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Research Article

Development And Evaluation Of Pressed Coated Floting Pulsatile Tablet Of Atenolol

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ABSTRACT

Atenolol is an Synthetic Beta-1 selective blocker, primarily used in management of hypertension and Chronic angina and to reduce mortality in known or suspected myocardial infarction. It belongs to BCS class III having a half-life of 7hrs and 50% bioavailability. The purpose of the present work was to design and optimize compression coated floating pulsatile drug delivery systems of Atenolol as an antihypertensive agent. The prepared system was composed of two components: an active ingredient-containing core tablet and an erodible outer shell with a gas-producing agent. The active component was combined with super disintegrates to create the rapid release core tablet (RRCT). By using polymer, the optimized RRCT was press coated. The optimization procedure made use of a 32 complete factorial design. As independent variables, Avicel pH 102 and the quantity of HPMC K200M were used. Lag time and hardness were selected as dependent variables. Floating pulsatile release formulation (FPRT) F8 at level +1 (100mg) for HPMC K200M and level -1 (20mg) for Avicel pH 102 showed lag time of 6 h with >90% drug release. The values of n were more than 1.

INTRODUCTION

The Drugs can be administered to the body orally, submucosally, parenterally, transdermally, pulmonaryly, etc. Oral delivery is a common method of delivery for these things. For these things, oral delivery is a typical way of delivery. The most favoured drug delivery method is oral since it is simple to administer, has flexible formulation options, and is well-liked by patients. The oral route is oldest and convenient route of administration of drugs because of low cost of

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therapy and ease of administration leads to higher level of patient compliance.[1-3]

Dosage forms that float have enough buoyancy to stay above the stomach's contents for a longer period of time.[4,5] Pulsatile drug delivery are the system in which rapid and transient release of an active molecule within a short time period immediately after a predetermined off release period. Such as lag time. Chrono pharmaceutics principally contains of Chronobiology of disease and pharmaceutical agents.[6-8]

MATERIAL AND METHOD:

Material:

Atenolol, Crospovidone, Magnesium Stearate, Talc, Lactose, Sodium bicarbonate, Citric acid, HPMC K-200M and Avicel PH 102

Method:[9-17]

❖ **Solubility Studies:**

Measure the solubility of the drug substance in different solvents and pH conditions. This helps determine the most suitable formulation approach.

❖ **Determination of Melting Point:**

Melting point of Atenolol was determined by capillary method. Fine powder of Atenolol was filled in glass capillary tube (Previously sealed on one end). The melting point was determined in Thieles tube using thermometer.

❖ **Drug – Excipients Compatibility Studies:**

Compatibility of Atenolol with its core material and the respective polymers that is HPMC K 200M and Avicel pH102 individual excipients and physical mixture of main formulation was established by Infrared Absorption Spectral Analysis (FTIR). With the help of IR spectral analysis, any modifications in the chemical composition following the addition of the excipients were looked at.

❖ **Differential Scanning Calorimetry (DSC):**

To characterise the thermal characteristics and potential for any interactions between the drug and excipients, differential scanning calorimetry (DSC) was employed. The DSC thermograms were recorded using a differential scanning calorimeter (DSC 823e, Mettler Toledo, Switzerland). Approximately 2–5 mg of each sample were heated in a pierced aluminum pan up to 300°C at a heating rate of 10°C/min under a stream of nitrogen at flow rate of 50 ml/min. Thermal data analyses were carried out.

❖ **Preparation of Core Tablet:**

Core tablet of 60 mg of weight containing drug Atenolol were prepared by direct compression method by using 6 mm punch. All ingredients passed through a sieve of 710 µm aperture size and blended for 15 min. Talc and magnesium stearate, passed through a sieve of 500 µm aperture size. Core tablet of atenolol contain crospovidone, magnesium stearate, talc and lactose. The total weight of core tablet was 60mg the composition of core tablet was shown in Table No.1

Table No.1 Composition of Core Tablet

Ingredients	C1	C2	C3	C4
Drug	30	30	30	30
Crosspovidone	6	8	10	12
Talc	1	1	1	1
Magnesium stearate	1	1	1	1
Lactose	22	20	18	16
Total weight	60	60	60	60

*All quantity are in mg.

