Formulation of Azithromycin Suspension as an Oral Dosage Form

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Abstract

Azithromycin is the drug of choice in the treatment of several bacterial infections, most often those causing middle ear infection, bronchitis, pneumonia, typhoid and sinusitis. It's also effective against certain urinary tract infections and venereal diseases. This study was carried out to prepare an acceptable suspension either as dry physical mixture powder or granules to be reconstituted, through studying the effect of various type and concentration of suspending agent (xanthan gum, hydroxypropyl methylcellulose (HPMC), either alone or in combination) on the release profile of the drug. The best prepared suspension formulas (H& III) were selected depending on the dissolution profile of each formulas and then compared with the reference suspensions (Zithromax and Azi-once).The viscosity, sedimentation volume, Resuspendability and expiration date were evaluated for the chosen formulas (H&III) and compared with references Zithromax® and Azi-once®.The result indicated that the chosen formula – H had better dissolution rate compared with references suspensions, Also it was less viscous than them.While other chosen formula – III had lower dissolution rate compared with Zithromax® and higher dissolution rate than AZi – once, also it was less viscous than both references.It was found that the dry physically mixed powder (formula – H) was more stable than the granular suspension (Formula III) since the expiration date for formula H and formula III were 3.24 and 2.7 years respectively.

Key words: Azithromycin, suspending agent, suspension.

تحضير الازثرومايسين كمعلق فموي

صبا عبد الهادي جابر*[1] ، زينب ثابت صالح* و هبة موفق سلمو*

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الخلاصة

الازثرومايسين هو الدواء المفضل لعلاج التهابات الجهاز التنفسي وحمى التيفوئيد هذا بالاضافة الى فعاليته في علاج العديد من امراض المسالك البولية والامراض الانتقالية . تم اجراء هذه الدراسة لتحضير معلق ثابت (بشكل حبيبات او مسحوق جاهز للحل) من الازثرومايسين من خلال دراسة تأثير انواع وتراكيز مختلفة من المواد المعلقة (زانثان كم وهايدروكسي بروبل مثيل سليلوز) على سرعة تحرر الدواء . ان الصيغ التركيبية المختارة (III & H) اختيرت اعتمادا على مقارنتها مع الصيغ الاخرى من خلال قياس سرعة تحرر الدواء ثم تمت كذلك مقارنتها مع التركيبة التجارية (ازي – اونس و زثروماكس) . كذلك تمت دراسة الكثير من الخواص الفيزيائية للصيغ التركيبية المختارة (III & H) وتتمثل بجريان المحلول، حجم المواد المترسبة،اعادة التجانس للمحلول بعد الرج وفعالية المواد الحافظة ومقارنتها مع التركيبات التجارية المرجعية (ازي - اونس وز ثروماكس) . وقد اظهرت النتائج ان الصيغ التركيبية التي اعطت سرعة تحرر اعلى من التركيبة المرجعية هي اقل لزوجة. وكذلك وجد ان معلق الازثرومايسين المحضر بشكل مسحوق جاهز للحل هو نوعا ما اكثر استقرارية من المعلق المحضر على شكل حبيبات حيث ان فترة انتهاء الصلاحية كانت 3.2سنة للمسحوق و 2.7 سنة للحبيبات .

الكلمات المفتاحية : أزثرومايسين ، مواد معلقة ، معلق.

Introduction

Suspension is preparation containing finely divided drug particle (Suspensoid) distributed uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility [(1)].Some suspensions are available in ready liquid form that is, already distributed through a liquid vehicle with or without stabilizers and other additives. This preparation is termed as an "Oral Suspension "in the united state pharmacopeia (USP). Other preparations are available as dry powders to be reconstituted when desired. This preparation is termed as "For Oral Suspension "in USP [(1)].There are many physical and chemical consideration in the preparation and development of a suspension to satisfy its pharmaceutical requirements.Some suspending agents are generally added to the dispersion medium in order that their structures help to maintain uniform dispersibility [(2)] or to prevent caking of the drug particles during shelf – life [(3)]. Pharmaceutical suspension usually defined as a coarse dispersion [(4)].

