IJPSR (2024), Volume 15, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 July 2024; received in revised form, 02 August 2024; accepted, 24 October 2024; published 01 December 2024

FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC TABLET OF DILTIAZEM HYDROCHLORIDE

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Keywords:

Osmotic System, Controlled porosity osmotic tablet, FT-IR, *In-vitro* dissolution, Leachable component

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ABSTRACT: Diltiazem HCl is a newer class of antiarrhythmic agent and available in market tablets as a controlled and extended-release formulation. The release pattern is influenced by atmosphere, pH, the presence of food and other physiological conditions of GI tract. This is possible by formulating and osmotic tablets. A controlled porosity osmotic tablet of diltiazem HCl was formulated by incorporating leachable polymer Eudragit in a PEG-400 semipermeable coating membrane. The core tablet was prepared using the drug, mannitol, MCC, PVP K-30, talc and mg. stearate. The core tablet was evaluated using bulk and tapped density, carr's index, angle of repose, hardness, weight variation, *in-vitro* dissolution. The thickness of PEG-400 coating was optimized to give a desired release of drug. The drug release study was done by USP-II dissolution apparatus (paddle). 2^3 factorial design used to optimized the formulation. The release pattern was concluded from kinetics models as a zero-order release. Osmotic tablet of diltiazem can be successfully formulated using diltiazem HCl (120mg), HPMCK100M (100mg), PEG 400(20%), mannitol (3.5mg) giving 6% weight gain which give zero order release for 24 hrs.

INTRODUCTION: Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens. Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food intake or that are dependent on patient age.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(12).3623-37

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(12).3623-37

In a typical therapeutic regimen, the drug dose and the dosing interval should be dictated by needs of body to maintain drug concentration within therapeutic window, thus ensuring efficacy while minimizing toxic side effects. Surveys indicated that frequent dosing and side effects caused due to therapeutic regimen greatly reduces patient compliance.

The problems with conventional dosage form are significant enough to make drug therapy with conventional dosage form less desirable than modified release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage form to achieve spatial placement is a compelling stimulus for development of controlled drug delivery.

Thus, controlled drug delivery has taken an important place in pharmaceutical development, improving tolerability and patient compliance with reduced adverse side effects.

The objective of the work is to get zero-order drug release and Formulation and development of stable controlled porosity osmotic pump of Diltiazem HCl [1, 2].

Basic Components of Osmotic Systems:

1. Drug
2. Osmogen
3. Semipermeable membrane
4. Suspending agents
5. Plasticizers

MATERIAL AND METHOD: Diltiazem HCl, MCC, Magnesium Stearate, Talc, mannitol, PEG were used in work done at V.B Manvar College of Pharmacy, Dumiyani, Rajkot.

Development of Analytical Method (UV Spectrophotometry): UV spectroscopic method is chosen for the analysis of Diltiazem HCl. Absorbance of each solution was measured at 224.8 nm was selected for further study.

Formulation of Core Tablets: The batches A1 to A3 were prepared by direct compression technique. The ingredients were individually passed through 40# and mixed for 15 minutes in mortar and pestle as per the formula shown in **Table 1**.

The blend pass to the sieve was again passed through 40# and lubricated with magnesium stearate and talc in glass bottle for 2 minutes. The blend was compressed into tablets using at single rotary multi punch tablet machine.

TABLE 1: FORMULATION OF CORE TABLETS

Sr. no.	Name of excipients	A_1	A_2	A_3
		mg/tab	mg/tab	mg/tab
1	Diltiazem hydrochloride	120	120	120
2	HPMC K100 M	50	100	150
3	MCC	150	100	50
4	$NaHCo_3$	50	50	50
5	Mg. Stearate	5	5	5
6	Talc	10	10	10
	Avg. core wt.	385	385	385

Coating Process:

Preparation of Polymeric Coating Solution: Coating polymer was hydrated in acetone by overnight storage. The solution was stirred for 15 min. Plasticizer (PEG 400) was added into the polymeric solution. The solution of color (Sudan red III) in acetone was gradually mixed stirrer bar as per given formula **Table 2.** At the end pass the filtrate through the sieve of fine pore diameter so that if any insoluble particle if remained in the coating solution will get removed.

TABLE 2: PREPARATION OF POLYMERIC COATING SOLUTION

Ingredients	% Of Each Ingredient			Uses
	B_1	B_2	B_3	
Microcrystalline Cellulose (W/V %)	1.5	1.5	1.5	Semipermeable, pH independent polymer
PEG – 400(W/W %)	12	24	36	Hydrophilic pore former, plasticizer
Sudan red III	q.s.	q.s.	q.s.	Colour
Acetone: IPA(80:20)	q.s.	q.s.	q.s.	solvent

Evaluation of Film Properties: Here the film of MCC was only evaluated. The free films were prepared by film casting method (8.5 ml in Petri dish of diameter 7.3 cm).

