



OPTIMIZATION AND EVALUATION OF TIME PROGRAMMED PRESS COATED TABLETS FOR ATENOLOL

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ABSTRACT

The role of chronotherapeutics in hypertension management is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. An oral press-coated tablet was developed by means of direct compression to achieve time-controlled tablet with a distinct predetermined lag time. This press-coated tablet containing; Atenolol in the inner core tablet which is formulated with various types and concentrations of superdisintegrants, and an outer shell tablet which is formulated with different weight ratios of hydrophobic (Ethylcellulose) and hydrophilic polymers (Hydroxy propylmethylcellulose). The effects of the formulation of core tablet and outer shell of press coated tablets; on drug release and the lag time were investigated. The Formulation was optimized on basis of acceptable tablet properties and in vitro drug release. The results indicate that press-coated tablet composed of C8 (as core tablet formula) and T4 (as coat formula) achieve a burst release within 4 minutes after 6 hours lag time which is promising applicable pulsatile drug delivery for Atenolol to control morning blood pressure surge through providing appropriate concentration at time of its maximum need.

Keywords: Chronodelivery, Hypertension, Superdisintegrant, Lag time.



INTRODUCTION

Chronodelivery systems (Pulsatile delivery systems), based on biological rhythms, are a state of art technologies for drug delivery[1]. These systems are non-conventional dosage forms designed to release the active ingredient after a lag phase according to circadian rhythm of disease states[2,3]. Pulsatile delivery system is necessary for diseases which show circadian rhythms in their pathophysiology [4,5]. Ischemic heart disease constitutes a paradigmatic example of the importance of biological time[6]. Cardiovascular events occur more frequently in the morning, and ambulatory blood pressure exhibits a diurnal variation with increase in the morning (morning blood pressure surge). The morning blood pressure surge was reported to be associated with high risk

of cardiac death, ischemic and hemorrhagic stroke [7, 8, 9]. Blood pressure rises sharply in the morning in response to the activation of the sympathetic nervous system, so when one arises, plasma norepinephrine level and plasma renin activity are elevated [9,10]. The early morning blood pressure surge is associated with other important hemodynamic and neurohormonal changes including increases in heart rate, vascular tone, and blood viscosity and decreases in vagal activity [11]. Hence; the rationale of chronotherapy for hypertension is to deliver the drug in higher concentrations during the early morning post awakening period when the blood pressure is highest and in lesser concentrations in the middle of a sleep cycle, when blood pressure is low. Thus, night-time antihypertensive medication that is more specific for the early morning surge of blood

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pressure in addition to 24-h control would be useful for the prevention of cardiovascular events in hypertensive patients [12].

Time programmed drug delivery system is one of chronodelivery systems which release the drug at appropriate time by means of an internal pre-programmed clock that is initiated when the dosage form come in contact with gastrointestinal fluids. Drug release from these systems is primarily activated by plug ejection or a barrier coating that dissolves, erodes, or ruptures after a certain lag time [13,14].

The most frequently used technique for preparation of time programmed tablet dosage form is press coating technique which is novel, simple, and unique that involves compaction of coating materials around a preformed core[1,15].

Soluble or erodible membrane time controlled drug delivery system based on a drug reservoir device coated with a soluble or erodible barrier. The barrier erodes or dissolves and the drug is subsequently released rapidly from reservoir core after specific preset time period [16, 17]. The lag time of this system can be maintained by using coat composed of combination of hydrophobic and hydrophilic polymer. When the barrier layer is exposed to dissolution media, the hydrophilic polymer swells and erodes, the retardation of drug release varies depending upon the quantity of hydrophobic polymer present demonstrating that manipulation of both components controls the erosion rate [18].

Atenolol is a second generation β_1 selective antagonist[19]; inhibits stimulation of β_1 -receptor sites, located mainly in the heart; decreasing cardiac excitability, cardiac output, and myocardial oxygen demand. Atenolol also acts to decrease release of renin from the kidneys; aiding in reducing blood pressure. Atenolol used in treatment of angina pectoris, cardiac arrhythmias and control hypertension[20].

The administration of Atenolol conventional tablets may cause fluctuations in plasma concentration, resulting in side effects or a reduction in drug concentration at receptor sites[21, 22]. The main aim of the present study is to develop, optimize, and evaluate Atenolol pulsatile release tablets intended for chronotherapy of cardiovascular diseases using press-coating technology by combination of hydrophilic and hydrophobic polymers as a coat around a rapid release core tablet in order to provide maximum drug plasma concentrations at time of its maximum need.

