Int. J. Drug Res. Tech. 2016, Vol. 6 (3), 150-163 ISSN 2277 - 1506

International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Original Research Paper

FORMULATION DEVELOPMENT, OPTIMIZATION AND EVALUATION OF BILAYER PUSH-PULL OSMOTIC PUMP TABLET OF ATENOLOL USING 3^2 FACTORIAL DESIGNS

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ABSTRACT

The objective of this study was to Formulate, Optimize and Evaluate Bilayer Push Pull Osmotic Pump Tablet of Atenolol Using 3^2 Factorial Designs. The main aim is to improve the site specification and to provide the controlled release of drug for once-a-day drug delivery system. The push pull osmotic tablets were prepared by double compression method; this study evaluates that regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by some factors as, the plasticizer proportion in the membrane, the osmotic agent proportion and the drug layer polymer grade. The influence of each factor was investigated defining their acceptability range. Results, shows that the use of suspension agent in drug layer affects the drug release. The formulation batch F3 was taken as ideal optimized batch. On the basis of results the effect of orifice diameter, polymer concentration in drug layer, coating composition and plasticizer amount was tested and promising results were found. The drug release was independent of pH but dependent on the osmotic pressure of the dissolution medium. The release kinetics followed the peppas model.

Keywords: Atenolol, Polyethylene oxide, Polyvinyl pyrrolidione K-30, Osmotic pump, Oral osmotic systems, *In-vitro* study.

INTRODUCTION

One of the common ways to reach drug in systemic circulation is via oral route. Oral drug delivery poses problem of multiple dosing for drugs for which half-life is less. Multiple dosing per day is leading cause of reduced patient compliance. To solve this there are two approaches could be explored, first is invention of drug for which half-life is more and second is to extend half-life of drug. Controlled Drug Delivery System (CDDS) helps to get desired drug release pattern for long period of time so that rate and extent of drug release from oral drug delivery could be predicted. Controlled Drug Delivery System is classified as Physical, Chemical and Biochemical processes. Physical controlled drug delivery includes Osmotic pressure activated drug delivery system, Hydrodynamic pressure activated drug delivery system, Vapour pressure activated drug delivery system, Mechanically activated drug delivery system, Magnetically activated drug delivery system, Sonophoretic activated drug delivery system, Iontophoresis activated drug delivery system and Hydration activated drug delivery system. Hypertension means the abnormally raised arterial blood pressure. There are many conditions which elevate arterial pressure including primary renal disease, hyperthyroidism, hyper aldosteronism leading to secondary hypertension. The primary hypertension causes are not known. In these patients although the cause is not completely understood, heredity, emotional factors and various physiological factors play a major role in raising blood pressure. If this condition is not treated, complication like left heart failure, congestive heart failure, cerebrovascular disease, kidney damage and atherosclerosis may develop. Normal blood pressure is defined as levels

<120/80 mmHg. Systolic blood pressure of 120–139 mmHg or diastolic blood pressure 80–89 mmHg is classified as prehypertension. These patients are at increased risk for progression to hypertension. Hypertension is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

MATERIAL AND METHODS

Material

Atenolol, Polyethylene Oxide was obtained as a gift sample from Lupin Pharmaceutical, Mulshi, Nande Village, Pune, Maharashtra (India). PVP-K30 from OZONE International, Mumbai; Lactose, Magnesium stearate, Magnesium stearate from LOBA Chemie Pvt. Ltd., Mumbai, All other chemicals and reagents used were of AR grade.

Method

Formulation Development, Optimization and Evaluation of Bilayer Push-Pull Osmotic Pump Tablet of Atenolol Using 3^2 Factorial Designs.

UV-Visible Spectroscopic Scanning-Spectral Analysis

Determination of UV Spectrum in Methanol

The stock solution of atenolol was prepared by dissolving it in methanol. A dilution of 15µg/ml was kept in cuvette. In UV spectrum was recorded using double beam UV-visible spectrophotometer in the wavelength range 200-400 nm with methanol.

Calibration Curve of the Drug

Preparation of Standard Curve in Methanol: The stock solution of atenolol was prepared by dissolving 5 mg of drug in methanol and final volume was made to 100 ml. The solutions in concentration range of 2-10µg/ml were prepared by appropriate dilution of stock solution. The UV absorbance of these solutions was determined spectrophotometricaly at ƛ max 226 nm.

Table 1: Variables and their levels in 3^2 factorial design

A) Independent variables	Levels		
	Low	Medium	High
Amount of osmopolymer (X1)	38mg	40mg	42mg
Amount of osmotic agent (X2)	15mg	20mg	25mg
Transformed value	-1	0	+1
B) Dependent variable (Y): % Cumulative drug release at 8 Hrs.			

Table 2: Variable level in coded form

Batch code	Amount of osmopolymer (X1)	Amount of osmotic agent (X2)
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table 3: Formulation of push-pull osmotic pump tablet

	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
A)	**Drug Layer 300 mg**									
	1) Atenolol	50	50	50	50	50	50	50	50	50
	2) PVP K – 30	25	25	25	35	35	35	45	45	45
	3) PEO 200K	70	75	80	70	75	80	70	75	80
	4) Lactose	143	138	133	133	128	123	123	118	113
	5) Mag. Stearate	12	12	12	12	12	12	12	12	12
	6) Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
B)	**Push Layer 200 mg**									
	1) PVP K – 30	15	15	20	20	20	25	25	25	25
	2) KCL	40	40	40	40	40	40	40	40	40
	3) PEO 200K	38	40	42	38	40	42	38	40	42
	4) Lactose	101	99	97	96	94	92	91	89	87
	5) Ferric O. (Red)	6	6	6	6	6	6	6	6	6
	6) Mag. Stearate	6	6	6	6	6	6	6	6	6
	7) Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**
	Total Tablet	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Preparation of Drug Layer and Push Layer Granules

- Fist sieved all ingredients trough sieve number 100.
- Drug layer ingredients and push layer ingredients were separately blended except the lubricant
- The alcoholic solution was added to drug layer ingredients to form a damp mass and a coloring agent Ferric oxide was added to the drug layer.
- Then it was passed through a sieve number 16 meshes and was dried in hot air oven. In this dried granules mixed with lubricant.
- Push layer granules were also prepared in a similar manner.
- Then add lubricant before going for compression.

