Formulation and Clinical Evaluation of Orphenadrine citrate as a Plain Tablet

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ABSTRACT

Orphenadrine is an anticholinergic ,antimuscarinic , centrally acting skeletal muscle relaxant .It presents in the form of citrate and HCl salts which are used in treatment of the symptoms of mild Parkinson's disease and also it is used as adjuvant with other drugs in the therapy .

Many trials were made to formulate Orphenadrine citrate as a plain tablet using wet granulation or direct compression technique in order to get a satisfactory formula through studying the effect of various factors such as binders , diluents and disintegrants types .

The best formula was obtained by using Poly Vinyl Pyrolidine (PVP) as a binder also the results indicated that starch and mannitol gave acceptable physical properties to the tablets when they were used as diluents . At the same time , the results showed that Avicel which was used as a disintegrant gave an acceptable disintegration and dissolution time in comparison with the reference tablet DISIPAL ®. In addition , the selected formula was used to study the effect of method of incorporation of disintegrant on the physical properties of tablets .It was found that the intragranular incorporation resulted in a shorter disintegration and dissolution times .The stability of Orphenadrine citrate prepared tablets was also studied upon storage at 50°C, 60°C and 70°C for four months .The drug was fairly stable and the expiration date for the prepared tablet was considered to be equal for 5 years .On the other hand , the results of clinical study on patients suffering from Parkinson's disease indicated that patients with tremor (regular rhythmic oscillation of extremities especially hand and finger) and mild symptoms of Parkinson's disease showed a good response to the prepared tablets , but it had no effect on patients of dystonia (fixed upward gaze , neck twisting ,clenching jaws) and akinesia (slow down of movement of voluntary muscle and difficulty of initiation of movement).

The overall results of this study indicate that the drug can be prepared as tablets , which fit the requirements of British Pharmacopoeia since the prepared tablets gave satisfactory results .

الخلاصة :-

الأورفينادرين (Orphenadrine) هو عقار مضاد لإفراز الكولين ويعمل كمسترخي مركزي للعضلات الهيكلية . يوجد على شكل أملاح السترات والهايدروكلورايد حيث يستخدمان في علاج الأعراض البسيطة لمرض باركنسون أو مساعد مع الأدوية الأخرى المستخدمة في العلاج . تم اجراء العديد من المحاولات للحصول على صبغة تركيبية مقبولة لسترات الاورفينادرين كأقراص سريعة التحرر باستعمال طريقة الحبيبيات الرطبة او الكبس المباشر من خلال دراسة تأثير العديد من العوامل مثل المواد الرابطة ، المواد المضافة و المواد المحطمة أو المفتتة .

أن أفضل النتائج قد تم الحصول عليها باستخدام مادة البولي فانييل بايروليدين (PVP) كمادة رابطة . كما أشارت النتائج إلى أن الذشا والمانيتول يعطيان خصائص فيزيائية مقبولة للأقراص عند استخدامها كمواد مخففة .

في نفس الوقت أظهرت النتائج بان السليلوز ألمجهري افيسيل (Avicel) المستخدم كمادة مفتتة أعطى زمن تفتت وتحرر مقبول مقارنة بالمصدر (حبوب ديسبال) اضافة الى هذا التركيبية المختارة قد استخدمت لدراسة تأثير طريقة اضافة المادة المفتتة على الخواص الفيزياوية للأقراص . حيث وجد بان ادخال المادة المفتتة ضمن الحبيبات ادى الى زيادة في سرعة التفتت والذوبان . كذلك تم دراسة استقرارية الدواء عند خزن الحبوب في درجات حرارة مختلفة 50 °م ، 60 °م ، 70 °م لمدة اربعة اشهر . حيث كان العقار مستقراً وان التاريخ الذي اعتمد لانتهاء مفعول الأقراص المحضرة هو خمس سنوات . من جهة اخرى ، اشارات نتائج الدراسة السريرية على المرضى الذين يعانون من مرض الباركسون بان المرضى الذين لديهم ارتعاش وبعض الاعراض البسيطة لمرض باركنسون اظهروا استجابة جيدة للتركيبة المختارة ولكن ليس لها تأثير على المرضى الذين يعانون من ضعف المقوية . أن نتائج هذه الدراسة تشير إلى إمكانية تحضير العقار على شكل حبوب كجرعة دوائية صلبة مطابقة لموصفات الدستور البريطاني طالما أن الحبوب المحضرة أعطت نتائج مقبولة .

