

Formulation of Tinidazole as an Oral Suspension Dosage Form

Lubna A.Sabri, Halah T. Sulayman and Dina W.Ameen
Dept of Pharmaceutics, College of Pharmacy, University of Baghdad

Abstract:

Tinidazole is an effective drug for the treatment of amoebiasis, giardiasis and anaerobic bacterial infections, it has a long half-life and it is practically insoluble in water thus it is suitable for suspension dosage form.

This study was carried out to prepare an acceptable suspension through studying the effect of different types and concentrations of suspending agent such as sodium carboxyethyl cellulose, xanthan gum, sodium alginate and avicel (RC 591).

The effect of these suspending agents was studied in 0.1N HCL and at 37°C. The obtained results were utilized to formulate different suspensions. The release rate, sedimentation volume and resuspendability were evaluated for these formulas.

The formula which gave best release and optimum sedimentation volume was chosen as the best formula.

The result showed that the release rate of the drug was dependent on the type and concentration of suspending agent. The best one was that containing 0.5%, xanthan gum as a suspending agent.

The rheology and expiration date were evaluated for this formula. The expiration date of the prepared suspension was about 2.2 years. The suspension of tinidazole was also extemporaneously prepared from Fasigyn® tablets. The prepared extemporaneous suspension should be used within 7 days after preparation.

Keywords: tinidazole, suspension, flocculation, suspending agents

الخلاصة:

التندازول هو دواء فعال يستخدم كمضاد حيوي لبعض الميكروبات مثل الجيارديا والاميبيا المعوية بالإضافة الى البكتيريا اللاهوائية. وبما ان الدواء غير قابل للذوبان عمليا في الماء فان تحضيره كمعلق صيدلاني معد للاستخدام الصيدلاني يعتبر مناسباً.

تم اجراء هذه الدراسة لتحضير معلق مقبول من الناحية الصيدلانية من خلال دراسة تحرر الدواء بوجود مواد مختلفة من المواد المعلقة وبعدها تراكيز مثل كاربوكسي مثيل سليولوز الصوديوم، صمغ الزانثان، الجينات الصوديوم والافسيل.

تمت هذه الدراسة بمحلول حامض الهيدروكلوريك عيارية 0.1 ودرجة حرارة 37 درجة مئوية. اشارت النتائج الى ان سرعة تحرر العقار بوجود المواد المعلقة يعتمد على نوع وتركيز هذه المواد، حيث استفيد من هذه النتائج لتحضير تراكيب عديدة لهذا المعلق. تم دراسة سرعة تحرر الدواء وحجم ترسب وتجانس المعلق بعد تحريكه لهذه التراكيب. اختيرت الصيغة التي اعطت احسن تحرر للدواء وفضل حجم ترسب كأحسن صيغة.

تم قياس جريان المعلق وتاريخ الصلاحية لهذه التركيبة. لقد وجد ان صلاحية هذه التركيبة كان بحدود 2.2 سنة. كذلك تم تحضير معلق التندازول أنيا من أقراص الفاسجين المتوفرة تجارياً. لقد وجد بأن هذا المستحضر يجب أن يستعمل خلال أسبوع من تاريخ تحضيره.

Introduction:

Intestinal protozoan infections are significant problem both in industrialized and developing countries, especially in the latter; where they may result in mortality in children^[1] Treatment with 5-nitroimidazole compound is recommended as first line therapy for adult and children^[2].

Tinidazole is an orally absorbed drug used in treatment of intestinal

protozoan infections. It has long $t_{1/2}$ which allows a simpler dosing schedule. Tinidazole also has fewer side effects and may improve compliance^[3].

The efficacy and safety of tinidazole in pediatric patient has been demonstrated for treatment of giardiasis^[4]. Until a child is 8 years old, swallowing tablet can be challenging.

This is often due to the smaller structure of child esophagus. Therefore children under the age of 8 are typically prescribed liquid medication^[5, 6].