Preparation of Core Push Pull Osmotic Tablet

To compressed drug layer and the push layer into bi-layer tablets using a Single rotary tablet machine (Lab Press) by double compression method, with 8 mm concave punches.

Coating of tablets

Preparations of Coating Solution: Cellulose Acetate as polymer 12 gm is dissolved in DCM as solvent 480 ml, Methanol as solvent 120 ml (4:1) using mechanical stirrer. Then add PEG-400 (Liquid-Solution) as plasticizer 2.0 ml, with constant stirring

Coating process

The core tablets were coated in a coating machine (Dolphin coater) by spray coating process. The coating process parameters were optimized with respect to pan speed, inlet air temperature and spray rate. Coating process was started when the required bed temperature was attained. Coating process parameters were set as coating pan speed 12-16 rpm, inlet air temperature 45-50^0 C (inlet), exhaust air temp.-35^0 C (outlet) and spray gun-3 ml/min.

Percentage Weight Gain of Tablet: Four percent (4%) weight gain of all tablets after coating to the initial wt. of tablet before coating.

Evaluation

Uniformity of Weight

The weight variation test is carried out in order ensure uniformity in the weight of the tablets in a batch. The total weight of 20 tablets from formulation was determined and the average was calculated. The individual weights of tablets were also determined and the weight variation was calculated by the formula.

% deviation= individual weight – average weight / average weight x 100

Hardness

To select ten tablets from each batch and hardness was measured using Monsanto Hardness tester to find the average tablet hardness.

Thickness

Five Tablets were selected at random from individual formulations and thickness was measured by using Digital Vernier calliper scale.

Friability (%F)

Twenty tablets from each batch were selected randomly and weighed. Then put 20 tablets in Roche Friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again.

% F = (Wi-Wr/Wi) 100

Drug Content

Five tablets were weighed individually and powdered. An amount equivalent to 5 mg of Atenolol was accurately weighed and placed in a 100 ml volumetric flask to prepare a 100 ppm solution in phosphate buffer pH. 6.8 or any solvent (as stock). From this 1ml dilute to 10 ml volumetric flask (10 ppm). The sample was measured at λmax 226 nm using a Shimadzu UV/Vis double beam spectrophotometer and Atenolol concentration was calculated from the standard curve prepared simultaneously.

Drug Excipients Interaction Study

Fourier Transform Infrared Spectroscopy (FT-IR)

It was determined by FT-IR (PRESTIGE-21, Shimadzu). The base line correction was done with blank background measurement. Then the spectrum of dried drug was run. FT-IR spectra were recorded in the wavelength region of 4000 to 500 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The 3.41 mg of sample was weighed and sealed in aluminum pan. Empty aluminum pan was used as a reference. DSC thermogram was recorded.

In-Vitro Drug Release Studies

The release rate of Atenolol from Push pull osmotic tablets was determined up to 12 hours using USP-type II dissolution testing apparatus (paddle type). The dissolution test was performed using the dissolution medium (900ml) consisted of 0.1N hydrochloric acid for first 2 hours and the phosphate buffer pH 6.8 from 3 to next 12 hours, maintained and at 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at specific time intervals (Each 1Hr) throughout the dissolution study of 12 hours for analysis and replaced with fresh dissolution medium thus maintained sink condition. In 5ml solution withdraw 1ml solution an dilute with phosphate buffer pH. 6.8. The samples were filtered using whatmann Filter Paper. The samples were analysed for Atenolol at 226 nm using a Shimadzu UV-1800 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release (% CDR) was calculated using an equation obtained from a standard curve and PCP Disso Software.

Kinetics of Drug Release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.

RESULT AND DISCUSSION

UV-Visible Spectroscopic Scanning-Spectral Analysis

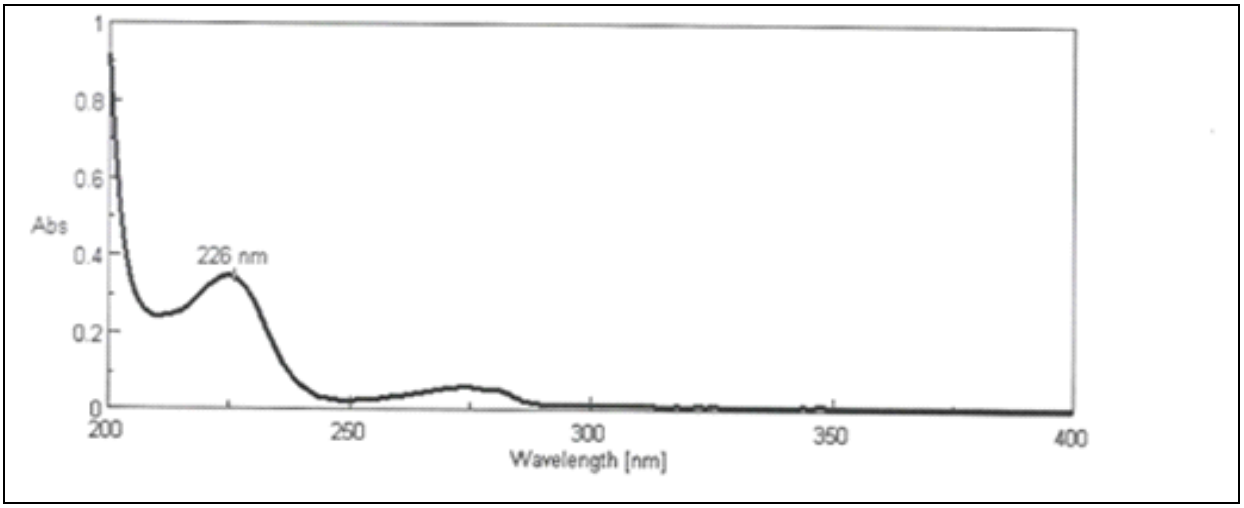

Figure 1: Wavelength maxima of Atenolol in Methanol (Conc. 20ppm)–226 nm

Table 4: Standard calibration curve data for atenolol

Conc. (ppm)	Abs. at (226nm)
0	0.0000
5	0.2104
10	0.4067
15	0.6231
20	0.7506
25	1.0456