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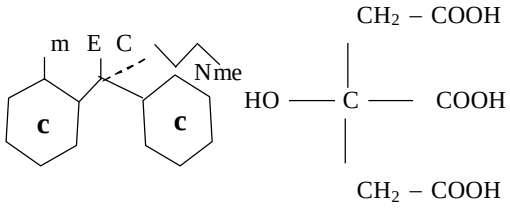
INTRODUCTION

The skeletal muscle relaxants are group of compounds used to relieve spasticity & abnormally high muscle tone [1,2] .They produce their effects by action on central nervous system (CNS) ,however , their mechanism of action not yet understood . There are many theories , which explain the mechanism of action or the clinical uses of muscle relaxants .One of these theories is that they reduce skeletal muscle spasm , possibly through an atropine like central action on cerebral motor centers or on the medulla but they do not have analgesic activity that contribute to their effects in patients with skeletal muscle spasm [3] . Anticholinergic drugs (Antimuscarinic drugs) were the most effective drugs for treatment of Parkinson's disease for more than a century , this is by blocking Acetyl choline receptors of the CNS , there by partially redressing the imbalance created by decreasing dopaminergic activity [4] , however , the introduction of the dopamenic drugs (Levodopa & decarboxylase inhibitors) has relegated anticholinergics to a supportive role in the treatment of the disorder .

Noverthless , the anticholinergric drugs are still useful for patients with minimal symptoms as patients unable to tolerate levopdopa because of side effects or contraindications , for those who are not benefited by levodopa [5] & for patients who had parkinsonian symptoms induced by antipsychotic drugs [6 , 7] . Orphenadrine citrate is white or almost white , odorless or almost odorless , crystalline powder with a bitter taste & followed by sensation of numbness . It melts in the range of 134 °C to 138 °C [8] .

Soluble 1 in 70 of water , slightly soluble in ethanol ; practically insoluble in chloroform and ether [9] .It should be stored in tight & light resistant containers [10] .



N,N dimetly [2 – (2 – methylbenzhydoxy) ethyl] amine dihyyd-rogen citrate [11] .$C_{18}H_{23}NO.C_6H_6O_7$ with M.wt of 461.5 gm .

Orphenadrine citrate is used for symptomatic treatment of Parkinson's disease [11] ,to relieve pain due to spasm of voluntary muscle [12] and as an alternative to quinon in treatment of noctural leg cramps [13] .Orphendrine may also be used in vertigo in patient with spontaneous vestibular disease[14] , and it may be combined with haloperidol in treatment of chronic schizophrenic patient [15] or with paracetamol in treatment of Myolgia [14] .

Orphenadine is contraindicated in patient with glaucoma [17],elderly people [18] and with antacid [19] .Its overdose is treated with physostigmine [20] or tetrahydroaminocrine [21] . on the other hand , Orphenadrine intoxication is potentiated by ethanol[22] and its use may cause dependence [23] . Orphenadrine citrate presents as an oral tablet extended release of 100 mg under the trade name of NORFLEX ® and parenteal injection of 30 mg/ml (ampoule of 2 ml) under the trade name of BanFLEX® and NORFLEX ®.

Also Orphenadrine citrate is found in combination such as ; NORFLEX ® oral plain tablet which contains Orphenadrine citrate 25 mg , aspirin 385 mg and caffeine 30 mg ; and Myogesic ® which contains Orphenadrine citrate 35mg and paracetamol 450 mg[24] .

This study was carried out to formulate Orphendrine citrate as a tablet dosage form , through preparing different formulas , and comparing them with reference tablets . Also the effect of excipients type (binders , disintegrants and diluents) on physical properties of the tablet was studied in addition to the effect of incorporation method of disintegrants .

Furthermore , the selected formula , which fitted the standard requirements ,was thoroughly investigated for its expiration date and clinical effects .