MATERIALS AND METHODS

Materials: Atenolol (Samara drug industry-Iraq), Avicel pH 102 (Samara drug industry-Iraq), Sodium Starch Glycolate (Aladdin-china), Crospovidone (Aladdin-china), PVP K30 (Samara drug industry-Iraq), Talc (Samara drug industry-Iraq), Magnesium stearate (Samara drug industry-Iraq), HPMC K100M (Aladdin-china), Ethylcellulose 100 mPa-s (Aladdin-china).

METHODS

Preparation of core tablets: All ingredients of core tablet (shown in table 1) were weighed and passed through 0.5mm standard sieve. All these ingredients (except magnesium stearate and talc) were blended for 20 minutes, followed by addition of magnesium stearate and talc then powder mixture was further blended for 10 minutes. 75 mg of the resultant powder blend was compressed directly using Riva mini-press tablet machine with 6mm die size [18].

Formulation of coating powder blend for press – coated tablet: Coat layer blend for coating the core tablet was prepared by dry blending using different ratios of the EC100 mPa-s and HPMCK100M as shown in table 2. These powders were dry blended for 10 minutes and the mixture is then used as coating material for core tablet to prepare press-coated pulsatile tablets [18].

Preparation of press-coated pulsatile release tablets: The core tablets were press-coated with coat blend where half of the coating material was weighed and transferred to tablet machine then the core tablet was placed manually at the center of the die. The remaining quantity of the coating material was added into the die over the core tablet and compressed by Riva mini-press tablet machine using 9 mm die size [18].

Evaluation of the core powder blend: The core powder blend was evaluated for angle of repose, Carr's index and Hausner ratio according to USP.

Evaluation of the prepared core tablets: The prepared core tablets were evaluated for thickness, hardness, friability, weight variation, and disintegration time.

In vitro release (dissolution) studies of core tablets: Prepared core tablets were placed in vessels of dissolution test apparatus containing 900 ml phosphate buffer (pH 6.8) solution as dissolution medium. Dissolution studies were performed using USP type 1 apparatus (basket method) at 50 rpm and $37 \pm 0.5^\circ\text{C}$. At 2 minutes

intervals, 5ml samples were withdrawn and replaced with equal volumes of fresh buffer medium. Withdrawn test samples were filtered and analyzed by using UV spectrophotometer (Shimadzu 1650 pc-Japan) at λ max= 274 nm and drug content was determined. The procedure was triplicated for each run test and the mean was calculated [23]. The best core tablet formula was selected according to the release profile of drug by using different types and quantities of superdisintegrants.

Evaluation of the coat powder blend: The coat powder blend was evaluated for angle of repose, Carr's index and Hausner ratio according to USP.

Evaluation of the prepared press coated tablets: Press coated tablets were evaluated for thickness, hardness and friability.

In vitro release studies of press-coated pulsatile tablets: The in vitro release from press-coated tablets were carried out using USP dissolution apparatus type I (basket method) at 50 rpm and $37 \pm 0.5^\circ\text{C}$, 0.1 N HCl and phosphate buffer (pH 6.8) was used as the dissolution medium. Initially, tablets were subjected to dissolution medium in 0.1 N HCl for 2 hours and after that medium were changed to phosphate buffer (pH 6.8). The samples were withdrawn at 15 minutes interval and analyzed by using UV spectrophotometer (Shimadzu 1650 pc-Japan) at λ max= 274 nm and drug content was determined. The procedure was triplicated for each run test and the mean was calculated [23].

Effect of coat thickness on lag time of press coated tablet: The selected coat formula was used to study the effect of coat thickness on press coated tablet. The total weight of coat blend was increased to 180 mg instead of 150 mg.

Effect of rotational speed of dissolution apparatus on lag time of press-coated tablet: To determine the effect of peristalsis and contraction movement of gastrointestinal tract on lag time and drug release, a study was carried out using different rotational speeds (25 and 100 rpm) of basket on the selected press coated tablet and the changes in lag time were examined.

Drug-excipient interactions: The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. Pure Atenolol, selected core and press coated tablets (previously grinded); were mixed thoroughly with potassium bromide. The potassium bromide discs were prepared by compressing the powder in a hydraulic press [24].

Accelerated stability studies: The stability of the selected press coated tablets was studied at three different temperatures: 40, 50 and 60°C for 16 weeks. Samples were taken at 14 days interval and tablets of the selected press coated tablet were grinded and dissolved in methanol then filtered through filter paper. Solution was analyzed for Atenolol content by UV Spectrophotometer at 279 nm using methanol as blank [24].

