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# Polymer–Drug Interaction: Stability of Aqueous Gels Containing Neomycin Sulfate

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**Abstract** □ A method for preparing aqueous gels containing neomycin sulfate is described. Gels of synthetic polymers containing polyionic or polar reactive sites were prepared and stabilized by adsorbing the drug molecule onto a cationic-exchange resin prior to incorporation into the bases. The binding capacity of the drug for the polymers was determined, and the activity of the drug–resin was substantiated and compared relative to an inert gel containing the free drug.

**Keyphrases** □ Neomycin sulfate aqueous gels—preparation, polymer–drug interaction, viscosity and drug activity □ Polymer–drug interaction—neomycin sulfate gels

Neomycin, an epimeric drug molecule, has been shown to interact with numerous macromolecules of biological importance (1–6). Inhibitory activity of the antibiotic toward DNA-dependent RNA polymerase of *Escherichia coli* was shown (1), and formation of a DNA–neomycin complex was found to be a linear function of the DNA concentration (2). Gubernieva and Silaev (3), using heparin as a model, concluded that interaction with basic antibiotics was due to complex formation. They also demonstrated the complex-forming ability of polymyxin, neomycin, and albamycin with plasma proteins, albumin, and γ-globulin in man, rabbits, and rats (4).

Steiner *et al.* (5), using the property of antibiotic complexation, studied the effect of antibiotics on serum cholesterol levels when given orally. When injected, neomycin had no cholesterol-lowering effect. However, when taken orally, the serum cholesterol level was lowered; this suggests a local effect in the GI tract. Oral aureomycin and bonamycin had similar but lesser lowering effects; achromycin, bacitracin, chloromycetin, streptomycin, mycostatin, and penicillin failed to cause any significant lowering of serum cholesterol (6).

Polymeric antibiotics such as neomycin, viomycin, and polymyxin were studied for their interaction with condensed phosphates. The binding capacity of neomycin for these higher phosphates was the strongest (7).

**Table I**—Aqueous Gel Systems

| Polymer | Concentration, % | pH | Gel–Resinate Viscosity, cps. |
|---|---|---|---|
| Methylcellulose 400 cps.[a] | 5 | 7.00 | 36,850 |
| Ethylene maleic anhydride | 4 | 2.55 | 27,410 |
| Carboxyvinyl polymer | 1 | 3.58 | 42,120 |
| Ethylene oxide copolymer | 5 | 7.20 | 35,381 |
| Heteropolysaccharide | 2 | 6.78 | 31,560 |
| Sodium carboxymethylcellulose | 5 | 6.80 | 51,840 |

[a] Reference standard.

Many naturally occurring clays or earths of pharmaceutical importance in liquid or semisolid dosage forms are anionic polyelectrolytes in nature and, therefore, strongly bind medicaments cationic in nature. Physicochemical studies of antibiotic–clay complexes were carried out by Pinck *et al.* (8). They studied the chemical and physical properties of 10 antibiotics; their adsorption by montmorillonite, vermiculite, illite, and kaolinite; and the X-ray diffraction patterns of some of the formed complexes. Streptomycin sulfate, dihydrostreptomycin sulfate, and neomycin sulfate formed complexes to varying degrees with the four clays; X-ray diffraction studies of the complexes indicated monolayer adsorption for strongly basic and dilayer adsorption for amphoteric antibiotics. Danti and Guth (9) studied cation-saturated bentonites and showed that neomycin sulfate was inactivated as a result of an ionic incompatibility with this pharmaceutical agent. Nakashima and Miller (10) qualitatively demonstrated ionic incompatibilities of 18 suspending agents of pharmaceutical importance with several therapeutic agents. Neomycin sulfate showed an immediate precipitating or coagulating action with more than 50% of the agents studied.