EXPERIMENTAL PART :-

Materials

- Orphenadrine citrate powder.(Dar AL Dawa , Amman , Jordan), Starch , Mannitol (Merk , Darmstadt ,Germany) , Microcrystalline cellulose (Avicel PH101 , FMC corporation , Pennysylvania , USA), Polyvinyl pyrolidine (PVP ,K_{30}),Ethanol ,Hydrochloric Acid (HCl) , Carboxy methylcellulose sodium salt (CMC) , Isopropyl alchohol ,(BDH Chemicals Ltd, ,pool, England),Magnesium strearate , (Barloches ,GMBH, Germany), Acacia arabique ,Dextrose , Talc.(Riedel – De – HAEN AG Seelze – Hannover , Germany),Dibasic calcium phosphate (Emcompress ®,Edward Mendell Co., USA), Explotab (AVEBA, Veendom ,Netherlands),DISIPAL® tablets as a reference (Yamanouchi Pharma Ltd. , UK).

Formulation of Orphenadrine citrate Tablets

Different formulas (Table I) were prepared to find the most satisfactory formula using wet granulatiom teghnique except formula 7 which was prepared by direct compression technique , in which the drug and excipients (except lubricant)were dry blended for at least 5 minutes and then mixture was compressed into tablets using F_3 Manesty tablet machine with a single 7 mm normal concave punches .

In case of using wet granulation method , the following procedure was followed : after 5 minutes dry blending of drug & excipients , the binder solution was added to the formula gradually in the mixing mortar until a satisfactory wetting was achieved (Ball test).The wet mass was then granulated through a sieve no. 10 and dried in a tray oven at 45C° for 30 minutes. The granules were then reduced in size and homogenized by passing them through a sieve no.16.

A known weight of the granules was then mixed with specified amount of disintegrant extra – granularly for 10 minutes in well closed container and then mixed with magnesium stearate (200 mesh in size)for 2 minutes . The final mixture was compressed.

Physical Parameter Measurement of Orphenadrine Tablets

Hardness :- The hardness of Orphenadrine citrate tablets were measured using Monsanto and Erweka hardness testers normal range between 4& 8 kg[24] .

Weight Variation : It was determined for all prepared formulas by taking 20 tablets , weighed individually and the average weight is calculated .For the tablets to be acceptable by not more than 2 of the 20 tablets may differ from the average weight by not more than 7.5% and no tablet may differ by more than double the percent [25].

Friability Test : The friability of tablets was performed using Roche friabilator and Erweka fribilator for 4 minutes at 25 r.p.m by weighing 10 tablets then place them inside the tester for 4 minutes and weigh them again .The difference in weight should not exceed 1% .

Disintegration Time : The disintegration time was measured using U.S.P disintegration apparatus . It consists of a basket rack assembly containing six open – ended glass tubes with a 10 –mesh screen on the bottom .The basket was immersed in an appropriate fluid (0.1N HCl) at 37 °C .The basket rack was raised and lowerd at a rate of 30 stockes per minute[25] .

Table (1)
Schedule of Different Formulations of Orphenadrine Citrate as a Plain Tablet

Materials	Formula No.								
	1	2	3	4	5	6	7	8	9
Orphenadrine.citrate (mg)	75	75	75	75	75	75	75	75	75
PVP10%w/v in ethanol	Q.S	Q.S		Q.S	Q.S	Q.S			
Avicel pH101	X	X	X	X				X	X
Starch	Y		Y		Y	Y	0.5Y	Y	Y
Mg.stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.7	1.5	1.5
Dextrose		D							
Acacia 20%			Q.S						
Mannitol				M					
Explotab					E				
Starch (disintegrant)						S			
Emcompress							68.5		
Starch paste								Q.S	
CMC									Q.S
Total weight	150	150	150	150	150	150	150	150	150

Q.S = sufficient quantity , X=amount of Avicel ,Y= amount of Starch ,D=amount of Dextrose , M =amount of Mannitol , E= amount of Explotab ,S= amount of Starch (disintegrant)…

Dissolution Test : The USP Basket Method [26] was used to study the release of the drug from the prepared tablets and from the reference tablet DISIPAL ® (Yamanouchi) . The studies were carried out in shielded apparatus to protect the solution of drug from light using 900 ml of 0.1N HCl solution as the dissolution medium at 37°C with a constant stiring speed of 50 r.p.m [26,27] .Samples were withdrawn at five minutes interval for one hour . The sample volume was replaced immediately by a fresh 0.1N HCl . The samples were filtered by microfilter and analyzed spectrophotometrically at its λ_{max} 264 nm[28] .

