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PREFORMULATION OF ANTITUBERCULOUS DRUGS IN POLYMERIC BASED FILMS

S.M. Safwat[1], S.S. Tous[1] and I.A. Hassan[2]

[1] *Department of Pharmaceutics, Faculty of pharmacy;*
[2] *Department of Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt*

يتناول هذا البحث رقائق من المبلمرات تحتوى على إثنين من العقاقير المستخدمة فى علاج الدرن وذلك للتحكم فى إنطلاق كل من الريفامبيسين والأيزونيازيد - وقد أستخدم فى هذا البحث ثلاثة أنواع من المبلمرات وهم (أ) مبلمر إيثيلين خلات الفينيل ، (ب) عديد خلات الفينيل ، (ج) بيوثيرات خلات السليلوز.

تم فى هذا البحث تقييم رقائق المبلمرات بحساب الخصائص الميكانيكية للرقائق بدون عقار ومن هذه الخصائص مقاومة الشد ومعامل المرونة وقد وجد أن رقائق بيوتيرات خلات السليلوز غير مرنة وتقطع بسهولة بينما رقائق خلات الفينيل وإيثيلين خلات الفينيل تكون مرنة وإضافة أى من العقارين لمحتويات الرقائق عند التحضير يؤدى إلى إنقاص معامل المرونة.

وتم حساب معامل النفاذية لكل من العقارين من خلال هذه الرقائق ووجد أن هذا المعامل يعتمد على نوع المبلمر ونوع العقار من حيث درجة قابليته للماء ووجد أن معدل نفاذ عقار الأيزونيازيد فى خلال إيثيلين خلات الفينيل أعلى منه خلال بيوتيرات خلات السليلوز - بينما الريفامبيسين له نفاذية أقل منه خلال هذين المبلمرين.

وقد تناول هذا البحث أيضا دراسة معدل إنطلاق العقارين من هذه الرقائق وتأثير تركيز العقار على معدل الإنطلاق وقد وجد أن هناك علاقة خطية بين الكمية المنطلقة للعقار فى وحدة المسافة المربعة والجذر التربيعى للزمن. وإن معدل إنطلاق الريفامبيسين من الرقائق المستخدمة يقل كثيرا عن معدل إنطلاق عقار الأيزونيازيد بالإضافة إلى أن معدل انطلاق الأخير من رقائق مبلمر إيثلين خلات الفينيل أعلى منه فى حالة إستخدام عديد خلات الفينيل. وإمتدت الدراسة لتشمل تأثير بعض المواد على معدل إنطلاق الريفامبيسين ولهذا الغرض إستخدم الإيثيل سليلوز كمحتوى من محتويات الرقائق كذلك إستخدم ثنائى ميثيل الفورماميد كمادة مساعدة لذوبان الريفامبيسين. وأوضحت النتائج أن معدل إنطلاق هذا العقار من الرقائق المستخدمة يزداد بزيادة تركيز إيثيل سليلوز وأيضا معدل إنطلاق هذا العقار من الرقائق يزداد بإستخدام ثنائى ميثيل الفورماميد وهذا يعتمد على نسبة الأخير فى الرقائق وهذه الزيادة تظهر جليا عند إستعمال رقائق مبلمر إيثيلين خلات الفينيل عند إستخدام رقائق عديد خلات الفينيل.

وقد إستخدمت الأشعة تحت الحمراء لدراسة إحتمالية وجود تفاعل بين عقار الريفامبيسين والمبلمر المستخدم فى تحضير الرقائق وقد أيد هذا ملاحظة بعض التغيرات فى طيف الأشعة تحت الحمراء للعقار بعد خلطه بهذه المبلمرات.

وأمتدت الدراسة لتشمل دراسة تأثير عقار الريفامبيسين المنطلق من رقائق المبلمرات كمضاد للبكتريا على بعض الكائنات الدقيقة - وأوضحت النتائج أن عقار الريفامبيسين المنطلق من الرقائق له فاعلية فى قتل الكائنات الدقيقة وذلك بحساب قطر منطقة عدم نمو هذه الكائنات الدقيقة فى الوسط المعد لذلك.

وقد شوهد أن العقار المحتوى فى رقائق مبلمر إيثيلين خلات الفينيل له قدرة على الإنطلاق والتأثير على البكتريا أكثر من ذلك المحتوى فى رقائق عديد خلات الفينيل.

والخلاصة أن هذه النتائج لها قيمتها التطبيقية المستقبلية وذلك لعمل تغطية لأقراص الأيزونيازيد للتحكم فى الإنطلاق أو عن طريق صياغة عقار الريفامبيسين للعلاج الموضعى والحروق.

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Controlled - release rifampicin (RF) and isoniazid (INH) polymeric films were cast from ethylene-vinyl acetate copolymer (EVA), polyvinyl acetate (PVA) and cellulose acetate butyrate (CAB) polymeric solutions. Evaluation of the films was done by determining Young's modulus of elasticity, tensile strength and permeability parameters. Hard and brittle films were obtained with CAB films while, PVA and EVA form soft and tough films. The incorporation of drugs in either polymers resulted in a decrease in the modulus of elasticity. The rate of permeation depended on the hydrophilicity of the drug and the polymer type. The permeation rate of INH through EVA is higher than CAB films while RF has low permeability across both films. The effect of initial drug concentration on the release rate from films was determined for each drug. There was a linear relationship between released amount of drug per unit surface area and square-root of time. The release rate of RF from EVA and CAB polymeric films is lower than that of INH. The release rate of INH from EVA films was higher than from PVA films. While that of RF from EVA and PVA films was enhanced by incorporating different concentrations of ethylcellulose (EC) as a film component. The slow release of RF from polymeric films was attributed to the possible interaction of RF with the polymer used in the preparation of the film as indicated from infrared spectral studies. The effect of dimethyl formamide (DMF) as a solubility modifier for RF in the films was indicated by increasing the release rate of the latter from EVA rather than from CAB films. The enhancing effect of DMF on the release rate of RF from polymeric films was found to be dependent on the level of DMF incorporated in the film. The antibacterial effect of RF released from polymeric films was found to be greatest from EVA followed by PVA films. The results were promising for topical formulation of RF.

INTRODUCTION

Polymeric membranes are used in pharmaceutical industry to moderate the rate of drug release. Ethylene-vinyl acetate copolymers (EVA) do not degrade *in situ* and are examples of non-biodegradable polymers[1,2]. Langer and Folkman[3] reported the release Kinetics of macromolecules from EVA copolymers. Subsequently, Langer *et al.*[4] reported the biocompatibility of this polymer in rabbit cornea. Polyvinyl acetate (PVA) is a good adhesive, binding and coating materials[5]. Another polymer which is celluloseacetate butyrate (CAB) is a pH sensitive polymer used as enteric coating polymer.

Incorporation of drugs in inert polymer films affords a possible method of awieving controlled release. Such product can be adopted to topical, oral, transdermal and other routes of administration. These polymer films can be utilized in the form of coating[6-8]. Drug release rate from polymeric films must be studied. This may be altered by variations of the dimensional parameters of the film, the polymer matrix material and the drug concentration in the film. Thus, in order to have a fundamental approach to compare results for different drugs and different polymers it is necessary to study the polymer as isolated film even if the final device is not a polymeric film.