RESULTS AND DISCUSSION

Pre-compression parameters of core powder blend: The resulted values of angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio for the prepared core powder blend of each formula was illustrated in table 3 and the results estimated according to USP. The results show that the prepared core mixtures have acceptable flow properties and compressibility.

Evaluation of core tablets: The results of thickness, hardness and friability, weight variations, and disintegration time of all the prepared core tablets are shown in table 4.

Dissolution test for Atenolol core tablets: The results of dissolution tests for (C1-C8) core tablet formulas are shown in fig.1 and 2. Results indicated that as the concentration of superdisintegrants increases; the drug release increases. The C8 formula was selected as the best core tablet formula to be coated with different coat blend to prepare pulsatile press coated tablets since it produced the fastest drug release (100% release within 4 minutes) of Atenolol.

Pre-compression parameters for coat powder blend: The resulted values of angle of repose, bulk density, tapped density, Carr's index and Hausner ratio for the prepared coat powder blend of each formula was illustrated in table 5 and the results estimated according to USP. The results showed that the prepared coat blends have acceptable flow properties and compressibility.

Evaluation for the prepared press coated tablets: Table 6 shows the result of thickness, hardness and friability tests for the press coated tablets.

Dissolution profile for Atenolol press coated tablets: The results of dissolution test for press coated tablet formulas shown in fig 3. It was found that as the concentration of hydrophilic polymer (HPMC) decreased; the lag time increased this is because the mechanism of drug release for these formulations based upon the hydration of the outer barrier layer. The hydrophobicity of EC retards the hydration of HPMC, therefore dissolution medium

did not penetrate the outer coating layer, and the coat eroded slowly. The active erosion rate of outer barrier layer depends upon the composition of the formulation which determines the lag time of press coated tablets. The HPMC is responsible for active erosion of barrier layer as its characteristic of absorption of water followed by swelling; thus as the weight ratio of HPMC was decreased, the lag time was increased. (T4) was selected as the best coat formula (compressed around C8 core tablet formula) to prepare the best pulsatile press coated tablet which produced 100% drug release after 6 hours lag time.

Effect of coat thickness on lag time of press-coated tablet: The results showed in fig.4 indicated that as the thickness of the coat increased; the lag time increased since the time required to complete the erosion of the outer shell would be longer.

Effect of rotational speed of dissolution apparatus on lag time of press-coated tablet: As shown in fig.5, the results indicated that the lag time decreased by increasing the rotational speed, this was due to the increase in coat erosion rate which lead to faster liberation of the core.

Content uniformity test for press coated tablets: The content uniformity test was done for the selected press coated tablets formula and the result

was 99.95%. This result agrees with the requirements of the United States pharmacopeia.

Drug – Excipients Compatibility Studies: The FTIR spectra for the pure Atenolol powder showed characteristic absorption bands at 3356, 3174, 2966, 1666, 1583, 1516, and 887 cm^{-1} which represent the following groups: OH, NH, C-CH₃, C=O, O=C-NH₂, C=C (aromatic) and C=CH₂; respectively. The results showed that these bands do not change significantly in the FTIR spectra of the grinded core, and selected press coated tablets; indicated that no drug interaction occurred with the component of the formulas.

Stability study (determination of expiration date): Accelerated stability of the selected press coated tablet was studied at three different temperatures (40, 50, and 60 °C) for 4 months, and Arrhenius plot was conducted (as shown in fig.6). The time required for a drug to lose 10% of its potency at 25°C was found to be 4.49 years.

CONCLUSION

The overall results offer pulsatile press coated tablets for Atenolol that might be useful as night time antihypertensive to overcome the early morning surge of blood pressure. This would be helpful for prevention of cardiovascular events in hypertensive patients.

