A Study on the Stability of Different Frusemide Liquid Dosage Formulas: Oral Solution, Syrup, Elixir, Suspension and Emulsion

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Abstract

The present study aim at preparing frusemide in liquid form suitable for oral use. This is achieved through preparing different liquid forms of frusemide. The frusemide liquid is prepared in the following forms: oral solution, syrup and elixir with intensity of 1, 0.4 and 0.8% weight /volume respectively and in combination with potassium carbonate, polysorbate 80, alcohol and phosphate buffer solution of pH8 to dissolve the frusemide in the above mentioned forms. The different forms of the prepared medicine have been stored in glass bottles that can provide protection against light and at 40, 50, 60^{0}C for four months. Besides the pH has been checked to decide the period of validity. The results show that the expiration date of frusemide have lasted for 1.8, 1.07 and 1.22 years respectively for the oral solution, the syrup and the elixir. The suspensions of frusemide are formulated in combination with the following: polyvinyl pyrolidine, xanthan gum, the combination of (xanthan gum and sodium carboxymethyl cellulose), the combination of (xanthan: methyl cellulose) and chitosan. The formulas which give suitable release of the drug are chosen for assessment according to the following considerations: The rat of sedimentation and apparent zero order degradation constant at 25^{0}C. In conclusion, it is found the best formula is that which includes poly vinylpyrolidine, tween20, glycerol, sorbitol, cocoa syrup and parabens at pH7. the fluidity of this chosen formula is psendoplastic type and its validity has lasted for about three years. The emulsion of frusemide is also prepared extemporaneously by using the commercial frusemide tablets in combination with acacia and olive oil. This should be consumed within 45 days of the date of production.

Key word: frusemide, elixir, suspension, emulsion.

الخلاصة

تهدف الدراسة تحضير سائل فموي مقبول للفروسيمايد من خلال تصنيعه بمختلف الاشكال السائلة الفموية .حضر الفروسيمايد كمحلول فموي وشراب والكسير بقوة1، 0.4 ، 0.8 % وزن/حجم على التعاقب مع كاربونات البوتاسيوم والبولي سوربات 80 والكحول ومحلول الفوسفلت الدارئة رقم 8 لاذابة الفروسيمايد في الاشكال المذكورة اعلاه. خزن الدواء المحضر باشكاله المختلفة في قناني زجاجية مضادة للضوء بدرجات حرارة 40، 50، 60 درجة مئوية لمدة أربعة أشهر مع ضبط الاس الهيدروجيني بحدود 8 لتحديد الفترة الزمنية للصلاحية. اظهرت النتائج بأن مدة صلاحيات الفروسيمايد كانت 1.8 ، 1.07 ، 1.22 سنة في المحلول الفموي والشراب والكسير بالتعاقب. ثم تصنيع معلقات الفروسيمايد مع بولي بايرولدين وصمغ الزانثان ومؤتلف)صمغ الزانثان والصوديوم مثيل سليلوز(ومؤتلف)صمغ الزانثان :المثيل سليلوز (والكيتوسان. التراكيب التي اعطت تحرر مناسب للدواء تم اختيارها للتقييم من خلال قياس سرعة الترسب وثابت التفكك لمرتبة الصفر الظاهرية الحركية بدرجة حرارة الـ25 مئوية وقد وجد بان احسن تركيبة هي التي كانت تحتوي على بولي فينل بابرولدين وتوين 20 وكليسرول وسوربتول وشراب الكاكاو والبرابينات عند اس هيدروجيني 7 وشكل جريان هذه التركيبة المختارة سلوك سيدوبلاستيكي اما صلاحياتها كانت بحدود ثلاث سنوات. حضر مستحلب الفروسمايد انياً من اقراص الفروسيمايد التجارية مع الصمغ العربي وزيت الزيتون على ان يتم تداوله خلال45 يوم من تحضيره.