Isoniazid is the ministry of regimen used for the treatment of tuberculosis and to reduce the risk of failure due to initial drug resistance during therapy. It is always administered with one or more other antituberculous agents[9] e.g. rifampicin. Various studies[10,11] in determining isoniazid acetylator phenotype have classified the subjects as slow or fast inactivators according to the rate at which they convert the drug into metabolites. In order to compensate for the rapid acetylation, isoniazid has been formulated in sustained release tablets[12-14].

In the present study, the possible use of EVA, PVA and CAB as polymeric films to control the release rate of isoniazid was examined. The study was extended to incorporate RF in these polymeric films as a trial for its preformulation for topical use. DMF was included in different concentrations in EVA and CAB films to improve drug release. EC was included in different concentrations to study its influence as a film component on the drug release. The mechanical properties of medicated

and nonmedicated films were studied. The release rate and permeation parameters for both drugs were calculated. IR spectral studies were used as a tool to detect the possible interaction that may occur between the polymer and drug *per se*. The studies were extended to evaluate the microbiological efficiency of rifampicin after its inclusion in polymeric films under investigation.

EXPERIMENTAL

Materials

- Isoniazid (Isonicotinic acid hydrazide, Elli Lilly Co., U.S.A.); Rifampicin (Ciba Geigy Co., Egypt); Ethylenevinyl acetate copolymers (Merck sharp, Germany); Polyvinyl acetate (Searle Co., England), Cellulose acetate butyrate (Scientific polymer product, Inc. Ontario, Canada); Ethylcellulose (BDH chemicals, Ltd. Poole England). All other chemicals were of reagent grade and used as received. Phosphate buffer of PH 6.8 was used[15].

Methods

Film preparation

Solutions of 2.5% (w/v) CAB or PVA polymers in acetone were prepared. Solutions of EVA polymer 2.5% (w/v) in methylene chloride was also prepared. Ten ml of the prepared solutions were poured into circular teflon mould (7.3 cm in diameter and 3mm in depth). The mould was covered with an inverted funnel to control solvent evaporation. Solvent was permitted to evaporate for 24 h. at room temperature. The dried films were then transferred to a desiccator containing silica gel for further 24 hours before test. Medicated films were prepared by adding certain amount of alcoholic solution of the drug (INH or RF) to the specified amount of polymer solution with stirring. The medicated films were obtained as above. Film thickness was determined at ten random points on the film by means of a micrometer and the mean thickness was calculated[16].

Mechanical properties of films

The Load deformation behavior of EVA, PVA and CAB free films was determined by clamping a film strip (2x4 cm) between two jaws of tensile-testing or dynamometer machine. Weights were added gradually to the movable lower jaw and the corresponding elongation in the film was recorded until the break point of the film. The load-deformation curves were plotted. Modulus of elasticity, percent elongation and the tensile strength were calculated[17].

Permeation rate determination

Drug permeation rate through free films (exposed film area 12.57 cm^2 and thickness 19.8 μm) was determined. Films of EVA and CAB were used for the study. Thirty percent (w/v) alcoholic solution of RF or INH were introduced in the donor compartments and phosphate buffer solution of pH 6.8 in the acceptor compartment. Permeation experiment was conducted by suspending the diffusion cells into a thermostated water bath with shaker at temperature 37$\pm$ 0.5°C and a rate of 50 rpm. No measurable permeation rate was obtained for films of PVA which had tear irrisistance from the aqueous contact with the buffer solution at 37°C. The amount of drug transferred into the acceptor compartment was determined at time intervals for two hours. Using the spectrophotometry at a wavelength of 262 nm. and 475 nm for INH and RF, respectively. Each experiment was carried out in 4 replicates and the results were used to calculate the mean permeation rate. Drugs permeation rates; mg h^{-1}; were calculated from the slopes of linear portions of plotting cumulative amounts of drug transferred from the donor to acceptor compartment as a function of time.

Drug release from medicated films

The medicated film was immersed in beaker 250 ml; containing 150 ml phosphate buffer of pH 6.8 as the release medium preheated to 37$\pm$0.5 C. To avoid water evaporation, the beakers were covered during the experiment. This situation generate the surface position of the film in the release medium and the continuous shaking of the medium at rate of 50 rpm during the time of experiment. The exposed area of the membrane was 44.2 cm^2. Aliquots (5ml) were withdrawn at various time and

replaced by equal volume of fresh buffer. The amounts of drug released was determined spectrophotometrically as mentioned above.

IR spectral studies

IR spectra of rifampicin; its physical mixture with either CAB or PVA and the mixture prepared by kneading method were examined as KBr discs using Pye Unicam Sp 1025 infrared spectrophotometer.

Determination of susceptibility of micro-organisms

Staphylococcus aureus; E.coli; Klepsiella pneumonae; Proteus vulgaris, Pseudomonas aerogunosa and *Candida albicans*, all these organisms were tested against the antibiotic discs obtained from the polymeric membranes by using special sterile cutter. The sensitivity was done by preparation of the inoculum by an over night broth culture prepared from the reference strains of microorganisms and inoculated on Muller Hinton agar Plates. The excess broth was removed and the plates were allowed to dry for 10 minutes. The discs were placed on the inoculum. Inoculated plates were then incubated immediately at 37 C for 24 hours. The zone diameters were recorded and interpreted according to the resistance and sensitivity depending on the diameter of inhibition zone per mm[18].

RESULTS AND DISCUSSION

Evaluation of polymeric films

Polymers are viscoelastic and their mechanical behavior is dependent upon many factors. The tensile test is often a guide to the behavior of a polymer in its finished application. Moreover,it gives an indication of elasticity, strength and toughness. The tensile test has been used to study the effects of solid filler whether it is drug or excipient on the tensile properties of polymeric film coatings for tablets.

Load-deformation relationship for EVA, CAB and PVA films medicated with 2% w/v or non-medicated are shown in Figs. 1-3 and table 1.

Tensile parameters such as the ultimate tensile strength and Young's modulus were calculated[17]. The incorporation of RF or INH in polymeric films affect the modulus of elasticity and tensile strength. The modulus increased with oriented films (non-medicated films) than for unoriented ones (medicated films). These results are in agreement with Kellaway *et al.*[19] who demonstrated the importance of orientation

Table 1: Effect of rifampicin and isoniazid in polymeric films on the mechanical properties.

Type of polymeric film	Type of drug	Conc. of drug	Film thickness (cm)±0.010)	Tensile strength kg/mx10^7	Young's modulus (N/m^{-2})
PVA	--	---	0.070	183	$7.760x10^{-3}$
	INH	2.00%	0.070	230	$2.837x10^{-5}$
	RF.	2.00%	0.070	170	$1.790x10^{-3}$
CAB	--	---	0.057	599	$5.300x10^{-3}$
	INH	2.00%	0.057	166	0.0387
	RF.	2.00%	0.057	127	0.1871
EVA	--	---	0.130	$1.14x10^{-2}$	$2.046x10^{-4}$
	INH	2.00%	0.130	$1.40x10^{-2}$	$1.857x10^{-5}$
	RF.	2.00%	0.130	$2.60x10^{-2}$	$2.900x10^{-6}$