❖ **Preparation of Preliminary Trial Batches of Press Coated Floating Pulsatile release tablet of Atenolol:**

Atenolol floating pulsatile release tablets were prepared in preliminary trial batches by press-coating the core tablets with a 300 mg powder mixture of coating material. A 9 mm die was filled with 150 mg of coating material after being weighed, and the core tablet was then manually positioned in the centre. One tablet compression machine was used to crush the press-coated tablet after the remaining 150 mg of coating material had been placed to the die.

❖ **Optimization by Using 3^2 Full Factorial Designs:**

In the present study, a 3^2 full factorial design was employed to study the effect of independent variables, i.e. amount of HPMC K200M(X1) and Avicel pH102 (X2) on dependent variables i.e. Lag time, in vitro drug release and floating time. A statistical model (see equation) Incorporating interactive and polynomial terms was utilized to evaluate the responses.

Table No.2 Layout of coating material by 3^2 full factorial design

Batch no	X1	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 No.3 Translation of coded value in an actual unit

Coded value	HPMC K 200 M (X1)	Avicel PH-102 (X2)
-1	80	20
0	90	30
+1	100	40

Table No.4 Composition of Optimized batches of coating material

Coating Material	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K200M	80	100	80	100	80	100	90	90	90
Avicel PH 102	20	20	40	40	30	30	20	40	30
NaHCO3	70	70	70	70	70	70	70	70	70
Citric acid	20	20	20	20	20	20	20	20	20
Lactose	110	90	90	90	100	80	100	80	90
TOTAL	300	300	300	300	300	300	300	300	300

*All quantity is in mg.

❖ **Evaluation of the Floating-Pulsatile Release Tablets:**

➢ **Thickness:**

Thickness was measured using a Vernier caliper. Five tablets of the formulation were picked randomly and thickness was measured individually.

➢ **Weight Variation Test:**

Select the twenty tablets were randomly from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

➢ **Hardness Test:**

Hardness was measured using Monsanto hardness tester. The hardness expressed in kg/cm2 . For each batch three tablets were tested.

➢ **Friability test:**

Twenty tablets were weighed and put in the Roche friabilator, which was circulated for 4 minutes at a speed of 25 rpm. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula,

% F = (Wt./W) ×100

Where, % F = Friability in percentage W = Initial weight of tablets Wt. = Weight of tablets after revolution

➢ **Drug Content Uniformity**

5 Tablets are weighed and powdered, from its average weight equivalent is weighed and added into 100 ml volumetric flask, this powder is dissolved in 0.1 N HCl and sonicated for 10 min. To obtain a concentration of 50 g/ml, 1 ml of the previous solution is taken and diluted to a volume of 10 ml with 0.1 N HCl. Then this solution is analyzed on UV Spectrophotometer using 220.8 nm wavelengths.

➢ ***In-vitro* Buoyancy Studies:**

The prepared tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200ml 0.1 N HCl (pH 1.2, temp. 37±0.5℃). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium called Floating Lag Time or Buoyancy Lag Time and total duration of time by which dosage form remain buoyant is called Total Floating Time.

➢ **Swelling Index Study:**

The absorption of a liquid produces an increase in weight and volume in the excipient particles used in tablet manufacturing. Liquid uptake by the particle may result via hydration of macromolecules or saturation of capillary spaces inside the particles. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. One tablet from each formulation batch was weighed and put into a beaker with 200 ml of buffer media. The tablet was taken out of the beaker and weighed once more up to 12 hours after each interval. The swelling index was calculated using following formula.

Swelling index (S.I) = {(Wt-Wo) /Wo} ×100

Where, S.I. = Swelling index Wt. = Weight of tablet at time t and Wo = Weight of tablet before placing in the Beaker.

➢ ***In-vitro* Dissolution Study of Atenolol:**

The release rate of atenolol from floating-pulsatile tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml 0.1N HCl, at 37 ± 0.5°C and 50 rpm/min. A sample (1ml) of the solution was withdrawn from the dissolution apparatus hourly for 10 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 220.8 nm.

➢ ***In-vitro* Drug Release Study:**

Drug release studies of press coated tablets were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 50 rpm, 37 °C) in 0.1 N HCl (900 ml). At the end of the time period 1ml of the samples were taken and analyzed for atenolol content. A 1ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal. Sample was analyzed using UV spectrophotometer at 220.8nm respectively.