Introduction

Frusemide which belongs to the group of loop diuretic is very effective indraining all kinds of oedemas (of cardiac, hepatic or renal origin), in mild or moderate hypertension or used in greater doses in acute and chronic renal failure, oliguria. [(1)] Commerrically available as tablets (20, 40, 80 and 500mg) and injection (10 and 20 mg/ml) and frusemide oral solution which mentioned in USP. [(2)] Many studies concered frusemide to prepare it in defferent pharmaceutical dosage forms as frusemide containing rectal suppositories to increase the drug liberation with the use of non-ionic surfactants (solutol of HS 15, cremophor RH60 and montanox 60DF).[(3)] Frusemide adhesive micro-spheres in hard gelatin capsules, frusemide granules with dika fat with maize starch and microcapsules of frusemide with Acrycoat E30 acrylic polymer were prepared and evaluated in man resulting in sustained release. [(4)] To the patients who have difficulty in swallowing the oral liquid dosage forms (syrup, elixir, suspension and emulsion) and rectal are offen supplied.

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Received : 14/4/2008
Accepted : 9 / 7/2008

Frusemide is week organic acid such as barbiturates and the sulfonamide. Its solubility in water is increased as the pH is increased by addition of a base. Therefore syrups which are sweet viscous oral solutions can be prepared as well as elixir which is sweet hydroalcoholic solution containing flavoring materials. [5] Also frusemide as insoluble materials can be prepared in liquid media by means of appropriates suspending agents or mix with oil which dispersed as small globules in water in presence of emulsifying agent to form emulsion. [6] In hospitals because the absence of commercial liquid dosage forms solutions and suspensions of frusemide are prepared extemporaneously from injections and tablets respectively may be susceptible to sedimentation of insoluble frusemide, chemically degraded by gastric acid and impractical in case of injection due to many ampoules required.[7] The aim of this study is to prepare frusemide in different liquid dosage forms (syrup, elixir, suspension and emulsion) because these forms are not commercially available. Then test its stability and compatibility to decide on an appropriate formulation and assigne an expire date.

Materials, Instruments and Methods

Frusemide (USP), xanthan gum, cherry flavor and sorbitol supplied by SDI, Iraq; sodium carboxy methylcellulose, methylcellulose, methyl and propyl paraben from Hopkin and Williams LTD, England; Tween20 and 80 (Merck-Schanchard Germany); Ethanol GCC Gainland chemicals company, U.K.; polyvinyl pyrrolidin (PVP) and potassium carbonate from BDH chemical LTd. Pool, England. Sodium saccharin and aspartam (BDH limited pool, England); sodium hydroxide (Fluka-AG); Disodium hydrogen phosphate and potassium dihydrogen orthophosphate (Atlas chemie, W-Germany); frusemide 80 mg tablets (Hoechst Marion Roussel) and date of production is 9-2007. Sartorius balance AG Gottingen, BL210S, CE, Germany; pH meter, Orchidis Labrotaries, France and Hanna instruments type, France; Dissolution apparatus type II, Dis 6000, Copley scientific, Nottingham, U.K.; UV. Visible spectrophotometer, Gitra 5,GBC scientific equipment, U.S.A.; Oven 50, 40^0C Memmert 854 Schwabach, W. Germany; Oven 60^0C Gallenkamp, B5 size one, England.

Experimental

Formulas I, II and III which are summarized in table (1) were prepared according to the following methods.

Table (1): Different formulas of frusemide prepared as solution, syrup and elixir (I, II and III respectively)

Matarials	formulas		
	I	II	III
Frusemide (gm)	1.0	0.4	0.8
Potassium carbonate (gm)	0.5	--	--
Tween 20 (ml)	--	--	5
Tween 80 (ml)	--	6	--
Sodium carboxy methyl cellulose (1%w/v)	--	5 ml	--
Aspartam (gm)	--	0.054	--
Sodium saccharin (gm)	--	--	0.08
Glycerol (ml)	30	--	--
Sorbitol 70% w/w (ml)	--	32.4	10
Alcohol 95% (ml)	--	10	40
Citric acid (gm)		0.1	
Cherry flavor (gm)		0.05	
Phosphate buffer 8 (ml) QS	--	100	100
Purified water (ml) QS	100	--	--

Frusemide oral solution (formula I)

0.5 gm potassium carbonate was dissolved in 45 ml purified water. Then frusemide 1gm and citric acid 0.1gm were added with stirring. Glycerine 30 ml was measured by graduated cylinder and added to previous mixture. Before the volume was completed to 100ml, the cherry flavor was added. Finally the pH was adjused by using pH-meter. [6]

Frusemide free sugar based syrup (formulaII)

0.4 gm of frusemide was mixted with *6m1 tween80 and ethanol 10ml with stirring.* Aspartame and citric acid were added to previous mixture.