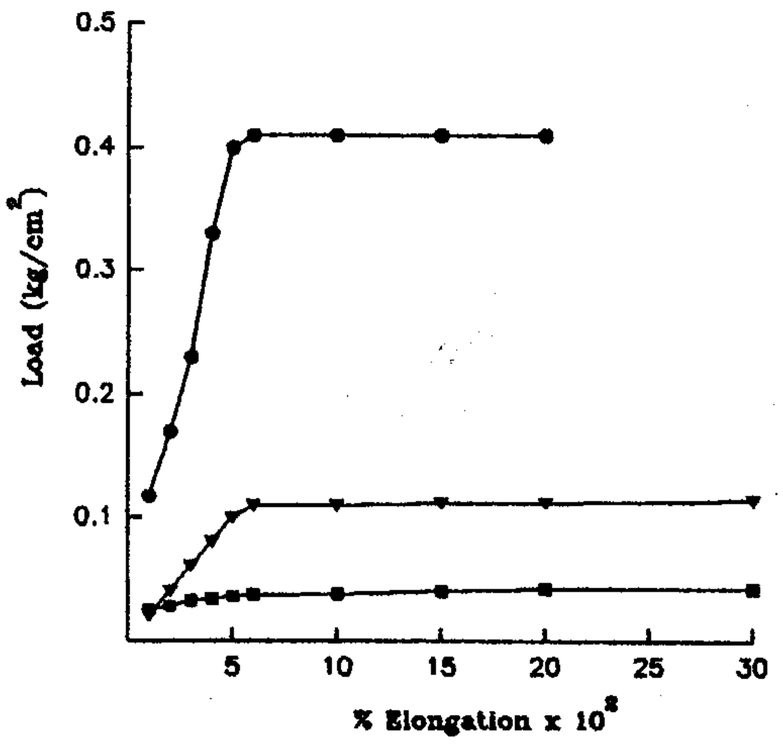

Fig. 1: Load–deformation profile of EVA films (●) plain film; (▼) INH film and (■) rifampicin film.

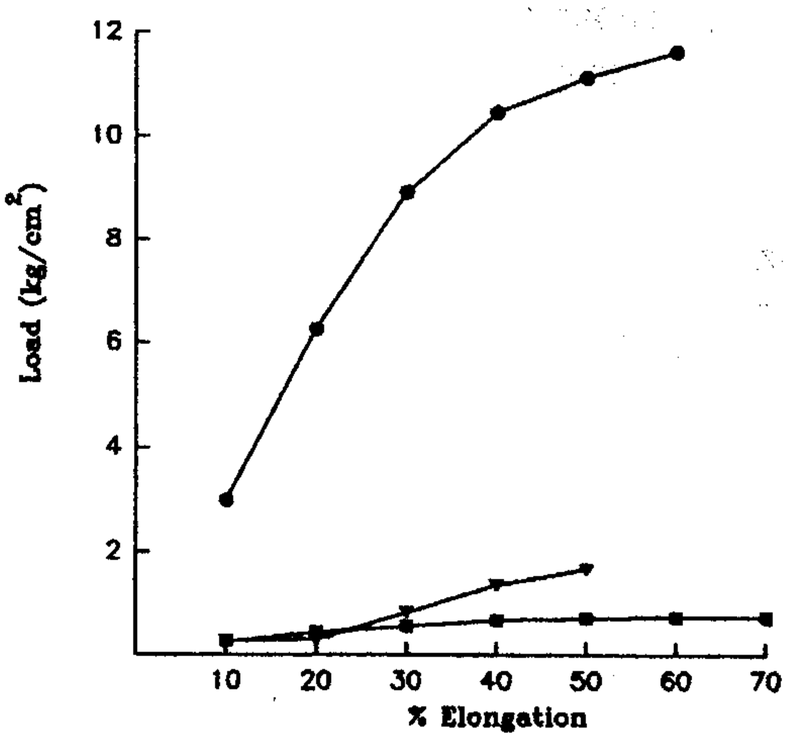

Fig. 2: Load–deformation profile of CAB films (●) plain film; (▼) INH film and (■) rifampicin film.

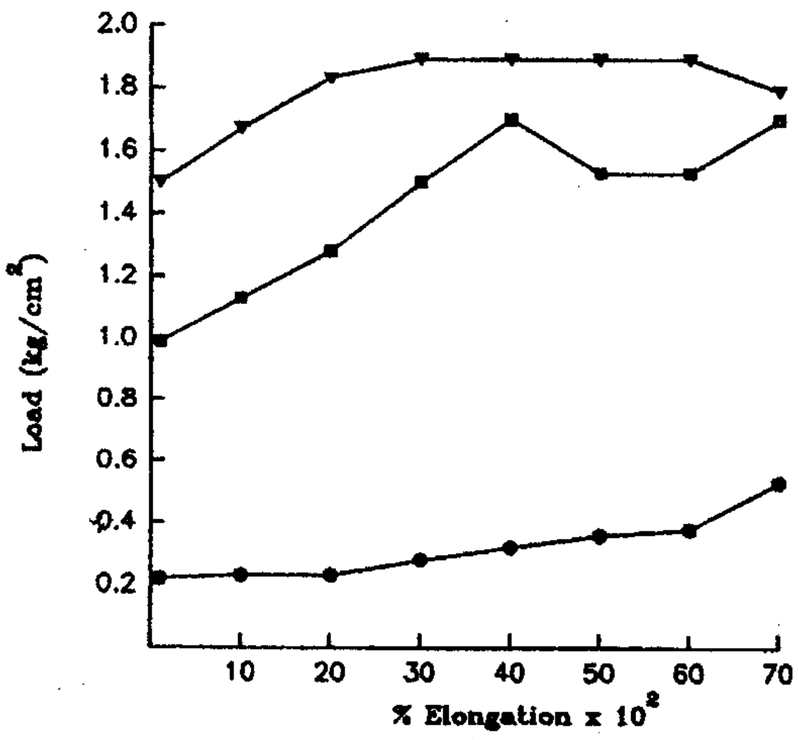

Fig. 3: Load deformation profile of PVA films (●) plain film; (▼) INH film and (■) rifampicin film.

effects on collagen systems. The change in profile of load-deformation of EVA film can be interpreted as follows: The small size of INH molecule compared to that of RF may be responsible to the ordered orientation which may affect the elasticity of EVA films. From table 1, it is clear that stronger films were produced by EVA, CAB and PVA. The profile of load-deformation of non medicated CAB film can be described by hard and brittle while PVA and EVA films are soft and rubbery films. In all cases, the properties tough and soft do not reflect completely the behavior of a film when subjected to shear and compression.

Permeability studies

The results in Figure 4 suggest that INH has the highest permeation profile across the CAB and EVA films than RF. The apparent permeation rate can be estimated from the slope of the amount permeated of the drug per unit surface area against time[20]. The permeability constant can be calculated from the following equation[21].

$$P = \frac{slop \; x \; v}{A \; C^2}$$

Where **p** is the permeability coefficient, which is a measure of the transfer rate of a drug from bulk solution where the membrane acts as a barrier; **x** is the thickness of the film in (cm); C_2 is the concentration of drug in the permeating solution; A is the surface area of the film in cm^2 [21].

Rifampicin is a lipophilic molecule with low permeability across the hydrophilic EVA and CAB films, so its mass transfer process across the film surface plays a significant rate-limiting role.Permeation of RF through CAB is higher than through EVA films. EVA copolymer film has higher polar component arising from the very polar acetate group. This polarity makes it relatively more hydrophilic film than CAB film.

INH is a water soluble drug, so the permeation rate is higher than rifampicin from both polymers (AB and EVA (Figure 4 and table 2). The results indicated that the permeation of INH through EVA films is higher than CAB films.

Table 2: Permeability parameters of rifampicin and isoniazid.