A review of the literature, therefore, supports the proposal that neomycin has the greater binding capacity of the antibiotics in common use and presents a more

Table II—Viscosity Measurements for Polymer–Drug Interaction[a]

| Polymer | Concentration, mg./ml. | Viscosity, cps. Polymer Solution | Polymer–Resinate | Polymer–Drug |
|---|---|---|---|---|
| Carboxyvinyl polymer | 1.5 | 13.5 | 13.5 | 0.695 |
| Heteropolysaccharide | 0.5 | 3.13 | 3.13 | 0.704 |
| Sodium carboxymethylcellulose | 1.0 | 2.67 | 2.67 | 0.695 |
| Methylcellulose 400 cps. | 1.0 | 1.13 | 1.17 | 1.17 |
| Ethylene oxide copolymer | 0.5 | 0.956 | 0.956 | 0.956 |
| Ethylene maleic anhydride | 1.0 | 0.776 | 0.776 | 0.695 |

[a] Viscosity of water at 37° is 0.6947 cps.

serious problem when considering drug activity and the physical stability of gel vehicles.

Gels prepared with polyionic macromolecules can be used as vehicles for complex-forming drugs. This may be accomplished by adsorbing the drug onto a stronger complexing agent prior to incorporating it into the gel vehicle. The agent of choice might be ion-exchange resins, which have been used effectively as carriers for drugs. Baruffini (11) initially indicated their use. He utilized hydrated resins in ointments to control ionic variations, to absorb noxious skin secretions, and as carriers of medicinal substances. The resinates were studied in water-in-oil and oil-in-water emulsion vehicles. The resin (Amberlite IRC-50) was shown to give the most effective adsorption of neomycin; a prolonged and uniform release of the drug was also found. Fiedler and Sperandio (12) further studied the activity of ion exchangers in hydrophilic bases and suggested their use for controlled drug release in topical ointments (13).

The objectives of this investigation were, therefore, to: (*a*) study the stabilization of neomycin-containing gels prepared from a selected group of synthetic macromolecules, each possessing reactive sites; (*b*) determine the binding capacity of neomycin sulfate with the polymers; and (*c*) determine the relative activity of the resinate in the gel bases as compared to a free neomycin-containing gel base.

## EXPERIMENTAL

**Materials**—The polymers used in this study were: (*a*) the free acid derivative of ethylene maleic anhydride[1]; (*b*) a carboxyvinyl polymer[2]; (*c*) an ethylene oxide copolymer[3]; (*d*) an anionic heteropolysaccharide[4]; and (*e*) sodium carboxymethylcellulose[5], a natural polymer chemically modified by carboxymethylation. Each polymer was of commercial grade and used as received from the suppliers.

The resin employed for adsorbing the antibiotic was a pharmaceutical grade sulfonated polystyrene-type cation-exchange resin[6]. The resin is a micropowder, has a particle-size specification of 95% through a 325-mesh screen, and is a very strong acid having an apparent pKa of 1.3.

Neomycin sulfate, commercial (pharmaceutical) grade, was used[7]. All other chemicals were of reagent grade.

**Drug Assay and Microbial Activity Measurement**—A spectrophotometric method of drug assay, developed by Dutcher *et al.* (14), was used in portions of this study. The method is based on the observation that neomycin, when heated with strong mineral acid, yields furfural as one of the decomposition products. The quantitative measurement of the furfural formed is made by measurement of the intensity of absorption at 280 nm.

The absorption densities of the standard and unknowns were determined in the Beckman DU[8] spectrophotometer with 40% sulfuric acid in the reference cell. The standard solutions were found to follow the Beer–Lambert law at concentrations of 25–500 mcg./ml.

The microbiological activity of the neomycin-containing gels was determined using the official cylinder-plate method, as described in USP XVIII (15), with several adaptations. The test organism was *Micrococcus pyogenes* var. *aureus* (ATCC 6538P) obtained commercially[9]. Nutrient agar was prepared with an artificial plasma electrolyte solution as described by Fiedler and Sperandio (13). This provided a simulated system for intact skin and allowed an electrolyte exchange with the resinate in the aqueous gels and subsequent release of drug.