Sorbitol 32.4ml and 5ml dispersion of sodium carboxy methyl cellulose (1% w/v) were measured in graduated cylinder and added to resulting product with stirring. After the product was filtered by cotton the cherry flavor was added. The volume was completed to 100ml by phosphate buffer 8. finally the pH was adjusted by using pH-meter.[8]

Frusemide elixir (formula III)

0.8gm of frusemide was dissolved in 10ml sorbitol plus 40ml ethanol. Then citric acid 0.1 gm and sodium saccharin 0.08gm were mixed in 20 ml purified water puls 5 ml tween 20. Then the aqueous solution was added to the alcoholic solution to maintain the highest possible alcoholic strength at all times so that the minimal separation occurs when the two solutions were completely mixed, the cherry flavor was added. Then the volume was completed to 100ml by phosphate buffer 8. The elixir was permitted to stand for a few hours to ensure saturation of alcoholic solvent. The product was filtered by using talc as filter aid to prevent cloudy appearance. Finally the pH was adjusted by using pH-meter. [6] Phosphate buffer pH8 was prepared by mixing 50ml of a solution of 0.2 M potassium dihydrogen orthophosphate with 46.8ml of 0.2M sodium hyproxide then diluted to 200ml with water.[2]

Formulation of frusemide suspension

Table (2) shows 6 formulas of frusemide suspension prepared by the following method: frusemide, methyl plus propylparaben, sorbitol and glycerol were Levigated in the mortar with tween20 and part of prepared dispersions of suspending agents (PVP, xanthan gum, sodium carboxy methyl cellulose, methylcellulose and chitosan) in different concentration as summarized in table (2). The remaining amounts of the dispersions were added in divided portions to the mixture. The mortar was rinsed several times with purified water and the rinsed volume of dispersion was added to cylinder, cocoa syrup was added before the volume was completed to 100ml by adding purified water.

[5]***Comparison studies of formulas A, B, C, D and E***

The following parameters were used to compare the prepared formulas A, B, C, D and E.

Table (2): Different formulas of frusemide prepared as suspension (A, B, C, D and E). and emulsion (F).

Matarials	formulas					
	A	**B**	**C**	D	E	F
Frusemide (gm)	2.5	2.5	2.5	2.5	2.5	-
Frusemide tablet (80mg)						5
PVP (gm)	10					
Xanthan gum (gm)		0.5	0.5	0.5		
Sodium carboxy methyl cellulose (gm)			0.5			
Methyl cellulose (gm)				0.25		
Chitosan (gm)					1.5	
Acacia (gm)						6
Olive oil (ml)						18
Tween 20 (ml)	1					
Glycerol (ml)	10					
Sorbitol (ml)	5					
Cocoa syrup (ml)	20					
Methyl + propyl paraben (gm)	0.18 +0.03					
purified water Qs(ml)	100					90

Dissolution rate measurement

The dissolution medium was 900ml of phosphate buffer 6.8. The temperature of study was 37^0C and the rotating velocity was 100 rev. min^{-1}. 5 ml of each formulas A, B, C, D and E was transferred to the jar bottom using a syringe. At appropriate intervals samples of 5ml were taken from the jar and analyzed for total content of frusemide by UV-spectrophotometer. Detection was done at 330nm. 5ml of fresh phosphate buffer was added to the jar with each time intervals to keep the volume constant.[10]

Sedimentation volume

100 ml of each formulas (A, B, C, D and E) was transferred to the stoppered graduated cylinder. The suspension were shaken vigorously to ensure uniformly then left undistributed. The sedimentation volume was measured at selected time intervals during storage without agitation for a period of 8weeks and was calculated in terms of the ratio of ultimate settled height (Vu) to the original height (Vo).[11]