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Azithromycin is one of the worldś best selling antibiotics, and is derived from erythromycin. Azithromycin is used to treat or prevent certain bacterial infections , most often those causing middle ear infection ,tonsillitis, throat infections, laryngitis, bronchitis, pneumonia, Typhoid and sinusitis [5,6].In recent year it has primarily been used to prevent bacterial infections in infants and those with weaker immune system.It is also effective against certain urinary tract infection and venereal diseases, such as non – gonococcal urethritis, Chlamydia, gonorrhea and cervicitis [7,8].Unlike erythromycin, azithromycin is acid stable and can therefore be taken orally with no need of protection from gastric acids.It is readily absorbed, but its absorption is greater on an empty stomach [9].Azithromycin is practically insoluble in water, freely soluble in anhydrous ethanol and methylene chlorid [10].

Materials and Equipments

Materials

Azithromycn powder (supplied by Kanawati Medical products – Syria) Artificial flavor (raspberry flavor), Xanthan gum , hydroxy propyl methyl cellulose (HPMC) , colloidal silicon dioxide, methyl paraben (M.P.) , propyl paraben (P.P.), disodium EDTA (supplied by Samara drug Industries (SDI)), tribasic sodium phosphate dodecohydrate, sucrose, polyvinyl pyrrolidone (PVP) (supplied by BDH chemical LTD. pool, England),absolute ethanol (supplied by GCC Gain land Chemical Company, U.K.)

Azi-once® powder for oral suspension (supplied by jam joom pharma).

Zithromax® powder for oral suspension (supplied by Pfizer - Italy).

Equipments

Miller Hinton agar (supplied by Rashmi – Diagnostics, Danglorc , India), sartorious balance (sartorius AG. Gottingen , Germany), pH 211 micro processor pH meter (HANA, Italy), uv\vis –spectra photo meter – UV-9200 (SEDICO LTD .P.O.BO 20961, Nicosia-1665 – Cyprus), dissolution apparatus (Erweka G.M.B.H. type DT6, w.Germany), viscometer (NDJ – 55 Digital Viscometer),oven (Mem meter 854 schw bach, W. Germany), oven (Gallen kamp, Bs size one, England), autoclave (webco F.G. Bade of CO Laboratory Equipment, Hamburg, Germany).

Method of preparation

Formulation of azithromycin suspension

Several formulas of Azithromycin aqueous suspension were prepared, either as dry physical mixture powder for reconstitution or as granules for reconstitution.

Suspension prepared by physical mixing (as dry powder)

Table (1) shows different formulas of azithromycin suspension each was prepared as: Ablend of 4.0 %(w/v) azithromycin was mixed with different excipients stated in the above table, in a dry amber bottle [11].

Table 1 : Different formulas of azithromycin powder prepared as physical mixture to be reconstituted as suspension (% w/v).

Materials (gm)	Formulas									
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
Azithromycin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Xanthan gum	0.3	0.5	-	-	0.3	0.5	0.3	0.5	0.5	0.5
Hydroxy propyl methyl Cellulose (HPMC)	-	-	0.3	0.5	0.5	0.5	0.3	0.3	0.3	0.3
Colloidal silicon dioxide	-	-	-	-	-	-	-	-	0.5	0.1
The following substances have been added to each of the above formulas in the same quantities										
Tribasic sodium phosphate dodecohydrate	0.8									
Methyl paraben (M.P)	0.18									
Propyl paraben (P.P)	0.03									
Disodium EDTA	0.1									
Artificial flavor (raspberry flavor)	0.49									
Sucrose	93									
Water for reconstitution	40 ml									

Suspension prepared as granular for reconstitution

Table (2) shows different formulas of azithromycin granules prepared by granulation method to be reconstituted as suspension as follows:-

A blend of 4.0 %(w/v) Azithromycin was mixed with different excipients mentioned in the above table, followed by levigating with alcoholic PVP solution (0.5% w/v) as a granulating agent.The powder mixture passed through a sieve (300µm) to a petri dish for drying at 37°C before being transferred to an amber bottles[12,13]. The evaluation of prepared suspension and comparative studies of different variables affecting the selected formulas with marketed references (Azi-once® and zithromax® suspension) were done.