Physicochemical stability is an important requirement for pharmaceutical suspension. The irreversible aggregation of the particle must be avoided and, at most, the suspension should be in flocculated state thus making it possible to reversibly change it to homogenous dispersion before dispensing^[7].

Polymers can be used to control the degree of flocculation by forming gel – like net work within the system and become adsorbed on the surface of the dispersed particles thus holding them in flocculated state^[8].

Hydrophilic colloids such as xanthan gum, acacia and cellulose derivatives have been used as suspending agents. Xanthan gum is a high molecular weight polysaccharide gum.

It is soluble in water at all temperatures. Avicel[®] RC-591 is a water dispersible organic hydrocolloid used in the preparation of pharmaceutical suspensions and emulsions^[11]. It consists of a spray-dried blend of microcrystalline cellulose and carboxymethyl cellulose sodium.

The colloidal microcrystalline cellulose, accounting for approximately 90 % of the combination, provides a structured dispersion vehicle while the carboxymethyl cellulose sodium facilitates dispersion and serves as a protective colloid^[1]

The objective of the present work is to prepare acceptable 4% and 7% w/v tinidazole (TDZ) suspensions through studying the effect of different type and concentration of suspending agents [xanthan gum (XAT), sodium carboxymethyl cellulose (SCMC), avicel 591(AVC) and sodium alginate (SAG)] on the release of tinidazole and the

sedimentation volume of the prepared suspensions. The rheology and expiration date were evaluated for the best formula. Tinidazole suspension was also prepared extemporaneously from tablet.

The dissolution profile, sedimentation volume, and chemical stability were evaluated for this suspension.

It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity over a wide pH and temperature range^[9]. Carboxymethyl cellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties^[10].

Materials and Methods:

Materials:

Tinidazole (Sigma Chemical Co), Sodium carboxymethyl cellulose (BDH Chemical, LTD, Pool, England), Sodium alginate (Himedia Lab, Mumbai, India), Xanthan gum, Methylparaben, and Propylparaben were supplied from Samara Drug Industries, Avicel 591 (Microcellulose Weissenborn GmbH Germany), Tween 80 (Merck Sanchard, Germany), Sorbitol (Riedel DeHaen A G, Seelze-Hannover, Germany).

Methods Preparation of stock dispersion of suspending agent:

Stock dispersion of each suspending agent used (SCMC, XAT, SAG and AVC) was prepared by dispersing (1.5, 1, 3 and 4gm) of the suspending agent respectively, in 75 ml of distilled water using an electrical mixer at 150 r.p.m.

The volume of dispersion was made up to 100 ml with distilled water. The resultant dispersion was allowed to hydrate for 24 hours^[13]. Then sorbitol, raspberry flavor and sodium saccharin were added, finally by adding sufficient quantity of distilled water, the volume was made up to 100ml^[15].

Physicochemical characterization of suspension-Determination of pH:L

pH measurement was carried out using pH meter (Hanna, pH211 microprocessor, Italy) by dipping the electrode into the suspension for one minute^[15].

Characterization the effect of type and concentration of suspending agent:

To obtain the optimum quantity of different suspending agents, in order to be used in formulation of TDZ suspension. Four grams of TDZ was levigated in a mortar with each, 24 hour aged, dispersions of suspending agents, separately, as shown in table (1).

When a smooth paste is formed, the remainder of vehicle is added in divided portions.

The mixture was then transferred to a stoppered graduated cylinder then rinsed the mortar with distilled water and the volume was completed to 100ml, shaken vigorously then allowed to stand for 24 hours^[14].

Formulation of TDZ suspension:

Different formulas of suspension of TDZ were prepared as shown in table (2) as follows: TDZ, metylparaben (MP) and propylparaben (PP) were levigated with glycerol and a part of the prepared dispersion of suspending agent.

The remaining amount of dispersion was added in divided portions to the mixture with continuous triturating for one minute, and then the mixture was transferred to a stoppered graduated cylinder.

The mortar was rinsed several times with distilled water and the rinsed volume of dispersion was added to the cylinder.