Gels of the synthetic polymers described were prepared in the concentrations shown in Table I. A gel of methylcellulose 400 cps., which by preliminary experimentation did not show any interaction with neomycin sulfate, was prepared as a reference standard to determine the relative activity of the resinate-containing gels. The six gels were freshly prepared. Neomycin sulfate and drug–resin equivalent to 1% neomycin were incorporated into separate portions of the methylcellulose gel. Drug–resin was also incorporated into the remaining gels in an amount equivalent to 1% neomycin.

Samples of standard and unknown containing free neomycin sulfate and drug resinate, respectively, were transferred asceptically with 10-ml. sterile syringes for filling the stainless steel cylinders. The plates were incubated for 20 hr. at 37°, and the diameters of the zones of inhibition were measured.

**Resin–Drug Preparation**—Neomycin was adsorbed onto the cation-exchange resin by agitating a solution of the drug containing an equivalent of 800 mg. base wth 1 g. of resin. The resin and drug mixture was placed in 4-oz. ointment jars which were tightly sealed with plastic tape. The jars were then agitated in a rotating-bottle-type water bath at 37°. Studies showed that 1 g. of the resin was capable of adsorbing 790 mg. of neomycin base after an equilibration period of 24 hr. under the conditions described.

**Polymer–Drug Interaction Studies**—Fresh aqueous gels were prepared with each of the synthetic polymers. Initial qualitative tests were carried out with 50-g. samples of these gels by adding 300 mg. of neomycin sulfate and making observations for physical gel breakdown.

The degree of polymer–drug interaction was then determined quantitatively by preparing a 100-mg. solution of each polymer, adding to this a solution containing 250 mg. of neomycin sulfate[10], and assaying for remaining drug. The resulting precipitates were centrifuged, the supernatant was decanted, and the precipitates were washed. The washings were mixed with each respective decanted solution, and then each solution was assayed spectrophotometrically for loss of neomycin.

[1] EMA-71, Monsanto Co., St. Louis, Mo.
[2] Carbopol 934, B. F. Goodrich Chemical Co., Cleveland, Ohio.
[3] Polyox, Union Carbide Chemicals Co., New York, N. Y.
[4] Biopolymer XB-23, General Mills, Inc., Minneapolis, Minn.
[5] Cellulose Gum, Hercules Powder Co., Wilmington, Del.
[6] Amberlite IRP-69M, Rohm & Haas Co., Philadelphia, Pa.
[7] Supplied by The Upjohn Co.
[8] Beckman Instruments, Fullerton, Calif.
[9] American Type Culture Collection, Rockville, Md.
[10] An arbitrary amount chosen but in excess, as substantiated in the results.

Table III—Relative Activity of Neomycin Ointments

| Polymer–Resinate | Inhibition Diameter, mm. |
|---|---|
| Ethylene maleic anhydride | 15 |
| Methylcellulose 400 cps. | 24 |
| Carboxyvinyl polymer | 25 |
| Sodium carboxymethylcellulose | 28 |
| Heteropolysaccharide | 30 |
| Ethylene oxide copolymer | 35 |
| Methylcellulose-free drug[a] | 50 |

[a] Reference standard.

**Gel Stability Studies**—Six gels (Table I) were freshly prepared, and drug–resin was incorporated into each in an amount equal to 1% neomycin base. Immediately after preparation, the viscosity was taken of each gel–resinate at 27° using a Haake Roto-Visco rotating bob viscometer. Twenty-five grams of gel was used for each measurement. The gels were stored in tight containers at 27°, and their viscosity was measured weekly for a period of 6 weeks to determine physical stability. Fresh solutions of each polymer were prepared in concentrations shown in Table II. Resinate equivalent to 1% neomycin was added to 100 ml., and 1% of neomycin sulfate was added to another 100 ml. of each solution. Viscosity measurements were taken of the pure polymer, the resinate–polymer, and the drug–polymer at 37° in an Ostwald–Fenske viscometer, using 20 ml. of test solution. Distilled water was used as the reference standard. Observations for change in viscosity were made.