Table 2 : Different formulas of azithromycin prepared as granules to be reconstituted as suspension (% w/v).

Materials (gm)	Formulas			
	I	II	III	IV
Azithromycin	4.0	4.0	4.0	4.0
Xanthan gum	0.3	0.5	0.3	0.5
Hydroxry propyl methyl Cellulose (HPMC)	0.5	0.3	0.3	0.5
The following substances have been added to each of the above formulas in the same quantities				
Tribasic sodium phosphate dodecohydrate	0.8			
Methyl paraben	0.18			
Propyl paraben	0.03			
Disodium EDTA	0.1			
Artificial flavor (raspberry flavor)	0.49			
Sucrose	93			
Alcoholic- PVP solution (0.5% w/v)	60 drops (for granulation)			
Water for reconstitution	40 ml			

Dissolution profile

The dissolution rate of azithromycin drug from suspensions was studied using USP dissolution apparatus rotated at 50 r.p.m. The dissolution medium was 0.1N HCl (500 ml) maintained at 37°C, 5 ml sample of suspension was added to the medium. Then a sample of dissolution medium was withdrawn at different time intervals (1, 2, 3, 4, 5, 7, 9, 12, 20, 30 minutes) through a pipette fitted with a filter paper. The same fresh dissolution medium was added to the jar each time to replace with drawn samples. Each sample was suitably diluted and assayed spectrophotometrically at 210nm [10] for azithromycin content [14].

Measurement of viscosity

The viscosities were obtained at 37°C with NDJ – 55 digital rotational viscometer using spindle number 2 at 60 rpm. [15].

Sedimentation volume measurement

Fifty ml of each suspension was diluted with distilled water to a volume of 100 ml in a stopper graduated cylinder. The suspensions were shaken vigorously to ensure uniformity, and then left undisturbed. The sedimentation volume was measured every 4 hours for a period of 48 hours [16].

Re– Suspendability of suspension

The test consisted of manually shaking the cylinder after the sedimentation experiment was completed. Based on the effort required to convert the sediment system to a homogenous suspension, the prepared product was rated as: resuspendable , resuspendable with difficulty or not resuspendable [17].

Antimicrobial activity of suspension

The antimicrobial activity of azithromycin suspensions were studied by the agar diffusion method [18, 19]. The basic of the diffusion test includes the diffusion of the material under test from a central reservoir into the surrounding agar which has been inculated with a sensitive organism. The growth of the organism is inhibited, and manifested as zone of inhibition.The relationship between the applied dose , kind of suspension and size of the inhibition zone in the basis of comparisons the gram +ve and the gram –ve bacteria which are sensitive to azithromycin were used .

Gram + ve ⟶ staphylococcus aureua .
Gram – ve ⟶ Escherichia coli.

Suspension tested

Azi – once®.
Zithromax®.
Formula H.
Formula III.

The test procedure

Steril Miller – Hinton agar media were poured in to flat bottom steril petri dish under aseptic technique and were allowed to harden , then incubated at 37°C for 24 hours after inoculated with the appropriate microorganism , all of these plates are divided into four sections as shown in figure (a) [14].0.05ml (one drop) of each suspension formulas were inoculated in each sector of the agar media using a micropipette, each drop contains the equivalent of 2mg of azithromycin.

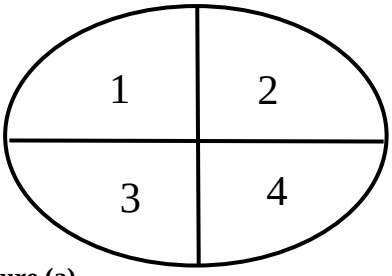

Figure (a)
1-Represent Azi – once® suspension.
2-Represent Zithromax suspension.
3-Represent Formula H .
4- Represent Formula III .

Stability study

The accelerated stability study was done in order to determine the expiration date of formula H and formula III by placing the samples of both formulas in ovens at 40°C, 50°C and 60°C for 90 days.Samples (dry physical mixture powder or granules) were taken and assayed for their drug content at a suitable time intervals using UV spectrophotometrical method for the two accepted formulas (H and III)[20]. Furthermore, physical stability (color, odor and pH) change for the samples were also examined .