Parameter	Film type	Rifampicin cm^2h^{-1}	INH
Permeability coefficient p(cm^2/h)	EVA	3.288×10^{-4}	3.0336×10^{-3}
	CAB	2.248×10^{-4}	5.6480×10^{-4}
Apparent permeability rate	EVA	0.0411	0.3792
Slope of (Q/t)	CAB	0.0281	0.0706

Table 3: Effect of concentration of isoniazid and rifampicin from EVA, PVA and CAB polymeric films on the release rate.

EVA				PVA			
Drug conc. %w/v	Apparent release-rate	Correlation coefficient	intercept	Drug conc. %w/v	Apparent release-rate	Correlation coefficient	intercept
INH 1%	0.0352	0.9897	0.0156	2%	0.0435	0.9724	0.0262
2%	0.0765	0.9903	0.0337	4%	0.0432	0.9939	0.0174
3%	0.1261	0.9919	0.0467	6%	0.0574	0.9831	0.0302
				CAB			
RF 2%	0.0163	0.9819	0.0029	INH 1%	0.01168	0.9934	0.00399
4%	0.0336	0.9873	0.0144	2%	0.02522	0.9952	0.00930
6%	0.0651	0.9881	0.0274	3%	0.14623	0.9931	0.05228
8%	0.0742	0.9881	0.0308	4%	0.40320	0.9937	0.14242

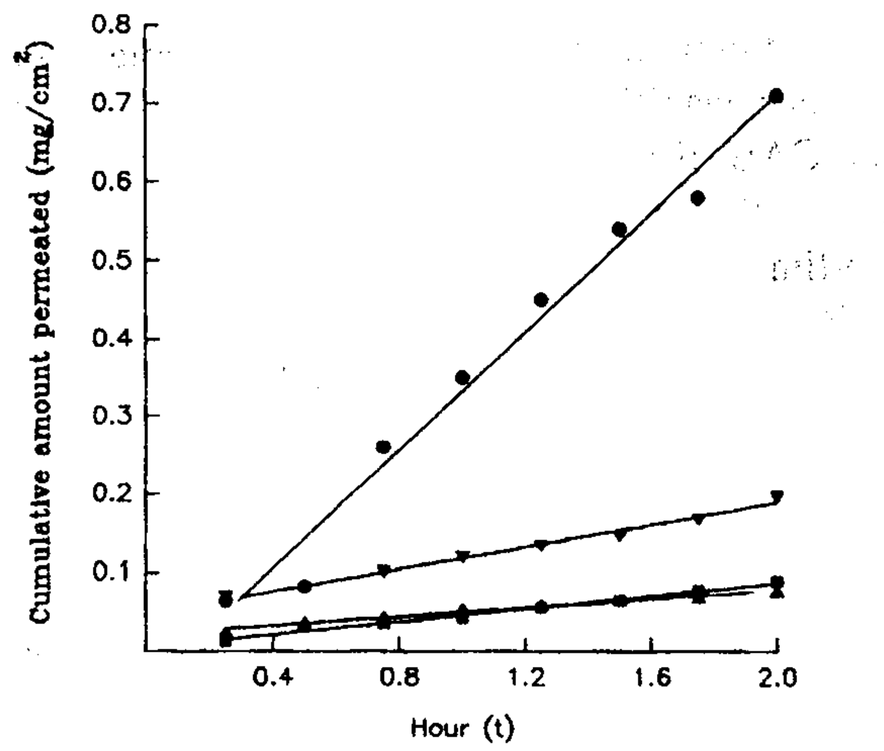

Fig. 4: Permeability profile of INH from (●) EVA film; (▼) CAB film and rifampicin from (■) EVA film; (▲) CAB film.

The rate of permeation depended on the hydrophilicity of the drug and the polymer type.

Release-Rate Studies

Effect of initial drug concentration on the release-rate

Figure 5 (A,B and C) shows the comparative release profiles of INH (A) and RF (B) of different concentrations from EVA and CAB films. The corresponding release-rates are shown in Table 3, figure 5 (A, B and C) that shows plots of the amount of drug released per unit surface area, Q, against the square root of time, t, for each drug. A linear relationship between Q and t existed for both drugs.The correlation coefficient was 0.9987 and 0.9857 in

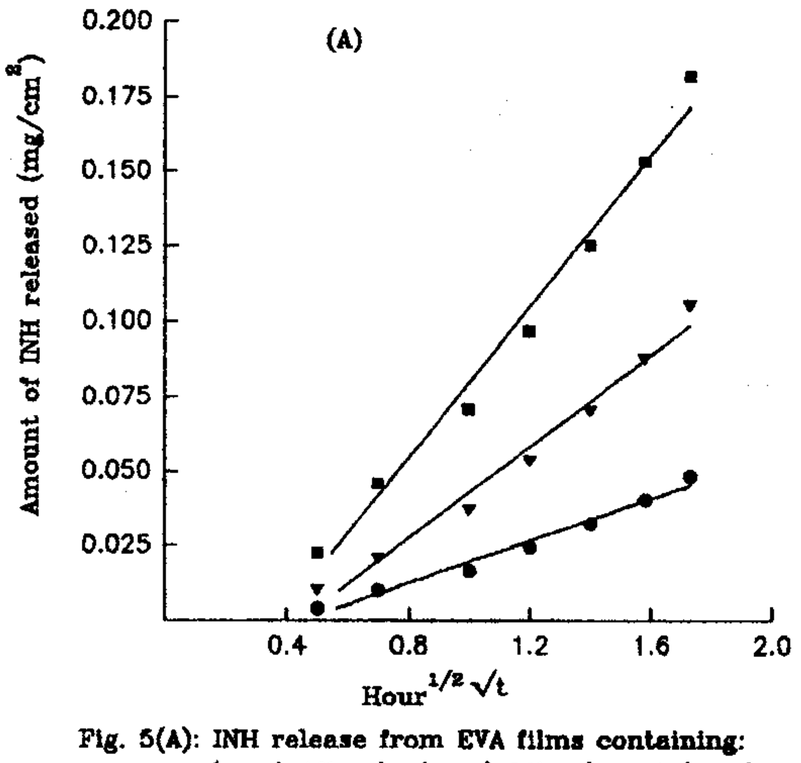

Fig. 5(A): INH release from EVA films containing: (●) 1% w/v; (▼) 2% w/v and (■) 3% w/v INH

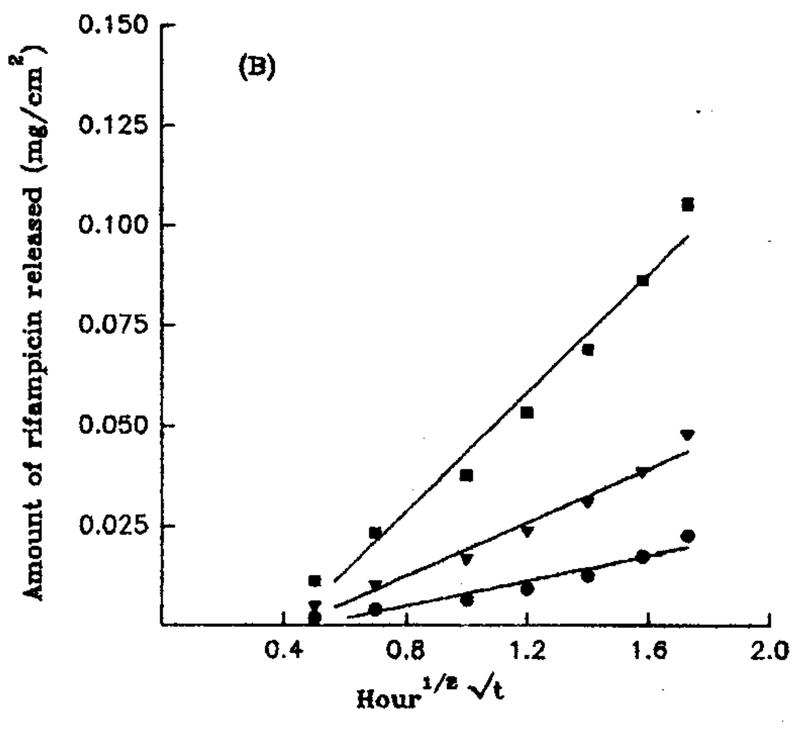

Fig. 5(B): Rifampicin release from EVA films containing: (●) 2% w/v; (▼) 4% w/v; (■) 6% w/v rifampicin.

