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FORMULATION OF RIFAMPICIN SUPPOSITORIES

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ABSTRACT

Rifampicin is a powerful bactericidal antitubercular drug. The drug was formulated as suppositories. Witepsol H_{12} was used as the formulating base. Certain other bases as witepsol H_{15} and W_{35} and Massa estarinum B and BC as well as cacao butter replaced witepsol H_{12}. Non-ionic surfactants with different chemical compositions, different HLB values as well as different physical and solubility properties were incorporated into witepsol H_{12} at 5% concentration. Of the tested surfactants were polysorbates, Spans, Myrjs and Brijs. Drug dialysis into saline solution at 37°C was studied through cellophane membrane. Of the tested bases, witepsols gave the highest dialysis rates. Polysorbates proved to be superior among the tested surfactants.

INTRODUCTION

Refampicin is a powerful, bactericidal antitubercular drug[1]. It is active against a wide range of microorganisms, including Mycobacterium tuberculosis, Mycobacterium leprae, Gram positive bacteria especially staphylococci, the Gram negative Neisseria meningitides, Neisseria gonorrhoeae, Haemophilus influenza and legionella sp. [2]. Also, it is active against some other bacteria which are resistant to other antibiotics. The drug has an equal activity after oral or parenteral administration. Higher blood levels were obtained with smaller doses in comparison to other antibiotics. Drug's activity is higher than that of erythromycin, lincomycin or cephloridine. The drug is less active than penici-llin [3].

Rifampicin is used for the treatment of pulmonary tuberculosis. Also, it has been used in the treatment of extrapuimonary lesions including tuberculosis, meningitis as well as in the elimination of meningococci from the carriers and in the treatment of leprosy. The usual dose is 600 mg daily before meals as a single dose. In patients with impaired liver function

the dose should be reduced [2]. It is readily absorbed from the gastrointestinal tract. Peak plasma levels of about 9 mcg/ml were attained 2 hours after a dose of 600 mg and 27 mcg/ml after a dose of 900 mg. About 75 to 80% of the drug is bound to plasma proteins [2-4]. The biological half-life is about three hours, increased with dose and in patients with liver diseases [5].

Gastrointestinal side effects have been reported and were sometimes severe enough to necessitate drug withdrawal. There have been rare reports of pseudomembraneous colitis associated with the use of rifampicin [6]. The drug is mainly metabolized in the liver to the active deacetylated derivative. Some of the adverse reactions associated with the drug were attributed to its metabolites [7]. The bioavailability of the drug is significantly reduced upon change in gastric pH after oral administration [8].

As it was reported that once the drug is released into the aqueous solution in the rectum, the mechanism of passage through the mucosa and tissues into the blood stream is the same as in higher regions of the gastrointestinal tract [9]. Therefore, this work represents a trial for the formulation of rifampicin in suppository dosage forms.

EXPERIMENTAL

Materials:

Rifampicin < 50 um (Lepetit, Milano, Italy). Semipermeable cellophane membrane 30/32 (Fischer Sci. Co., London. UK). Non-ionic surfactants (Atlas Chem. Ind., U.S.A.) and different suppository bases. The other chemicals were of analytical reagent grade.

Equipments:

Thermostatically controlled water bath fitted with mechanical shaker (GFL-England), and Double beam spectrophotometer (Shimadzu-150-02-Japan).

Procedure:

1-Preparation of Rifampicin Suppositories:

Suppositories of infantile size (about 1 gm) each containing 200 mg of the drug, were prepared. The spositories were prepared according to the fusion method. The suppositories were placed in a refrigerator for three days, then removed and left at room temperature for 24 hours before testing.

2-Dialysis of Rifampicin through Cellophane Membrane:

The dialysis technique was adopted as follows: An open glass cylinder; 2.2 cm internal diameter was used as the donor. Moist cellophane membrane, previously soaked in distilled water over night, was firmly stretched over the lower end of the cylinder. The cylinder was then clamped in an inverted position in 50 ml beaker containing 25 ml of saline solution (the acceptor). An additional 10 ml of saline solution was added into the donor cylinder. The whole system was placed in a mechanically shaken (50 shake/minute) and thermostatically controlled water bath, at 37°C. After equilibrium, the test suppository was introduced, into the donor. At specified time intervals, 2 ml of dialysis medium was withdrawn and replaced by an equal volume of fresh one. The UV absorbance of the withdrawn sample was measured at 338 nm. after appropriate dilu-

tion using fresh saline solution as a blank. Drug concentration was calculated using a standard caliberation curve. It is worthy to note that no interference due to either bases or surfactants at this wave length.