➢ **Kinetic Study**

In order to gain insight into the drug release mechanism, the release data were examined for best fitting into zero-order, first-order, and Higuchi's square root of time mathematical models, the Hixson and Crowell powder dissolution method, and the Korsmeyer and Peppas model.

➢ **Stability Studies of Optimized Formulation:**

A pharmaceutical preparation is said to be stable if it can maintain its physical, chemical, microbiological, therapeutic, and toxicological requirements during the course of its shelf life in a particular container or closure system.

Stability testing is used to establish recommended storage conditions, re-test intervals, and shelf lives by demonstrating how the quality of a drug substance or drug product changes over time under the influence of various environmental factors, including temperature, humidity, and light.ICH specifications for stability study.

- **Accelerated testing: 40°C ± 2°C /75% RH ± 5% RH for 6 months.**
- **Procedure:**

In the present study, stability studies were carried out at room temperature 40 ± 20C and 75 ± 5% RH for a specific time period up to 3 Months for selected formulations. The tablets were placed in

aluminium container that had a polyethylene coating inside for stability testing. These sample containers were placed in Stability chamber maintained at 60% RH.

RESULT AND DISCUSSION

➢ **Solubility Profile:**

Atenolol was found to be Soluble in ethanol; sparingly soluble in water; slightly soluble in dichloromethane; practically insoluble in ether.

➢ **Melting point determination:**

The melting point of the drug sample was found to be 154℃, which is within the reported value of 154℃. It complies with standards thus indicating the purity of drug sample.

➢ **Drug –excipients compatibility studies:**

✓ **FT-IR Study**

From IR spectra of pure drug and the combination of pure drug with polymers, shows that all the characteristic peaks of atenolol were present in the combination spectrum thus indicating compatibility of the drug and polymer. IR spectra of pure drug and in combination with the polymers are shown in spectrum.

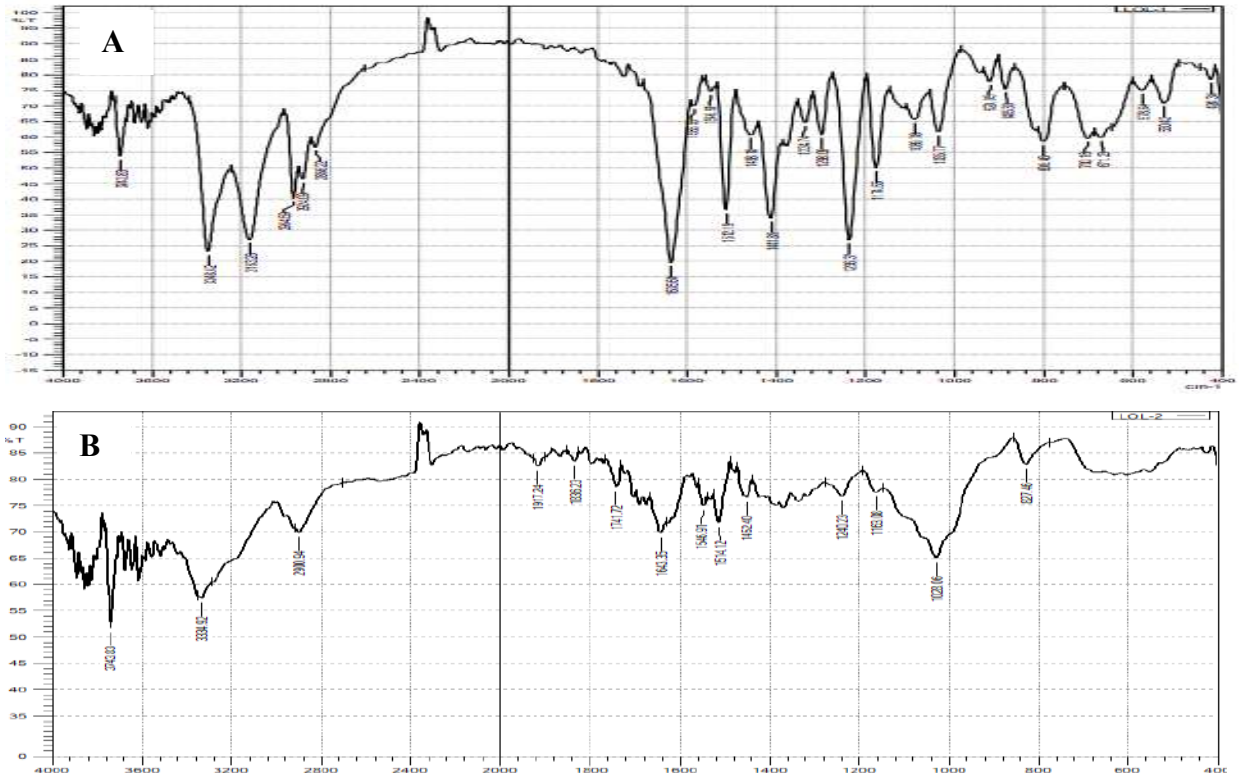
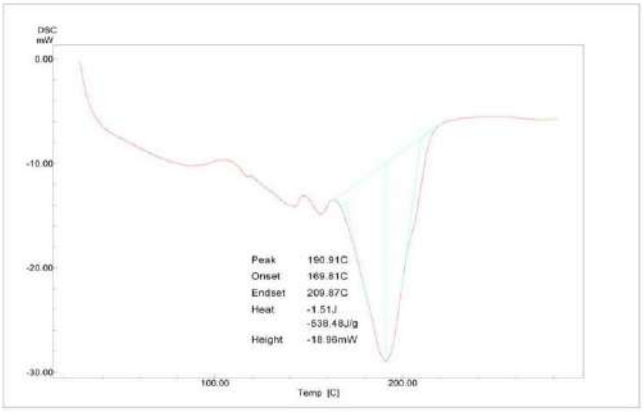


