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IN VITRO RELEASE OF NEOMYCIN SULFATE FROM POLYMERIC FILMS

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ABSTRACT

A study was made of the release of neomycin sulfate from films containing ethyl cellulose or a polyamide. These films were plasticized using hexadecyl alcohol and/or tributyl citrate. Neomycin

sulfate was incorporated into the film, and the release of neomycin in a desorbing media of distilled water was measured by periodically removing a sample of desorbing media and determining the neomycin sulfate content spectrophotometrically. The release of neomycin sulfate from these films was also determined microbiologically. This was carried out by measuring the zone of inhibition surrounding a circular disc containing neomycin sulfate which had been placed onto the surface of a Petri dish containing suitable media inoculated with Bacillus subtilis. Hexadecyl alcohol was noted to suppress or decrease the release of neomycin sulfate from ethyl cellulose and polyamide films. Release of neomycin sulfate from films of ethyl cellulose plasticized with tributyl citrate showed an increase. The results of the microbiological determination were similar to the spectrophotometric results and indicated that the release of neomycin sulfate from ethyl cellulose/tributyl citrate systems was time dependent.

INTRODUCTION

The use of chemical adhesives in the management of wounds has been demonstrated by several workers[1-3] and included inert flexible surgical dressings containing an acrylic resin and tetramethyl thiuramidi-

sulfide[4]. This was noted to be impervious to bacteria and was capable of adhering to the wound edge without maceration of the tissues. Others reported the use of similar preparations as ideal dressings for abdominal and other wounds[5-8]. Plasticized cellulosic compounds have been utilized as sterile plastic dressings[9] alone or combined with polymixin, neomycin and bacitracin in aerosol form[10]. This aerosol was sprayed onto wounds and used to prepare various body surfaces prior to surgery. The results showed a reduction of major sepsis from 7.2% to 0.4% and in minor sepsis from 1.2% to 0.8%. It was found that gentle scrubbing and irrigation of wounds with neomycin solution was significantly more effective in preventing an infection than was the use of saline or hexachlorophene solutions.[11] The use of topical antibiotics in the prevention of experimental wound infection has also been reported.[12]

Ethyl cellulose and sodium carboxymethylcellulose solutions containing several antibiotics were employed as bactericidal filmforming liquids and used in the treatment of cuts, bruises and wounds.[13] Beaseley, et al[14] have reported the effect of various combinations of antibiotics and isobutyl cyanoacrylate on the healing of soft tissue wounds.

A specially designed apparatus and method for the *in vitro* determination of the rate of release of cetylpyridinum chloride and benzalkonium chloride from various films was reported.[15] A kinetic model based on the Noyes-Whitney relationship was used and the rate of drug release in aqueous media from various films was determined. Since the chemical adhesives are retained in the area of application for a number of days it was felt that the incorporation of selected antibiotics into the adhesive material would enhance the healing process. The present investigation was undertaken to develop a polymer-antibiotic system which could be dispensed as a spray-on-bandage. This system was then evaluated to determine the *in vitro* release of neomycin from the polymeric film and the resulting biological activity.

EXPERIMENTAL

Film-forming agents such as ethyl cellulose[a] and a polyamide resin[b] along with suitable plasticizers such as dexadecyl alcohol and tributyl citrate[c] were selected for use in this study on the basis of the results obtained in previous studies.[15] Neomycin sulfate, U.S.P. (micronized) was selected as the model antibiotic.

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a - Ethyl cellulose N-10, Hercules Powder Co., Wilmington, Delaware
b - Polyamide 1155, Lawler Chemicals, Inc., Chicago, Ill.
c - Citroflex 4, Chas. Pfizer & Co. Inc.,New York,N.Y.

Preparation and Treatment of the Model drug-films:

The films were cast from solutions containing 5% by weight of ethyl cellulose and varying amounts of plasticizers in a solvent of absolute alcohol. Polyamide films were cast using isopropanol as the solvent. A specified amount of neomycin sulfate was added to the polymer-plasticizer-solvent system. The concentration of drug in the film was varied from 150 mg to 200 mg per 5 g of solid resin content in order to produce a good quality film free of any fissures or cracks. The films were cast onto a mercury substrate as previously reported.[15] The neomycin containing films were stored in a desicator overnight. Table 1 indicates the polymer-plasticizer combinations used in this study.