Assay for total Orphenadrine citrate present in the Tablets

Preparation of standard :150 mg of pure Orphenadrine citrate was dissolved in 75 ml 0.1N HCl , shaken for 15 minutes and filtered , then the volume was completed to 100 ml with 0.1N HCl . A sample of 20 ml was taken and diluted to 100 ml with 0.1N HCl .

The absorbance of the diluted solution was determined spectrophotometrically at its λ_{max} which is 264 nm[28] .

Assay of the Prepared Tablets : 20 tablets of Orphenadrine citrate were triturated and an accurate weight equivalent to 0.15 gm of Orphenadrine citrate was added to 75 ml of 0.1N HCl , shaken for 15 minutes and filtered .The final volume was completed to 100 ml with 0.1N HCl

The absorbance of diluted solution was determined spectrophotometrically at 264 nm , and the quantity of drug per tablet was calculated according to the following equation :

Test /Std. × 100 =% Orphenadrine citrate present in tablet [29] .

Kinetic Study

Effect of temperature on Orphenadrine citrate tablets was studied by storing some tablets of the selected formula (1) at different temperatures (50 °C 60 °C 70 °C **)** for four months .Samples of tablets were taken at desired time intervals and assayed for contents of Orphenadrine citrate according to the method mentioned before .The friability , disintegration and dissolution time were also checked at the end of four months , and organoleptic properties were also examined .

STATISTICAL ANALYSIS

Students t – test was used to examine the difference in the mean of the results of parameters tested . A p – value of less than 0.05 was considered significant .

PRELIMINARY CLINICAL STUDY

The selected prepared formula (1) in addition to DISPAL® were given to seven patients suffering from tremor (legs and arm) , stiffness and autonomic dysfunction which are clinical symptoms of Parkinson's disease .They were also given to three patients with dystonia , at the same time the study was done using placebo tablets . The treatment was followed up to three months with a dose of one tablet 3 times daily . The study was done in Nahrain College of Medicine Teaching Hospital to determine the clinical symptoms and the clinical parameters used to asses the therapy .

RESULTS and DISCUSSION :

Effect of Binder Type

Different formulas (1,3,8 and 9) were prepared to study the effect of binder type on the hardness , friability , disintegration and dissolution times as shown in table (2) and fig

Table (2)
Effect of Binder Type on the Hardness ,
,Friability , Disintegration Time and Dissolution Time of the Suggested Orphenadrine Citrate Formula in Comparison with the Reference Tablet

Suggested formula	Type of binder	Hardness (kg)	Friability (%)	Disintegration Time(min)	Dissolution Time(min)to 100%
1	10% PVP	8.25	0.539	5	20
3	20%Acacia Mucilage	7	0.7	6	20
8	10% Starch paste	5	1.1	5	15
9	5% CMC	3	2.8	4	30
DISIPAL® Reference				10	25

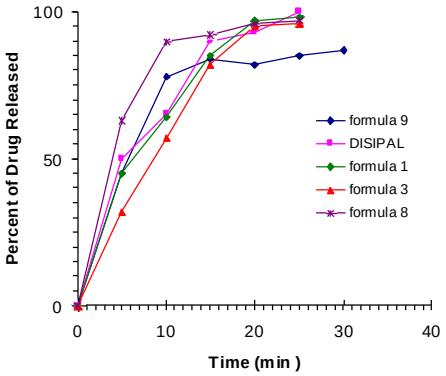


Fig .1 :Effect of binder on the release of Orphenadrine from prepared formulas in comparison with the reference tablet DISIPAL®

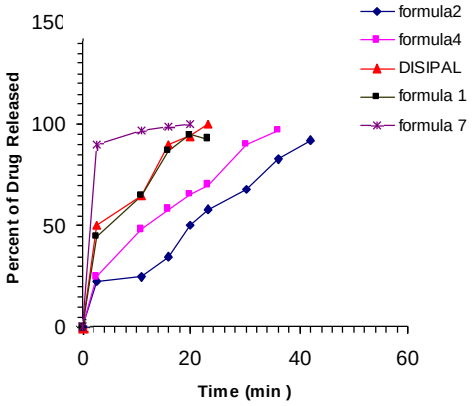


Fig. 2 : Effect of diluent on the release of Orphenadrine from prepared formulas in comparison with the reference tablets DISIPAL® in 0.1N HCl and 37° C

The results obtained indicate that using different types of binders affect the physical properties and the release of drug . For example , formula 1 in which PVP was used as a binder , showed a good hardness (8.25kg) , friability (0.5%),disintegration time (5 mins.) and dissolution time up to 100% (20 mins.) in comparison with the reference tablet DISPAL® .This may be due to the use of PVP in ethanol which has the same viscosity as P.V.P in water[30] .Also hydgroscopicity of PVP prevents the tablet from being harder with age [31] .