Extemporaneous preparation of frusemide emulsion (formula F)

Acacia was triturated in mortar to be in powder form. 12ml water was added to get primary emulsion. 18ml olive oil was added drop by drop with continuous trituration in same direction until clickuing sound was heard. Spread frusemid powder from grinded (5) tablets of 80 mg strength. The primary emulsion was diluted to 90ml by purified water. The contents of formula F are showed in table (2) as well as the dissolution rates of formula F were measured as described previously.[8]

Stability study

2ml samples of formulas I, II and III were stored in closed tubes at 40, 50 and 60 ^{0}C measurement on: 0, 7, 15, 30, 60, 90, and 120 day.Sample of 100ml suspension was inspected for change in color, odor, pH and precipitant. Analysis for remaining frusemide was carried by diluting 2ml of sample with distilled water to 200ml. The 5 ml of resultant solution was taken and completed to 50 ml with 0.1 N NaOH. The absorbance of later solution was detected by a UV-method at 271 nm.[9] The accelerated stability test were also carried out on the suspensions showing the heighest sedimentation volume which were formulas A and D. the suspension of each formula was centrifuged to get supernatant solution. 1 ml samples of the resultant solution were stored in closed tubes at 40, 50 and 60 ^{0}C measurement on: 0,7, 15, 30, 60, 90 and 120 day. Samples of 100ml suspension were inspected for change in color, odor, pH and precipitant. Analysis of remaining frusemide was carried out by diluting 1ml of supernatant solutions with phosphate buffer 6.8 to 25 ml. The absorbance of latter solutions were determined by a spectrophotometer at 330 nm.[9,12] The shelf life calculated from the initial concentration [A_0] and the apparent zero-order rate of degradation (k_0) accordings to the following equations.[13]

$$K_0 = Kx[\,frusemideso\,\mathrm{lub}\,ility\,]$$

$$t_{10\%} = \frac{0.10[A_0]}{K_0}$$

The stability of extemporaneous frusemide emulsion was done as those of suspension which mentioned previously.

Rheogram

Rheogram was obtained for the selected formula at 37^{0}C with Brook field DV-II+Pro viscometer which read shear stress versus shear rate.

Results and Discussion

Oral frusemide solution was claimed to produce agreater diuretic with congestive heart failure than tablet so formula I prepared as oral solution containing potassium carbonate which added to increase pH up to 7. The effect of pH on solubility is critical in the formulation of liquid dosage forms. The solubility of frusemide (PKa=3.9) is often pH dependent. Furthermore, the pH control is at least as important to fully control the crystallize habit and the stat of agglomeration to ensure quality, efficacy and safety of the drug.[10,14] Also frusemide prepared as syrup(formula II) which containing tween 80 to increase solubility of frusemide. Alcohol is present in formula II to serve as a solvent and preservative. While benzoates and parabens was excluded from this formula (pH8) because they are ineffective as preservative in alkaline solutions which frusemide freely soluble in it. Sorbitol is compatible with alcohol as much as 10 percent (v/v) before crystallization is observed. [8, 15] Formula III having a high alcoholic content (elixir) contains saccharin which is required only in small amount rather than sucrose which is only slightly soluble in alcohol and required greater quantities for equivelant sweetness. This formula is self preserving and don't require the addition of antimicrobial agent because it contains more than 10-12% of alcohol. The carboxymethylcellulose, a derived gum function as viscosity builder agent.[6] The presence of glycerine and sorbitol in formula I, II and III contributes to solvent effect, assists in the dissolution of the solute and enhance the stability of the preparation. However, the presence of these materials also adds to the viscosity. [6] The effectiveness of cherry flavour in masking the taste of frusemide is enhanced by presence of weak acid (citric acid). [8] The accelerated studies applied on formulas I, II and III at higher temperatures (40, 50, and 60^{0}C) were employed to predict the expiration date of these formula using UV-spectrophotometer. The degradation of frusemide in these formulas shows first order kinetics since straight lines were obtained by plotting the logarithm of percent remaining of frusemide versus time as shown in figures (1,2 and 3) according equation (1).