Fig No.1 (A) FTIR Spectrum of Atenolol and (B) FTIR Spectrum of Physical Mixture

Table No.5 Interpretation of IR spectra of Blend

Sr. No.	Wave Number (cm-1)	Functional Group
1	**2900.94**	C- H stretching
2	**1643.35**	C = C stretching
3	**3334.92**	O - H bending
4	**1240.23**	C - O stretching

✓ **Differential Scanning Calorimetry (DSC)** DSC Study was carried out for Atenolol as given in Figure no. 2. DSC thermogram of Atenolol showed sharpen endothermic peak with onset temperature 147.41°C and peak temperature 153.54°C corresponding to melting point.



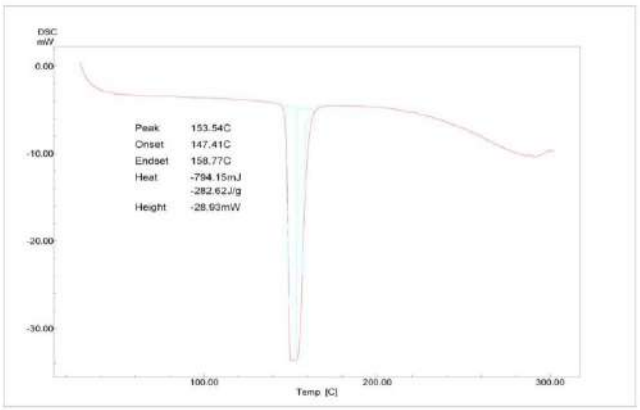


Fig No.2 (A) DSC Spectrum of Atenolol and (B) DSC Spectra of Physical Mixture

DSC studies were carried out for Atenolol and Blend. Figure no.3 and 4 Showed DSC studies Thermogram of Atenolol and Blend respectively. The DSC Thermogram of Atenolol showed sharpen endothermic peak with onset temperature 147.41○C and peak temperature 190.91○C corresponding to melting point, while the Blend of drug and excipients exhibited an endothermic peak at 190.91○C. The presence of same peak in the blend indicates that there was no interaction between drugs and excipients during the formulation process. By comparing the Thermogram of drug and drug- excipients it was found that it has a suitable compatibility for further formulation.

❖ Evaluation of Core Tablet

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Weight variation, hardness, thickness, friability, drug content and in vitro drug release study of Tablet are shown in Table No.8. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeia limits of ±10%. Hardness or crushing strength of the tablets found to be in the range of 2.1 to 2.8 kg/cm^2. The obtained results were found to be well within the approved range (<1%) in all the designed formulations. The drug content uniformity was examined as per I.P specification.