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Table 1: Core tablet formulas composition

Ingredients (mg)	C1	C2	C3	C4	C5	C6	C7	C8
Atenolol	50	50	50	50	50	50	50	50
Avicel	20	18	16	14	20	18	16	14
Sodium Starch Glycolate	2	4	6	8	-	-	-	-
Crospovidone	-	-	-	-	2	4	6	8
PVP K30	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Total Weight	75	75	75	75	75	75	75	75

Table 2: Coat powder blend composition

Coated powder formula	weight of coat mixture (mg)	HPMC K100M (%)	EC100 mPa*s (%)
T1	150	80	20
T2	150	60	40
T3	150	50	50
T4	150	40	60
T5	150	20	80

Table 3: Results of the Pre-compression parameters for core powder blend

Formula	Angle of repose (degree)±SD	Bulk density (gm/cm ³)±SD	Tapped density (gm/cm ³)±SD	Carr's Index (%)	Hausner ratio	Type of flow
C1	31.15±0.63	0.364±0.04	0.408±0.01	10.78	1.12	Good
C2	37.65±0.8	0.357±0.01	0.426±0.02	16.19	1.19	Fair
C3	38.65±0.74	0.364±0.04	0.435±0.04	16.32	1.19	Fair
C4	36.75±0.79	0.339±0.02	0.408±0.05	16.91	1.2	Fair
C5	26.56±0.62	0.377±0.05	0.417±0.05	9.59	1.11	Excellent
C6	24.52±0.62	0.385±0.02	0.417±0.03	7.67	1.08	Excellent
C7	28.96±0.57	0.377±0.05	0.417±0.02	9.59	1.11	Excellent
C8	26.44±0.69	0.388±0.01	0.415±0.05	6.51	1.07	Excellent

Table 4: Results of thickness, hardness, friability, weight variation and Disintegration time tests for coated tablets

Formula	Thickness (mm)	Hardness (kg/ cm ²)	Friability %	Weight variation (mg)	Disintegration time (seconds)
C1	2.58±0.08	3.7±0.06	0.65±0.05	73.6±0.01	260±4
C2	2.63±0.04	3.7±0.01	0.67±0.03	74±0.03	180±2
C3	2.56±0.02	3.5±0.04	0.63±0.04	75±0.03	150±2
C4	2.72±0.05	3.3±0.06	0.63±0.02	73±0.02	120±3
C5	2.74±0.09	4.1±0.09	0.55±0.03	74.8±0.05	99±1
C6	2.78±0.04	4.1±0.07	0.52±0.05	73.4±0.04	72±4
C7	2.80±0.03	4±0.05	0.47±0.02	73.9±0.02	40±2
C8	2.81±0.06	4±0.03	0.5±0.04	74.1±0.04	30±1

Table 5: Results of the Pre-compression parameters for coat powder blend

Formula	Angle of repose (degree)±SD	Bulk density (gm/cm ³)±SD	Tapped density(gm/cm ³)±SD	Carr's Index (%)	Hausner ratio	Type of flow
T1	32.85±0.79	0.364±0.01	0.422±0.05	13.74	1.16	Good
T2	31.34±0.61	0.368±0.05	0.42±0.05	12.38	1.14	Good
T3	30.63±0.51	0.374±0.01	0.404±0.05	7.43	1.08	Excellent
T4	31.42±0.52	0.375±0.04	0.398±0.03	5.78	1.06	Excellent
T5	34.81±0.76	0.381±0.01	0.4±0.06	4.75	1.05	Excellent

Table 6: Results of thickness, hardness and friability tests for coated tablets

Formula	Thickness (mm)	Hardness (kg/ cm ²)	Friability (%)
T1	4.33±0.03	9.5±0.04	0.64±0.03
T2	4.33±0.01	9.5±0.03	0.58±0.01
T3	4.35±0.05	9.75±0.05	0.51±0.06
T4	4.36±0.03	9.75±0.08	0.45±0.04
T5	4.38±0.01	10±0.04	0.42±0.04