$$Log\ C = Log\ Co - \frac{kt}{2.303} \qquad \text{---------- } 1$$

In which Co is the initial concentration; C is the remaining undecomposed concentration at time t; and k is the first order rate constant and –k/2.303 is the slope of the line from which the value of the rate constant is obtained. [12]

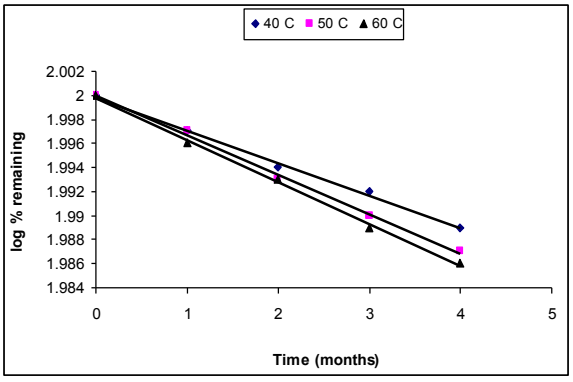

Figure (1): Degradation curve of frusemide oral solution (formula I) at 40, 50, 60 ^{0}C

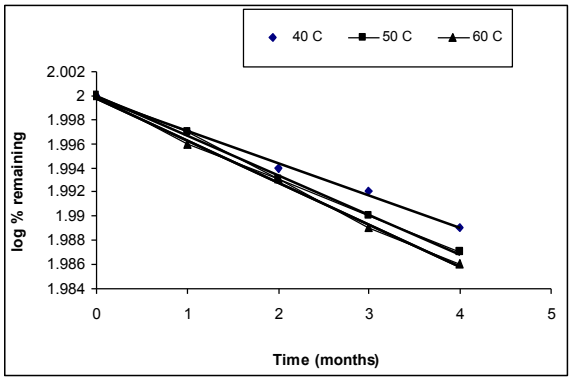

Figure (2): Degradation curve of frusemide syrup (formula II) at 40, 50, 60 ^{0}C

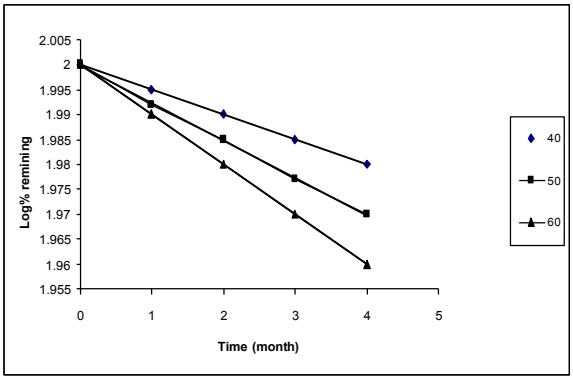

Figure (3): Degradation curve of frusemide elixir (formula III) at 40, 50, 60 ^{0}C

Table (3) summarized the degradation rate constant of formulas I, II and III. Arrhenious plots were constructed to predict the degradation rate constant of frusemide at 25^{0}C as shown in figures (4, 5 and 6). The results indicate no significant differences (P>0.05) between K_{25^0C} for formulas (I, II and III). The expiration data of frusemide was calculated according to first order reaction equation:

$$t10\% = \frac{0.104}{K_{25^0\,C}} \quad \text{----------2}$$

Table (3): Degradation rate constants of frusemide in formulas I, II, III at 40, 50 and 60 ^{0}C.

Formulas	$K_{40}(x10^{-3})$ month^{-1}	$K_{50}(x10^{-3})$ month^{-1}	$K_{60}(x10^{-3})$ month^{-1}
I	5.9	7.1	8.0
II	10.7	26	35
III	10.1	15	20

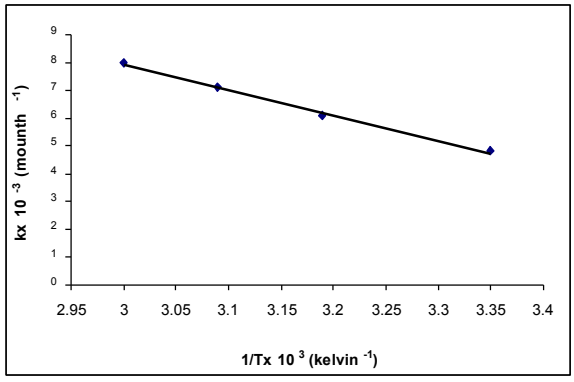

Figure (4): Arrhenious plot for estimation of the expiration date of formula I at 25 ^{0}C.