Polymeric coating solution was poured onto glass petridishes. Petridishes with polymeric coating solution were then left overnight (18 hr) for air drying [8]. Film was lifted from petridish. The film properties like folding endurance, tensile strength, elasticity and appearance were evaluated on the next day. In **Table 3** maintain parameters during coating process.

TABLE 3: LIST OF PARAMETERS MAINTAINED DURING COATING PROCESS

Batch size	20 tablets
Pan diameter	30 cm
Pan rotating speed	40 RPM
Inclination pan angle (^{o})	30
Inlet air temperature	70^{o}C
Distance between tablet bed and spray gun	15 – 20 cm

Preliminary Studies:

Formulation of Coated Tablets: Spray coating of MCC was performed on the core tablets (Batch A1) using single pan coater according to parameters given in **Table 4** procedure.

TABLE 4 FORMULATIONS FOR PREPARATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS

Excipients (mg)		Batch Code					
		C_1	C_2	C_3	D_1	D_2	D_3
Core tablet							
Diltiazem HCl	mg	120	120	120	120	120	120
HPMC K 100 M	mg	50	50	50	100	150	100
MCC	mg	150	150	150	100	50	100
$NaHCo_3$	mg	50	50	50	50	50	50
Mg stearate	mg	5	5	5	5	5	5
Talc	mg	10	10	10	10	10	10
Total wt	mg	385	385	385	385	385	385
Coating							
Mannitol	%W/V	3.5	3.5	3.5	3.5	3.5	3.5
PEG 400	%W/W	12	24	36	24	12	24
Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s
% wt gain	%	3	6	9	3	6	9

Optimization of Controlled Porosity Osmotic Pump Tablet of Diltiazem Hydrochloride using 2^3 Full Factorial Design: In the present work, a 23 full factorial design was adopted to find out the optimum combination of independent variables (Drug: osmogen ratio, concentration of pore former and the % wt gain) to obtain desired values of the T90 i.e. the average time required to release 90 % of Diltiazem hydrochloride.

The reason for selecting this factor is that we ultimately require the release of drug for the long period. 2 Levels selected: high and low for all three factors. The drug: osmogen ratio, concentration of pore former and the % wt gain were selected for different levels were based on the preliminary work done on the formulation of controlled porosity osmotic pump tablet of Diltiazem hydrochloride [4].

TABLE 5: FORMULATIONS FOR PREPARATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLET OF DILTIAZEM HYDROCHLORIDE AS PER 2^3 FULL FACTORIAL DESIGN

Excipients (mg)		Batch Code							
		AB_1	AB_2	AB_3	AB_4	AB_5	AB_6	AB_7	AB_8
Core tablet									
Diltiazem Hcl	mg	120	120	120	120	120	120	120	120
HPMC K 100 M	mg	50	50	50	50	150	150	150	150
MCC	mg	150	150	150	150	50	50	50	50
$NaHCo_3$	mg	50	50	50	50	50	50	50	50
Mg stearate	mg	5	5	5	5	5	5	5	5
Talc	mg	10	10	10	10	10	10	10	10
Total wt	mg	385	385	385	385	385	385	385	385
Coating									
Mannitol	%W/V	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
PEG 400	%W/W	24	24	24	24	24	24	36	36
Acetone:IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
% wt gain	%	3	9	3	9	3	9	3	9

Development of Formulation (using design expert software, the optimized formulation was received to have desired parameter like T90):

TABLE 6: DEVELOPMENT OF FORMULATION (BATCH AB9):

Excipients (mg)		Batch Code
		AB_9
Core tablet		
Diltiazem Hcl	Mg	120
HPMC K 100 M	Mg	100
MCC	Mg	100
$NaHCo_3$	Mg	50
Mg stearate	Mg	5
Talc	Mg	10
Total wt	Mg	385
Coating		
Mannitol	%W/V	3.5%
PEG 400	%W/W	24%
Acetone: IPA (80:20)	q.s	q.s
% wt. gain	%	6%

***In-vitro* Dissolution Profile:** In dissolution test using a USP paddle type II apparatus at 37°C ± 0.5°C in 900 ml of distill water with a speed of 50 rpm [3, 12]. Samples were withdrawn after predetermined time intervals and Diltiazem hydrochloride content was measured using a spectrophotometer (Systronics double beam spectrophotometer – 2203 SMART, UV-Visible Spectrophotometer) at a wavelength of 224.8 nm [7].