Formula 3 , which utilizes acacia mucilage in water as a binder ,showed good hardness (7kg), acceptable friability (0.7%) , disintegration time (6mins.) and dissolution time up to 100% (20mins.) in comparison with the reference tablet DISPAL®.These may be due to the fact that gum acacia generally produce hard granules but without producing tablets of increasing hardness[31] . Formula 8 which contains starch paste as a binder , showed reasonable hardness (5kg) and disintegration time of (5mins.)with unacceptable friability (1.1%) and fast dissolution time up to 100% (15mins.) .This may be due to the property of starch paste , which forms generally soft and brittle tablets[31] . Finally formula 9 in which CMC. was used as a binder , showed low hardness (3kg)and unacceptable friability (2.8%)with an acceptable disintegration time (4mins.)and long dissolution time (30mins.)since CMC. sodium is viscosity controller ,it is conceivable that it forms a highly viscid systems that resist dilution by dissolution fluid which might impede drug release[32].

Effect of Diluent Type

Formulas 1,2,4 and 7 were used to study the effect of diluent type on the hardness , friability ,disintegration and dissolution times of the prepared tablets .

Table (3) shows the effect of diluent type on physical properties of the prepared tablets , while fig (2) shows the release of Orphenadrine citrate from the prepared tablets (formula 1,2,4 and 7) in comparison with the reference tablets DISIPAL® .

Formula 1 in which starch was used as diluent gave a good hardness(8.25kg), friability (0.539%) , disintegration (5min) and dissolution time up to 100% (20min) .

Formula 2 which contains dextrose as a diluent ,showed a good friability (0.1%), hardness (7kg) and disintegration time (4 mins.) but long dissolution time (40mins.), although brown spots was seen on the tablet after a while which may be due to the interaction of dextrose with amines (Orphenadrine)[30] . Formula 4 in which mannitol was used as a diluent , gave a good friability(0.5%), hardness (7.25kg), disintegration time (6mins.),with a reasonable dissolution time (35mins.). This may be due to non – hygroscopicity of mannitol [30].

Formula 7 ,which was prepared by direct compression technique , showed a weight variation .This is because of poor flow of powder in spite of presence of Emcopmress .Also it showed unacceptable friability (1.1%)
and hardness (3kg)with a rapid disintegration time (50-sec) and dissolution time of 20 min .

Effect of Disintegrant

Effect of Disintegrant Type

Formulas 1,5 and 6 were utilized to study the effect of disintegrant type on physical properties of the prepared tablets as shown in table (4) and fig (3) .

Table (3)
Effect of Diluent on the Physical Properties of Orphenadrine Citrate Plain Tablets

Formula No.	Diluent Type	Hardness(kg)	Friability (%)	Disintegration time (min)	Dissolution Time (min)to100%
1	Starch	8.25	0.539	5	20
2	Dextrose	7	0.1	4	40
4	Mannitol	7.5	.5	6	35
7	Emcompress	3	1.1	0.5	20

Table(4)
Effect of Disintegrant Type on the Physical Properties of Prepared Orphenadrine tablets

Formula No.	Diluent Type	Hardness(kg)	Friability (%)	Disintegration time (min)	Dissolution Time (min)to100%
1	Avicel	8.25	0.539	5	20
5	Explotab	4	0.1	5	25
6	Starch	3.5	0.01	4	30

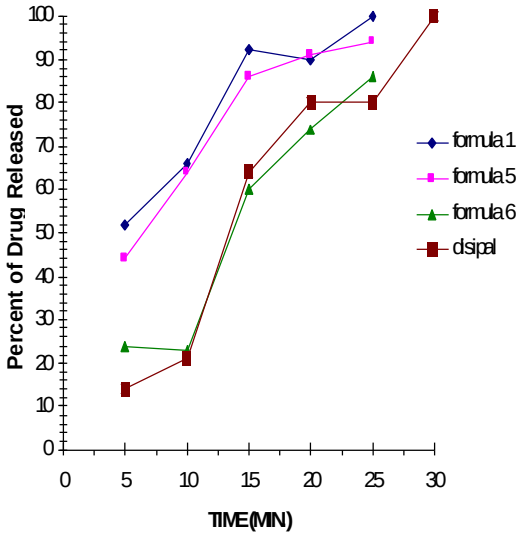


Fig. 3 : The effect of disintegrants type on the release of Orphenadrine in comparison with the reference tablets DISIPAL ®