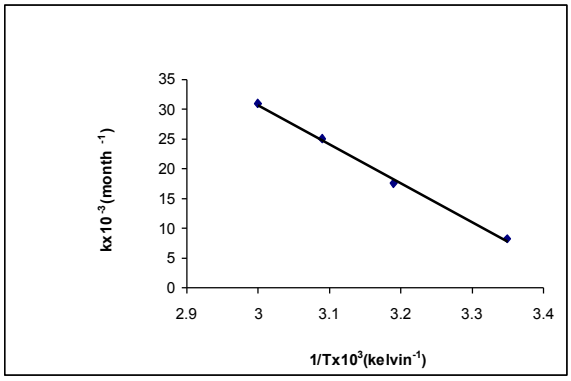

Figure (5): Arrhenious plot for estimation of the expiration date of formula II at 25 ^{0}C

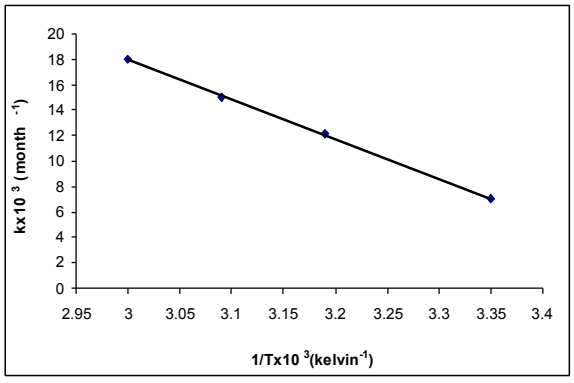

Figure (6): Arrhenions plot for estimation of the expiration date of formula III at 25 ^{0}C

The expiration dates were found to be equal to 1.8, 1.07 and 1.22 years for formulas I, II and III respectively as shown in table (4).

Table (4): Degradation rate constants at 25^{0}C and the corresponding expiration dates of the prepared formulas.

Formulas no.	$K_{25}(x10^{-3})$ month^{-1}	$t_{10\%}$ (years)
I	4.8	1.8
II	8.09	1.07
III	7.0	1.22

Figures (7 and 8) show the dissolution rate profile of frusemide for formulas A, B, C, D, E and F. The results showed that frusemide amounts released increases in the following order:
F<E<C<D<B<A. The differences was significant (P<0.05). Formula A showed the highest dissolution rate for a short periods of time (10 minutes), this could be due to the wetting effect of water soluble polymer (10%PVP) solution with intrinsic rapid dissolution properties especially in the practice of the presence solubilizer glycerol and sugar alcohol such as mannitol and mixture thereof . Optionally a surfactant such as tween 20 may be added to facillate wettability within formulation. [16] Figure (9) shows the sediment volume of formulas A, B, C, D and E during 8 weeks after 48 hours undisturbed.

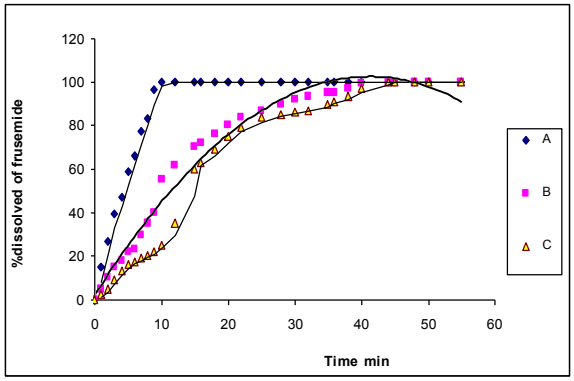

Figure (7) : Dissolution rate profile of frusemide formula (A, B and C)