TABLE 1

Polymer-Plasticizer Combinations

Polymer	Plasticizer	Plasticizer % W/W **
Ethyl Cellulose	Tributyl citrate	20
Ethyl Cellulose	Hexadecyl alcohol	20
Ethyl Cellulose	Tributyl citrate Hexadecyl alcohol	10 10
Polyamide Resin*	Tributyl citrate	20
Polyamide Resin*	Hexadecyl alcohol	20
Polyamide Resin*	Tributyl citrate/ Hexadecyl alcohol	10/10

*Polyamide 1155 **Based upon weight of polymer

Analytical Procedure: The concentration of neomycin sulfate in the film was determined by the method of Hoodless.[16] This method, as modified for our study, was based on the reaction of ribose with phloroglucinol in a mixture of concentrated hydrochloric acid and glacial acetic acid. The absorbance of the resulting solution was determined at 552 nm. A calibration curve was prepared by plotting absorbance versus the known concentration of neomycin sulfate. The concencentration of neomycin sulfate followed the Beer-Lambert relationship. Appropriate blanks were prepared and the absorbance determined on a double beam Coleman-Hitachi spectrophotometer, model 124. This method was found to be sensitive and yielded reproducible results in a concentration range from 100 g/ml to 400 g/ml.

Determination of Initial Concentration of Neomycin Sulfate in the Model Film: The initial concentration of neomycin sulfate in the ethyl cellulose film was determined colorimetrically using the above procedure. A circular film 4.5 cm in diameter, and containing neomycin sulfate was prepared and dissolved in n-butanol. A sample of the model film without neomycin sulfate was used as a blank. After appropriate dilutions, the absorbance of the sample against a reference was measured and the concentration of neomycin sulfate was determined from the Beer-Lambert plot. The results represent the average of three determinations on each sample.

In Vitro Release Rate of Neomycin Sulfate from the Film: The method used was similar to the one previously reported.[15] The ethyl cellulose film containing neomycin was mounted on a flat glass surface. The assembly was immersed into 300 ml of distilled water which was used as the desorbing medium and stirred at a temperature of 37° C. ± 0.5°. Figure 1 illustrates the apparatus used to determine the drug release. Aliquot samples of the dissolution medium were withdrawn at various time intervals and analyzed colorimetrically for concentration of neomycin sulfate. The aliquot of desorbing medium used to determine the drug concentration was returned to the container in order to maintain a constant volume. Two determinations were made on each sample and the results are shown in Figure 2.

Microbiological Method for the Release of Neomycin Sulfate from the Film: The potency of a sample of neomycin sulfate in the film was determined by comparing the zone of inhibition of growth of Bacillus subtilis with the zone produced by the control model film without any neomycin sulfate.

Sterilized Petri dishes were filled with a Trypticase Soy Broth Medium* and allowed to solidify. The surface of the solidified medium was innoculated with Bacillus subtilis. A circular disc, 10 mm in diameter,