Formula 5 , in which Explotab (low substituted carboxymethyl starch [32]) was used as a disintegrant showed a relatively low hardness (4kg) with an acceptable friability (0.1%), disintegration time (5mins.) and dissolution time (25 mins.) , however , its dissolution profile showed no significant difference with formula 6 fig(3) (p – value > 0.05).

This is may be due to Explotab properties since its granules absorb water rapidly and swell but do not break . In general , the swelling granules remain intact , causing disintegration without bursting (unlike starch) and consequently release of the soluble starch fraction .This might lead to increase the viscosity and delay moisture penetration into the tablet [29] .

Formula 6 showed a good friability (0.01%) , disintegration time (4mins.) and dissolution time (30mins.), with relatively low hardness(3.5kg) .This may be due to the fact that tablets containing high amount or concentration of starch are often soft and may be difficult to dry [33] . Formula 1 in which Avicel ® was used as disintegrant , showed a good hardness (8.25kg)and friability (0.5%) with an acceptable disintegration time (5mins.),and a fast dissolution time(20mins.).

This is because Avicel® is a super disintegrant which is highly porous ,with strong " wicking" tendencies [23] ,this will allow water to enter the tablets matrix by means of capillary forces which breaks the hydrogen bonding between adjacent bundles of cellulose microcrystals[33]

Effect of Mode of Incorporation of Disintegrant

Formula 1 , was used to study the effect of method of incorporation of disintegrant .It was prepared by three methods of incorporation , they were : extragraunlar 1, intragranular 1_b , and combination of both types 1_c .The data are displayed in fig (4) and table (5).

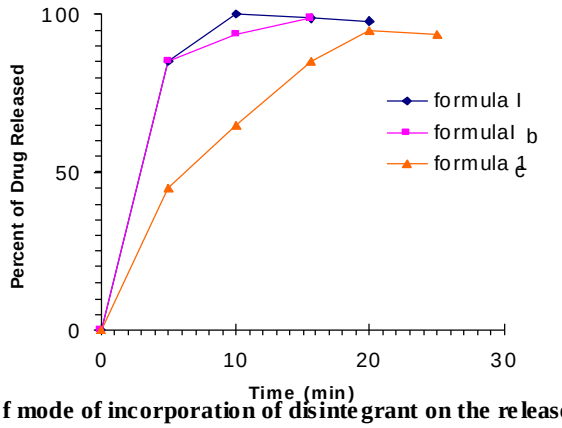


Fig. 4 : Effect of mode of incorporation of disintegrant on the release of Orphendrine from prepared formulas

Table (5)
A Comparison Between the Effect of Method of Incorporation of Disintegrant Extra or Intra or Combination of Both

Formula No.	Disintegrant Location	Hardness (kg)	Friability(%)	Disintegration Time (min)	Disslution Time (min) to 100%
I	Avicel Extra	8.25	0.539	5	20
I_b	Avicel intra	3	0.1	3	19
I_c	Avicel Extra & intra	3.5	0.15	4	15

The results showed that faster disintegration (3mins.)and shorter dissolution time (10mins.)for formula 1_b compared with that of formula 1_c and formula 1. This is in agreement with Gordon et al[34] who stated that incorporation of super disintegrant in the intragranular phase resulted in faster tablet dissolution than did incorporating it in the extragranular phase or both phases . Based on the overall results ; it seems that formula 1 and 5 are the promising formulas compared with the reference tablet DISPAL® .Since both of them showed good disintegration and dissolution times . However , regarding the economic part of production and the cost of mannitol [33] , formula 5 was excluded .

Kinetic Study

The stability of formula 1 which was chosen as the promising formula was studied at different temperatures (50 , 60 and 70 °C) for four months . The degradation of Orphenadrine citrate follows first order kinetic since straight lines were obtained when the logarithm of percent remaining of Orphenadrine citrate was plotted versus time (fig.5) . The degradation rate constants (K) for different temperatures were calculated from the slopes of the lines as shown in table (6) .

