Article

A Study of The Stability And Kinetics of The Azithromycin Drug For Five Different Companies & Shelf Life Determine

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Abstract :
In this study, the stability of azithromycin, which is considered one of the most important macrolide antibiotics, was identified; which means that it is a broad-spectrum antibiotic effective against both Gram-positive and Gram-negative microorganisms. The stability of the drug azithromycin was studied for five different companies: (Jamjoem Pharma, LDP Laboratories, Torlan S.A. Ajanta Pharma Ltd, GET and Brawn), and the decomposition of the drug was studied at different temperatures (40, 50, 60 and 70) Celsius; and the Shelf Leaf value was calculated. The reaction rate constant for the drug was determined using the Arrhenius equation and the first-order reaction equation for each drug manufacturing company ;It was found that LDP is considered the best among the five companies for the drug azithromycin in resisting temperature during storage and can be stored for a longer period than the drug belonging to other companies; while ZAHA showed the reduction. The lowest resistance to change at high temperature and greater decomposition of the drug, in addition to its lack of resistance to heat and its stability when stored for a certain period.

***Keywords*:** stability studies , Azithromycin dehydrate, shelf life, expiry date, chemical stability, Azithromycin solubility, chemical kinetics, Temperature effects.

I. Introduction:

A pharmaceutical product's stability can be defined as a formulation's capacity to stay within its physical, chemical,microbiological,toxicological, protective, and informational criteria in a certain container/closure system. In other words, it is the amount to which a product retains the same features and attributes as when it was packaged, within prescribed limits, during its storage and use term [1]. The USP defines pharmaceutical product stability as "the extent to which a product remains within prescribed limits" during storage and usage [2]; Chemical instability refers to chemical changes in the solid state that lead to drug degradation and possible therapeutic potency loss, as well as the production of toxic degradation products; however, molecules in the solid state, particularly the crystalline state, are thought to be less susceptible to chemical degradation than molecules in solution. example of chemical reactivity are, thermal decompositions such as decarboxylation; hydrolysis; oxidative reactions [3].

1.1. SHELF-LIFE / EXPIRATION DATE:

The Food and Drug Administration (FDA) has mandated that pharmaceutical manufacturers include expiration dates on all of their products since 1979. These dates range from 12 to 60 months from the date of manufacturing for the majority of medications supplied in the United States. Expiration dates are merely suggestions. Even though most medications do not become hazardous after they expire, they might nevertheless harm your health [4]. The shelf life often known as the expiration date, of a medication refers to the amount of time it has been shown safe and effective despite exposure to various environmental conditions such as temperature, humidity, and light. The FDA does not mandate long-term testing, despite the fact that expiration dates ensure a certain amount of stability. Many pharmaceuticals may have a substantially longer shelf life than what is stated on the label [5].

The proper storage of pharmaceuticals, as well as the incorrect storage of medications in places like the bathroom and medicine cabinet, can aid to prolong their potency due to heat and humidity. Medications are best kept in dry, cool, and dark places away from light. Keep prescription bottle tops completely secured and out of children's reach [6].

1.2. Azithromycin:

A macrolide antibiotic called azithromycin is available in a variety of crystalline forms, including anhydrous, monohydrate, and dihydrate, as well as an amorphous form [7]. It's a 15-membered lactone ring formed from erythromycin with a methyl-substituted nitrogen atom integrated into the lactone ring. It's used to prevent endocarditis in at-risk patients who can't take penicillin in some countries. Trachoma and typhoid are also treated with it [8].

Azithromycin Dihydrate ((2R,3S,4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-[(2,6-dideoxy-3-Cmethyl-3-O methyl-a-L-ribo-hexopyranosyl) oxy]-2-ethyl -3,4,10 - trihydroxy - 3,5,6,8,10,12,14 - heptamethyl - 11 - [[3,4,6, - trideoxy - 3(dimethylamino) -β- D - xylo - hexopyranosyl]oxy] - 1 - oxa - 6 azacyclopentadecan-

15-one) is a white crystalline powder with the chemical formula C38H72N2O12•2H2O and a molecular weight of 785.0 [9.] It is a white crystalline powder with the molecular formula C38H72N2O12•2H2O Azthiromycin is a white or almost white powder that is practically insoluble in water but readily soluble in anhydrous ethanol and methylene chloride , white or almost white powder[10]. It's a broad-spectrum antibiotic with antibacterial activity against both Gram-positive and Gram-negative bacteria. It's been widely used to treat lower respiratory tract infections, and the FDA has approved it for the treatment of community-acquired pneumonia and chronic obstructive pulmonary disease exacerbations [11]. As a result of the pandemic, medication repositioning has emerged as a short-term strategy for developing a COVID-19 treatment. The fact that patients with COVID-19 have pneumonia and acute respiratory distress supports azithromycin's therapeutic suitability for the cur rent pandemic [12]. The molecular structure of azithromycin dihydrate. Show Figure.1 .