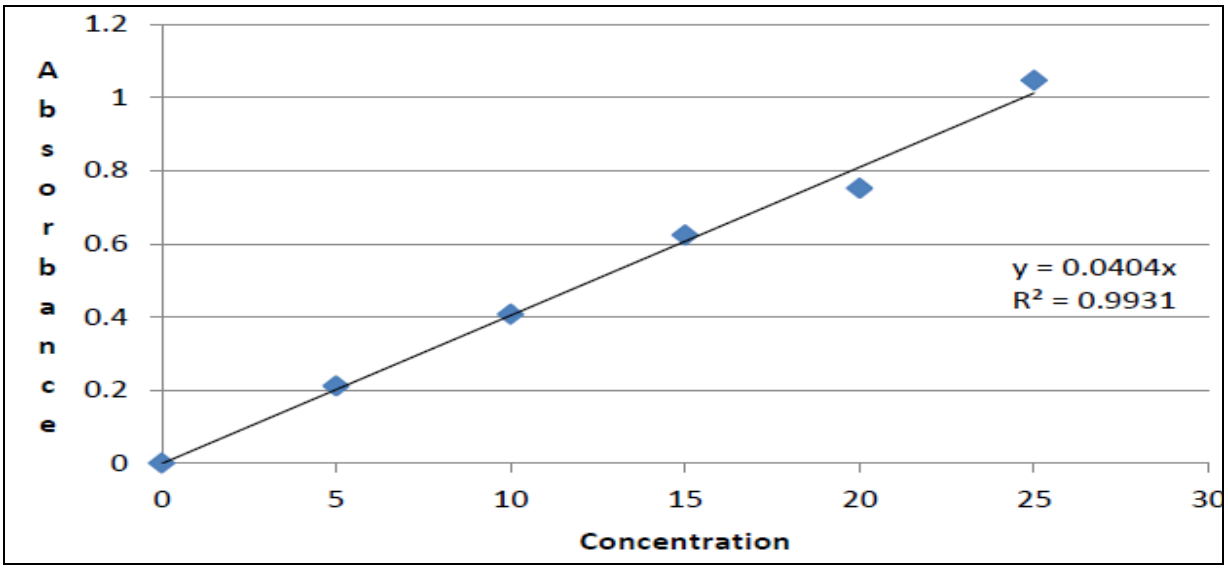

Figure 2: Calibration curve of atenolol

Drug-Polymer Interaction Study

FT-IR

The drug was found compatible with polymer.