Kinetics of Drug Release: Various models are available for explaining the kinetics of drug release [6]. They are listed below:

- Zero order model
- First order model
- Higuchi model
- Hixon crowell model
- Korsmeyer and Peppas model
- Weibull distribution model

RESULT AND DISCUSSION:

Preformulation Study:

Preformulation Study of Diltiazem HCl:

TABLE 7: PREFORMULATION STUDY OF DILTIAZEM HCL

Sr. no.	Study	Parameter	Results
1	Physical state	Color	White to off white
2		State	Solid
3		Odor	Odorless
4	Powder characteristics(physical properties)	Angle of repose	32.57
5		Bulk density	0.20 g/ml
6		Tapped density	0.28 g/ml
7		Carr's index	28.57%
8		Hausner's ratio	1.4

Preformulation Study of Blend:

TABLE 8: PREFORMULATION STUDY OF BLEND

Sr. no.	Property of a blend	Observe value
1	Bulk density	0.53-0.62 g/ml
2	Tapped density	0.61-0.71 g/ml
3	%Carr's index	13.11-17.39
4	Hausner's ratio	1.15-1.25
5	Angle of repose	25.63-29.98

Fourier Transform Infrared Spectroscopy (Ft-Ir) Results of the Optimized Formulation:

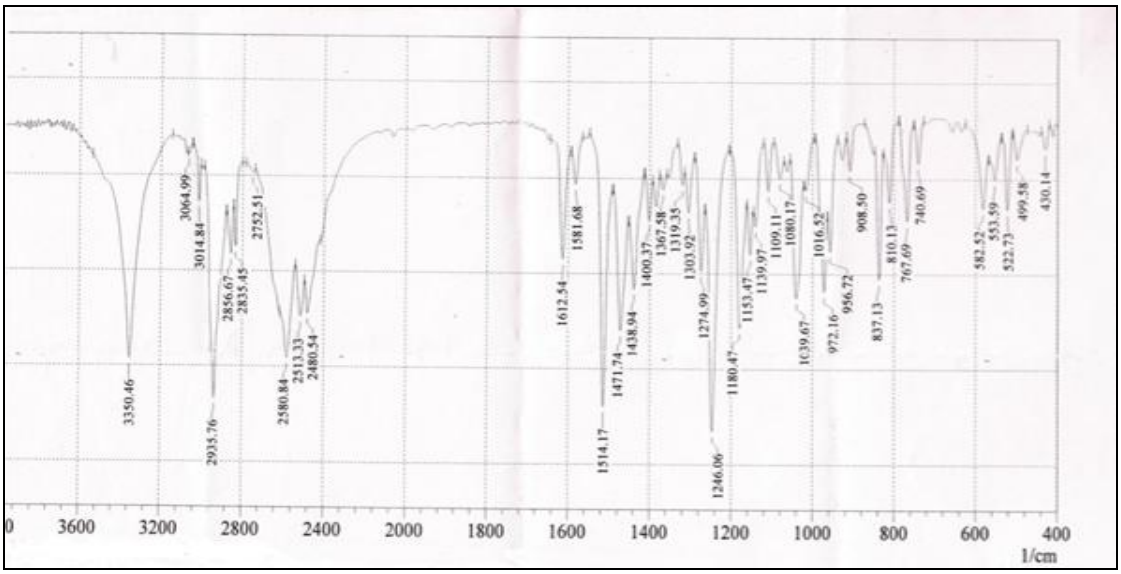

FIG. 1: FT-IR SPECTRUM OF DILTIAZEM HYDROCHLORIDE

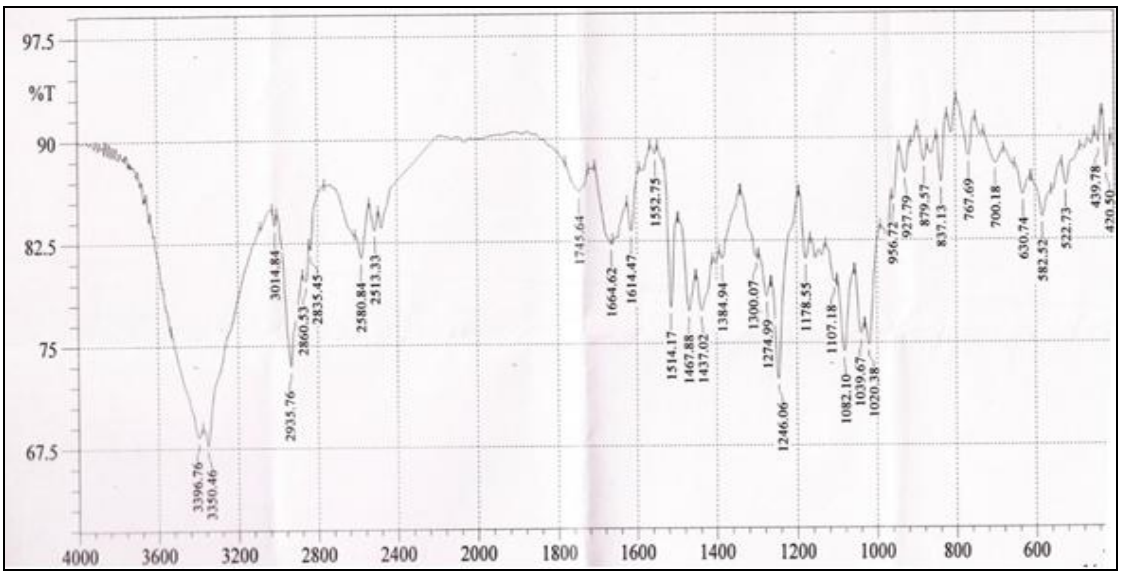

FIG. 2: FT-IR SPECTRUM OF OPTIMIZED FORMULATION OF DILTIAZEM HYDROCHLORIDE