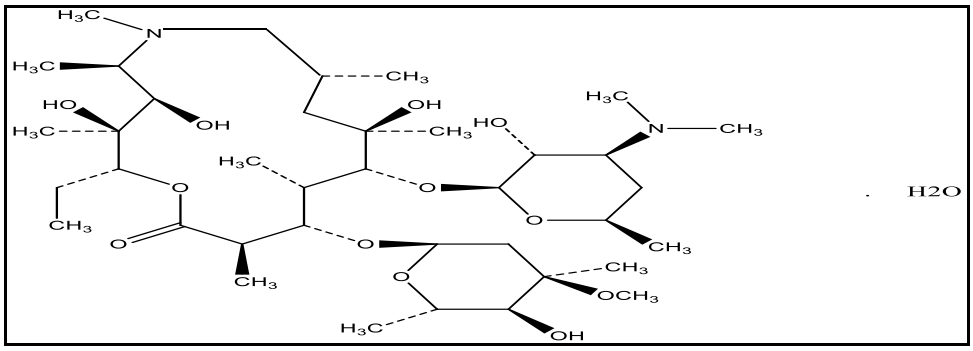

Fig. 1 : show the Azithromycin Dehydrate structure

1.3.Objectives Of Stability Studies :

1. Stability testing is done to give information on how different environmental elements, such temperature, humidity, and light, affect a drug product's quality over time.
2. To choose suitable formulas and container closure systems (in terms of stability).
3. To ascertain storage conditions and shelf life.
4. To verify the stated duration of use.
5. To confirm that no modifications have been made to the production process or formulation that could have a negative impact on the product's stability.
6. The primary goal of an expedited stability study is to forecast a drug product's stability profile and estimate its shelf life prior to commercialization [13].

2. Material and Method :

2.1.Prepare 5 Samples of Azithromycin Dehydrate From Different 5 Company:

A. Prepare 5 samples of Azithromycin dehydrate from different 5 companies:
- Azi-once capsules 250mg (jamjoem pharma), Batch number : XE0145.
-LDP Azoxine capsules 250mg (LDP Laboratories Torlan S.A), Batch number : UI80020.
-Zaha tablets 250mg (Ajanta Pharma Ltd), Batch number : DJ0579G.

-Azibru capsules 250mg (Brawn Laboratories Limited), Batch number : BNC1120020.
-Zithroget capsules 250mg (Getz Pharma), Batch number : 163C21.

2.2.Preparation of 0.1n Of Hcl Standard Solution:

Using 10ml pipette, transfer 2.2ml of HCl stock solution into 250ml volumetric flask with a small amount of distal water to avoid the release of heat during the addition of distal water than Complete the volume with distal water to acquire 0.01N of HCl standard solution.

2.3. Preparation of The Azithromycin Solutions :

Transfer 25ml of ethanol stock solution to 100ml volumetric flask then add 75 ml of distal water to prepare the solvent. taken 2g of azithromycin (for different 5 companies) and add 100 ml of solvent in the volumetric flask, Transfer the solutions to the water bath , take 10ml of solutions at time (0 min , 15min , 30min, 45min, 60min) respectively solution (for all companies taken sample of solution after passes 15 min then 30min then 45min and 60min) then add 2-3 drops of Methyl red to titrate with 0.1N HCl until the color change from red to yellow to get the end point, record the observation ,Repeat the above steps for each temperature at (40^{o}c, 50^{o}c, 60^{o}c and 70^{o}c) then record the observation .