Table No.8 Post-Compression Parameters of core tablet

BatchNo.	Wt. variation (mg) ±SD*	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegrtion time (sec)	Drug Content (%)
C1	57.90±5.05	2.3	2.5	0.35±0.025	38	98.2
C2	60.40±4.43	2.8	2.9	0.38±0.015	39	99.8
C3	55.35±5.46	2.6	2.7	0.39±0.020	46	99.4
C4	61.90±3.08	2.1	2.2	0.41±0.031	37	97.2

*** n=3**

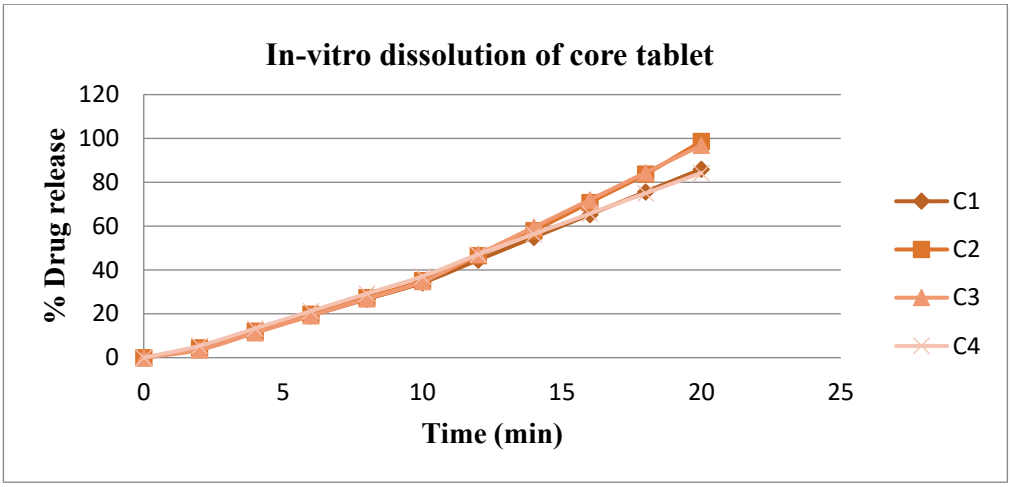


Fig No.6 Graph of Drug Release of Core Tablet

Dissolution of core tablet C1 to C4 formulations varies in drug release. Out of all formulations C2 98.67 of drug release within 20 minutes. The Time v/s Cumulative % Drug release graph of all formulations C1-C4 shows in fig No.6.

❖ Evaluation of Optimized Press Coated Tablets:

All the tablet formulations were subjected for evaluation according to various official specifications and other parameters. Weight variation, hardness, thickness, friability, drug content and in vitro drug release study of Tablet are shown in Table No.9.

All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeia limits of ±10%. Hardness or crushing strength of the tablets found to be in the range of 5.8 to 7.2 kg/cm^2. The obtained Friability results were found to be well within the approved range (<1%) in all the designed formulations. Buoyancy study of batches F1 to F9 shows good buoyancy properties. The drug content uniformity was examined as per I.P specification.

Table No.9 Evaluation Parameters of Press coated table

Batch No.	Weight Variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Floating lag time (sec)	Drug Content (%)
F1	309.23±2.42	5.8	4.5	0.59±0.015	15.33±0.57	96.5
F2	340.30±3.41	7.2	4.3	0.64±0.032	17.00±1.00	97.4
F3	318.15±4.86	6.3	4.3	0.56±0.032	15.33±0.57	98.2
F4	318.10±5.69	5.9	4.4	0.64±0.030	17.66±1.15	97.8
F5	305.85±4.86	6.2	4.5	0.58±0.040	16.00±1.00	98.4
F6	358.25±5.17	6.8	4.8	0.59±0.015	15.00±1.00	97.2
F7	312.36±4.05	7.0	4.7	0.60±0.055	15.23±0.45	98.2
F8	322.15±3.86	5.9	4.8	0.64±0.026	15.66±2.08	99.8
F9	317.82±4.15	6.1	4.3	0.60±0.055	16.66±1.15	97.9

❖ Swelling Index

Swelling index of all batches shows good results, the swelling index varied between 51.3 to 158.3 respectively. The results are tabulated in Fig. No.10.

