Formulation of Rifampicin Suspension

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Abstract

Rifampicin is the drug of choice in treatment of tuberculosis. Also, it is effective in treatment of various bacterial infections.This study was carried out to prepare a stable suspension for rifampicin through preparation of different formulas of rifampicin aqueous suspension either as ready to use or as granular powder to be reconstituted.The selected formula (A) was evaluated and compared with commercial brand of rifampicin (Rifactine®) as a reference through measuring their dissolution rates and other physical properties.The results indicated that the selected formula had better dissolution rate compared with the reference suspension and the rheogram showed that the selected formula was less viscous than the reference one.Also, it was found that the granular rifampicin was more stable than the ready to use suspension, since the expiration date of granular rifampicin was 2.6 years, while the expiration date of ready to use suspension was 1.8 years.

Key words : Rifampicin , Suspending agent ,Powder for reconstitution , Aqueous suspension

الخلاصة

إن الريفاميسين هو الدواء المفضل في علاج التدرن الرئوي والالتهابات البكتيرية المختلفة. تم إجراء هذه الدراسة لتحضير معلق ثابت للريفامبيسين من خلال تحضير صيغ تركيبية مختلفة لمعلق الريفامبيسين أما بشكل معلق جاهز للاستعمال أو كمسحوق جاهز للتعليق. أن الصيغة التركيبية المختارة (أ) اختيرت للتقييم والمقارنة مع المستحضر المرجع (الريفاكتين) من خلال قياس سرعة التحرر و الخواص الفيزيائية الأخرى. أوضحت النتائج أن الصيغة التركيبية المختارة أعطت افضل سرعة تحرر مقارنة مع المستحضر المرجع و تعيين التدفق أظهر أن الصيغة المختارة هي اقل لزوجة من المستحضر المرجع. وكذلك وجد أن معلق الريفامبيسين الحبيبي هو اكثر استقرارية من المعلق الجاهز للاستعمال ، حيث أن مدة انتهاء مفعول المعلق الحبيبي هي (٢,٦) سنة بينما مدة انتهاء مفعول المعلق الجاهز للاستعمال هي(١,٨) سنة.

Introduction

An oral pharmaceutical suspension has long been one of the most favorable dosage forms for pediatric patients or patients unable to tolerate solid dosage forms [(1)].

There are many physical and chemical considerations 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)].

Rifampicin is bactericidal agent against wide range of microorganism [(4)]. It is one of the very slightly soluble drugs, thus is suitable for suspension dosage form. But rifampicin is poorly wetted with water due to its hydrophobic nature.

El-bary et al. studied the wettability of rifampicin powder using different concentrations of various surfactants and polyhydroxy compounds .The wettability of rifampicin was found to be directly proportional to surfactant HLB and concentration [(5)]. In this study, rifampicin is formulated as an aqueous suspension either as ready to use or as dry powder and the selected formula is compared with the reference suspension.

Experimental

Materials and Equipments

Rifampicin powder, Polysorbate 80, Raspberry flavor, Xanthan gum, Guar gum , Methylparaben, Propylparaben (Supplied by Samara Drug Industries (SDI)).

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Received 26-11-2005

Accepted 24-5-2006

Rifactine® suspension (Supplied by Medical Union Pharmaeutical, Egypt)
Sodium saccharin, Sorbitol 70%, Sodium citrate (Supplied by Ibn- seina Drug Research Center, Baghdad).
Citric acid monohydrate (Al-Rahma Pharmaceutical Co., Jordan).
Disodium edetate, Sodium metabisulphite, Hydrochloric acid, colloidal Silicone dioxide (Aerosil), Methylcellulose, Sodium carboxymethylcellulose (BDH chemicals Ltd, Poole, England).
Spectrophotometer (Pye-Unicom-sp-8-100 model 292MK, England).
Dissolution apparatus (Erewka G.M.B.H. type DT6, W.Germany).
pH meter (Orchidis laboratories, France).
Viscometer (Cole-parmer, rotational viscometer U.S.A).
Ovens (Memmert 854 Schwabach, W.Germany).

Method of preparation

Formulation of Rifampicin Suspension:

Several formulas of rifampicin aqueous suspension were prepared, either as ready-to-use aqueous suspension or dry powder for reconstitution.