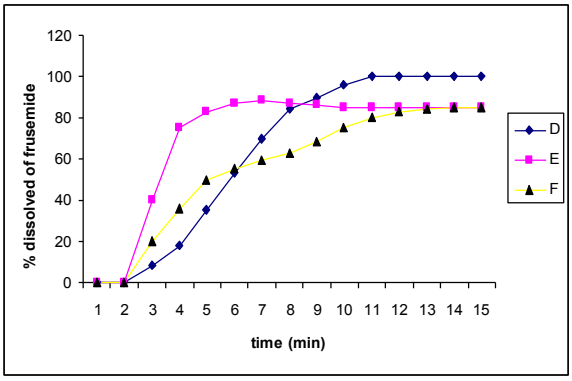

Figure (8) : Dissolution rate profile of frusomide formulas (D, E and F)

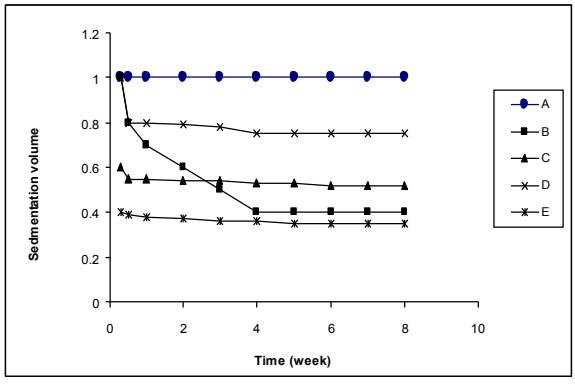

Figure (9): Sedimentation volume of formulas (A, B, C, D and E)

The sediment volume measured according to the ratio of the final height of the sediment after settling (Vu) to the initial height of the total product (V_0).

$$F = \frac{Vu}{Vo} \quad \text{--------} (3)$$

The results show that the sediment volume increases in the following order: E<B<C<D<A

The sedimentation volume depends on the types and concentrations of suspending, wetting and viscosity enhancing agents used. As a result, a high sediment volume observed in formula A could be a result of the increase in the viscosity of the PVP dispersion in alkaline media which may be caused by the expansion resulting from electrostatic repulsion between negatively charged carboxylate group. [17, 18] In formula D the increase in viscosity due to strong cross-linking between the nonionic gum (methylcellulose) and anionic gum (xanthan gum).[19] The presence of glycerol, sorbitol and cocoa syrup adds to the viscosity of suspension especially cocoa syrup (chocolate syrup) which is a suspension of cocoa powder in vehicle containing liquid glucose, glycerine, vanillin and sucrose. It is effective because of its high viscosity and enhance the palatability by coating the tongue and thus it tends to inhibit diffusion of the frusemide to the taste buds. [8] The resultant solutions from centrifuging of formulas A and D suspension was with no reservoir of frusemide to replace that depleted so frusemide degradation in them follows the first-order expression as in equation (4).

$$-\frac{d[c]}{dt} = k[c] \quad \text{-------- (4)}$$

In which C is the concentration of frusemide remaining undecomposed at time and k is known as a first-order rate constant. When the concentration [c] is rended constant as in the case of a suspension, the equation (5) is applied.

$$k[c] = k_o \quad \text{------- (5)}$$

In which K_0 is apparent zero order rate constant, [c] is the solubility of frusemide at 25^0C which equal 0.086 gm/100ml at pH 7 and K is first order rate constant at 25^0C The first order rate constant for frusemide degradation in supernatant centrifuged solution of formula (A and D) were calculated from slopes of straight lines which result from plotting log% remaining of frusemide in these solutions versus time at elevated temperatures (40, 50 and 60 ^{0}C) as shown in figure (10). Then by plotting the log of these rate constants versus reciprocal of the absolute temperature. First order rate constant $K_{25}{}^0{}_C$ was obtained by extrapolating the straight line in Arrhenious plot as shown in figure (11).