Sedimentation volume:

Each sample was shaken to ensure uniformity prior to the study, and then transferred to the measuring cylinder (100 ml capacity), where it was allowed to stand undisturbed for 48 hr.

Sedimentation height was measured after 2, 4, 6, 8 and 48 hr. The sedimen-

tation volume (SV) was calculated from the ratio of the ultimate height (H_u) of the sediment to the initial height (H_o) of total suspension^[17].

Redispersibility:

The redispersibility of a suspension was evaluated qualitatively. The test consisted of manually shaking the cylinder after the sedimentation experiments were completed. Based on the time and the effort required to convert the sediment to homogenous suspension, the formulations were evaluated. One inversion was considered as 100% easy to be redispersed. Every additional inversion decreased the percent ease of redispersibility by 5%^[18].

Rheology:

Rheogram was obtained at 37°C with NDJ 5S Digital LCD viscometer. The suspension was left undisturbed for 10 minutes then was sheared with spindle 2 initially at a rate of 6 rpm. The scale reading was taken at the end of 30 sec for the viscometer to stabilize^[19].

Drug content analysis:

An accurately measured 5ml of suspension was placed in 250 ml volumetric flask. The volume was made up to 250 ml with 0.1 N HCL and shaken vigorously for 10 minutes.

The resulting sample was filtered and 1 ml of the filtrate was diluted to 50 ml with 0.1 N HCL. The resulting solution was assayed spectrophotometrically for TND at 277nm. The drug content was determined using preconstructed calibration curve of TDZ in 0.1N HCL^[16].

Stability study:

To assess the stability of TDZ in the selected formula, the suspension was centrifuged to get the supernatant solution. 5 ml samples of the resultant solution were stored in several closed amber glass bottles at 40°C, 50°C, and 60°C for 120 days^[20, 21]. Samples were assayed for drug content at suitable time intervals.

In addition, the selected formula was stored at room temperature and was

inspected at specified time intervals for any physical changes (color and pH).

Preparation and evaluation of extemporaneous TDZ suspension:

Four tablets containing TDZ (*Fasigyn*[®] 500 mg) were accurately weighed and ground to fine powder by using mortar and pestle.

A weight of powder equivalent to 4 gm of TDZ was levigated in a mortar with 5 ml cherry syrup.

Then, the mixture was transferred to a graduated cylinder, the volume was completed to 30 ml using cherry syrup, and the resultant suspension was stored in amber glass bottle^[22].

The dissolution profile of TDZ from this suspension, and sedimentation volume were evaluated by applying the same methods which were prescribed previously. The chemical stability of the prepared suspension was studied following storage in amber glass bottle for one month at room temperature.

Result and Discussion:

Effect of type and concentration of suspending agent:

The effect of various types and concentration of suspending agents on dissolution rate of TDZ was investigated and illustrated in Figures (1-4).

The effect of XAT on dissolution rate is shown in figure (1), the order of dissolution enhancement was $0.7\% < 0.00 < 0.3\% < 0.5\%$. while figure (2) shows the dissolution profile in the presence of 0.5, 0.75 and 1% w/v of SCMC. The order was $1\% < 0.0 < 0.75\% < 0.5\%$.

It has been postulated that the higher the dissolution rate was that from 0.5% dispersion of either XAT or SCMC because these anionic polymer behaves as a protective colloid by coating the hydrophobic particles of drug with multimolecular layer, this will impart hydrophilic character to the solid and thus promote wetting but to a certain concentration (above 0.5%), the dissolution of TDZ decreased which is

attributed to the fact that at high polymer concentration, the polymeric flocculating agent coat the whole surface of TDZ or solid particles films formed around the drug particles^[11,21].

there is a possibility of formation of regions of high viscosity, both in the tightly bound layer surrounding the drug particles as well as in the bulk dissolution medium due to the hydrated polymer chains causing resistance in the diffusion process^[23].