RESULTS AND DISCUSSION

Rifampicin auppositories were prepared using witepsol H_{12} as the formulating base. Certain other bases were used without additives. Mixtures composed of witepsol H_{12} and different non-ionic surfactants (95:5) were also used to formulate the rifampicin suppositories. The prepared suppositories were found to be in accordance with the pharmacopoeial requirements as regard to both the uniformity of weight and uniformity of drug contents. The in *vitro* dialysis of drug through cellophane membrane was studied. The results showed that (Tables I-V & Fig. 1) substituting witepsol H_{12} with either witepsol H_{15} or witepsol W_{35} resulted in insignificant change in the dialysis rate of the drug. However, the use of cacao butter led to a marked slowing in the drug dialysis rate. Massa estarinum bases exhibited an intermediate dialysis rates characterized with a slow initial phase. Thus, the tested bases can be arranged according to the rate of drug dialysis as witepsols > Massa estarinum > cacao butter. It is worthy to note that all the tested bases are of nearly the same melting range. Therefore, the melting behaviour of the base seemed to be ineffective variable. On the other hand, the chemical composition of the base seemed to be a determinant factor on drug dialysis. In this respect, witepsol; H_{12}, H_{15} and W_{35} which have the same chemical composition were found to have nearly the dialysis pattern. The higher dialysis rates obtained with witepsols may be attributed to the presence of monoglycerides as a self emulsifying agents, in their composition. Cacao butter which is mainly composed of triglycerides exhibited the lowest dialysis rate.

The incorporation of 5% of non ionic surfactants into witepsol H_{12} base was found to significantly modify the dialysis pattern. All the tested surfactants were found to enhance the drug dialysis rate. An effect which may be attributed to the reduction in the water repellent effect of both base & drug by the used surfactants. An exception was found with Span 60 which lowers the dialysis rate of the drug. A result that can be attributed to both insolubility of the surfactants in the aqueous media and its low HLB value (4.7). Generally, the tested surfactants can be arranged according to their enhancing effect on drug dialysis rate as follows: Polysorbates > Spans > Brijs or Myrjs. A result which suggests that the chemical composition and not the HLB value of the surfactant is the determinant factor. Of the tested surfactants; Polysorbate 20, Polysorbate 40, Polysorbate 80, Brij 35, Brij 58, Myrj 52 and Myrj 53 of nearly the same HLB values (15-17.9) showed different dialysis rates of the medicaments. Other surfactant properties as solubility in aqueous media as well as in the formulating base can be regarded as an effecting parameters in determining the drug diffusion profile. Finally, a base composed of witepsol H_{12} and any of polysorbate 20, 60 or 61 (95:5) can be suggested for formulating rifampicin in suppository forms.

Table I: Effect of Formulating Base on Rifampicin Dialysis through Cellophane Membrane at 37°C.

Base used	Amount of Rifampicin Dialysed (mg/100 ml) after the following specified time intervals in hours					
	½	1	1½	2	2½	3
Witepsol H_{12}	0.72	1.12	1.60	2.16	2.72	3.36
Witepsol H_{15}	0.64	1.04	1.44	2.16	2.88	3.60
Witepsol W_{35}	0.72	1.04	1.52	2.10	2.80	3.44
Massa Es B	0.08	0.26	1.20	1.92	2.64	3.76
Massa Es BC	0.00	0.16	0.40	0.72	0.96	1.44
Cacao Butter	0.00	0.00	0.16	0.32	0.48	0.72
Suspension*	0.76	0.90	1.44	1.50	2.52	3.14

* Suspension form (200 mg/10 ml).

Table II: Effect of Incorporating Spans into Witepsol H_{12} (5:95) on Rifampicin Dialysis through Cellophane Membrane.

Span used	Amount of Rifampicin Dialysed (mg/100 ml) after the following specified time intervals in hours					
	½	1.0	1½	2.0	2½	3.0
Control	0.72	1.12	1.60	2.16	2.72	3.36
20	1.12	2.48	3.92	5.12	6.64	7.84
40	0.64	1.68	2.80	4.00	4.96	6.40
60	0.40	0.72	1.04	1.68	2.00	2.80

Table III: Effect of Incorporating Polysorbates into Witepsol H_{12} (5:95) on Rifampicin Dialysis through Cellophane Membrane

Polysorbate used	Amount of Rifampicin Dialysed (mg/100 ml) after the following specified time intervals in hours					
	½	1.0	1½	2.0	2½	3.0
Control	0.72	1.12	1.60	2.16	2.72	3.36
20	2.48	4.16	7.44	8.56	9.76	11.68
40	2.72	4.96	6.40	7.28	8.08	9.12
60	2.48	3.84	5.92	7.36	9.12	11.04
61	2.16	3.84	5.84	7.36	9.12	11.04
65	2.32	4.16	5.76	7.28	8.72	9.92
80	2.40	3.20	3.68	4.08	4.48	5.04
81	1.52	3.36	4.96	6.64	8.56	10.00

Table IV: Effect of Incorporating Brijs into Witepsol H_{12} (5:95) on Rifampicim Dialysis through Cellophane Membrane

Brij used	Amount of Rifampicin Dialysed (mg/100 ml) after the following specified time intervals in hours					
	½	1	1½	2	2½	3
Control	0.72	1.12	1.60	2.16	2.72	3.36
35	1.28	2.72	3.60	4.16	4.32	4.80
52	1.36	3.20	4.88	6.48	8.16	9.68
58	1.28	2.88	4.00	4.72	5.28	5.92
97	1.16	2.72	3.36	4.08	4.48	4.96
99	1.20	2.16	2.80	3.12	3.60	4.00