Evaluation of Diltiazem Hydrochloride Core Material and Core Tablets:

TABLE 9: EVALUATION OF DILTIAZEM HCL CORE MATERIAL AND CORE TABLETS

Core material evaluation			
Test	**Batch No.**		
	A_1	**A_2**	**A_3**
Angle of repose	26	27.75	29.05
Hausner's ratio	1.24	1.15	1.25
Carr's index	19.51%	12.83%	19.87%
Tablets evaluation			
Test	**Batch No.**		
	A_1	**A_2**	**A_3**
Diameter (mm)	9	9	9
Thickness (mm)	5	5	5
Weight (mg)	385±5%	385±5%	385±5%
Hardness (kg/cm^2)	2.8	3	2.9
% Friability	0.3	0.3	0.3

In-vitro Dissolution Profile of Diltiazem Hydrochloride Core Tablets:

TABLE 10: *IN-VITRO* DISSOLUTION PROFILE OF DILTIAZEM HYDROCHLORIDE CORE TABLETS BATCH- A_1 TO A_3

Time (min)	%C.D.R.		
	Batch-A_1	Batch-A_2	Batch-A_3
0	0	0	0
10	11.77	27.05	43.34
20	26.28	43.21	79.95
30	40.96	60.53	80.07
40	59.98	75.35	93.20
50	74.06	92.96	94.04
60	80.47	93.63	94.55
70	91.85	94.74	96.31

%C.D.R. = Cumulative Drug Release

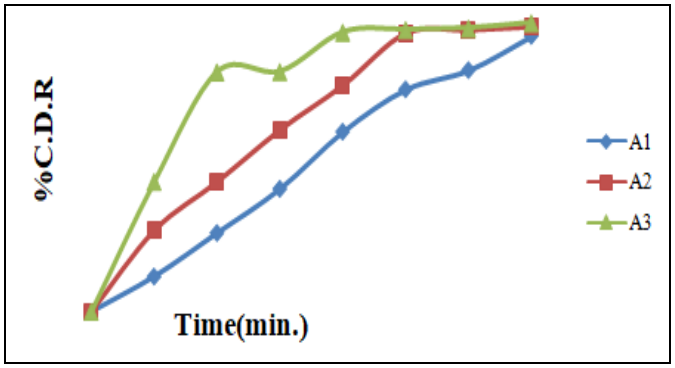

FIG. 3: *IN-VITRO* DISSOLUTION PROFILE OF DILTIAZEM HYDROCHLORIDE CORE TABLETS BATCH- A_1 TO A_3

Batches A1 to A3 having appropriate flow ability, compressibility, hardness and friability. From A1 to A3 with increasing amount of osmogen, the release rate was accelerated. All three batches having acceptable *in-vitro* dissolution requirement.