Results and Discussion

Xanthan gum was used as suspending agent because of its excellent suspending properties and also as an effective flocculating agent at relatively low concentration [21] . An increase in the concentration of xanthan gum (Formula B) gave no substantial change in flocculation behavior, good dissolution properties and it produced a sediment layer that was easily redispersed upon shaking as shown in figure (1).On the other hand, hydroxy propyl methyl cellulose (HPMC) was utilized as suspending agent and binder as shown in figure (2).

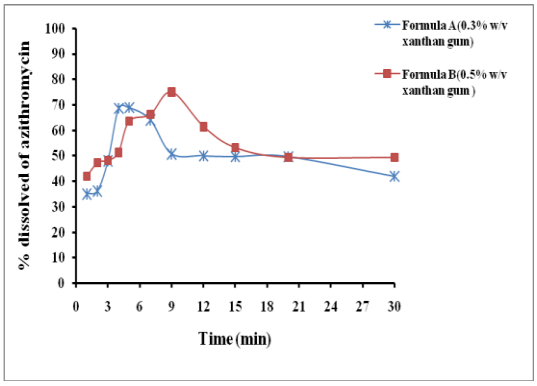

Figure 1: Effect of xanthan gum concentration on dissolution profile of azithromycin (Formula A and B) in 0.1 N HCl (pH=1.2) at 37 °C.

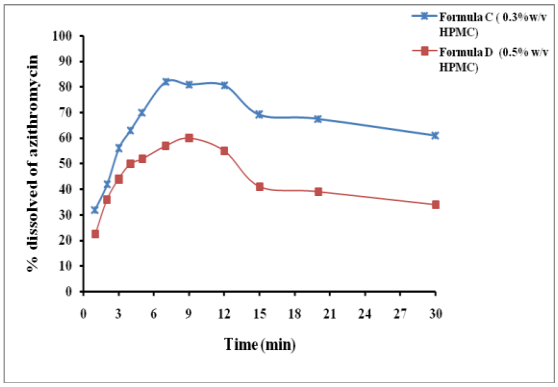

Figure 2: Effect of HPMC concentration on the dissolution profile of azithromycin (Formula Cand D) in 0.1 N HCl (pH=1.2) at 37 °C.

This polymer behave as a protective colloid by coating the solid hydrophobic particles with multimolecular layer, this will impart hydrophilic character to the solid and thus promote wetting[22]. But to a certain concentration, the dissolution of azithromycin decreased which is attributed to the fact that at high polymer concentration, the polymeric flocculating agent coat the whole surface of the suspended particles, so there is no free areas from adsorbate. These areas are necessary for cross-linking to be recure after the product was sheared[23]. The increase in the viscosity of the

system may also have an effect on the dissolution rate of the drug[24]. Furthermore, a combination of xanthan gum and HPMC (Formula E , F, G and H) resulted in a maximum enhancement in the dissolution of azithromycin , this could be due to the fact that their linear branched chain molecules form a gel – like net work within the system and become adsorbed on to the surface of the dispersed particles , thus holding them in a flocculated state (bridging effect) [20] as shown in figure (3) . Formula – H produced a suspension with good dissolution as shown in figure (3). This formula (H) gave the most optimum physical stability and remarkable release profile, therefore it was chosen for extensive study and to be compared with reference suspensions.The addition of colloidal silicon dioxide as a dispersing agent (formula I&J) results in too viscous suspension as listed in table (3), with difficulty to redisperse upon shaking. This was a result of using a combination of three polymers (xanthan gum +HPMC and colloidal silicon dioxide) which leads to rheological synergism to be occurred due to stronger cross linking between these polymers[25].These formulas (I &J) showed a substantial change in the dissolution behavior corresponding to the best formula –H and the releasing profile decreased by increasing the concentration of colloidal silicon dioxide as shown in figure (4)[26,27].