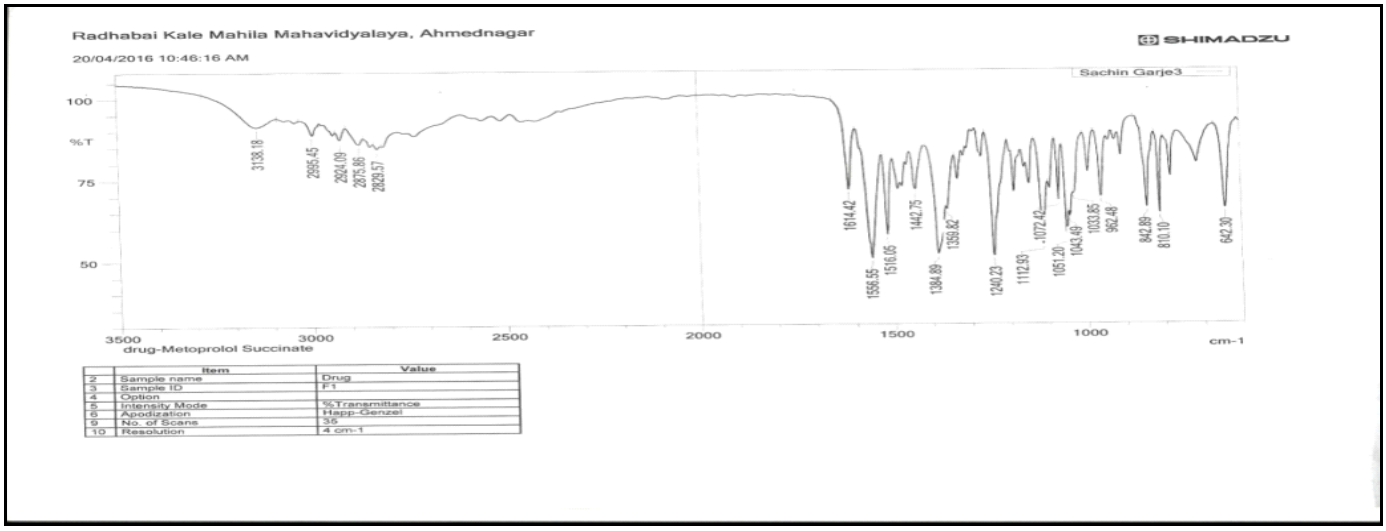

Figure 3: FTIR Spectra of API metoprolol succinate

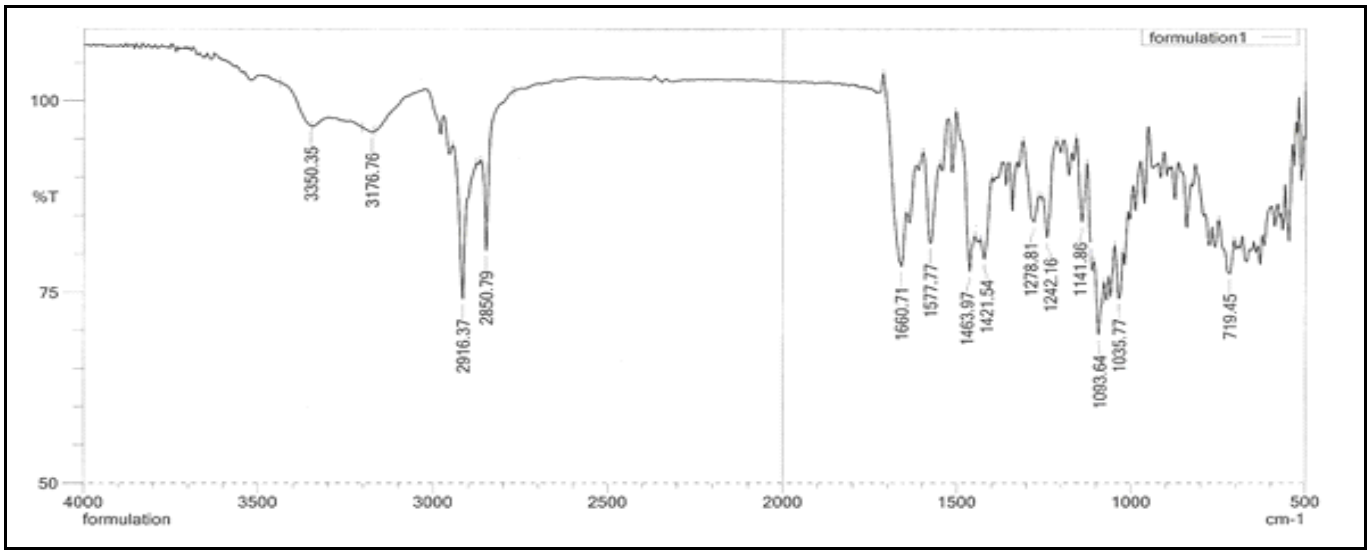

Figure 4: FT-IR spectrum of Formulation F3 Batch

Differential Scanning Colorimetry (DSC)

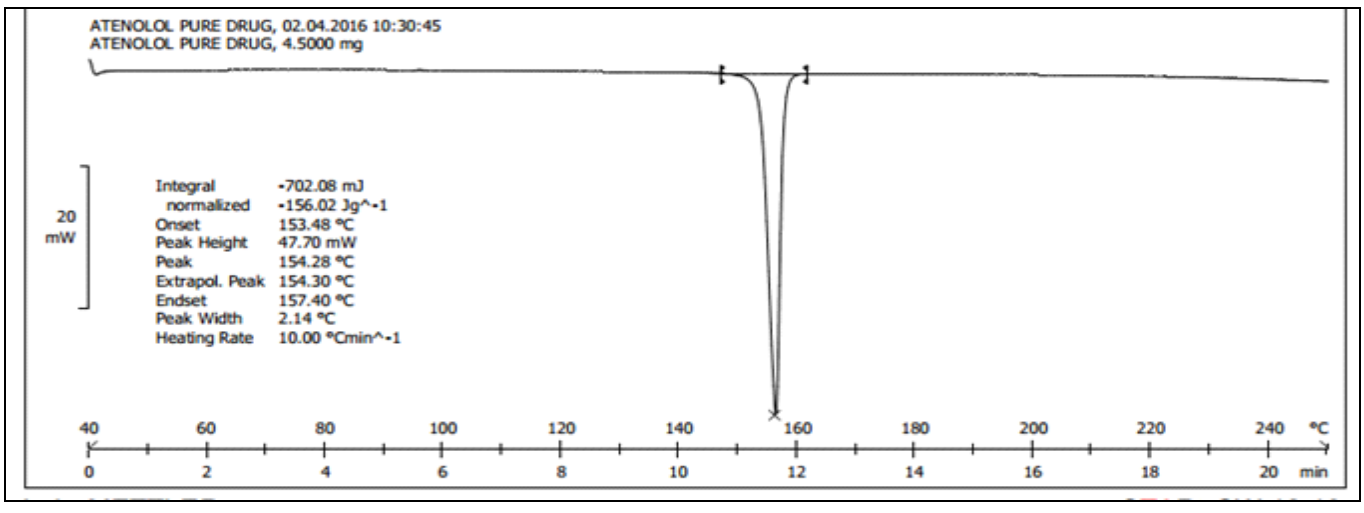

Figure 5: DSC Thermogram of API Atenolol

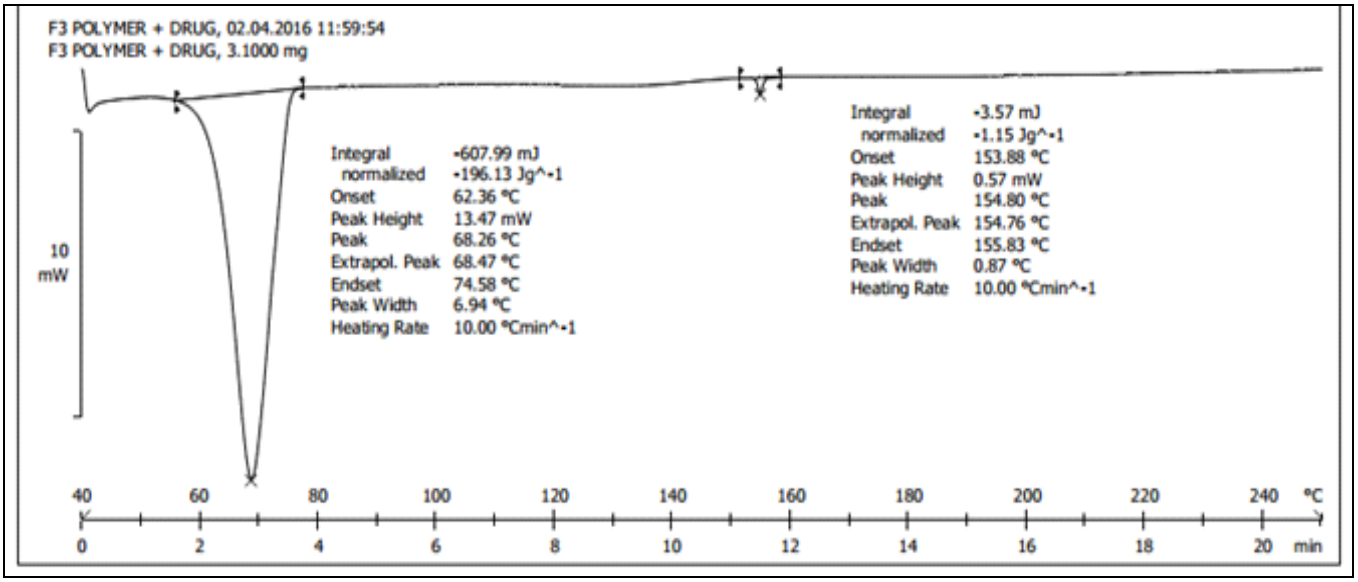

Figure 6: DSC Thermogram of Atenolol + Polymer

Evaluation

Pre Compressional Parameters for Granules

Precompressional parameters of granules of Drug layer and Push layer shows in (Table). Angle of repose, Carr's index, and Hausner's ratio are in the range given in official standards.