III. Calculations & Results:

After recording the end point, we calculate the azithromycin solutions at each time interval (0 min ,15 min ,30 min ,45 min ,60 min) for each temperature:

At time zero min the initial concentration of azithromycin (C_o) is equal to the end point at time zero min. At each interval (15 min ,30 min ,45 min ,60 min) the azithromycin concentration (C_t) can be calculated from the equation :

$C_t = 2x - y$	(1)

Where:
x = volume of HCl at time zero (C_o)
y = volume of HCl at each Period of time

the reaction dependent on the concentration of only one reactant; we use the first order equation to determine the rate constant of the reaction by calibrating the Ln(C_t) of each temperature with time (0, 15, 30, 45, 60) min. on the graph according to the equation:

$\ln C_t = \ln C_o - Kt$	(2)

Whereas the slope = -k
Intercept = $\ln C_o$

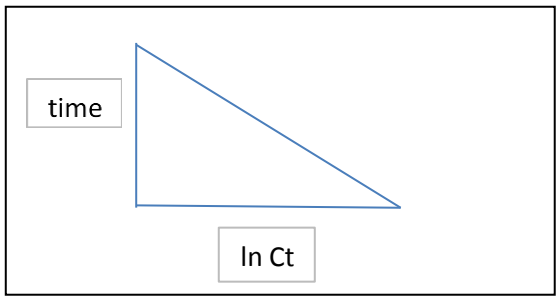

Fig. 2 : show the first-order equation

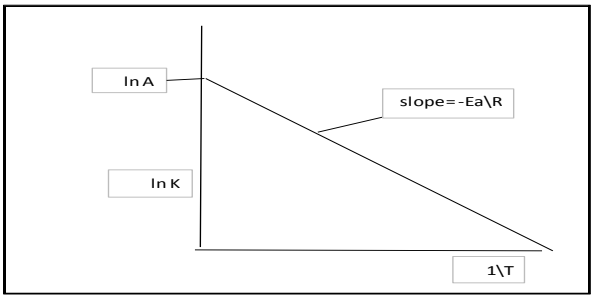

Fig. 3: show Arrhenius plot

The reaction is temperature dependence of reaction rates, by using Arrhenius equation [14] and by calibrating Ln(k) of all the temperature of each company against the inverse temperature in kelvin [1/T(k)], will allow us to determine the rate constant at temperature 25 ºC which will help to determine the shelf life of the drug.

lnK = lnA + E\RT	(3)

Where: K = reaction rate constant
A = frequency factor
ΔE = activation energy (kJ/mol).
R = universal gas constant (0.00831 kJ/mol).
T=absolute temperature (K).

2.4. Azithromycine Drug Company :

2.4.1.Jamjoom Laboratories Company:

Is the pharma began commercial activities in Saudi Arabia in the year 2000. The company has a track of of quick growth and expansion, and it has established itself as one of the fastest growing enterprises in the Middle East, Africa, and the Commonwealth of Independent States [15].

2.4.2. Ldp Laboratories Company:

LDP Laboratories Torlan S.A. is a pharmaceutical company dedicated to the manufacture of injectable. antibiotics for human use and is specialized in the production of Beta-lactamase in powder form. Located Cerdanyola del Vallès, Barcelona [16].

2.4.3.Ajanta Laboratories Company:

Pharma Limited (APL) Ajanta Pharma is a specialty pharmaceutical company engaged in development, manufacturing and marketing of quality finished dosages. Produce a comprehensive range of specialty products targeting different therapeutic segments for treatment of patients. [17].

2.4.4.Getz Laboratory Company :

is an international research-driven, branded generic pharmaceutical company specializing in the formulation development, manufacturing, testing and marketing of a wide range of quality, affordable medicines. they manufacture and market brands trusted by healthcare professionals around the world. their manufacturing

facility, located in Pakistan, and its approved by the World Health Organization, Geneva (WHO) [1].

2.4.5. Brawn Laboratory Company:

located in Faridabad from New Delhi, India, They manufacture a wide variety of pharmaceuticals, across the spectrum, to include Antibiotics – Antibacterials, Cardiovascular, Antidiabetics, Gastrointestinals, Cough & Cold, Anxiolytics & Antidepressants, Analgesics – Anti Tubercular, Anti-Inflammatories, Antivirals, Antifungals, Antihelminthics, Anti protozoals, Antimalarials, Corticosteroids, Antihistaminics, Nutritional supplements and others [19].

3. Discussion:

According to the first order of kinetics the rate of the reaction increases as the temperature elevate; in fact the rate of reaction is increased every 10 C^{o} by two to three times; But our result show that the rate of the disintegration [K] fluctuate due to technical during the titration; Some of these issues such as different in the pressure ; room temperature ; concentration and power shutdown during the experiment etc.