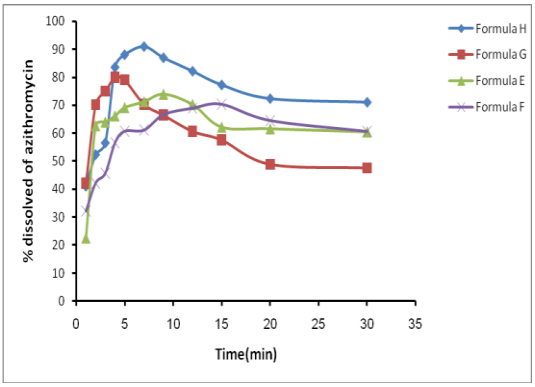

Figure 3: Effect of xanthan gum and HPMC on the dissolution profile of azithromycin (Formula E,F,G and H) in 0.1 N HCl (pH=1.2) at 37 °C.

-Formula H(0.5 % w/vxanthan gum + 0.3% w/v HPMC)
-Formula G (0.3% w/v xanthan gum + 0.3% w/v HPMC)
-Formula E (0.3% w/v xanthan gum + 0.5% w/v HPMC)
-Formula F (0.5% w/v xanthan gum + 0.5% w/v HPMC)

Table 3: The viscosities of the suspension formulas (H , III, I , J) and reference suspension, using spindle number 2 at 60 rpm.

Formulas	Viscosity (mpa.s)
Azionce®	268
Zithromax®	240
Formula – H	233
Formula – III	199.2
Formula – I	450
Formula – J	400

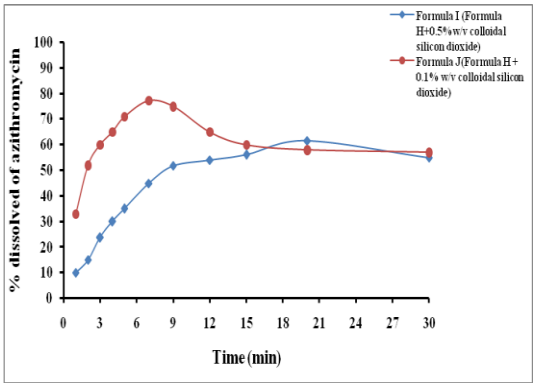

Figure 4: Effect of colloidal silicon dioxide concentration on the dissolution profile of azithromycin from the best formula – H (Formula I and J) in 0.1 N HCl (pH=1.2) at 37 °C.

Finally, azithromycin suspension (as dry physical mixture powder) when prepared using 0.5%(w/v) xanthan gum as a single suspending agent together with 0.3%(w/v) HPMC as suspending agent and binder (formula –H) resulted in a suspension that showed high sedimentation volume (0.99) and was easily redispersed upon simple shaking.Figure (5) shows the enhancement in the dissolution of azithromycin by the addition of a blend of different concentrations of xanthangum and HPMC (polymeric flocculation agent) to the formulas I, II, III and IV. These formulas were prepared as granules using alcoholic – PVP solution as a granulating agent [28]. The granules were found to be free flowing, not bulky, and of uniform size. The size of each granule was 300 µm according to the sieve number was used (no.50)[1,17]. Formula III was chosen since it gave good dissolution, stability although it produced sediment layer with simple shaking easily redispersable. Figure (6) show the dissolution profile of azithromycin suspension for formulas H & III compared with the reference Zithromax® and Azi – once® suspensions.

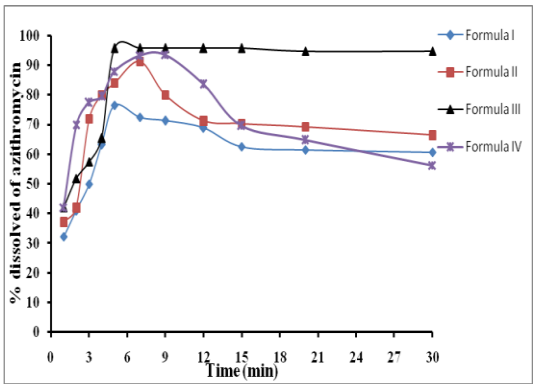

Figure 5: Effect of xanthan gum and HPMC concentration on the dissolution profile of azithromycin granules (Formula I,II,III and IV) in 0.1 N HCl (pH=1.2) at 37 °C.