*BBL, Division of BioQuest, Cookeysville, Maryland

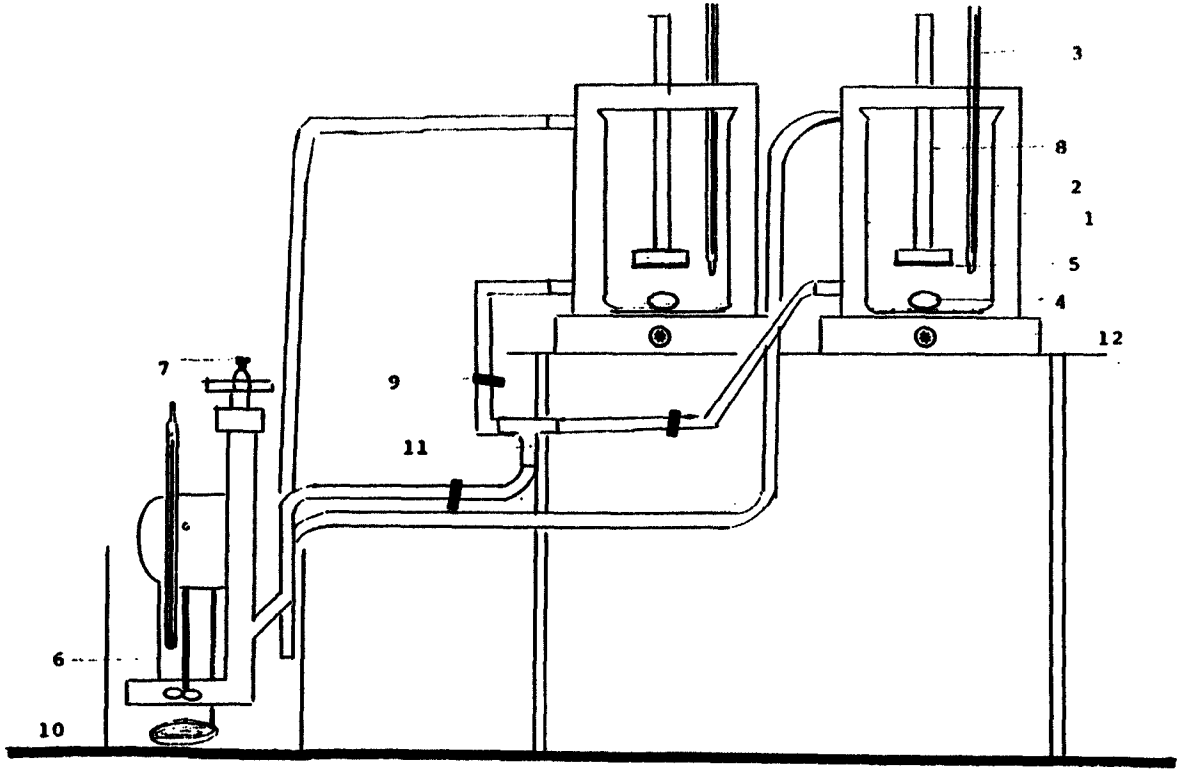

FIGURE 1
Schematic diagram for in vitro drug release determination, Key: 1, plastic jar; 2, 400 ml, beaker; 3, thermometer; 4, magnetic stirrer; 5, model drug film; 6, water circulating pump; 7, temperature variable; 8, plastic rod with a glass stopper; 9, pinch cock; 10, heating element; 11, glass T tube; 12, magnetic stirrer control.