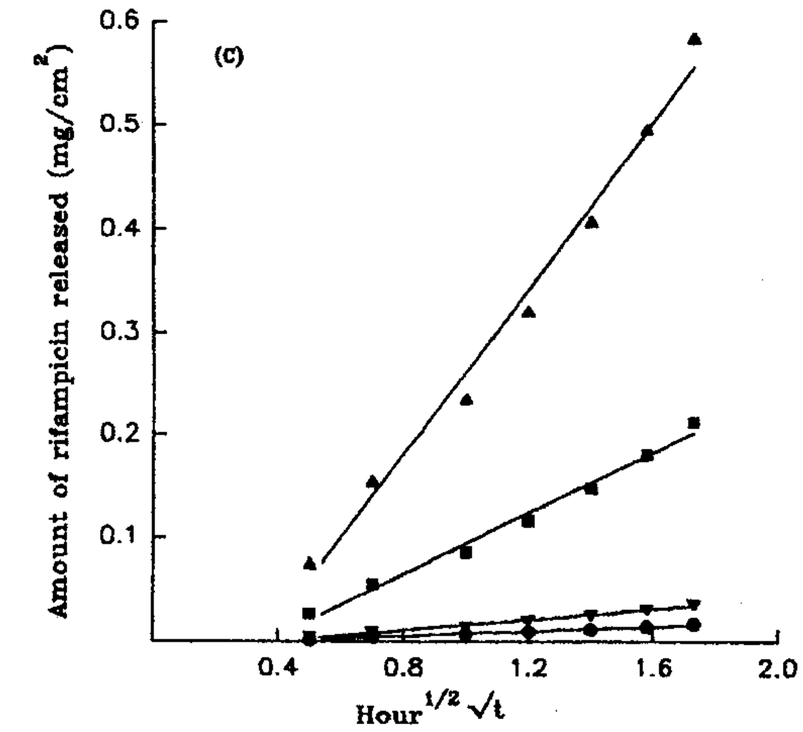

Fig. 5(C): Rifampicin release from CAB films containing: (●) 2% w/v; (▼) 4% w/v; (■) 6% w/v and (▲) 8% w/v rifampicin.

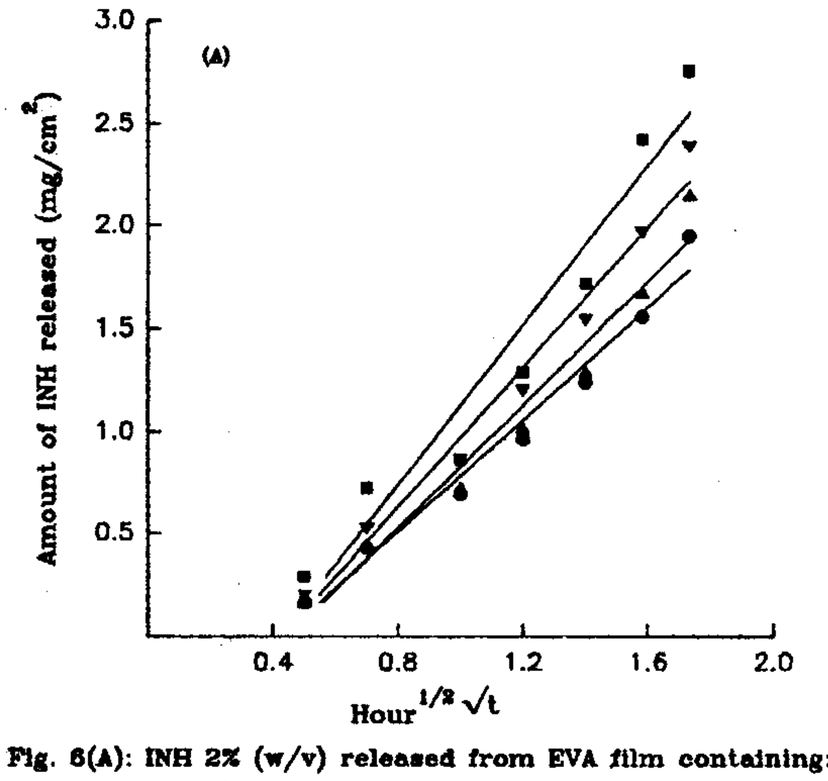

Fig. 6(A): INH 2% (w/v) released from EVA film containing: (●) 0.10% w/v; (▼) 0.15% w/v; (■) 0.20% w/v and (▲) 0.30% w/v EC.

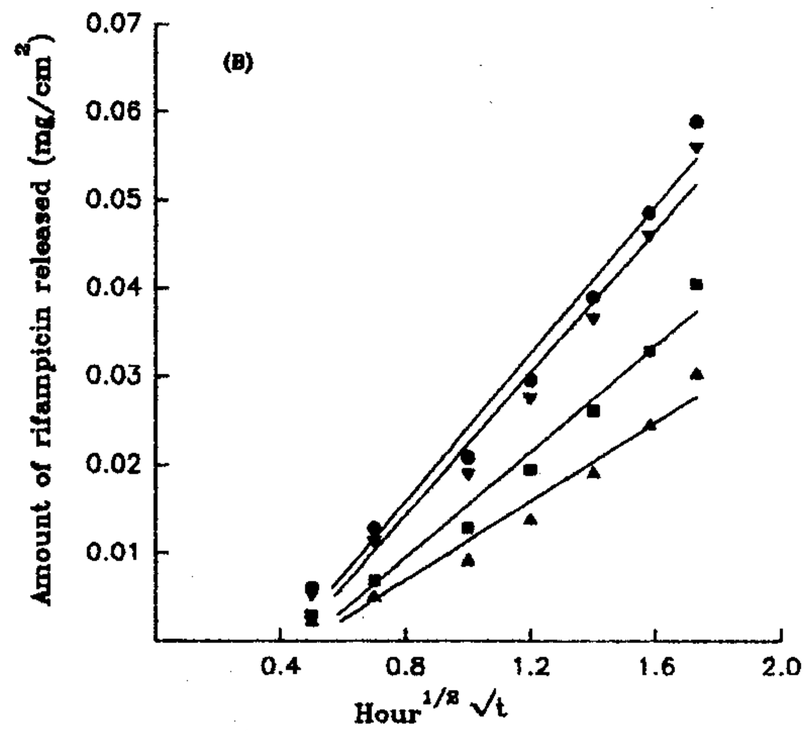

Fig. 6(B): Rifampicin 2% (w/v) released from EVA film : containing: (●) 0.10% w/v; (▼) 0.15% w/v; (■) 0.20% w/v and (▲) 0.30% w/v EC.

case of EVA containing INH and RF respectively, and was 0.9217 in case of CAB containing RF. These results indicate that, the release of the two drugs from EVA could be described by the diffusional model and hence, the rate-controlling stage in the release process is diffusion of the dissolved drug through the matrix[22]. Figure 5 and table 3 show that, as the concentration of drug is increased, the release rate is increased. The increase in the release of RF may be due to the numbers and dimensions of the aqueous channels and pores through which solutes diffuse[23]. The effect of polymer type on the release-rate of drugs was also studied (Figure 6 (A and B) and Table 3). Two

Table 4: Effect of ethylcellulose as film component on drug release from EVA and PVA polymeric films.