On other hand figure (3) shows that SAG enhanced the dissolution of TDZ only at 0.5% concentration. The order of release is $2\% < 1\% < 0.00 < 0.5\%$.

This result is related to the low solubility of SAG in acidic media or due to the formation of high viscosity regions due to the hydrated polymer surrounding drug particles which encounter high resistance to the dissolution^[24].

Finally, figure (4) illustrates the effect of AVC on the dissolution rate using different concentration of this polymer. The order was as follows: $1\% < 0.00 < 2\% < 1.5\%$. The enhancement in the release using 1.5% of AVC may be explained as the same effect using 0.5% XAT.

Formulation of TDZ suspension:

Xanthan and SCMC were chosen in concentration of 0.5% in formulas (I, II and VIII) as showed in Table (2) since this concentration enhanced the dissolution rate of TDZ as mentioned previously. A combination of polymers was utilized in formulas (III, IV, and V) to control flocculation and to improve the degree of thixotropy^[25]. Tween 80 was added with XAT in formula (VI) and with AVC in formula (VII) to improve the dissolution properties of TDZ.

The following excipient additives were also added to the prepared suspension; sorbitol and sodium saccharin as a sweetening agent They produced smooth taste and less viscous suspension. Glycerol act as a wetting and levigating agent^[26].

Raspberry flavor was added as a flavoring agent, methylparaben and propylparaben were added as preservatives. The pH of the formula was adjusted to 4.5 using citrate buffer.

Dissolution rate study:

The dissolution rate of TDZ from the prepared formulas was studied. Figure (5) shows the dissolution profile of formulas (I, II, III, IV and VIII). Formulas I, II and VIII had faster rate of dissolution due to the same reason described previously.

The decrease in dissolution rate in formula (III and IV) may be due to rheological synergism occurred due to stronger cross-linking between the two gum (XAT and SCMC), where the presence of carboxyl group on SCMC promote stronger hydrogen bonding^[27].

The addition of tween80 in formulas (VI and VII) resulted in the enhancement of the release as shown in figure (6).

This is due to its wetting effect; i.e. tween80 is adsorbed at the solid/liquid interface in such a way that the affinity of the particles for the surrounding medium is increased while the interparticular forces are decreased, and deflocculation occurs^[28].

Moreover, the dissolution rate constants of TDZ were calculated using Hixson- Crowell's cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify this effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is expressed by the following equation

$$W_0^{1/3} - W_t^{1/3} = K.t \quad \dots\dots\dots \text{eq. (1)}$$

Where W_0 is the initial weight of the solute, W_t is the undissolved weight at time (t) and K is the apparent dissolution rate constant having the unit $\text{weight}^{1/3}$ per unit time. So by plotting $W_0^{1/3} - W_t^{1/3}$ vs. t a straight line is obtained with a slope equals to the rate constant^[29].

Table (3) summarizes the dissolution rate constant for different TDZ formulas. It is obvious from the table that

the highest dissolution rate constant was achieved when 0.5% w/v of xanthan gum was used as compared with other formulas.

Sedimentation volume and resuspendability:

The flocculation behavior and resuspendability of TDZ suspensions is shown in table (3). The data indicated that formulas prepared using 0.5% of XAT gum (I, IV, and VIII) had the maximum sedimentation volume equal to 1. These formulations did not sediment but remained highly flocculated throughout the study.

The obtained results attributed to the network of floc formed in the suspension which is so loose and fluffy that can extend through out the vehicle^[21]. XAT is often used as flocculating agent to achieve non-sediment suspension with no need to other adjuvant^[9].

The result of such sedimentation volume achieved in suspension containing 0.5% XAT is consistent with that obtained in a study of metronidazole benzoate and diloxanide furate suspension^[14].

Flocculated suspension produces bulky sediments which redisperse easily with mild agitation while deflocculated suspension settle to form very compact sediment which does not redispere easily, a condition known as caking^[30].

The sedimentation volume increases in the following formulas order: VII<IX<II<VI<III<V. The low sedimentation volume of formula (VII) is indicative of a highly deflocculated system. At very low concentration of polymer; a large number of sites on the surface of the dispersed solids are available for adsorption of the polymer.