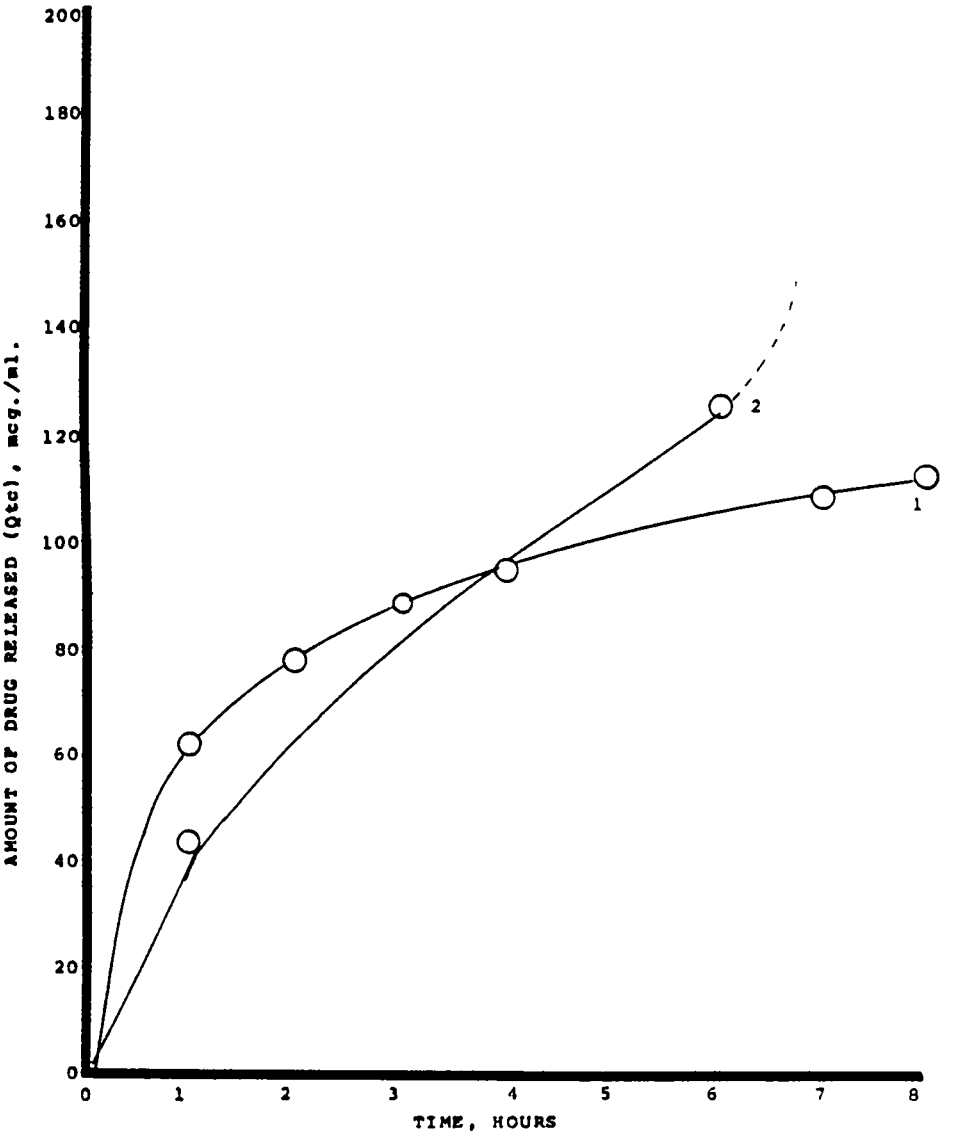

FIGURE 2
Release of neomycin sulfate from ethyl cellulose films in demineralized water: 1. Ethyl Cellulose and tributyl citrate (20 PHR); 2. Ethyl Cellulose and tributyl citrate/ hexadecyl alcohol (10/10 PRH).

of model film containing neomycin sulfate and disc without any drug was placed onto the surface of the innoculated medium. These Petri dishes were set aside for 2-4 hours and then incubated at 37° for 16-18 hours. The zone of inhibition produced by the disc containing the neomycin was measured and compared to the zone produced by the film alone. An attempt was made to relate the diffusion of neomycin sulfate from the film to time. These results are shown in Table II and Figure 3.

TABLE II

Microbiological Determination of Release of Neomycin Sulfate from Polymeric Films

Neomycin Sulfate mg/5 g Polymer Solid	Polymer	Plasticizer per cent	Zone of Inhibition mm
100	Ethyl cellulose	Tributyl citrate,20	36
200	Ethyl cellulose	Tributyl citrate, 20	41
100	Ethyl cellulose	Hexadecyl alcohol,20	25
200	Ethyl cellulose	Hexadecyl alcohol,20	29
100	Ethyl cellulose	Tributyl citrate, 10 Hexadecyl alcohol,10	24
200	Ethyl cellulose	Tributyl citrate, 10 Hexadecyl alcohol,10	31
100	Polyamide Resin*	Tributyl citrate, 20	26
100	Polyamide Resin*	Hexadecyl alcohol,20	29