Ready-to-use aqueous Rifampicin Suspension

Different formulas of rifampicin suspension were prepared using different suspending agents as shows in table (1), each formula was prepared as follows:

Rifampicin, methylparaben and propylparaben were levigated in a mortar with the prepared dispersion of the suspending agent. The mixture was triturated with a pestle until a smooth paste was formed. With continuous triturating, the paste was diluted with the remaining amount of the dispersion of suspending agent then transferred to graduated cylinder. The required amount of sodium saccharin and disodium edetate or sodium metabisulphite were dissolved in a small portion of distilled water and added to the graduated cylinder. Finally sorbitol, glycerol and raspberry flavor were added followed by adding sufficient distilled water to make up to volume. The suspension was shaken thoroughly and the pH was adjusted to 5 with few drops of 5M sodium citrate.

Table (1) Different Formulas of Ready-to-Use Rifampicin Suspension (% W/V)

Material	Formula						
	A	**B**	**C**	**D**	**E**	**F**	**G**
Rifampicin	2	2	2	2	2	2	2
Agar						x	y
Methylcel - lulose					x		
Xanthan gum	x	y	x				
SCMC			x	x			
Polysorbate 80	x	x	x	x	x	x	x
Disodium edetate	0.1	0.1	0.1	0.1	0.1		
Sodium metabisulphite						0.15	0.15
Glycerol	5	5	5	5			
Sorbitol 70 %	5	5	5	5			
Sodium saccharin	0.2						
Methylparaben	0.18						
Propylparaben	0.03						
Raspberry flavor	0.05						
Final volume	100 ml						

Powder for reconstitution

Different suspending agents were used to prepare rifampicin suspensions as powder form ready for reconstitution are shown in table (2). Each was prepared by triturating rifampicin powder with the selected components. The powder mixture was passed through a sieve (150 µm) before being transferred to amber glass bottles [6].There was an exception for formula I, in which a powder blends was moistened with (0.5 % polyvinylpyrrolidone in alcohol). The damp mass was then passed through the sieve (1000 µm) and the granules were dried at 37 ˚C. The dried granules were resieved through the same sieve before being transferred to amber glass bottles. The ease of reconstitution and stability were evaluated to select the proper formula, which will be subjected to further study.

Table (2) Different Formulas of Rifampicin Powder to be Reconstituted as Suspension. (% W/V)

Material	Formula			
	I	II	III	IV
Rifampicin	2	2	2	2
Guar gum		x	y	2y
SCMC	x			
Aerosil			x	x
polysorbate 80	x			
Sucrose	20			
Sodium saccharin	0.08			
Metylparaben	0.18			
Propylparaben	0.03			
Disodium edetate	0.1			
Sodium citrate	0.06			
Citric acid	0.03			
Raspberry flavor	0.05			

Comparative Studies of The Selected Formula with Rifactine® Suspension:

The selected formulas (A and I) were compared with the reference Rifactine® utilizing the following parameters:

Dissolution Profile

The dissolution rate of rifampicin suspensions was studied using USP dissolution apparatus. The dissolution medium was 0.1N HCl (900 ml), 5 ml sample of suspension was added. Then a sample of dissolution medium was withdrawn at different time intervals (2, 5,10,15,30 and 45 minutes) through a pipette fitted with a filter paper. Fresh dissolution medium was added to the jar each time to replace withdrawn samples. Each sample was suitably diluted and assayed spectrophotometrically at 475 nm for rifampicin content.

Measurement of Rheogram

Rheograms were obtained at 37 ˚C using Cole-parmer rotational viscometer.

Sedimentation Volume Measurement

Fifty ml of each suspension was diluted with distilled water to a volume of 100 ml in a stoppered graduated cylinder. The suspensions were shaken vigorously to ensure uniformity, then left undisturbed. The sedimentation volume was measured every 4 hours for period of 48 hours [7].

Resuspendability of Suspension

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

Stability Study:

The accelerated stability study was done in order to determine the expiration date of formula A and I by placing the samples of both formulas in ovens at 35 ˚C, 45 ˚C and 55 ˚C for 120 days.

Samples were taken and assayed for drug content at suitable time intervals (0, 15,30,60,90,120 days) using UV spectrophotometric method at 475 nm.