Preliminary Studies:

TABLE 11: *IN-VITRO* DISSOLUTION PROFILE OF PRELIMINARY BATCH:

Time (hr.)	%C.D.R.					
	C_1	C_2	C_3	D_1	D_2	D_3
0	0	0	0	0	0	0
1	6.97	1.75	1.52	2.03	1.57	4.25
2	11.12	12.33	8.18	5.32	9.98	14.33
4	25.07	20.02	14.27	13.19	14.09	21.01
6	32.09	22.44	21.55	20.10	20.63	31.65

%C.D.R.= Cumulative Drug Release

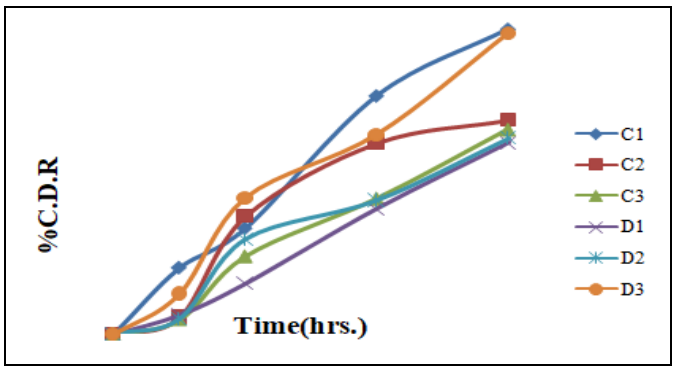

FIG. 4: *IN-VITRO* RELEASE PROFILE OF PRELIMINARY BATCH:

From dissolution profile of different batches C_1 to C_3, with increasing. So, release rate was controlled by adjusting the thickness of coating membrane. While with increasing in concentration of osmogen in core tablet and concentration of pore former in coating solution, $t_{90\%}$ was increased [5, 6].

So, release rate was accelerated, because generation of osmotic pressure in core tablet and formation of porous channels in the surface of the coating membrane, so, water could be imbibed into the membrane very quickly, accelerating drug release rate [10].

In batch C_1 (3%), % wt gain was very less, therefore, release rate was high. In batch C_3 (9%), % wt gain was high, so, retard release of drug as compare to C_1 (3%) was low. From batches D_1 to D_3 with increasing in concentration of pore former, increasing the number of pore which increased release rate. In batch D_1 (12%w/w), concentration of pore former was less, so, release rate was slower. In batch D_3 (36%w/w), concentration of pore former was high, so, release rate was higher.

Evaluation of Response Y (Time Required to Release 90% of Drug: As shown in **Table 12** and **Fig. 5**, independent variables Drug: osmogen ratio (X_1), Concentration of pore former(X_2), % wt gain (X_3) significantly influences the response Y (t_{90}) ranging from 1 hr to 24 hr. Refined model were generated using multiple linear regression analysis (EXCEL 2007) for the Y response.

TABLE 12: TIME REQUIRED TO RELEASE 90% OF DRUG FOR BATCHES AB_1 TO AB_8

Batches	Time required to release 90% of drug (hr)
AB_1	16.5
AB_2	22.31
AB_3	13.87
AB_4	24.11
AB_5	7.71
AB_6	21.97
AB_7	7.92
AB_8	20.10

TABLE 13: REGRESSION STATISTICS FOR Y (USING EXCEL 2007)

Regression Statistics for Y		
Multiple R		0.986116
R Square		0.972425
Adjusted R Square		0.806976
Standard Error		2.835498
Observations		8
Coefficients		**P-value**
β0	36.54375	0.278121
β1	-0.14435	0.339008
β2	-0.28552	0.643652
β3	-1.13792	0.644698
β12	0.001183	0.704429
β23	-0.00052	0.991
β31	0.014083	0.376294

Contour Plot: Using stat graphics centurion software.

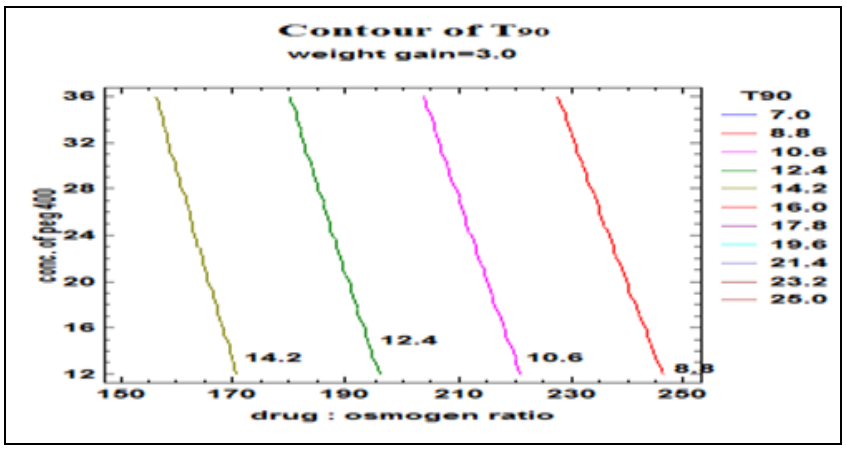

FIG. 5: CONTOUR OF ESTIMATED RESPONSE SURFACE

3D Surface Method: (Using stat graphics centurion software).