Table 5: Pre compression parameters for granules of drug layer

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hauseners Ratio	Angle of Repose (θ)
D1	0.35	0.45	8.62	1.01	26 .12
D2	0.39	0.39	10.00	1.09	28 .56
D3	0.36	0.48	6.55	1.18	22 .43
D4	0.33	0.49	12.15	1.12	25. 21
D5	0.34	0.40	14.36	1.16	20 .59
D6	0.36	0.39	17.03	1.20	30.47
D7	0.33	0.41	9.25	1.08	29 .39
D8	0.38	0.45	11.78	1.10	31 .76
D9	0.33	0.40	15.51	1.14	29 .65

Table 6: Pre compression parameters for granules of push layer

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hauseners Ratio	Angle of Repose (θ)
P1	0.35	0.40	6.23	1.16	27.92
P2	0.39	0.45	9.52	1.11	27.84
P3	0.38	0.32	8.6	1.21	29.57
P4	0.34	0.43	11.89	1.18	25.25
P5	0.32	0.42	15.65	1.34	29 .67
P6	0.33	0.40	13.81	1.10	26.43
P7	0.37	0.43	15.42	1.05	30.51
P8	0.38	0.42	12.06	1.07	31.03
P9	0.30	0.41	6.9	1.26	29.68

Evaluation of Post Compression Parameter

To shows post compressional parameters i.e. Hardness (7.26 to 7.50 kg/cm^2), Friability (0.22 to 0.28 %), Weight variation (0.490 to 0.510mg), Thickness (3.86 to 3.87 mm) and Diameter (9.02 to 9.04 mm). Drug content was (98.28 to 98.16%) within the acceptable official limits.

Table 7: Post compression parameters of tablet formulation

Batch	Weight variation (n=20)	Thickness (mm, n=10)	Diameter (mm, n=10)	Hardness (kg/cm2, n=10)	Friability (%, n=20)	% Drug Content (n=3)	Coating Thickness (mm, n=3)
F1	500 ± 0.5	3.86	9.02	6.18	0.22	98.23%	0.21
F2	500 ± 1.0	3.86	9.04	7.04	0.24	98.12%	0.22
F3	490 ± 1.0	3.85	9.02	6.15	0.23	99.04%	0.23
F4	510 ± 0.5	3.85	9.02	6.10	0.26	99.16%	0.22
F5	500 ± 0.5	3.87	9.03	6.16	0.27	98.74%	0.21
F6	500 ± 1.5	3.86	9.03	6.12	0.25	97.29%	0.23
F7	490 ± 1.0	3.85	9.02	6.16	0.28	98.65%	0.21
F8	490 ± 1.5	3.86	9.04	6.17	0.22	99.02%	0.23
F9	500 ± 0.5	3.85	9.02	6.18	0.25	98.34%	0.21

In-Vitro Drug Release Studies

Table 8: In-vitro % Drug Release of F1 to F9

	Percentage Cumulative Drug Release Profile of all formulations								
Time [hr.]	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	**0**	0	0	0	0	0	0
1	41.39	34.41	28.85	34.47	39.20	48.21	28.91	31.04	27.12
2	43.04	38.52	42.88	39.14	43.61	55.43	32.44	38.49	31.01
3	49.12	45.61	50.85	43.27	48.19	58.82	39.69	46.16	37.18
4	54.22	51.12	58.24	50.78	54.13	62.91	44.20	52.21	43.86
5	58.11	57.19	64.19	56.38	59.60	68.39	49.02	58.80	50.04
6	62.14	66.22	71.93	63.17	64.01	73.29	57.32	66.31	56.24
7	68.45	72.41	75.27	68.93	68.32	77.94	62.11	71.89	60.71
8	71.32	77.81	81.79	74.88	73.11	82.18	68.87	78.97	69.20
9	76.26	83.20	86.18	80.96	76.48	87.17	76.22	83.47	77.38
10	81.52	86.26	90.14	85.75	81.24	93.01	82.10	88.90	82.93
11	86.11	88.43	95.05	89.53	85.92	96.71	90.23	91.57	88.15
12	89.57	90.04	98.28	94.51	92.47	98.15	96.57	95.08	91.64

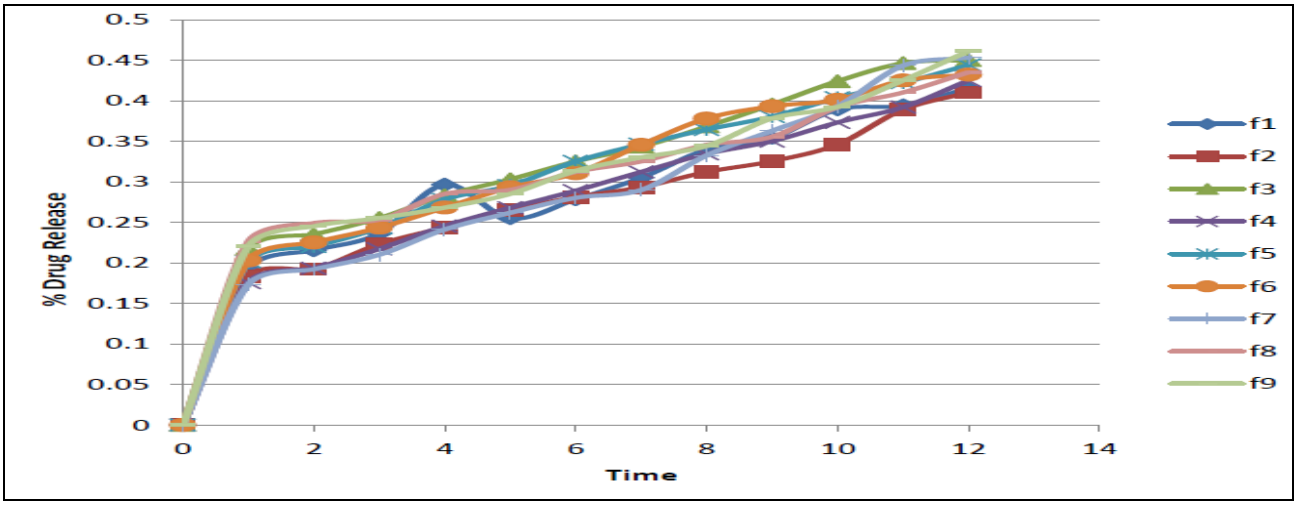

Figure 7: In Vitro Drug Release studies formulation (F1-F9)