The effect of temperature as previously stated; raised the reaction rate by two to three times as the temperature climbed by ten degrees according to two theories, Co can comprehend. collision theory: temperature impacts molecular movements when reactant molecules clash; transition-state theory: colliding molecules can join to form a stable intermediate state. The Arrhenius equation can be derived using these methods to account for temperature variation of the rate constant. In general, as the temperature rises, the frequency of collisions rises [20].

our result that illustrated in fig(4,6,8,10 and 12) show the change in the natural logarithm of the concentration Ln[Ct] for each sample of azithromycin at different temperature [40C, 50C, 60C and 70C] at each 15min time interval [0min, 15min, 30min, 45min and 60min] and according to the equation

[$lnCt = lnCo - Kt$], High temperatures were employed so that the researchers could be aware of all the circumstances, whether at home or at the pharmacy, that could lead to the drug's degradation and breakdown as a result of improper storage [21] which shows that as the temperature elevate the concentration continue to increase as time pass; except in LDP company show that When the temperature increases , duo to decrease in concentration , this leads to K value is decreases [22] , show figure (6) ; through these graphs it help us to identify the rate of disintegration for each temperature which are being calibrated against the inverse of time in kilven and by using Arrhenius equation [$lnK = lnA + E/RT$] that show in the fig (5,7,9 , 11 and 13) ; that ln[k] is being reduced a as the inverse temperature increases', and through this plot, it help us to identify the constant k for room temperature, and according to the first order kinetics the shelf life is calculated through the equation [23]:

T1/9 = 0.105/K25	(4)

as shown in table 6 ,show that ZAHA has the highest disintegration rate (K25=198.343) and the lowest shelf life (T0.9=0.000529) followed by brawn then

jamjom then gets and finally LDP (lowest constant rate (K25=0.000825) and the highest shelf life (T0.9= 127.27) , this is evidence that LDP is considered the best company in resisting the temperature during the storage and can be stored for longer and it is considered the most company [24] of them than the rest while ZAHA company show that is lower shelf life this means a drug was analysis through short time, and its cannot be safety for long time .

4. Conclusion :

Azithromycin drug , which is considered one of the most important macrolide antibiotics, was identified, The stability of the drug azithromycin was studied for five different companies and the decomposition of the drug was studied at different temperatures (40, 50, 60 and 70) Celsius, It was found that LDP is considered the best among the five companies for the drug azithromycin in resisting temperature during storage and can be stored for a longer period than the drug belonging to other companies, while ZAHA showed the reduction. The lowest resistance to change at high temperature and greater decomposition of the drug, in addition to its lack of resistance to heat and its stability when stored for a certain period, We conclude from this study that the issue of knowing the decomposition of medicines varies from one manufacturer to another, and therefore we must be careful not to use medicines belonging to unreliable companies, because the decomposition of medicines when exposed to heat, especially in the atmosphere of our country, will expose our lives to danger due to the change in the composition of the drug .

Table 1 : show the experiment result for jamjoom pharma Azithromycin [azi - once tablets 250mg

Temp.	Temp. (K)	1/T(K)	Time (min)	Vol. of E.P (ml)	Conc. at time (Ct)	ln Ct	K	ln K
40	313	0.0031	0	1.4	1.4	0.3364	0.0009	-7.01311
			15	1.2	1.942	0.6641		
			30	1.4	1.8	0.5877		
			45	1.5	1.728	0.5472		
			60	1.7	1.585	0.4610		
50	323	0.00309	0	1.4	1.4	0.3364	0.014	-4.268
			15	2	1.371	0.3158		
			30	2.2	1.228	0.2058		
			45	2.3	1.157	0.1459		
			60	3.2	0.514	-0.664		
60	333	0.003003	0	1.5	1.5	0.4054	0.008	-4.7795
			15	2	1.371	0.3158		
			30	2.2	1.228	0.2058		
			45	2.3	1.157	0.1459		
			60	3.2	0.514	-0.66		
70	343	0.002915	0	1.5	1.5	0.4054	0.006	-5.0359
			15	1.4	2.066	0.7259		
			30	1.2	2.2	0.7884		

			45	1.3	2.133	0.757		
			60	0.9	2.4	0.875		

Table 2 : show the experiment result for LDP pharma Azithromycin [azi - once tablets 250mg]