The simultaneous adsorption of the polymer molecule on to the surfaces of different particles creates a bridge.

At low polymer concentration the number of particle-particle bridges is relatively low.

At an intermediate concentration, sufficient binding sites are still available

on the particles, permitting more bridges to form.

It is this intermediate concentration that results to optimum flocculation and sedimentation volume. At a high concentration of polymer, there is complete coverage of remaining binding sites on the particles to form interparticulate bridges.

This consequently leads to deflocculation due to formation of adsorbed layers of polymer on different particles hence preventing close attraction .

These perhaps offer an explanation for the inconsistency in sedimentation volumes of TDZ suspensions suspended with different concentrations of different suspending agents^[31].

Based on the results obtained, formula (I) was chosen to carry out further study.

Rheological behavior:

The rheogram of the selected formula (I) is represented in figure (7).The profile showed that the viscosity of the prepared formula was shear rate dependent and the suspension exhibit pseudoplastic flow due to the suspending agent used which was XAT gum. Pseudoplastic flow behavior is a desirable property in the formulation of suspension, enhancing re-dispersion and pourability of suspension prior to administration^[32].

Evaluation of extemporaneous suspension:

The dissolution profile of TDZ from this suspension was low as shown in figure (6).The measured sedimentation volume was 0.42 and the prepared suspension was resuspended with difficulty.

The suspension was not uniformly distributed. The absence of suspending agent in the prepared extemporaneous suspension may explain these results. The suspension is stable for one week.

Estimation of expiration date of formula (I):

The accelerated stability study at higher temperature (40°C,50°C,and 60°C) were employed to predict the expiration date of formula (A).The degradation of TDZ in suspension follows zero order kinetics , in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles so that the concentration remain constant .This concentration is, of course the equilibrium solubility in a particular solvent at particular temperature which was found to be 14.4mg/ml.Once all the suspended particles have been dissolved, the system changes to a first order reaction. The zero order equation can be written as follows:

$$K_o = K_1 \times [A] \dots\dots\dots\text{eq. (2)}$$

In which K_o and K_1 are the zero and first order rate constant, respectively, and $[A]$ is the solubility of tinidazole at 25°C.

K_1 can be predicted by Arrhenius plots construction at 25°C which was equal to $3.5 \times 10^{-4} \text{ day}^{-1}$ as shown in figure (9).

The expiration date of TDZ in the prepared suspension was calculated according to the following equation:^[20]

$$T_{10\%} = 0.1 [\text{total dose}] / K_o \dots\dots\dots\text{eq.(3)}$$

The expiration date was found to be equal to 2.2 years.

Conclusion:

The results of this study show that tinidazole can be formulated as an oral stable oral suspension. Formula (I) was the best formula since it showed good release rate, optimum sedimentation volume in addition to being easily dispersed The stability study showed that formula (I) has an adequate expiration date. Oral tinidazole suspension is suitable for children and patients with difficulty in swallowing solid oral dosage form.

Table-1: Concentration of suspending agent prepared from stock solution to be used in preparation of aqueous TDZ suspension.

Suspending agent stock dispersion (% w/v)	Concentrations prepared (% w/v)
Xanthan gum 1%	0.3,0.5,0.7
Sodium carboxymethyl cellulose 1.5%	0.5,0.75,1
Avecil 4%	1,1.5,2
Sodium alginate 3%	0.5,1,2

Table-2: Schedule of different formulations of TDZ as a suspension dosage form

materials	formulas									
	I	II	III	IV	V	VI	VII	VIII	IX	
Tindazol	4	4	4	4	4	4	4	7		
Tindazol tablet (500 mg)										
Xanthan gum	0.5		0.3	0.5	0.3	0.5		0.5		
Sod.carboxymethylcellulose		0.5	0.5	0.3						
Avecil					1.5		1.5			
Tween 80						1.25	1.25			
Glycerol	10									
Sorbitol	7									
Sod.saccharine	0.25									
Methyl + propyl paraben	0.18 + 0.03									
Raspberry flavor	0.05									
Purified water Qs (ml)	100									
Simple syrup`										100