RSM Optimization Results

ANOVA

Table 9: ANOVA for Response Surface 2FI model

Source	Sum of Squares	df	Mean Square	F Value	p-value, Prob > F	
Model	64.91	3	21.64	12.63	0.0407	Significant
A-pvp k30	9.23	1	9.23	1.55	0.2688	
B-PEO 200k	9.18	1	9.18	1.54	0.2699	
AB	46.51	1	46.51	7.80	0.0383	
Residual	29.83	5	5.97			
Cor Total	94.74	8				

Std. Dev.	2.44	R-Squared	0.6852
Mean	94.26	Adj R-Squared	0.4962
C.V. %	2.59	Pred R-Squared	-0.1266
PRESS	106.74	Adeq Precision	5.711

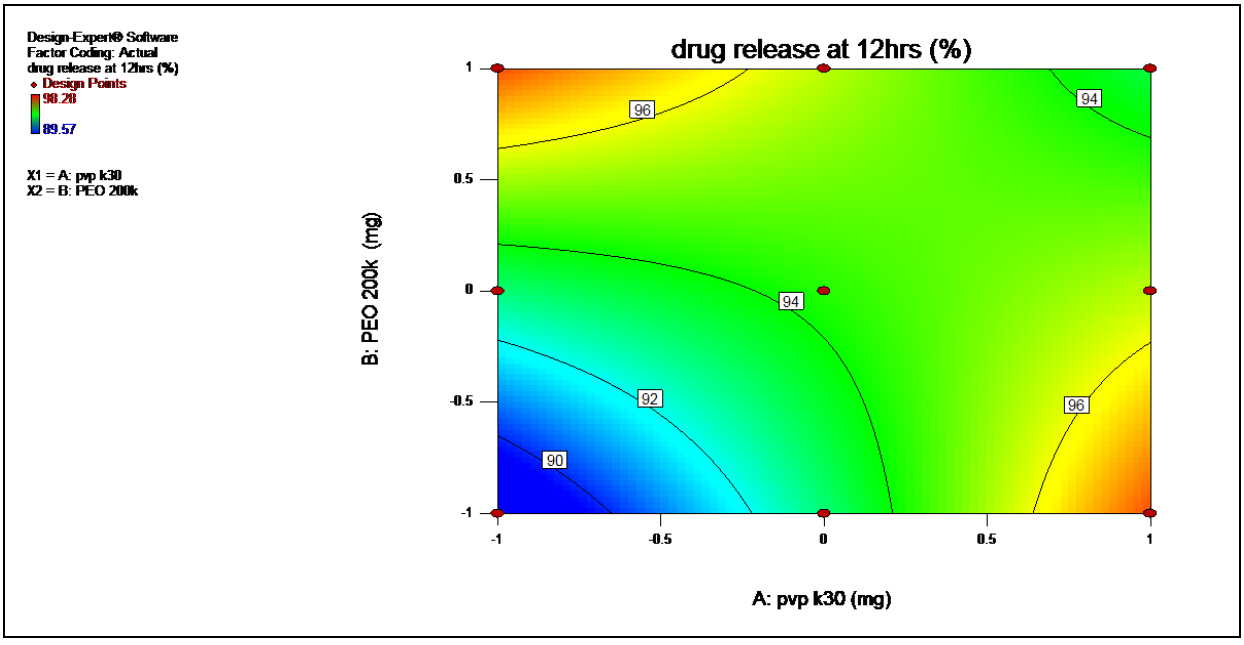

Figure 8: Contour Plot for showing the effect of pvpK30 (X1) and PEO (X2) on Percent CDR at 12 Hr