Temp.	Temp. (K)	1/T(K)	Time (min)	Vol. of E.P (ml)	Conc. at time (Ct)	ln Ct	K	ln K
40	313	0.00319	0	1.1	1.1	0.09531	0.002	-6.214
			15	1.2	1.109090	0.10354		
			30	1	1.290909	0.25534		
			45	1.1	1.2	0.18232		
			60	1.3	1.018181	0.01801		
50	323	0.00309	0	1.1	1.1	0.09531	0.002	-6.214
			15	1	1.29090	0.25534		
			30	1.4	0.92727	0.0755		
			45	1.2	1.109090	0.10354		
			60	1.3	1.01818	0.01801		
60	333	0.003	0	1	1	0	0.0087	-4.744
			15	1.1	0.9	-0.1053		
			30	1.3	0.7	-0.3566		
			45	1.5	0.5	-0.6931		
			60	1.3	0.7	-0.3566		
70	343	0.0029	0	1	1	0	0.0094	4.6691
			15	1.2	0.8	-0.223143		
			30	1.1	0.9	-0.105360		
			45	1.6	0.4	-0.916290		
			60	1.3	0.7	-0.356674		

Table 3 : how the experiment result for Ajanta Pharma Ltd . Azithromycin (ZAHA capsules 250mg)

Temp.	Temp. (K)	1/T(K)	Time (min)	Vol. of E.P (ml)	Conc. at time (Ct)	ln Ct	K	ln K
40	313	0.003194	0	2	2	0.693	0.0061	5.115
			15	1.8	3.1	1.131		
			30	1.9	3.05	1.115		
			45	1.6	3.2	1.16		
			60	1.8	3.1	1.131		
50	323	0.003095	0	2	2	0.693	0.0035	5.654
			15	1.4	3.3	1.193		
			30	1.5	3.25	1.178		
			45	1.6	3.2	1.163		
			60	2.7	2.65	0.974		
60	333	0.003003	0	2.1	2.1	0.741	0.0051	5.298
			15	1.4	3.533	1.262		
			30	1.6	3.438	1.234		
			45	1.7	3.390	1.220		
			60	2.2	3.152	1.148		
70	343	0.002915	0	2.1	2.1	0.741	0.005	5.278
			15	2	3.247	1.177		
			30	2.5	3.0095	1.101		
			45	2.4	3.0571	1.1174		
			60	2.2	3.1523	1.1481		

Table 4 : show the experiment result for GETZ pharma . Azithromycin zithroget capsules 250mg

Temp.	Temp. (K)	1/T(K)	Time (min)	Vol. of E.P (ml)	Conc. at time (Ct)	ln Ct	K	ln K
40	313	0.0031	0	1.5	1.5	0.4054	0.001	6.919
			15	1.4	2.06	0.7259		
			30	1.6	1.93	0.6592		
			45	1.7	1.86	0.6241		
			60	1.8	1.8	0.5877		
50	323	0.003	0	1	1	0	0.005	-5.318
			15	0.8	1.2	0.1823		
			30	0.9	1.1	0.095		
			45	1.1	0.9	-0.1053		
			60	1.2	0.8	-0.2231		
60	333	0.003	0	1.7	1.7	0.5306	0.01	-4.656
			15	2	2.22	0.7990		
			30	30	1.5	2.5176		
			45	0.9	2.87	1.0545		
			60	0.9	2.87	1.0545		
70	343	0.0029	0	1.8	1.8	0.5877	0.006	5.132
			15	1.2	2.93	1.0761		
			30	1.4	2.82	1.0375		
			45	1.5	2.76	1.0176		
			60	1.3	2.87	1.0570		

Table 5 : show the experiment result for BRAWN laboratory Limited . Azithromycin (Azibru capsules 250mg)

Temp.	Temp. (K)	1/T(K)	Time (min)	Vol. of E.P (ml)	Conc. at time (Ct)	ln Ct	K	ln K
40	313	0.00319	0	2.1	2.1	0.741	0.0048	-5.33
			15	2.3	3.104	1.132		
			30	2.2	3.152	1.148		
			45	2.3	3.104	1.132		
			60	2.5	3.009	1.101		
50	323	0.003095	0	2.1	2.1	0.741	0.0075	-4.892
			15	1.2	3.628	1.288		
			30	1.1	3.676	1.301		
			45	1	3.723	1.314		
			60	2.1	3.628	1.288		
60	333	0.003003	0	2.4	2.4	0.875	0.0071	-4.947
			15	2.3	3.841	1.345		
			30	2.6	3.716	1.312		
			45	2.1	3.925	1.367		
			60	1.8	4.05	1.398		
70	343	0.002915	0	2	2	0.693	0.002	-6.214
			15	3.7	2.15	0.765		
			30	3.5	2.25	0.810		
			45	3.6	2.2	0.788		
			60	3.4	2.3	0.832		

TABLE 6: show the values shelf life and rate constant at room temperature of the azithromycin for fife company