Result and Discussion

The nonionic surfactant (polysorbate 80) was incorporated in the formulation of rifampicin suspension as a wetting agent to increase dissolution rate of the drug [5]. In addition, xanthan gum was also used as a suspending agent because of its excellent suspending properties and also as an effective flocculating agent at relatively low concentration[8]. An increase in the concentration of xanthan gum (as in formula

B) gave no substantial change in flocculation behavior and a viscous suspension was obtained which pour with difficulty.

On the other hand, sodium carboxymethylcellulose (SCMC) was used as in formula D. It gave good dissolution properties and it produced sediment layer that was easily redispersed by shaking.

Furthermore, a combination of xanthan gum and SCMC resulted in too viscous suspension, which poured with difficulty. Methylcellulose utilized in formula E produced a suspension with low dissolution rate as shown in figure (1).

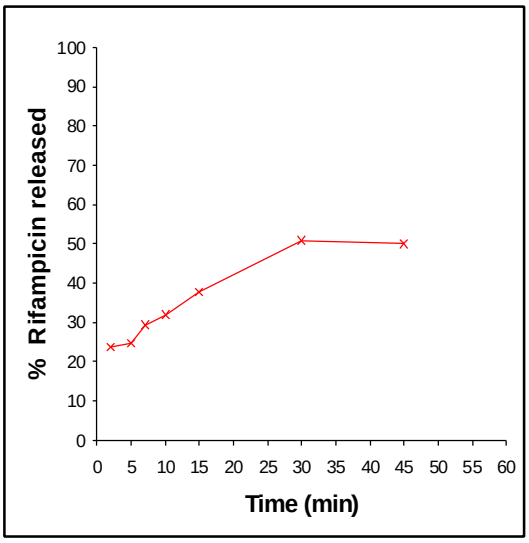

Figure (1) : Dissolution rate profile of rifampicin suspension (formula E) in 0.1 N HCl at 37°

Finally, agar was utilized as thickening agent and to control flocculation. Good results were achieved with formula F but hard cake was formed with formula G.

Formula A gave the most optimum physical stability and remarkable release profile, therefore it was chosen for extensive study and to be compared with reference suspension.

On the other hand, rifampicin suspension (as dry powder) when prepared using guar gum as a single suspending agent (formula II) resulted in a suspension that showed low sedimentation volume (0.2) but was easily redispersed. The addition of aerosil to formula III and IV resulted in easily redispersed suspensions with high sediment volume (0.8 and 0.9 for III and IV, respectively). Being finely divided, aerosil aggregates to form three dimensional network together with its ability to absorb large amount of water, hence it prevents caking [6].

In addition sodium carboxymethylcellulose was used as a suspending agent in combination with polysorbate 80 to enhance the dissolution (formula I). This formula was prepared as granules using alcoholic PVP solution as a granulating agent. The granules were found to be free flowing and not bulky. Also, rifampicin granules were found to be good in appearance and their particles were uniform in size.

Formula I was chosen since it gave good stability although it produced sediment layer with easily redisperability by shaking.

Figure (2) shows the dissolution rate of rifampicin suspension for formulas A and I compared with the reference rifactine suspension. The results showed that rifampicin released from formula A was higher than that from others. Formula I after reconstitution showed the lowest dissolution rate and this may be due to granulation process, since PVP was used as granulating agent which is water soluble binder and has good swelling and hydration capacity [9]. These properties result in high viscous region surrounding the drug particle.

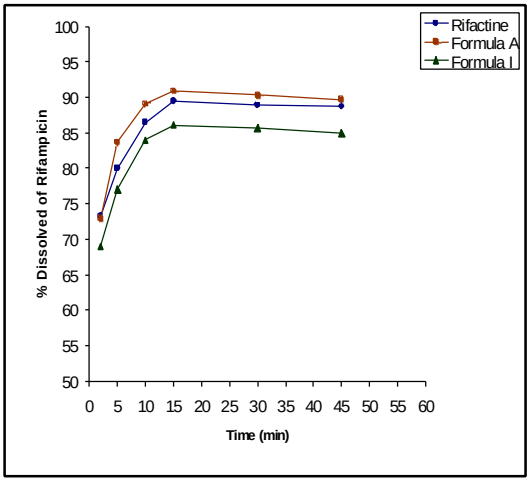

Figure (2) : Dissolution rate profile of rifampicin suspension (formulas A and I) and rifactine in 0.1 N HCl at 37°C.