$K_0 = K_{25}{}^0{}_C$ x [frusemide in solution] as in equation(5)

$K_0 = (8.07 \times 10^{-2}\ \text{month}^{-1}) \times (0.086\ \text{g/100ml})$

$K_0 = 6.94 \times 10^{-5}$ g/ml. month^{-1}

Then, the expiration date of frusemide suspension formula (A and D) which showed the best release and sedimentation volume than other formulas was calculated according to apparent-zero order reaction equation

$$t10\% = \frac{0.10[A_0]}{K_O} \quad \text{---------- (6)}$$

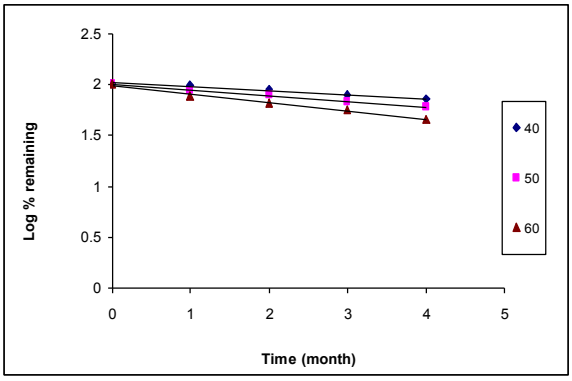

Figure (10): Degradation curve of centrifuged frusemide solution (formula A and D) at 40, 50, 60 ^{0}C

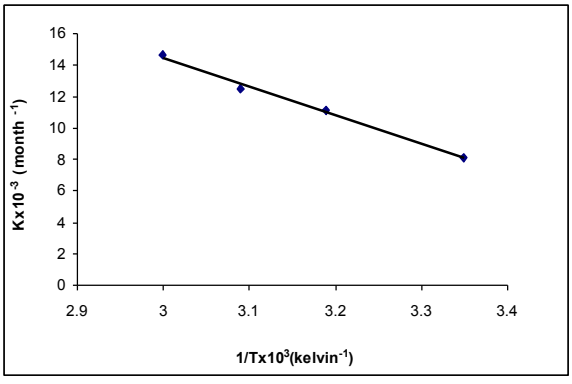

Figure (11): Arrhenenius plot of centrifuged frusemide solution (formula AandD)

The expiration dates were found to equal 3 years for both formula A and D. The shelf life of extemporaneously frusemide prepared emulsion (formula F) was calculated from the initial concentration and the apparent zero-order rate of degradation (K_0) as the steps followed by estimation of expiration data of formulas A and D frusemide

suspensions. The shelf life of formula F was 45 days. Acacia used in preparation of formula F because it is preferred in the formulation of the most extemporaneous prepared products. As well as the experimental studies in animal and clinical studies in humans showed that acacia gum has a urea lowering effects so this preparation is useful for patients suffering from hypertension with chronic renal failure. [20] Formula A was selected to study the rheology as shown in figure (12) because of it's highest release, sediment volume and shelf life than other formulas. The rheogram of formula A has a high viscosity at low shear stress while at higher shearing stress it has low viscosisty due to the flow behavior of PVP at concentration above 5% witch is typical pseudoplastic and thixotropic characteristics.[18] Therefore formula A which containing PVP, tween20, glycerol, sorbitol, cocoa syrup and parabens considered a well formulated suspension because it was physically and chemically stable due to PVP is compatible with many drugs such as frusemide, paracetamol, salicylic acid and testosterone. [16]

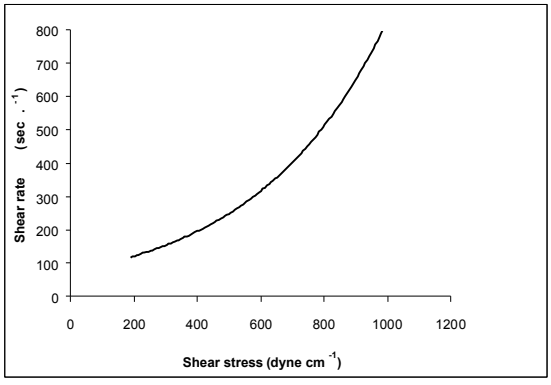

Figure (12): Rheogram of the selected frusemide suspension formula (A)

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