Tabel V: Effect of Incorporating Myrjs into Witepsol H_{12} (5:95) on Rifampicin Dialysis through Cellophane Membrane

Myrj used	Amount of Rifampicin Dialysed (mg/100 ml) after the following specified time intervals in hours					
	½	1.0	1½	2.0	2½	3.0
Control	0.72	1.12	1.60	2.16	2.72	3.36
52	1.52	2.32	2.64	2.88	3.28	3.60
53	1.60	3.04	3.84	4.40	4.64	5.12
59	1.52	3.04	4.32	5.12	5.68	6.16

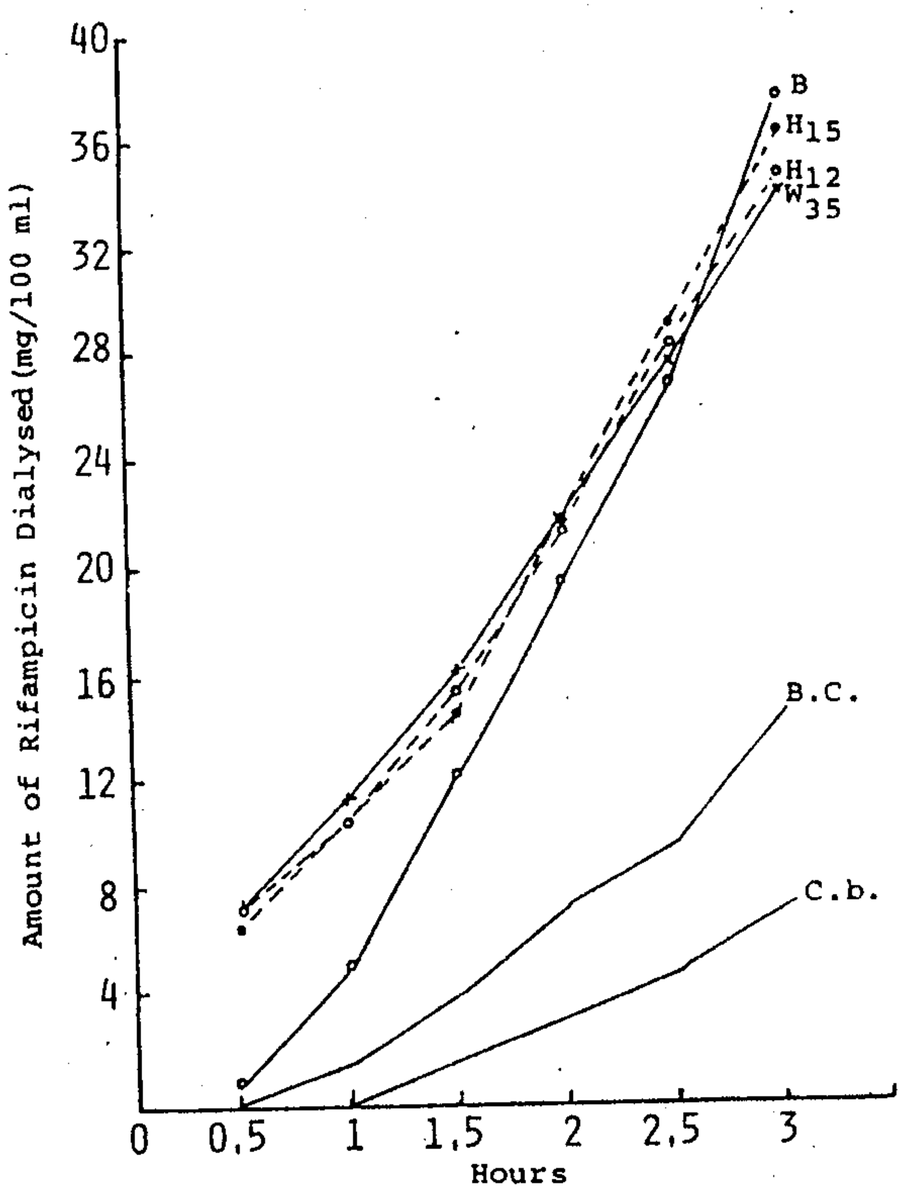

Figure (1): Effect of Formulating Base on the Dialysis of Rifampicin through Cellophane Membrane, at 37°C.

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صيانة اقماع الريفامبسين

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في هذا البحث تم صيانة عقار الريفامبسين في صورة الاقماع الشرجية باستخدام قاعدة الوتبسول H_{12} كما تم استبدال القاعدة السابقة بقواعد اخرى متمثلة في قواعد الوتبسول H_{15} و W_{35} والماسا استارينم B و Bc وكذلك زبدة الكاكاو. كما تم دراسة استخدام خليط من قاعدة الوتبسولH_{12} والعديد من منشطات السطح الغير متاينة بنسبة ٥:٩٥ كقواعد لاقماع العقار. وقيمت الاقماع المحضرة بدراسة معدلات انطلاق العقار منها وقد وجد ان القواعد المحضرة من خليط الوتبسول مع عديدى السوربات تعطى احسن النتائج من حيث معدلات انطلاق العقار منها.

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