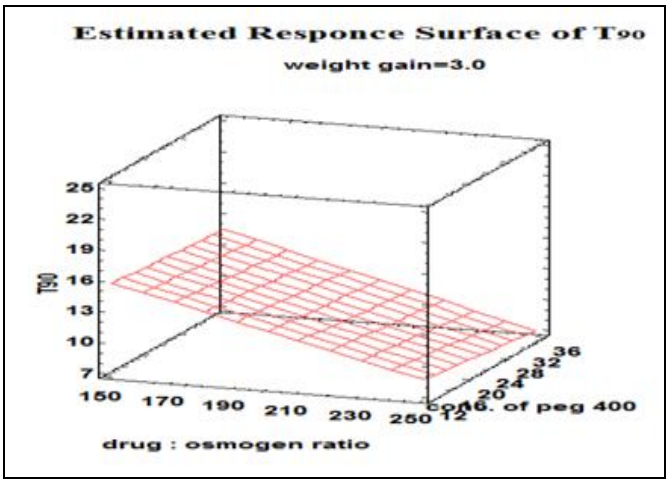

FIG. 6: 3-D GRAPH OF ESTIMATED RESPONSE SURFACE

As the Drug: Osmogen ratio and conc. Of PEG 400 increases the T90 decreases and as the %weight gain increases the T90 increases [9]. From above polynominal equation and graphical representation of two dimension (contour plot) and three dimension (3D method) following value of variable were optimize, ratio of drug to osmogen (1:1), concentaion of pore former(24%), and percentage of weight gain (6%).

Evaluation of Optimized Formulation: Selection the optimized batch basis of full factorial design and preparation of the optimized batch on the basis of it gave us the desired results in terms of time for 90% drug release (24 hr) and from the value of slop (4.117), optimize formulation release 2.951µg/hr in the body.

TABLE 14: EVALUATION OF DILTIAZEM HYDROCHLORIDE CORE MATERIAL AND CORE TABLETS

Core material evaluation	
Test	**Batch no.- AB_9**
Angle of repose	27.75
Hausner's ratio	1.24
Carr's index	19.87%
Tablets evaluation	
Diameter (mm)	9
Thickness (mm)	5
Weight (mg)	385 ± 5
Hardness (kg/cm^2)	3.5
% Friability	0.3

TABLE 15: *IN-VITRO* DISSOLUTION PROFILE OF BATCH- AB_9

Time (hr.)	%C.D.R.
0	0.000
1	6.37
2	12.27
4	17.04
6	31.07
8	42.42
10	44.82
12	52.59
14	55.37
16	65.08
18	76.79
20	88.01
22	96.33
24	99.62
%C.D.R. = Cumulative Drug Release	

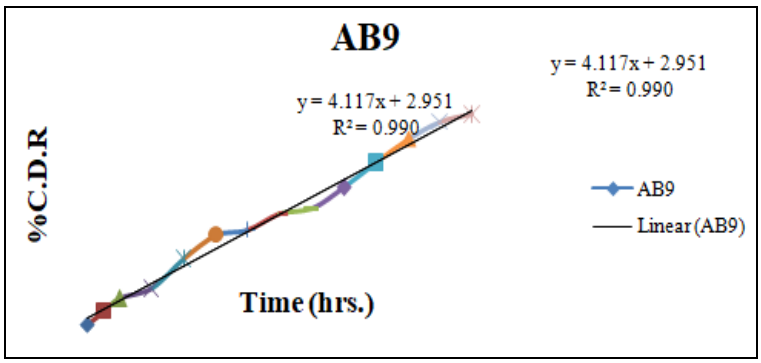

FIG. 7: *IN-VITRO* RELEASE PROFILE OF BATCH- AB_9

Kinetics of Drug Release: Table 15 shows that zero order model showed best fit for release of Diltiazem hydrochloride from dosage form because it shows highest R Square value (0.990). The K_0 release rate was 4.296.