Rheograms of the products are represented in figure (3). The graph showed that the viscosity of rifampicin suspensions was shear rate dependent and increased in the following order:

Formula A < Rifactine < Formula I

The results illustrated that the prepared formulas (A and I) exhibited pseudoplastic flow properties due to the suspending agents used, which were xanthan gum and sodium carboxymethylcellulose .

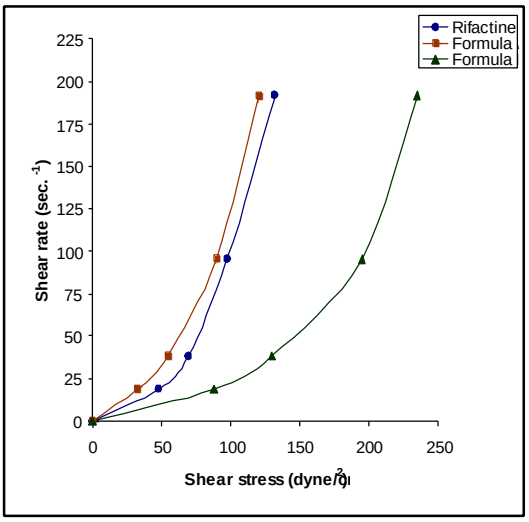

Figure (3) : Rheogram at 37˚C of rifampicin suspensions formulas and rifactine.

Tables (3 and 4) show the sedimentation volume and resuspendability after settling of rifampicin suspensions, respectively. The data indicated that formula A, which was prepared with xanthan gum, had sedimentation volume equal to 2. This result was attributed to the network of flocs formed in the suspension , which was so loose and fluffy that can be extended throughout extravehicle. The same result was reported by Jawad [(10)].

Table (3) Sedimentation Volume of Rifampicin Suspensions (formulas A, I and Rifactine)

Products	Sedimentation volume	
	F= Hu / Ho	F
Rifactine	45/50	0.9
Formula A	100/50	2
Formula I	20/50	0.4

Where: Hu is ultimate height of the sediment as suspension settle Ho is the initial height of the total suspension.

Table (4) Resuspendability of Rifampicin Suspensions (formulas A,I and Rifactine)

Products	Resuspendability
Rifactine	easily resuspended
Formula A	No sedimentation
Formula I	easily resuspended
Rifactine	easily resuspended

In the stability study of rifampicin suspension and granular rifampicin figures (4 and 5) showed that the degradation of rifampicin for formulas A and I respectively, which follows first order kinetics since straight lines were obtained by plotting the logarithm of percent remaining of rifampicin versus time.

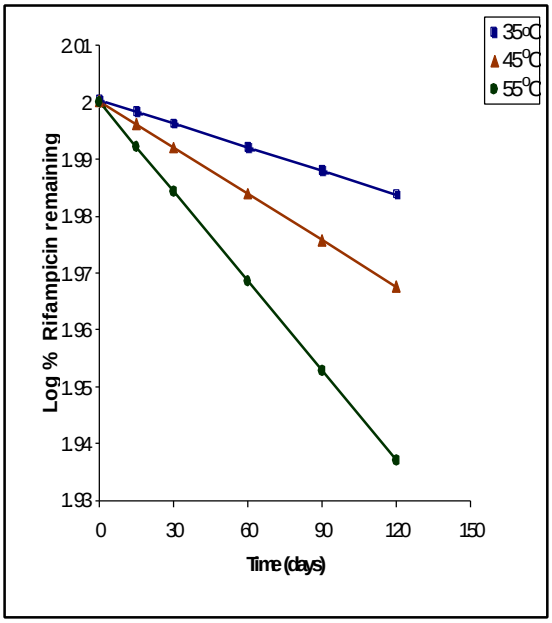

Figure (4) :Degradation curve of ready-to- use rifampicin suspension (formula A) at different temperatures.