Company Name	K25	T 1/9
JAMJOM	12.135	0.0086171
LDP	0.000825	127.27
ZAHA	198.343	0.000529
GETZ	4.481	0.0234
BRAWN	90.017	0.00116

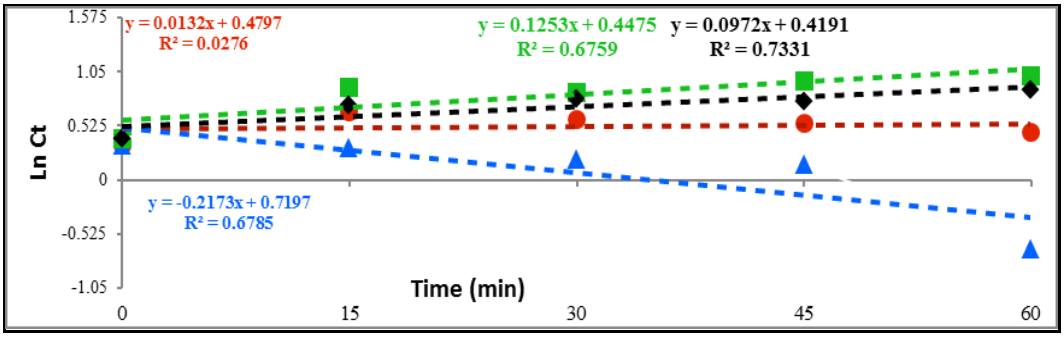

Fig. 4 : the first-order equation for jamjom tablets 250 gm

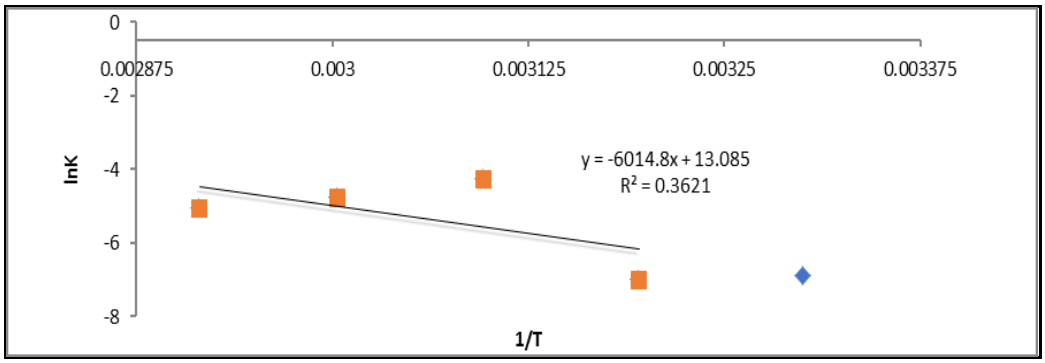

Fig. 5 : show Arrhenius plot for jamjom tablets 250mg

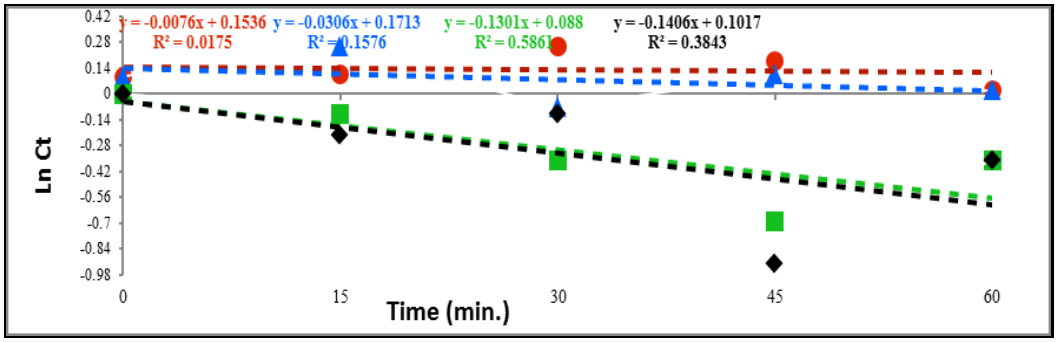

Fig. 6 : show the first-order equation for LDP capsules 250mg