Table-3: Sedimentation volume, redispesability and dissolution rate constants (K) of Tinidazole suspension formulations.

formulas	Sedimentation volume	$K \times 10^{-2} \text{ (mg}^{1/3}/\text{min)}$	Resuspendability
I	1	14.0479	100%
II	0.71	13.2504	75%
III	0.89	4.1975	80%
IV	1	4.8666	100%
V	1	2.9971	100%
VI	0.75	5.1775	80%
VII	0.2	8.2771	70%
VIII	1	17.0967	100%
IX	0.42	5.7584	45%

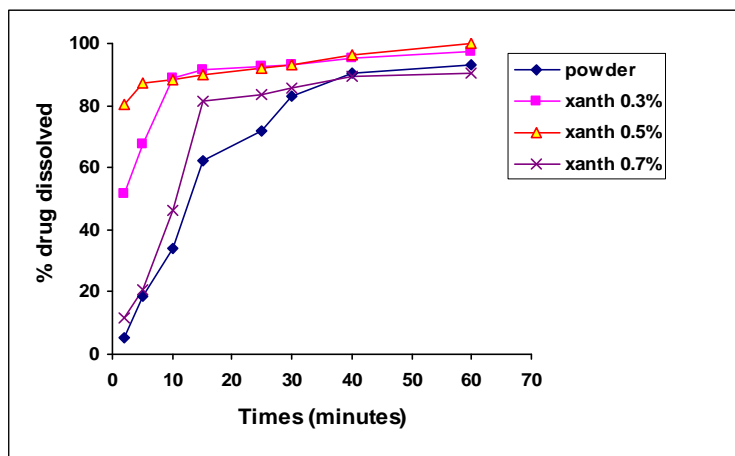


Figure-1: The effect of xanthan gum concentration on the percent of tindazole released in 0.1 N HCl (pH 1.2) at 37 °C.

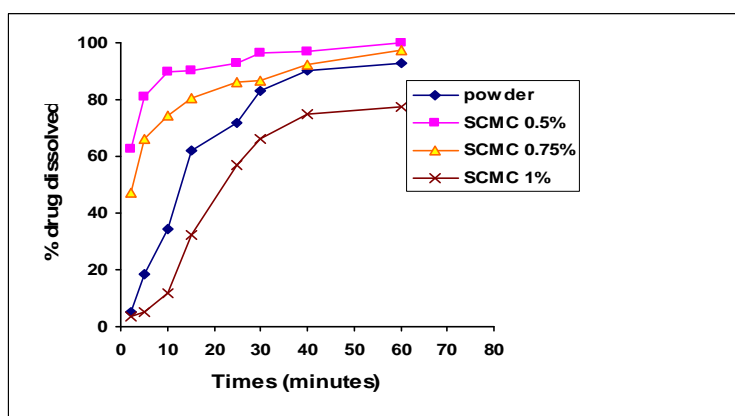


Figure-2: The effect of SCMC concentration on the percent of tindazole released in 0.1 N HCl (pH 1.2) at 37°C.