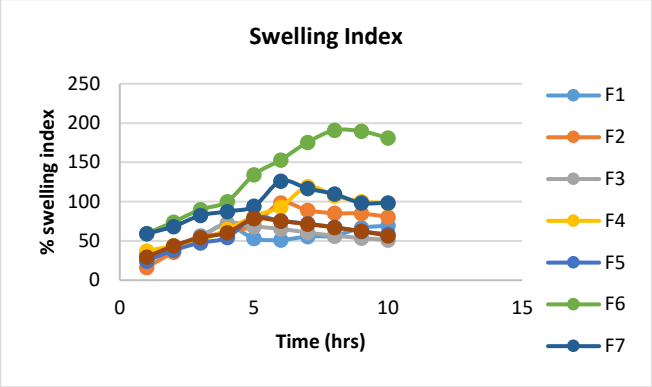


Fig No.7 Graph of Swelling Index

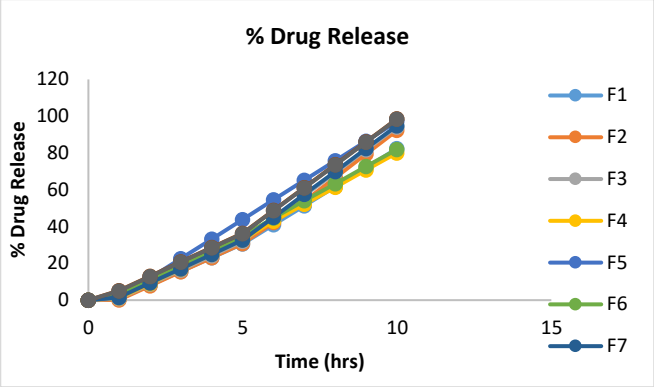


Fig No.8 Graph of Drug Release of Press coated tablet

❖ In-Vitro Drug release study

Dissolution of tablet F1 to F9 formulation shows varies in drug release. Out of all formulation F8 shows up to 98.6% of drug release with lag time of 6 hrs. The Time v/s % Drug release graph of formulation F1 to F9 shows in Figure No.8

❖ Kinetic study

The slope n was computed to know whether the release was Fickian or Non-Fickian. For Non-Fickian release the n values falls between 0.5 and 1.0, while for Fickian diffusion n is less than or equal to 0.5. The slope values are tabulated in below chart The values of n were more than 1 for all F8 formulations.

Table No.10 Kinetic Study of optimized batch F8

Batch Code	Zero order R^2value	First order R^2 value	Higuchi R^2value	Korsmeyer-PeppasR^2 value	'n'
F8	0.9836	0.6808	0.9369	0.9846	1.4313

❖ Stability Study

Stability study was carried out on optimized batch (F8) according to ICH guidelines. The tablet did not show any physical changes during the study period and the drug content was found to be 96.64% for atenolol at the end of 3 month on stability condition which is shown in Table No.18

Table No.11 Stability Study of Optimized Batch

Condition	Hardness (Kg/cm2)		Friability (%)		Drug content (%)		Floating lag time (sec)		% Drug release	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Accelerated temp. 40^{0}C and 75% RH	5.9	5.8	0.64	0.63	99.8	98.9	15	16	98.6	98

CONCLUSION

Oral route for drug delivery is considered as a most useful and most preferable, beneficial route for administration of Drugs and having advantages of ease of administration, patient compliance, pain avoidance etc. for this, the aim is to identify the orally active drug molecules which provide effective plasma concentration in body.

The results revealed that the drug and polymers were satisfactorily compatible, for making press coated atenolol floating pulsatile release tablet first formulate core tablet which contain drug.

Then Core tablets were coated with various concentration of HPMC K200 M and Avicel pH 102 optimization was done using 32 full factorial designs. From the optimization study it was found that formulation F8 (90 mg HPMC K200 M and

40 mg Avicel pH 102) was the best for floating pulsatile drug delivery system. F8 batch shows 6 hrs lag time which is required for pulsatile release. From the accelerated stability studies, it was observed that there was no significant change in the drug content and % release of drug, therefore the formulations are quite stable.

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