-Formula I (0.3% w/v xanthan gum + 0.5% w/v HPMC)
-Formula II (0.5% w/v xanthan gum + 0.3% w/v HPMC)
-Formula III (0.3% w/v xanthan gum + 0.3% w/v HPMC)
-Formula IV (0.5% w/v xanthan gum + 0.5% w/v HPMC)

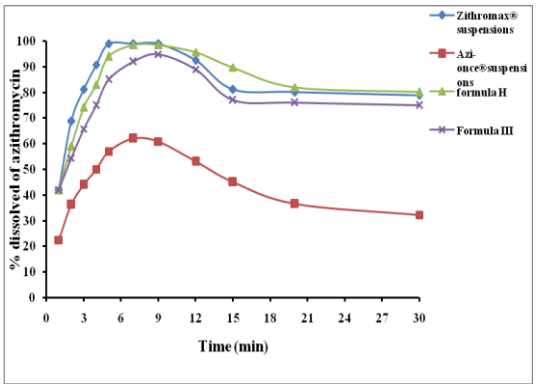

Figure 6: Dissolution profile of azithromycin suspension for Formulas H&III compared with the reference Zithromax® & Azi-once® suspensions in 0.1 N HCl (pH=1.2) at 37°C .

The results showed that azithromycin release from formula –H was higher than that form others (Azi-once and formula – III) but show approximately the same release as zithromax®. Formula – III after reconstitution showed lower dissolution profile than formula H – and zithromax®, this may be due to the granulation process, since PVP was used as a granulating agent which is water soluble binder and has good swelling and hydration capacity. These properties result in the high viscous region surrounding the drug particle[29,30].On the other hand the viscosities of the products are represented in table (3). The results showed that the viscosity of azithromycin suspension was shear rate dependent and increased viscosity in the following order:

Azionce® > Zithromax® > Formula – H > Formula – III

Table (4,5) show the sedimentation volume and resuspendability after settling of the chosen azithromycin formulas (H,III) and the reference suspensions after 48 hours undisturbing . The evaluation of azithromycin released as antibacterial agent was listed in table (6).

Table 4: Sedimentation volume of azithromycin suspensions (formula H,III,Azi-once and zithromax®)

Products	$F=H_u / H_0$
Zithromax®	0.99
Formula – H	0.99
Formula – III	0.9
Azi – once	0.6

Where H_u is the ultimat height of the Sediment as suspension settle ,H_0 is the intial height the total suspension .

Table 5: Resuspendability of azithromycin suspensions (formula H,III,Azi- once and zithromax®)

Products	Resuspendaloility
Zithromax®	Easily resuspendable
Formula – H	Easily resuspendable
Formula – III	Easily resuspendable
Azi – once	resuspendable with difficulty

Table 6: Zone of inhibition by azithromycin in different formulas on the sensitive gram +ve and gram –ve organism (mm).

Products	gram +ve staph. aureus inhibition zone	gram -ve E – Coli inhibition zone
Zithromax®	34 mm	33 mm
Formula – H	33 mm	28 mm
Formula – III	34 mm	28 mm
Azi – once	32 mm	28 mm

Formula – H has less antimicrobial effect against gram positive microorganism compared to the references, while formula – III has the same activity as references. Formulas (III and H) has the same antimicrobial activity against gram negative microorganism as Azi – once® but less than zithromax®[31].The accelerated stability study was applied on the chosen formula at higher temperatures(40°C,50°C and 60°C) to predict the expiration date of formulas H and III .

The degradation of azithromycin in these formulas followed first order kinetics since straight lines,were obtained by plotting the logarithm of percent remaining of azithromycin versus time as shown in figures (7, 8) [32,33].