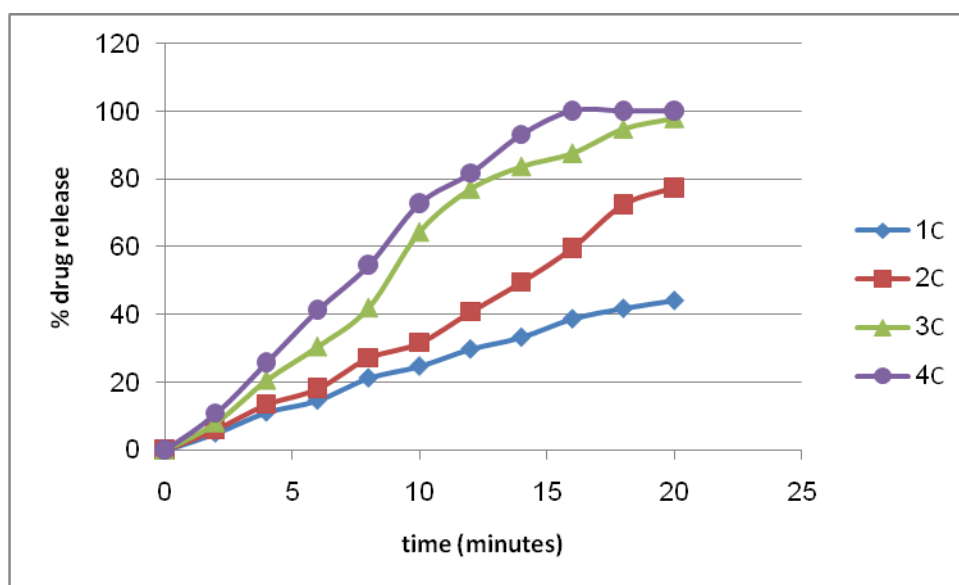


Figure 1: Effect of sodium starch glycolate concentration on drug release from core tablet