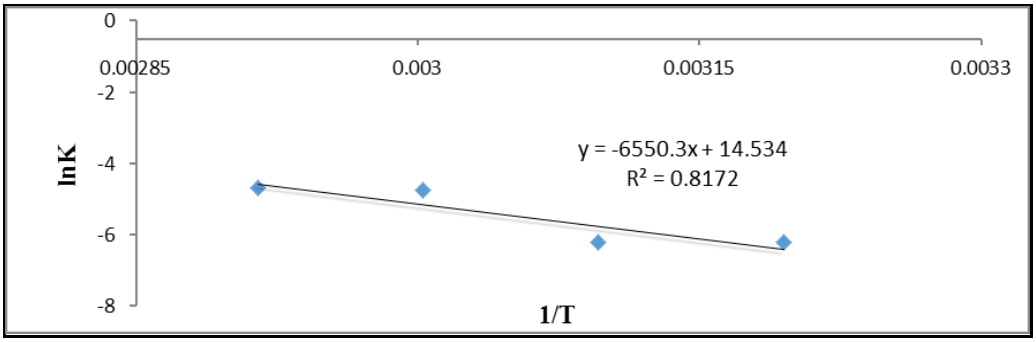

Fig. 7 : show Arrhenius plot for LDP azoxine capsules 250mg

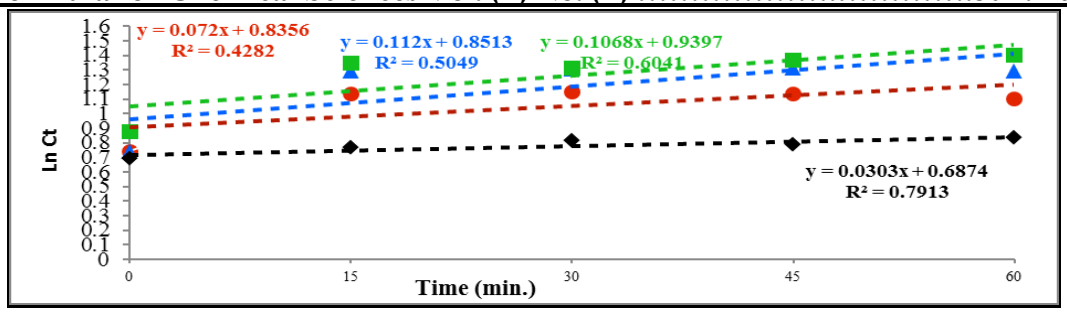

Fig. 8: first-order equation for Ajanta capsules 250mg

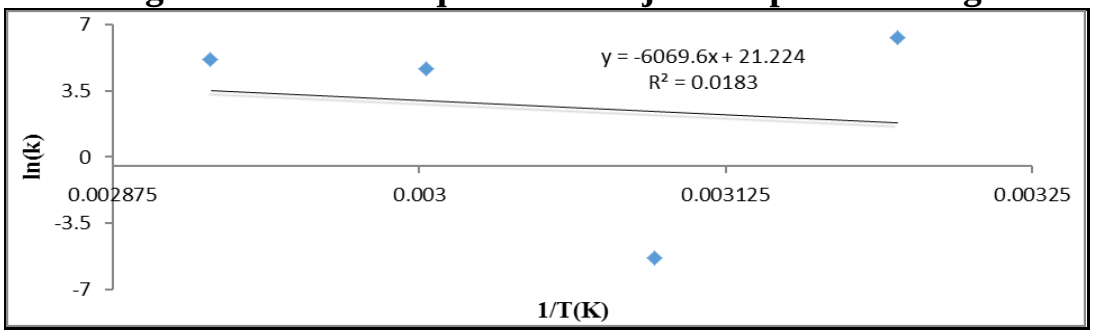

Fig. 9 : show Arrhenius plot for the Ajanta capsules 250mg

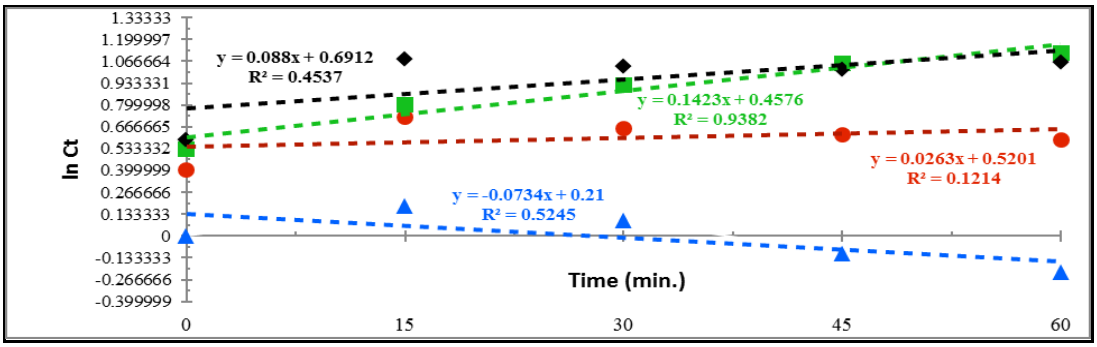