TABLE 16: MODEL FITTING FOR KINETICS OF DRUG RELEASE OF DILTIAZEM HYDROCHLORIDE FROM DOSAGE FORM

Batch code	Zero order		First order		Higuchi		Korsmeyer		
	R-square	K_z	R-square	K_f	R-square	K_h	R-square	K_k	N

AB_1	0.978	5.418	0.886	0.087	0.826	18.65	0.982	3.958	1.12
AB_2	0.961	3.907	0.961	0.065	0.912	15.79	0.979	6.980	0.802
AB_3	0.699	6.545	0.980	0.164	0.979	23.83	0.981	25.94	0.465
AB_4	0.964	4.054	0.902	0.066	0.819	16.05	0.964	3.361	1.38
AB_5	0.557	7.143	0.973	0.227	0.929	26.24	0.943	32.28	0.414
AB_6	0.893	4.327	0.972	0.083	0.933	17.70	0.962	11.13	0.670
AB_7	0.651	7.030	0.977	0.204	0.929	25.67	0.931	27.72	0.468
AB_8	0.980	4.441	0.936	0.080	0.895	17.84	0.987	6.364	0.875
AB_9	0.995	4.296	0.933	0.074	0.890	17.22	0.991	5.547	0.911

Stability Study of Optimized Batch (Batch-AB_9): The percentage of drug release before and after storage was found to be similar. Dissolution profiles before and after storage are nearly overlapable [11]. The change in the drug release pattern i.e. dissolution profile was not significantly different from the two months previous tablet dissolution profile.

TABLE 17: COMPARISON OF *IN-VITRO* RELEASE PROFILE OF BATCH AB_9 TABLETS BEFORE AND AFTER (60^{TH} DAY) STABILITY STUDY STORED AT 35 TO 40°C

Time (hrs)	%C.D.R.	
	Before	After 60 days
0	0.000	0.000
1	6.37	7.31
2	12.27	10.21
4	17.04	21.34
6	31.07	37.44
8	42.42	51.22
10	44.82	63.78
12	52.59	69.93
14	55.37	74.11
16	65.08	81.22
18	76.79	86.33
20	88.01	91.44
22	96.33	94.36
24	99.62	99.40

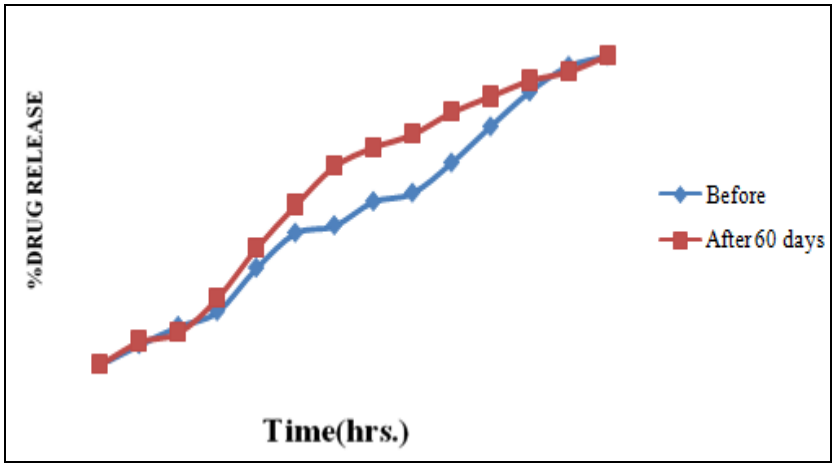

FIG. 8: COMPARISON OF *IN-VITRO* DISSOLUTION PROFILE OF BATCH AB9 TABLETS BEFORE AND AFTER (60TH DAY) STABILITY STUDY STORED AT 35 °C TO 40°C

TABLE 18: STUDENT T-TEST BETWEEN BEFORE AND AFTER 60 DAYS OF BATCH AB_9

t-Test: Paired Two Sample for Means		
	Variable 1	Variable 2
Mean	49.12714	56.29214286
Variance	1106.114	1224.648372
Observations	14	14
Hypothesized Mean Difference	0	
Df	26	

t Stat	-0.5553
P(T<=t) one-tail	0.291717
t Critical one-tail	1.705618
P(T<=t) two-tail	0.583433
t Critical two-tail	2.0555292

Student t – test between before and after 60 days of storage showed insignificant difference (t-cal< t-tab.). It conforms that there must be adequate storage container.