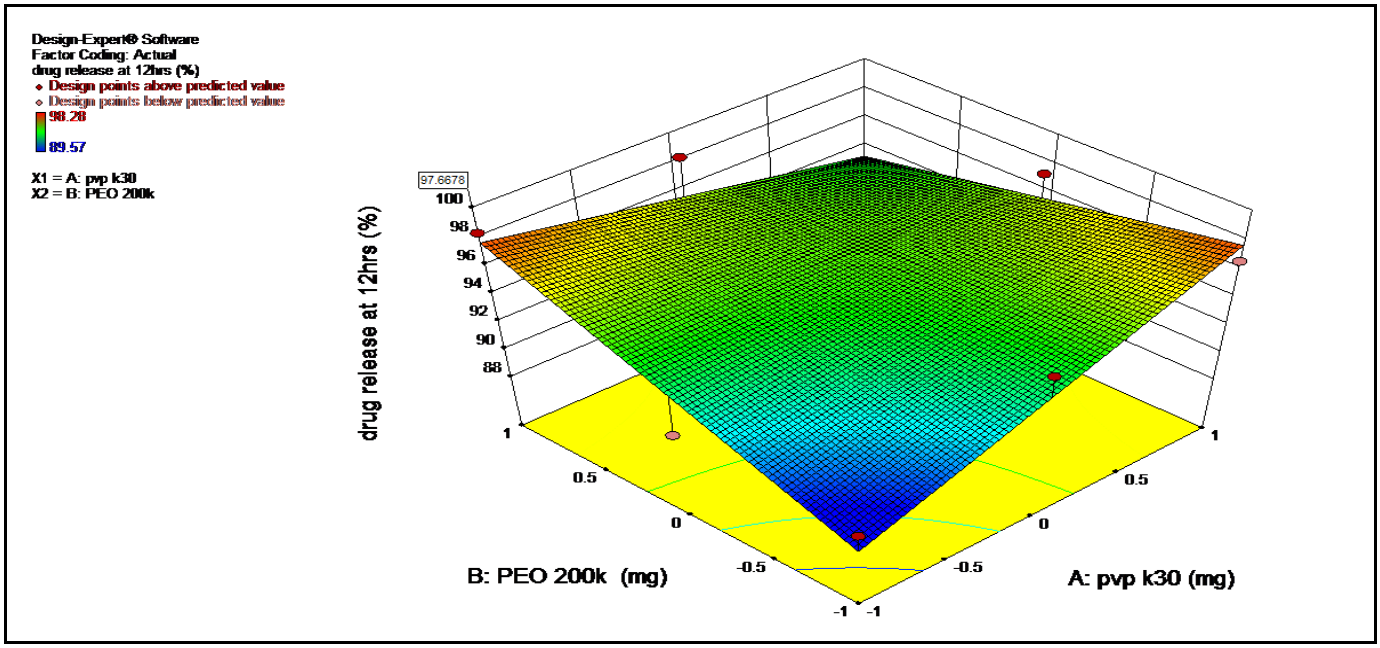

Figure 9: Response Surface Plot for showing the effect of pvpK30 (X1) and PEO (X2) on % CDR at 12 Hr

Checkpoint Analysis

Table 10: Checkpoint batches with predicted and measured % CDR at 12 Hrs.

Batch Code	Amount of (X1)	Amount of stabilizing agent (X2)	% CDR at 12 Hrs	
			Measured	Predicted
F3	-1	1	98.28	97.66
F4	0	1	94.51	93.02