	EVA				PVA		
Drug conc.	EC conc. conc. %	Release rate	Corr. coeff.	Intercept	Release rate	Corr. coeff.	Intercept
INH 2.00%	0.00	0.0439	0.9563	0.0599	0.04346	0.9724	0.02620
2.00%	0.10	1.3732	0.9875	0.5917	0.04781	0.9921	0.01990
2.00%	0.15	1.5409	0.9668	0.6666	0.05127	0.9942	0.19460
2.00%	0.20	1.8911	0.9734	0.7796	0.07156	0.9948	0.02680
2.00%	0.30	1.5090	0.9818	0.6826	0.06700	0.9947	0.02470
Rifampicin	0.00	0.01625	0.9819	0.0029	No Release		
2.00%	0.10	0.04179	0.9885	0.0176	0.00109	0.9719	0.00041
2.00%	0.15	0.04025	0.9873	0.0178	0.00207	0.9650	0.00090
2.00%	0.20	0.02991	0.9872	0.0144	0.00225	0.9819	0.00110
2.00%	0.30	0.02234	0.9830	0.0109	0.00362	0.9900	0.00166

Table 5: Effect of different concentration of dimethylformamide on the release rate of 2% w/v rifampicin from polymeric films.

	EVA			CAB		
DMF conc. %w/v	Release rate	Corr. coeff.	Intercept	Release rate	Corr. coeff.	Intercept
0.00	0.01625	0.9819	0.0029	0.01168	0.9934	0.00399
2.00	0.02765	0.9847	0.0133	0.01202	0.9351	0.00691
4.00	0.02822	0.9911	0.0109	0.01048	0.9138	0.00653
6.00	0.03894	0.9942	0.0139	0.01478	0.9593	0.00792
8.00	0.04427	0.9944	0.0159	0.02600	0.9699	0.01244

polymers were included in this study; EVA and PVA to test their effect on the release of INH. The rate of release of INH (2% w/v) from EVA films is higher than from PVA films. However, on using RF with PVA, there was no detected release at the same concentration.

Effect of EC as a film component on the drug release-rate

The success was achieved by incorporating EC in different concentrations up to 0.30% w/v into EVA and PVA films for the controlled-release of RF and INH. Factors determining the rate of drug release are important in the design and formulation of controlled-release preparations. The effect of incorporating EC in the composition of EVA and PVA films on the release of drugs was shown in Figures 6 (A&B), 7 (A&B) and table 4. The release rate was increased on incorporating different concentrations of EC in EVA and PVA films up to 0.20% and 0.15% for INH and RF respectively. On the other hand, the release rates of RF on using EVA and PVA films were increased. Generally, the release-rate of RF from both polymeric films is lower than that of INH.

There is a linear relationship between the amount of the drug released per unit surface area and square root of time (Figures 6 (A&B) and 7

(A&B). Different values of correlation coefficient were obtained of the range 0.9563, 0.9948 for both drugs with EVA and PVA polymers (Table 4). The observations indicate that the release of both drugs obtained from both polymeric films was a formulation factor dependency.

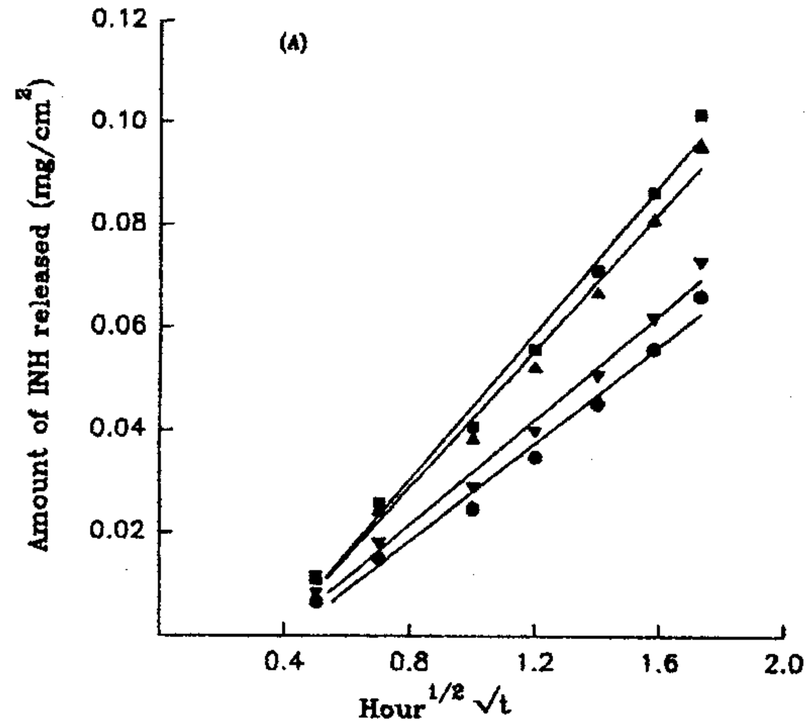

Fig. 7(A): INH 2% (w/v) released from PVA films containing: (●) 0.10% w/v; (▼) 0.15% w/v; (▲) 0.20% w/v and (■) 0.30% w/v EC.

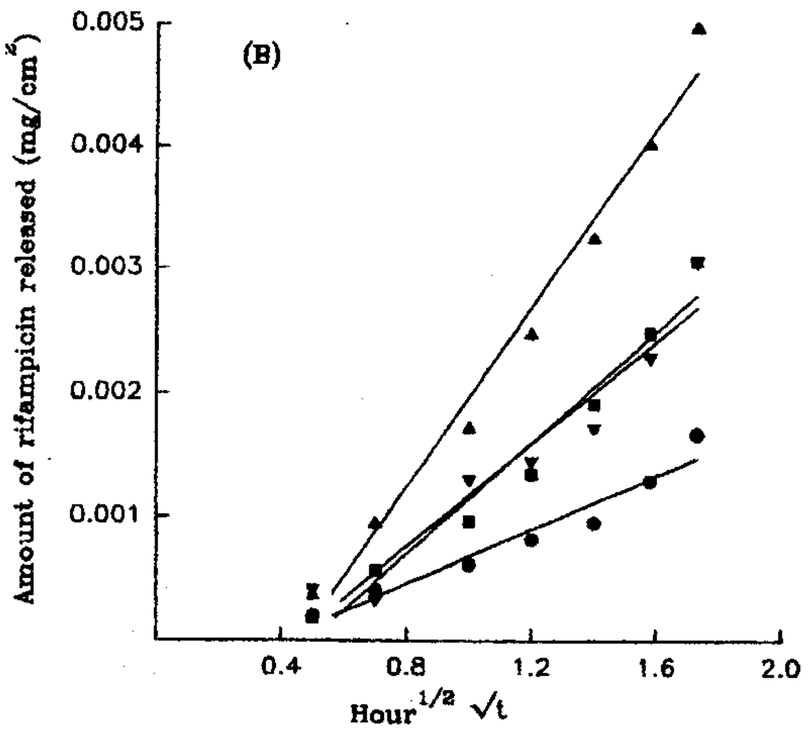

Fig. 7(B): Rifampicin 2% (w/v) released from PVA films containing: (●) 0.10% w/v; (▼) 0.15% w/v; (▲) 0.20% w/v and (■) 0.30% w/v EC.