Fig. 10: show the first-order equation for zithroget capsules 250mg

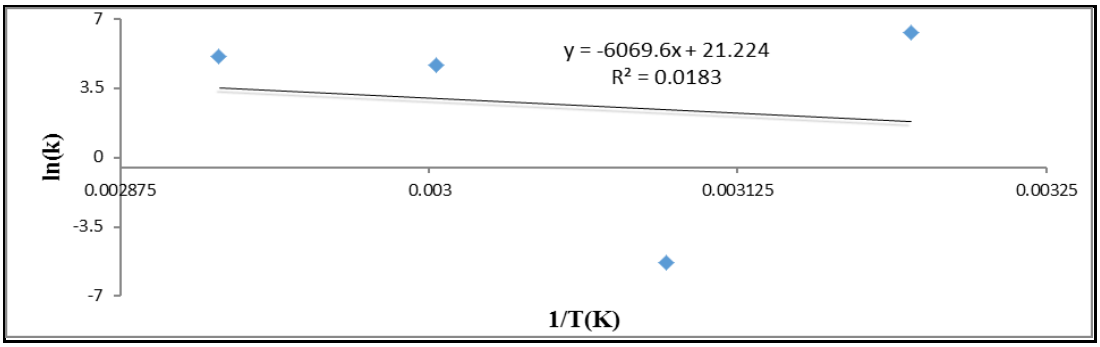

Fig. 11 : show the Arrhenius plot for zithroget capsules 250mg

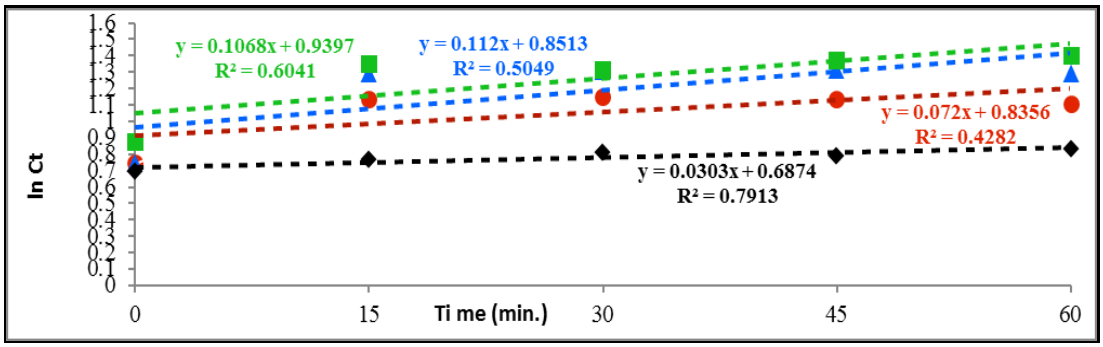

Fig. 12 : first-order equation for azibru capsules 250mg

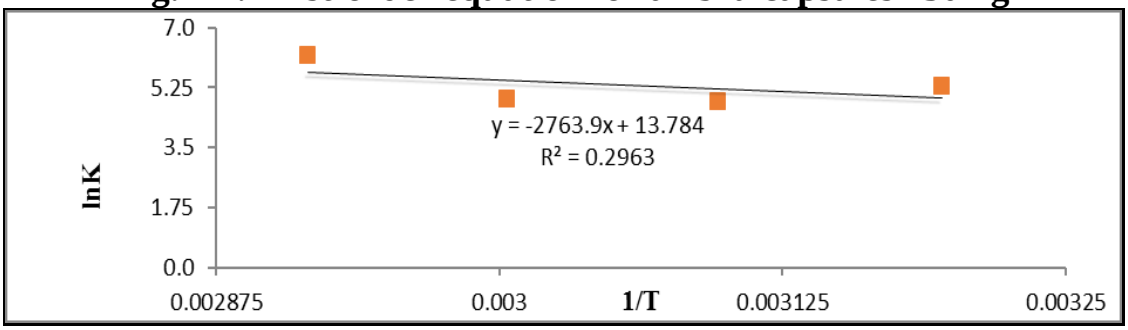

Fig. 13: show the Arrhenius plot for azibru capsules 250mg

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