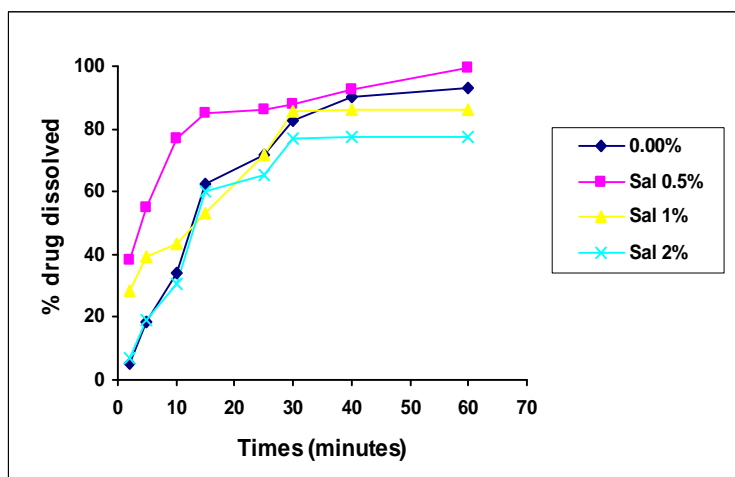


Figure-3: The effect of sodium alginate concentration on the percent of tindazole released in 0.1 N HCl (pH 1.2) at 37°C.

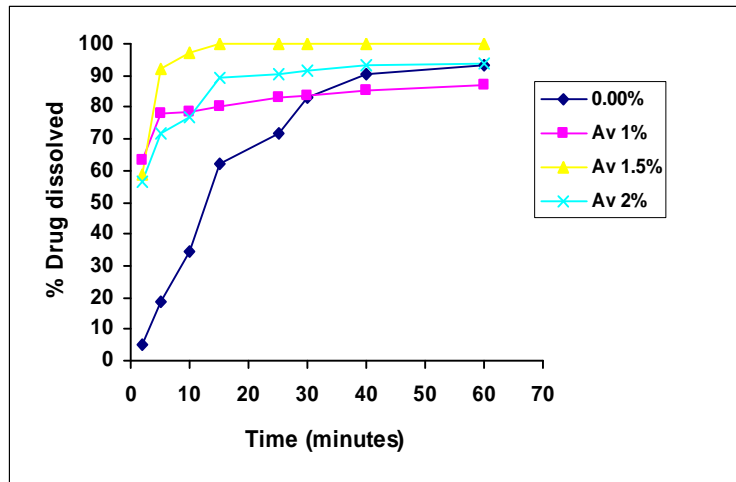


Figure-4: The effect of avecil concentration on the percent of tindazole released in 0.1 N HCl (pH 1.2) at 37 °C.

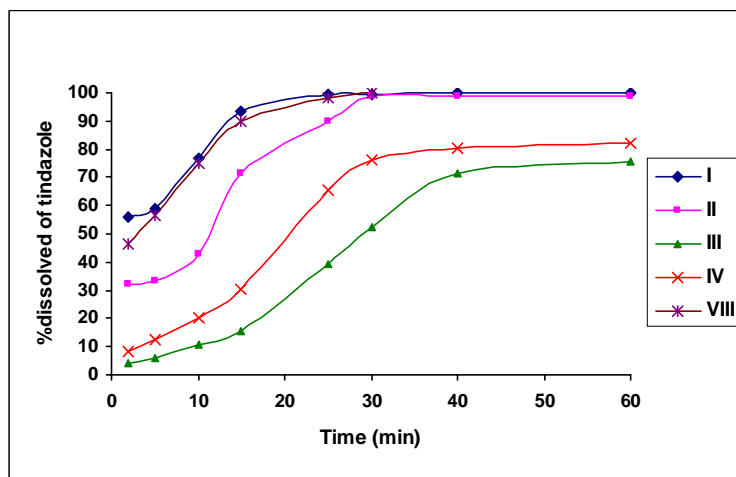


Figure-5: Dissolution rate profile of tindazole formulas (I, II, III, IV, and VIII) in 0.1N HCl at 37°C.