Effect of DMF on the release-rate of drugs from polymeric films (EVA and CAB)

The solubility of RF was found to be greatly enhanced in presence of 20% w/v DMF up to 25 mg/ml at 20 C. It is obvious that, the release rate of RF was increased from each of EVA and CAB films (Figs. 8 (A&B), 9 and Table 5). There is a direct correlation between DMF concentration (up to 8% w/v) and the drug release-rate. The increase in the release rate among the two types of polymeric films can be attributed to the hydrophilicity and drug solubility in DMF. Rifampicin solubilized by DMF (used as solubility modifier may be capable of increasing porosity of the film) which enhances drug release. It is worthy to note that, the increase in release-rate was observed with EVA films rather than CAB films. Generally, the level of the DMF was more important to affect the release of RF from polymeric films.

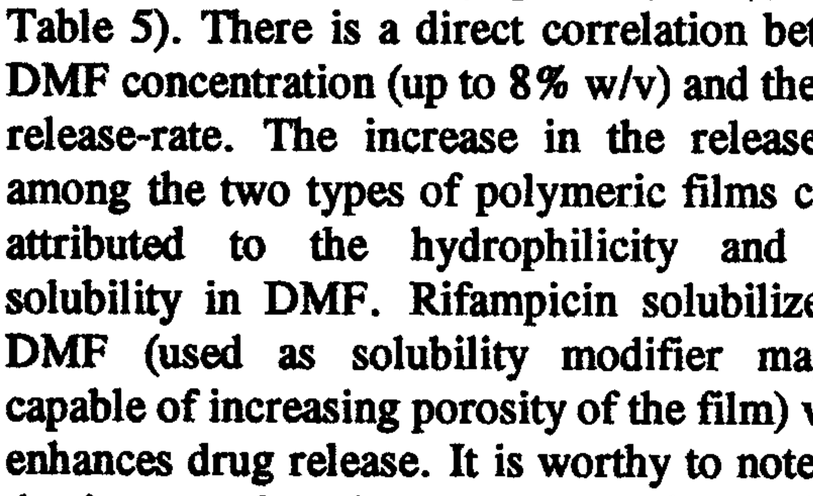

Fig. 8(A): Release of 2% (w/v) rifampicin from EVA films containing (●) 2% w/v; (▼) 4% w/v; (■) 6% w/v and (▲) 8% w/v DMF.

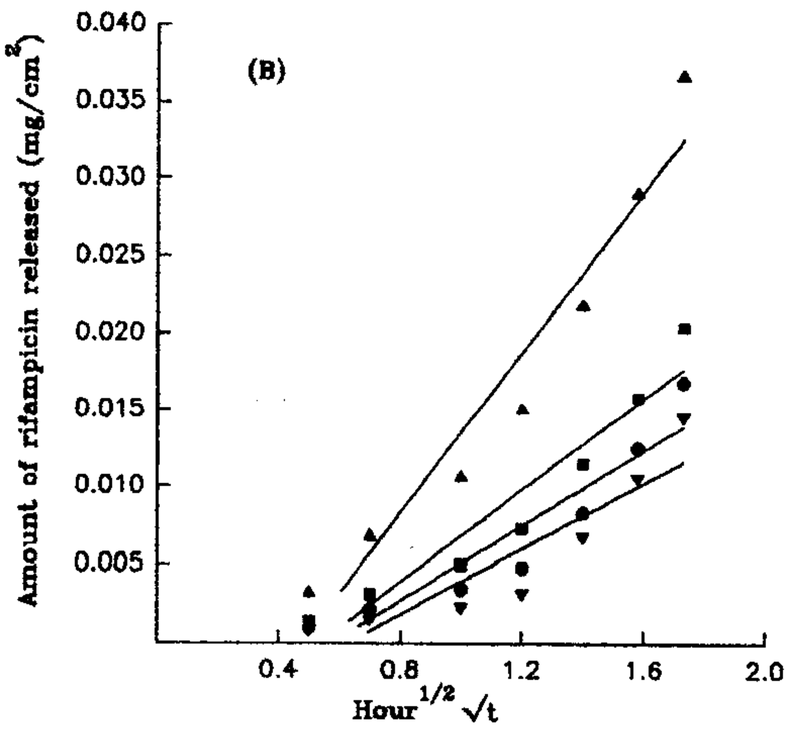

Fig. 8 (B) Release of 2% (w/v) rifampicin from CAB films containing: (●) 2% w/v; (▼) 4% w/v; ■) 6% w/v and (▲) 8% w/v DMF.

Table 6: IR spectra of rifampicin and its physical mixture as well as kneading sample with each of CAB and PVA.

Wave number cm^{-1}					
Sample	C-O-C Acetyl	C=C Vibration	C-O-C Acetyl	Amide	
Rf	1250	1538-1583	1097,1062	1649	1728
RF with CAB physical mix.	1249	1539-1586	1099,1063	1648	1716,1792
kneading mix.	1230-1253	1557 broad	1098,1060	1636	1731-1753
Rf with PVA physical mix.	1248	1539-1561	1096,1062	1635	1711-1734
kneading mix.	1250	1537-1583	1096,1058	1642	1734

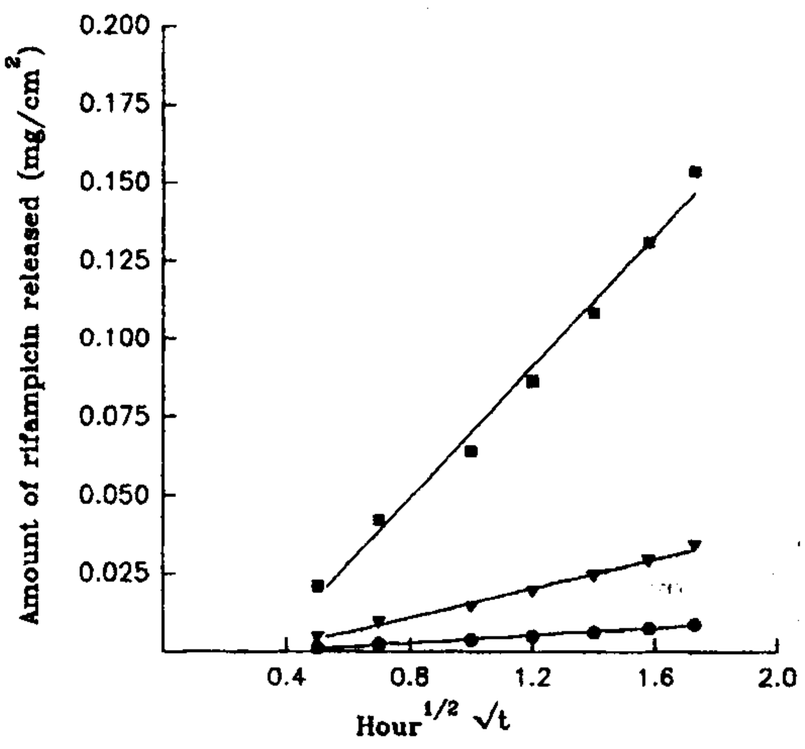

Fig. 9: Release of rifampicin from CAB films with 4% (w/v) DMF containing: (•) 2% w/v; (▾) 4% w/v and (▪) 8% w/v rifampicin.