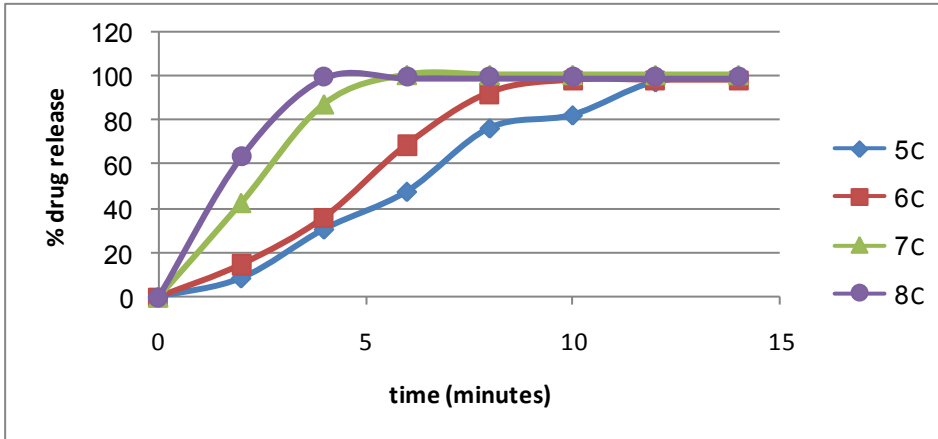


Figure 2: Effect of Crospovidone concentration on drug release from core tablet

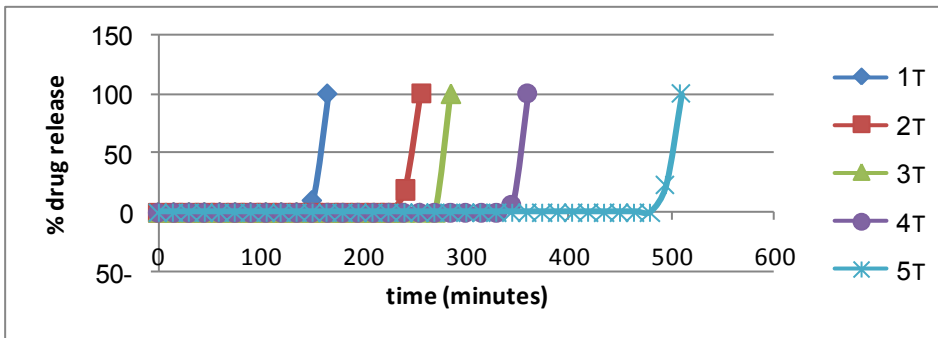


Figure 3: Effect of polymers ratio on lag time of press coated tablet

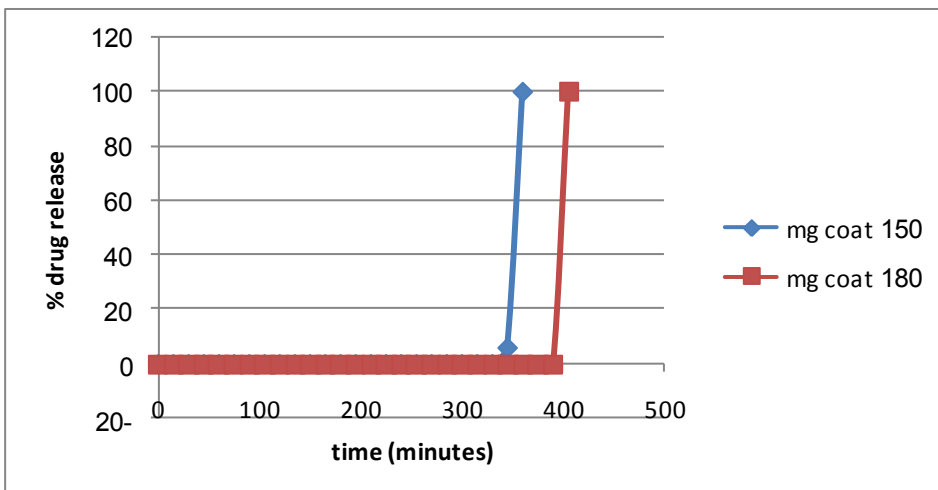


Figure 4: Effect of coat thickness on lag time of press-coated tablet

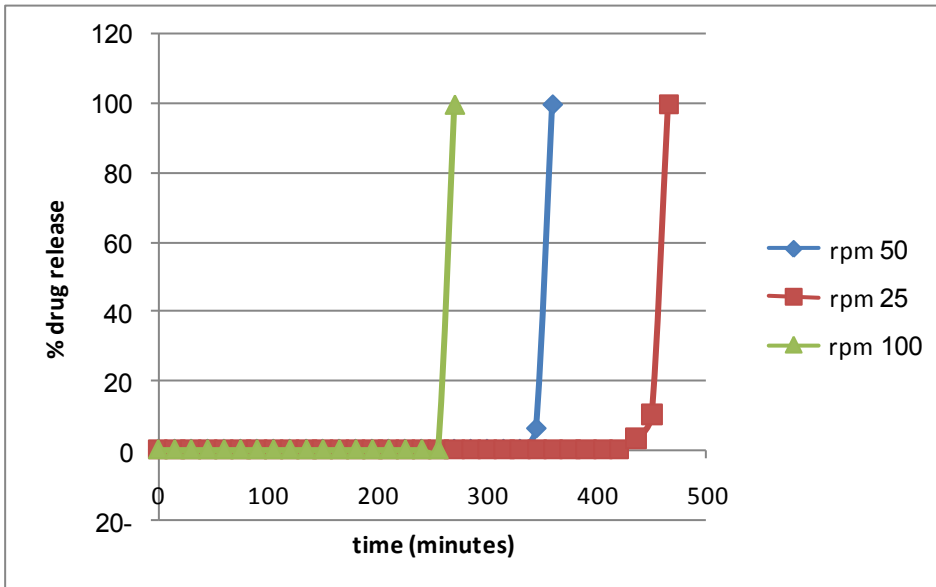


Figure 5: Effect of rotational speed of dissolution apparatus on lag time of press-coated tablet

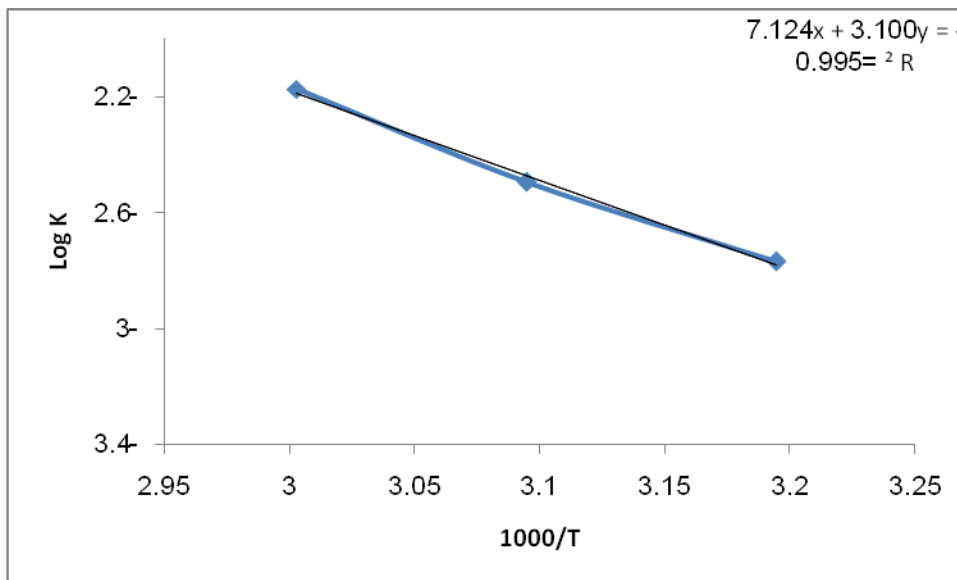


Figure 6: Arrhenius plot of Atenolol press coated tablet for the selected formula T4 for the estimation of the expiration date