*Polyamide 1155

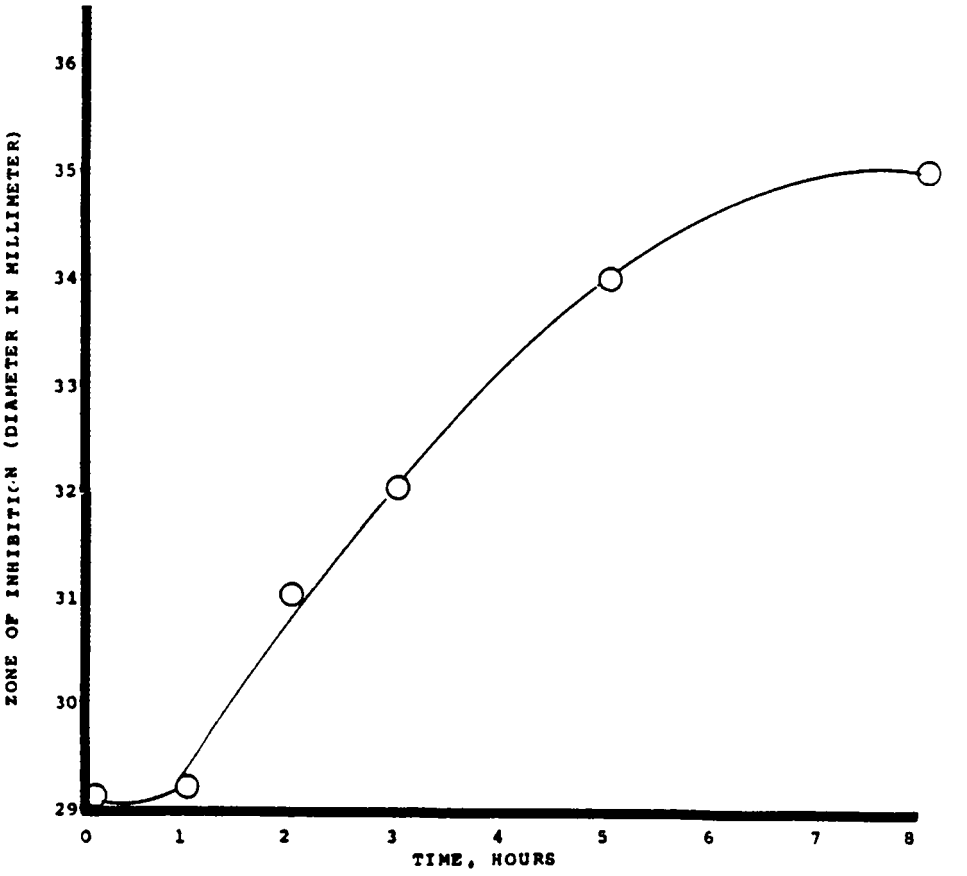

FIGURE 3
Zone of Inhibition produced by Neomycin Sulfate in Ethyl Cellulose - tributyl citrate (20 PHR) Film.

RESULTS

The incorporation of neomycin sulfate into ethyl cellulose and polyamide films showed a drug-polymer system that could be used in the formulation of spray-

on-bandages. The critical concentration of neomycin in the polymeric matrix was noted to be between 100 mg to 200 mg per 5 g of resin solids. Higher concentrations of neomycin produced a non-uniform film containing cracks and fissures.

Various concentrations of the two plasticizers were used to evaluate their effects on the drug profile. It was found that the release of neomycin sulfate was suppressed from the polyamide films plasticized with hexadecyl alcohol. Neomycin was readily released from ethyl cellulose films plasticized with tributyl citrate. Ethyl cellulose films plasticized with hexadecyl alcohol actually showed a decrease in drug release. The drug-polymer films subjected to microbiological testing for the evaluation of biological activity of the film showed a zone of inhibition in all cases. When compared to the lack of a zone of inhibition surrounding the control, one can quickly note the release of the neomycin under these conditions.

A plot of the zone of inhibition as a function of time is seen in Figure 3. This plot covers the ethyl cellulose/tributyl citrate system and clearly indicates that the release of neomycin from this system is time dependent.

CONCLUSIONS

This investigation indicated that neomycin sulfate mixed with ethyl cellulose and polyamide film plasticized with tributyl citrate and hexadecyl alcohol could be formulated as a spray-on-bandage and that the neomycin sulfate could be released from the film. Polyamide films and hexadecyl alcohol were noted to suppress the release of neomycin sulfate from the film while ethyl cellulose plasticized with tributyl citrate seemed to provide a good film for the neomycin. Microbiological evaluation of these drug-polyamide films indicated the biological activity of the system.

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