Table (6) Rate Constants of Degradation (K) of Orphenadrine Citrate (formula 1) at Different Temperatures

Temperature °C	K(month^{-1})
50	1.0×10^{-3}
60	1.413×10^{-3}
70	1.995×10^{-3}

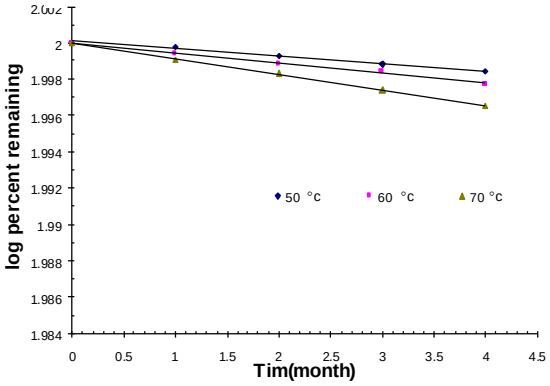


Fig.5: Accelerated breakdown of Orphenadrine citrate at different elevated temperatures (formula 1)

To compute the expected expiration date (t_{10}%), Arrhenius plot was made to predict the K_{25}°C as shown in fig (6). utilizing the following equation :

$$t_{10} = \frac{0.104}{K_{25}°C}$$

However , the calculated t_{10}% was long ,so its considerd to be equal for 5 years .In addition , at the end of four months , no change in physical properties of the prepared tablets was seen .

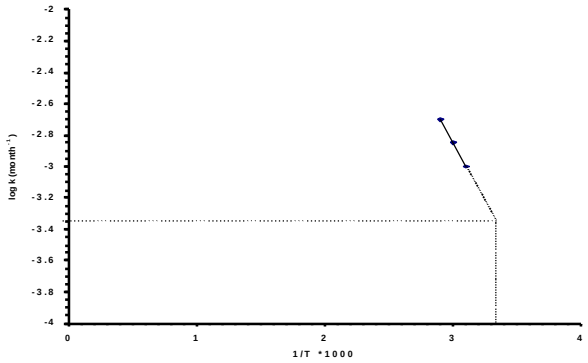


Fig .6 Arrhenius plot for expiration date estimation of Orphenadrine citrate (formula 1)

RELIMINARY CLINICAL STUDY

The results of this study as indicated in table (7) showed five out of seven patients had a good response to the drug after one week of treatment for the selected formula 1 as well as the reference tablets DISPAL® , while the rest two patients showed different behavior . i.e , one had no response to the drug and the other showed side effects such as hallucination and blurred vision after one day of treatment , therefore the therapy was stopped , on the other hand , the drug showed no effect on patients with dystonia as with the placebo tablets .

CONCLUSION

From all previous experimental work one can conclude that best binder is PVP in ethanol since it is cheap , available , compressible and compatible with drug . Starch and Mannitol are the best diluents but we prefer using starch because of its low cost . Avicel is a good disintegrant since it is compressible , highly porous giving a good disintegrating time although it is relatively expensive .Formula 1 is the most satisfactory formula in comparison with the reference tablets DISIPAL®.and the t_{10}% was considered to be equal for 5 years .

Table(7)
Clinical Responses to prepared Orphenadrine tablets and the reference

Patient	Age (year)	Sex	Chief complaint	Past treatment	Duration new treatment	Dose	Notes
1	60	Male	Tremor	Parkizol sinamet	One day	1×3	Patient develop hallucination and blurred vision stop treatment after one dose only
2	40	Male	Tremor	No	2 weeks	1×3	Moderate response
3	50	Female	Tremor	Sinamet	2 months	1×3	Good response
4	59	Male	Tremor	No	3 months	1×3	Good response
5	30	Female	Tremor	No	1week	1×3	No response
6	40	Female	Tremor and rigidity	Parkizol Sinamet artane	1 month	1×3	Good response
7	45	Male	Tremor	No	2 weeks	1×3	Moderate response
8	11	Female	Dystonia	No	3 weeks	1×3	No response
9	15	Male	Dystonia	No	1 month	1×3	No response
10	30	Male	Dystonia	No	2 weeks	1×3	No response
% response to Tremor							71.4
% side effect							14.28
% response to dystonia							0.0

Note : The difference between good & moderate responses is related to the examiner

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