TABLE 19: COMPARISON OF OPTIMIZED BATCH WITH MARKET FORMULATION OF DILTIAZEM HYDROCHLORIDE (CARDIZEM LA AND DILGARD XL)

Time (hrs)	%C.P.R.		
	Optimize batch	Market product (Cardizem LA)	Market product (Dilgard XL)
0	0.000	0.000	0.000
1	6.37	2.33	27.12
2	12.27	5.65	45.23
4	17.04	11.54	75.83
6	31.07	15.89	95.64
8	42.42	23.72	-
10	44.82	32.84	-
12	52.59	41.12	-
14	55.37	54.36	-
16	65.08	62.89	-
18	76.79	69.12	-
20	88.01	75.72	-
22	96.33	83.45	-
24	99.62	87.44	-

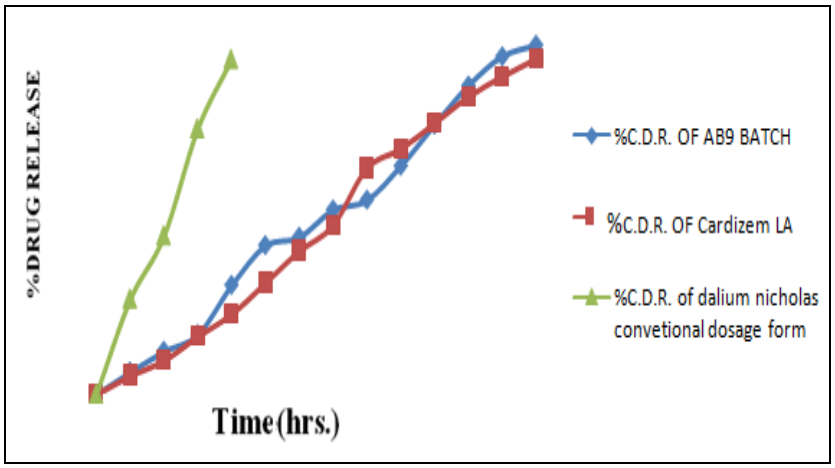

FIG. 9: COMPARISON OF IN-VITRO DISSOLUTION PROFILE OF BATCH AB_9 AND MARKET PRODUCT (CARDIZEM LA AND DILGARD XL)

The above comparison study showed that *in-vitro* dissolution profile of optimized batch was giving better release profile than marketed product.

CONCLUSION: The research work was aimed at formulating a controlled porosity osmotic pump tablets of Diltiazem hydrochloride. The developed extended-release formulation delivered a drug for 24 hr. In this developed formulation pores are formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves and pore formation occurs. Subsequently, water diffuses into the core through the micro porous membrane, setting up an osmotic gradient and thereby controlling the release of drug. The release rate from these types of systems was dependent on the concentration of osmogen in the tablet core, which generate osmotic pressure difference across the membrane, level of leachable components in the coating (conc. of pore former) and coating thickness (% wt gain).

Diltiazem hydrochloride having high solubility and relatively short half- life (3-4.5 hr) suggest its suitability for an extended formulation. Core tablets

were prepared by direct compression technique using mannitol as osmogen and MCC as filler showed excellent flowability and good compressibility. Directly compressible core tablets showed acceptable friability and were evaluated for in vitro dissolution. ($t_{90\%}$ for A_1- 58 min, A_2- 52 min. and A_3- 41 min). The core tablets were coated by coating agent mannitol (3.5%w/v) with PEG 400 (24%w/w) as water soluble pore former and plasticizer. 2^3 factorial design was employed to optimize the controlled porosity osmotic tablets of Diltiazem hydrochloride by selecting ratio of drug to osmogen, amount of pore former and membrane weight gain. Optimized batch (Batch AB_9) was formulated using 1:1 drug: osmogen, 24% w/w of pore former and 6% weight gain. It gave desired results in terms of time for 90% drug release Tt $_{90\%}$) for 24 hr. The compatibility of drug with excipients was studied by FT-IR. It shows that there was no chemical interaction between the drug and excipients. The stability study of optimized batch was carried out at room temperature for two months in a double plastic zip bags and it was found that there was no statistically significant difference in *in-vitro* drug release before and after stability study. No fracture of coat from any tablet of optimized batch was noticed during and after stability study. It can be concluded that a controlled porosity osmotic tablet can be successfully formulated using Diltiazem HCl (120mg), HPMC K100 M(100mg), PEG 400(24%) with mannitol (3.5%w/v) for thick coating giving 6% weight gain on coating Along with other convetional tablet. The developed controlled porosity of osmotic tablet of Diltiazem HCl can be utilized to deliver drug at a zero-order controlled rate for 24 hrs.

ACKNOWLEDGMENT: None

CONFLICTS OF INTERESTS: Authors declare no conflicts of interest.

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How to cite this article:
Agravat M and Devamurari P: Formulation and evaluation of controlled porosity osmotic tablet of diltiazem hydrochloride. Int J Pharm Sci & Res 2024; 15(12): 3623-37. doi: 10.13040/IJPSR.0975-8232.15(12).3623-37.