Optimal Formulation

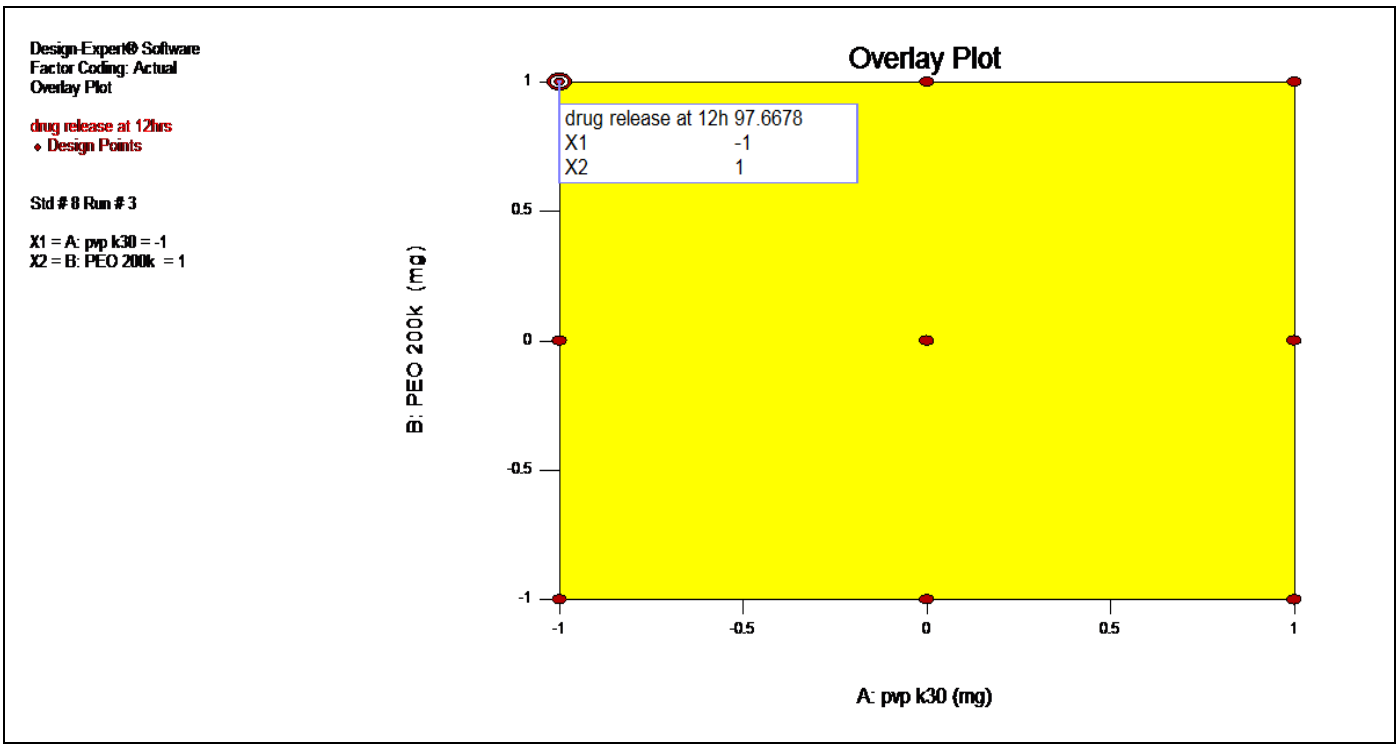

Figure 10: Overlay plot of response variables (F3 optimize batch) batch

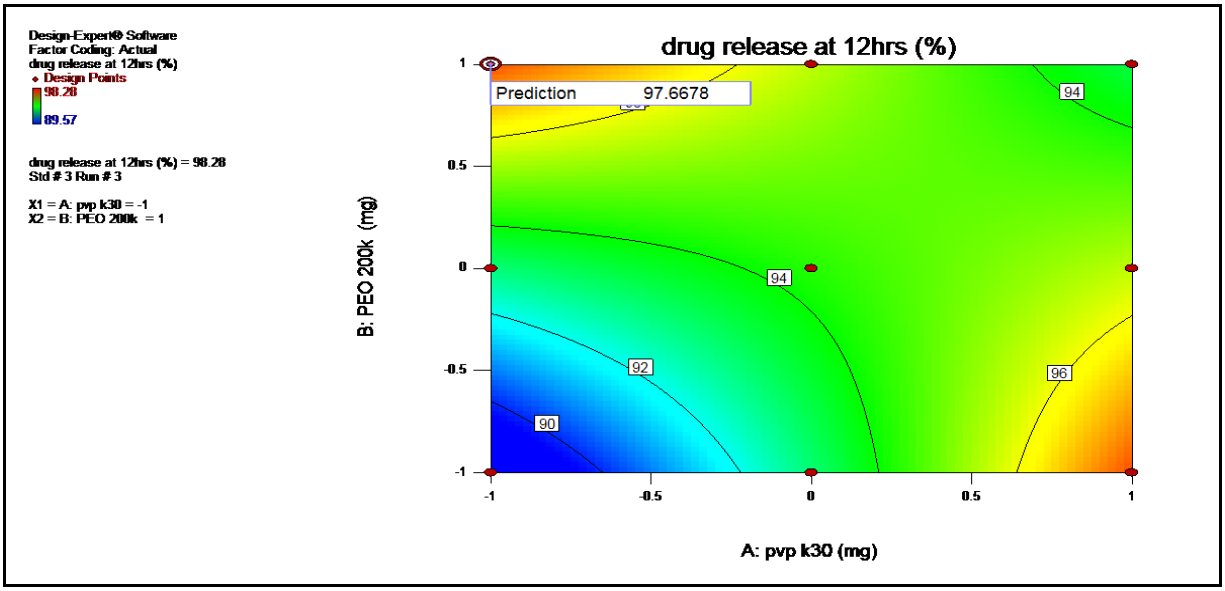

Figure 11: Contour Plot for showing the effect of pvpK30 (X1) and PEO (X2) %CDR at 12 hr with predicted value

Kinetics of Drug Release

To know the release mechanism and kinetics of optimized formulations (F3) were attempted to fit into mathematical models and R^2 values for zero order, first order, matrix Korsmeyer-Peppas and Hixon-Crowel models were represented in Table

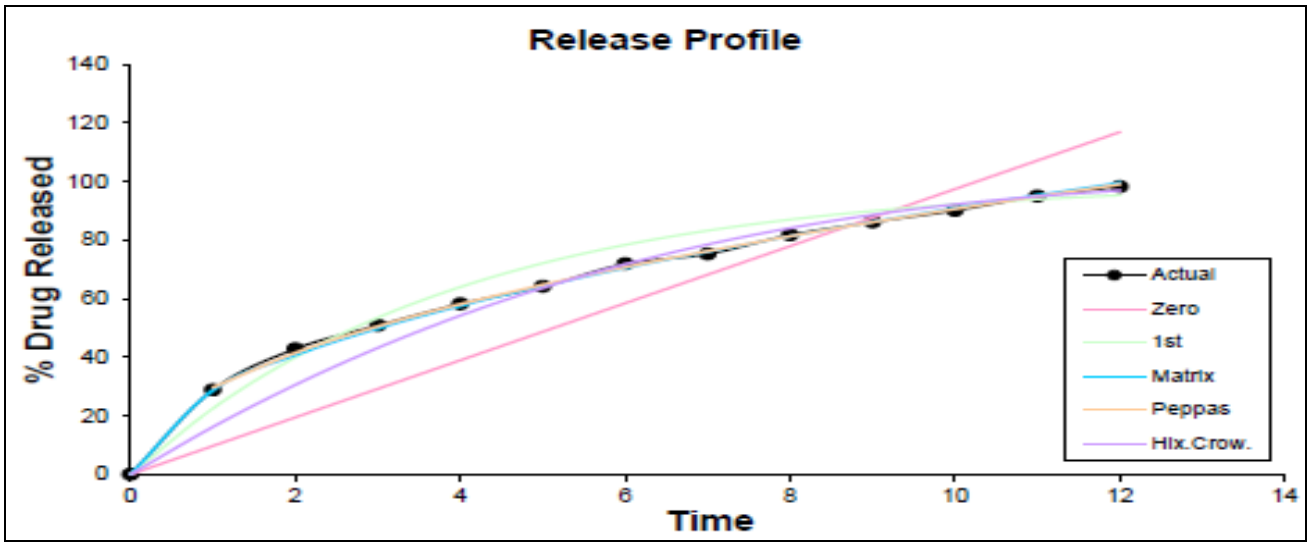

Figure 12: In Vitro Drug Release of F3 optimize Formulation

Model	R	K
Zero order	0.5668	10.0293
1st order	0.9415	-0.2717
Matrix	0.9565	30.0077
Peppas	0.9743	45.3292
	Best fit model	
Hix.Crow.	0.9479	-0.0601

Stability Study Of Optimize Batch (F3)

(Storage Condition: 40º C ± 2º C / 75% RH ± 5% RH, Time Period: 3 months)

Table 11: Stability study on the optimized formulation F3

Sr. No	Time (Days)	% Purity
1	30	99.21
2	60	99.16
3	90	99.07

CONCLUSION

Atenolol is a Beta-1 selected adrenoceptor blocking agent, for oral administration in the treatment of Hypertension, Angina pectoris and Heart failure. It has a half life of 6 to 7 hours. It gives once-a-day administration.IR and DSC study shows that there is compatibility between drug and excipients. The desired release profile was obtained by optimizing amount of osmotic agent, and osmopolymer. From the in vitro drug release study, it was inferred that drug release increased with the amount of osmotic agent and osmopolymer. To reduce the frequency of administration and to improve patient compliance, an osmotically controlled release formulation of Atenolol is desirable.

ACKNOWLEDGEMENTS

The authors are thankful to Lupin Pharmaceutical, mulshi, Nande Village, Pune, Maharashtra (India) for providing drug Sample and all The suppliers for gift samples and also sincere thanks to Prof. K N Tarkase Sir and Prof. Dr. Prabhakar Ghorpade Sir for their grand support in project.

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Cite This Article: Kailas, N Tarkase and Pooja, V Kadu (2016), "Formulation development, optimization and evaluation of bilayer push-pull osmotic pump tablet of atenolol using 3^2 factorial designs", ***International Journal of Drug Research and Technology***, Vol. 6 (3), 150-163.

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