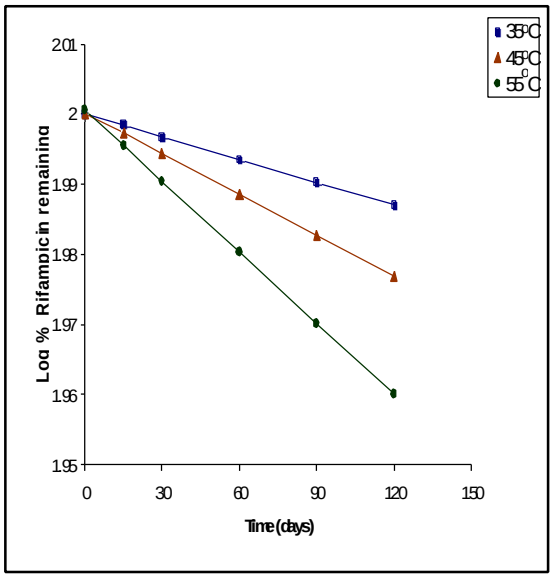

Figure (5): Degradation curve of granular rifampicin suspension (formula I) at different temperatures

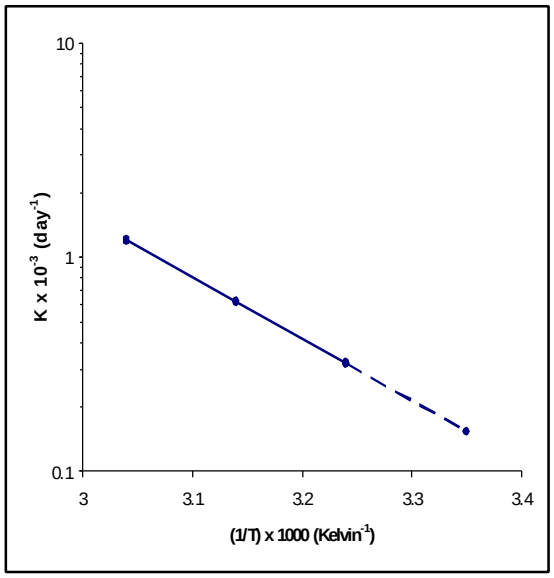

Figure (6) :Arrhenius plot for expiration date estimation of rifampicin suspension formula I at 25˚C.

The degradation rate constants (K) at different temperatures were calculated from the slopes of the straight lines and they were listed in table (5).

Table (5) Degradation Rate Constants of Rifampicin Suspensions Ready-to-Use (Formula A) and Granular Suspension (Formula I).

Temperature (˚C)	K x10^{-3} (day^{-1})	
	Formula A	**Formula I**
55	1.206	0.822
45	0.619	0.429
35	0.318	0.224
25	0.153	0.109

Arrhenius plots were then constructed and are shown in figures (6 and 7) for formula I and A, respectively. The linearity of the curves indicates their utility in predicting the rate of degradation at lower temperatures .

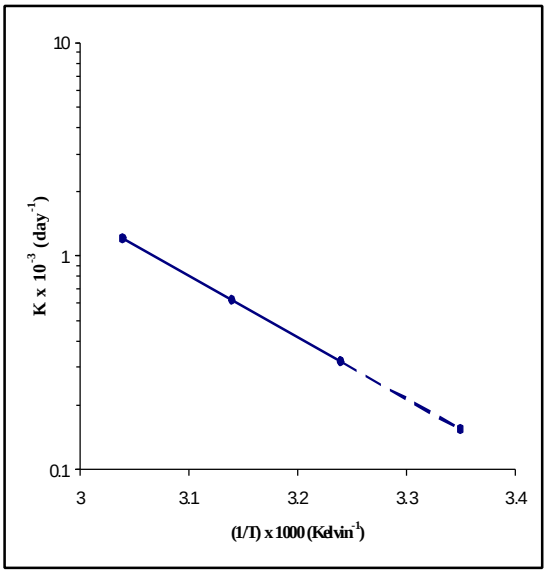

Figure (7) : Arrhenius plot for expiration date estimation of rifampicin suspension formula A at 25˚C.

The rate constants at 25˚C, obtained from those plots for ready-to-use (formula A) and granular suspension (formula I) were equal to 0.153 x 10^{-3} and 0.109 x 10^{-3} (days^{-1}) respectively.
Since the degradation of the drug followed first order kinetics, the expiration date t10% at 25˚C could be calculated using the following equation:

$$t10\% = \frac{0.105}{K_{25^\circ C}}$$

The expiration dates for formula A and formula I were 1.8 and 2.6 years respectively, indicating that rifampicin is more stable when it is prepared as granulated powder for reconstitution, as also indicated by Patankar and Bajaj [11]

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