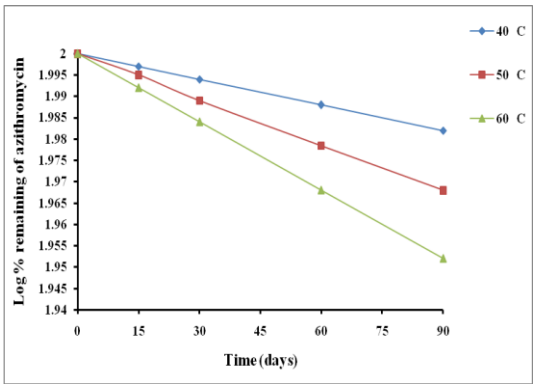

Figure 7: Degradation curve of dry physical mixture powder of azithromycin suspension (Formula – H) at different temperature.

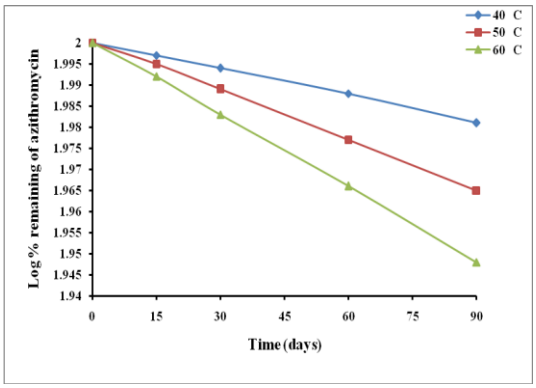

Figure 8: Degradation curve of granular azithromycin suspension (Formula – III) at different temperature.

Table 7: Degradation rate constant of Azithromycin suspension dry powder (Formula – H) and Granular suspension (Formula III)

Temperature	K X 10^{-3} (day $^{-1}$)	
°C	Formula – H	Formula – III
60	0.53	0.6
50	0.35	0.4
40	0.2	0.23
25	0.09	0.11

The degradation rate constants (k) at different temperatures were calculated from the slope of the straight lines and they were listed in table (7). Arrhenius plots were then constructed and are shown in figures (9,10) for formula H and III respectively.The Linearity of the curve indicates their utility in predicting the rate of degradation at lower temperature. The rate constant at 25°C, obtained from those plot for dry physically mixed powder (Formula – H) and granular suspension (Formula III) were equal to (0.09 x 10^{-3}) and (0.11 x 10^{-3})(day^{-1}) respectively.Since the degradation of the drug followed first order kinetics, the expiration date t 10% at 25°C could be calculated using the following equation.

$$t_{10} = \frac{0.105}{K_{25°C}}$$

The expiration date for formula – H and formula – III were 3.24 and 2.7 years respectively.

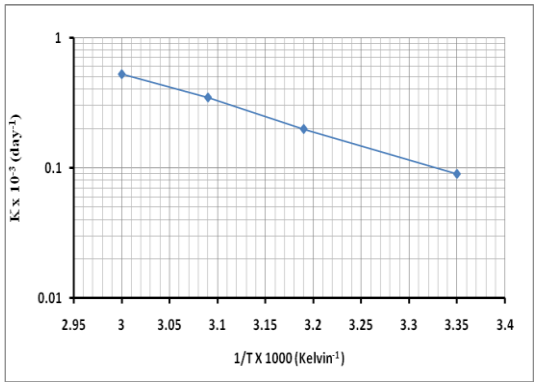

Figure 9: Arrhenius plot for expiration date estimation of azithromycin suspension (Formula – H) at 25°C .

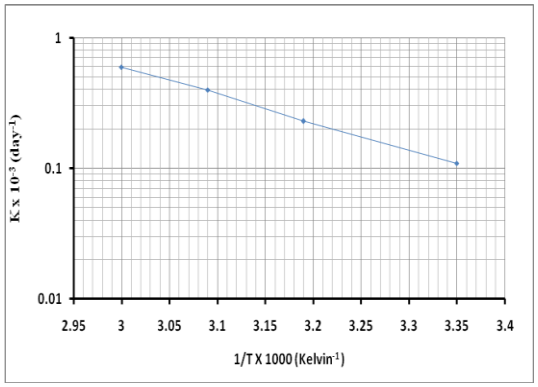

Figure 10: Arrhenius plot for expiration date estimation of azithromycin suspension (Formula – III) at 25°C

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