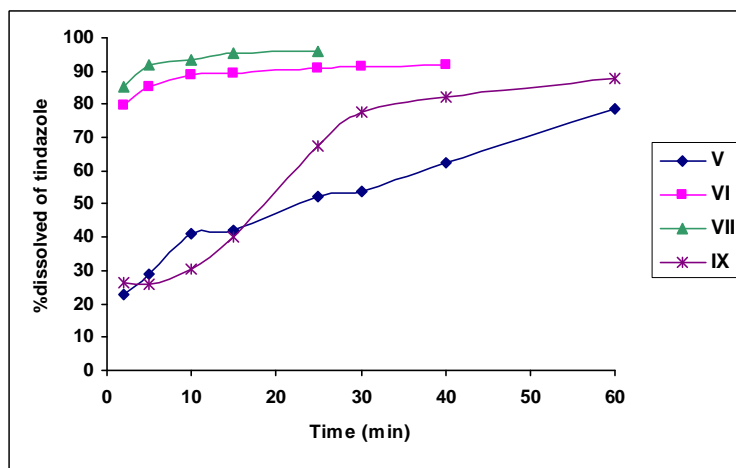


Figure-6: Dissolution rate profile of tindazole formulas (V, VI, VII and IX) in 0.1N HCL at 37°C.

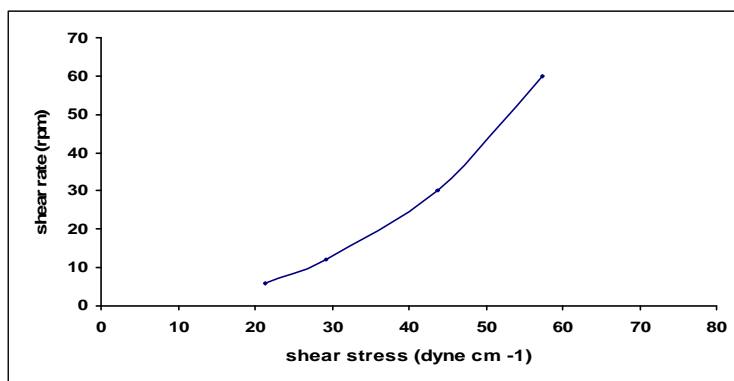


Figure-7: Rheogram of the selected tindazole suspension formula (I)

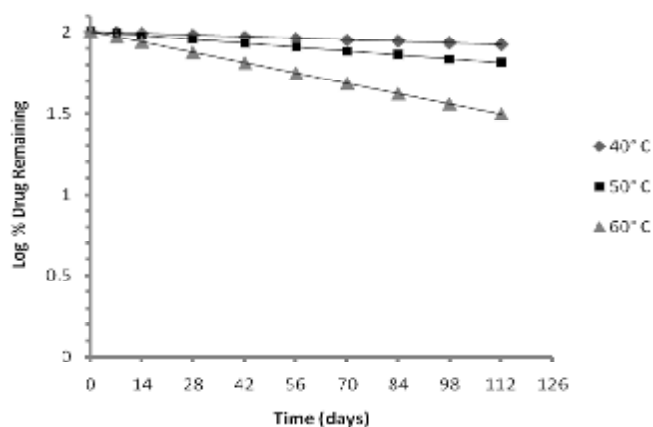


Figure-8: Accelerated stability study of TDZ in the prepared suspension (formula I) at elevated temperature.

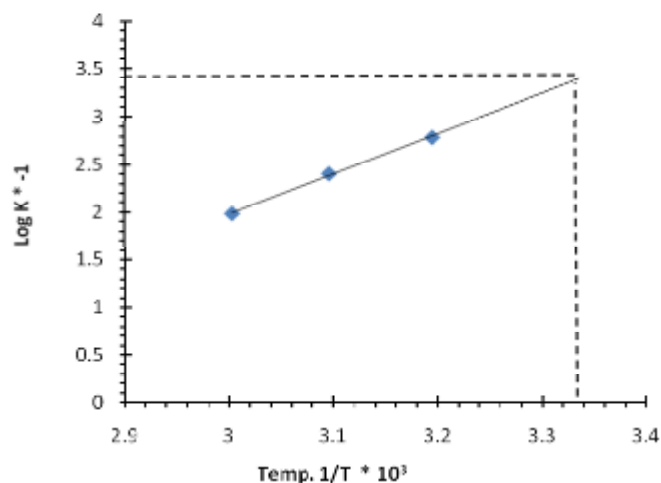


Figure-9: Arrhenous plot for Expiration date estimation of TDZ in suspension formula (I).

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