Infrared spectrophotometric studies

IR spectra of RF, RF carrier (PVA or CAB) mixture and RF carrier (PVA or CAB) prepared by kneading method were illustrated in figure 10 and table 6. The principal peaks of RF appear at 1250 (C-O-C acetyl), 1567 (C=C vibrational), 1098, 1054 (C-O-C acetyl); 1650 (Amide II) and 976 cm^{-1} [24]. These peaks underwent changes when RF is physically mixed or kneaded with PVA or CAB. For example the peaks of RF that appeared at 1649 cm^{-1} shifted to lower frequency when RF is physically mixed or kneaded with PVA or CAB. On the other hand, the peak at 1378 cm^{-1} in RF spectrum is shifted to higher frequency in PVA samples. The peak at 1250 cm^{-1} in RF spectrum became broad when it is physically mixed or kneaded with CAB. All these changes indicated that, there may be a sort of interaction between the drug and the carrier under investigation. These interactions may involve amide or acetyl groups of the drug. The slow release of RF from these polymer films may be due to this interaction.

Microbiology Studies

A comparative study of the antibacterial efficiency of RF released from different polymeric films; EVA, PVA and CAB has been performed by measuring the mean inhibition zone diameter in each type. Table 7 illustrates the effect of RF released from different polymeric films on different strains of bacteria compared to RF alone.

It is clearly observed that RF incorporated in EVA film gives the highest inhibition zone than with other films. The effect of RF in

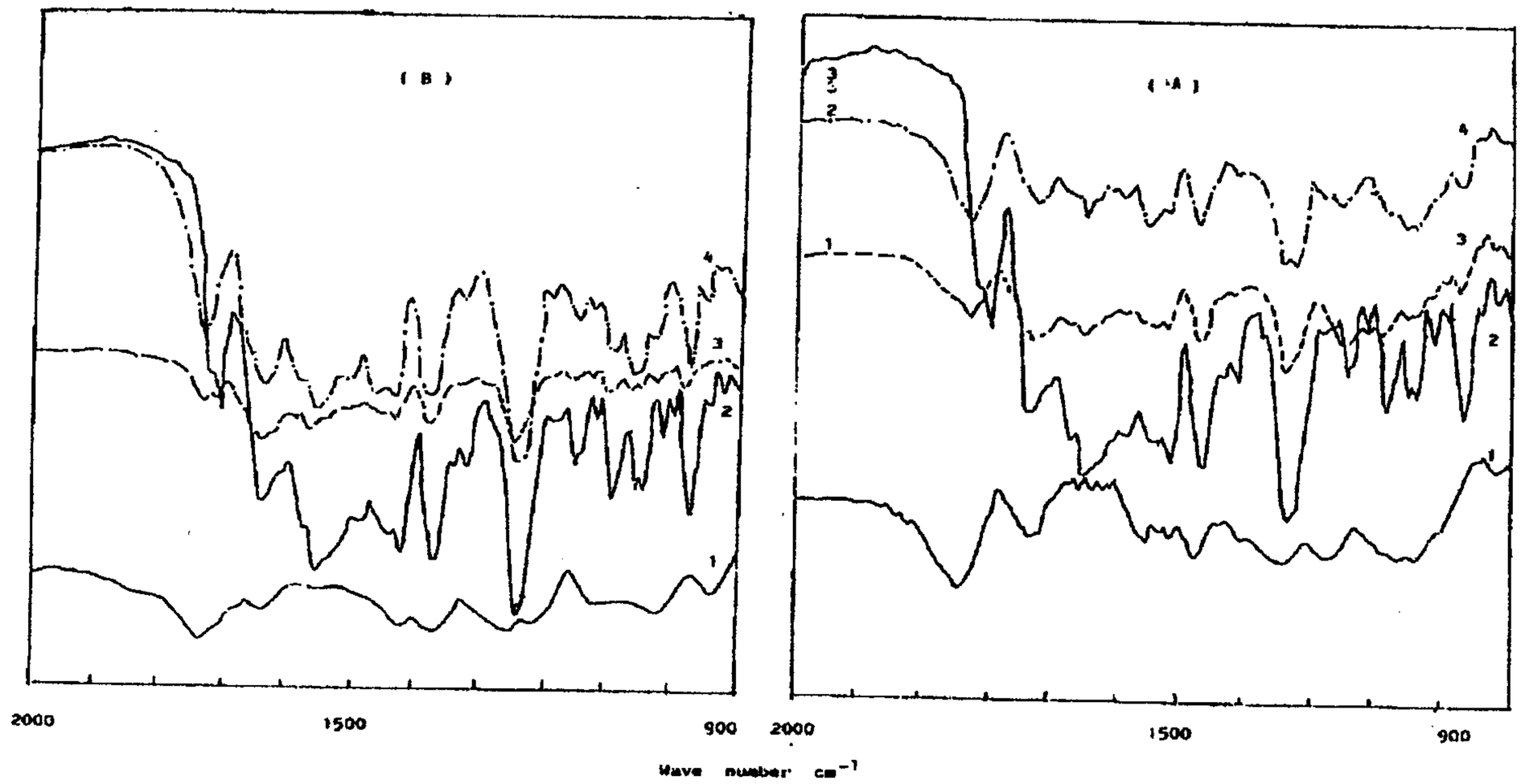

Fig. 10.: IR spectra of rifampicin (2) and its physical mixture (3) as well as kneeding sample (4) with each of CAB (1) Fig. (A) and PVA (1) Fig. (B).

Table 7: Antibacterial effect of rifampicin from polymeric films.

Bacteria strain type	Inhibition zone diameter (mm) using							
	Drug alone	ethyl-alcohol	CAB	CAB alone	PVA	PVA alone	EVA	EVA alone
Escherichia coli	7 +	--	--	--	--	--	--	--
Klebsiella pneumonae	7 +	--	--	--	--	--	--	--
Proteus vulgaris	7 +	--	--	--	--	--	--	--
Pseudomonas aerogunosa	19+	--	11+	--	7 +	--	13+	--
Staphylococcus aureus	19+	--	7 +	--	11+	--	13+	--
Candida albicans	19+	--	7 +	--	7 +	--	13+	--

(--) Resist type. (+) Sensitive type. Rifampicin conc. 30mg/Disk.

different films can be ranked in decreasing order as: EVA>PVA>CAB against *Staphylococcus aureus* and EVA>CAB> PVA against *Pseudomonas aerogunosa*. EVA/RF gave the highest inhibition zone than PVA and CAB. On using *E.coli*; *klebsiella pneumonae*; *Proteus vulgaris* there is no inhibition zone with the three types of medicated films compared to drug alone. The plain films have no effect on various strains listed in table 7. The results indicate that, it is possible to formulate RF in polymeric films for topical applications. So the study must be extended to formulate and evaluate such preparations. The stability of RF in these preparations must not be ignored.

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