## RESULTS AND DISCUSSION

**Polymer–Drug Interaction Studies**—The general reaction observed upon incorporating the drug into the gels was immediate loss of structure and formation of stringy, opaque masses which were insoluble except for the interaction with ethylene oxide copolymer. In this case, structure breakdown was evidenced by a decrease in viscosity from a gel to a free-flowing liquid. Initial qualitative tests showed that neomycin sulfate in 300-mg. amounts was sufficient to cause complete breakdown of 50 g. of gel.

Assay of neomycin remaining in the supernatant after having interacted an excess with 100 mg. of polymer indicated that 128.5, 102.5, 66.5, and 55 mg. of drug had interacted with 1 g. of carboxyvinyl polymer, sodium carboxymethylcellulose, ethylene maleic anhydride, and heteropolysaccharide, respectively. The amount interacting with ethylene oxide copolymer was indeterminable because no precipitate was formed.

**Gel Stability Studies**—The initial viscosity found for each freshly prepared gel–resinate (Table I) did not appreciably change over the 6-week period of observation, therefore suggesting no interaction between polymeric gel and drug. On the other hand, the viscosities determined for the polymer solutions (Table II) showed that for those polymers forming insoluble interaction systems, there was complete precipitation of polymer–drug from solution. The viscosities of the supernatent liquids were the same as that of the standard, distilled water. Ethylene oxide copolymer in this low concentration and methylcellulose showed no change in viscosity, indicating no drug interaction. The drug–resinate system was successful in stabilizing each polymer system that was sensitive to interaction with neomycin, as evidenced by no change in the viscosities of the polymer solutions.

**Drug Activity**—Results of the bacteriological studies indicated that neomycin was available for activity from the cation-exchange resin. The average diameters of the zones of inhibition (Table III) indicate a varying degree of drug availability from the ointment and/or resinate. Methylcellulose, which has no reactive functional groups, released the free drug to the largest extent. The release of drug in the methylcellulose–resinate mixture was approximately half that of the free drug, indicating the general effect that could be expected in the remaining group of gels which showed an activity of approximately one-third to three-quarters that of the standard gel, methylcellulose. Ethylene oxide copolymer, which indicated little or no interaction with neomycin, showed the second highest activity over that of the polymers containing active polyfunctional groups.

The viscosity of the gels apparently had little or no effect on drug diffusion to the surface of the simulated skin. The ethylene maleic anhydride–resinate system was the least viscous and also showed the lowest activity. However, the pH of the gel systems may have had an effect on neomycin activity. Neomycin shows optimum activity at about pH 7.0; therefore, one would expect the ethylene maleic anhydride gel (pH 2.65) to show the least activity and ethylene oxide copolymer (pH 7.2) to show the greatest activity. Drug activity appeared to be related to the binding capacity of the polymers. Sodium carboxymethylcellulose and carboxyvinyl polymer interacted with the largest amount of drug, as indicated here, but showed a smaller inhibition diameter (Table III) than the heteropolysaccharide which interacted with about half as much drug.

This study shows that a much lower amount of antibiotic than is necessary to interact ultimately with all the reactive portions of the polymer molecules is sufficient to break down the gel structure. Breaking of gel structure is, therefore, not dependent upon the degree of polymer–drug interaction. This was evidenced by 6 mg. of neomycin sulfate being capable of completely precipitating 1 g. of each polymer studied, whereas 55–128.5 mg. of drug was found to have interacted with each polymer.

A cation-exchange resin with a low pKa is readily capable of forming a complex with neomycin strong enough to prevent further interaction with polyfunctional polymers. The resin, therefore, serves to stabilize aqueous gels until they are applied topically. Recognizing the general principles of ion exchange, one could suggest that the resin exchanges the drug moiety for the electrolytes present in the aqueous portion of the skin or the exudate of open wounds.

Aqueous gel systems, which are becoming increasingly more popular in use, are not limited to use with nonreactive drugs whenever an ion-exchange resin can be used to stabilize them. In addition, this affords the formulator a greater number of possible materials to choose from in developing efficacious semisolid dosage forms.

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