Modification of Polyethylene Glycol Ointment U.S.P. XVI

By WINITA CHANDRANONDNAIWINIT and E. BLANCHE SOMMERS

The hydrophilic capacity of official polyethylene glycol ointment, modified by the addition of 0.5 per cent of dry unneutralized carboxypolymethylene compound, was increased 48 per cent. The relative effectiveness of the modified ointment as a vehicle for yellow mercuric oxide (1 per cent) and potassium penicillin G (1000 u./Gm.) using *Staphylococcus aureus* PS 81 as the test organism was determined. Antistaphylococcal activity was increased 23.3 and 31.3 per cent, respectively. The stability of penicillin in the modified and official bases was checked for 23 days. Antistaphylococcal activity declined to 18.8 and 13.5 per cent, respectively.

POLYETHYLENE glycol ointment U.S.P. XVI possesses such advantages as esthetic appearance, washability, inertness, and the ability to form an emollient base. However, its high degree of solubility precludes the addition of aqueous solutions much in excess of 5% of the total formula (1).

One of the criteria of an ideal ointment base is that of hydrophilic capacity. According to Beeler (2), various authors have described an ideal ointment base as being capable of holding at least 50% of water.

Due to the lack of this ability on the part of all of the polyethylene glycols, various additives have been tried with limited degree of success. For example, the addition of 5% of cetyl alcohol to the anhydrous base containing 47.5% each of polyethylene glycol (PEG) 4000[1] and polyethylene glycol 400 has been recommended (3). This addition increased the water absorption ability of the base 10%.

Since the official ointment in most respects is pharmaceutically and dermatologically acceptable except for its lack of water capacity, further study was prompted in regard to this characteristic. Different substances were tried in varying concentrations and carboxypolymethylene compound[2] proved to be the most satisfactory in regard to increasing the hydrophilic capacity of official polyethylene glycol ointment.

EXPERIMENTAL

Addition of Carboxypolymethylene Compound.—Polyethylene glycol ointment U.S.P. XVI was prepared and samples of the official ointment were modified by the addition of carboxypolymethylene compound in concentrations of 0.5, 0.75, 1, 2, and 5%. Aseptic techniques were observed and finished ointments were stored in closed jars at room temperature. The polymer was added according to the following methods.

Method 1.—One-half gram of unneutralized carboxypolymethylene compound reduced to a fine powder was thoroughly triturated into enough polyethylene glycol ointment to make 100 Gm. This process was repeated using 0.75, 1, 2, and 5 Gm. of the polymer.

Carboxypolymethylene compound owes much of its exceptional ability to thicken, suspend, and emulsify to its hydrophilic nature or affinity for water (4). It was used dry and unneutralized in an effort to increase its water absorption ability when present in the ointment base.

Method 2.—Method *1* was varied by adding the respective portions of unneutralized carboxypolymethylene compound to enough liquid polyethylene glycol 400 to make each portion weigh 60 Gm. The powder was first levigated with a small amount of the liquid glycol and successive portions of the latter were added until thorough incorporation was accomplished. Each 60-Gm. portion of the PEG 400 containing its respective concentration of the polymer was then heated with 40 Gm. of PEG 4000 on a water bath to 65°. The preparation was allowed to cool and was stirred until it congealed.

Method 3.—Carboxypolymethylene compound (0.5 Gm.) was neutralized with a solution of sodium hydroxide (10%). In order to avoid the presence of water to the greatest possible degree, the dry polymer was mixed with 10 ml. of the official ointment before it congealed. One milliliter of the sodium hydroxide solution was added and the mixture was allowed to stand for 30 min. It became very gelatinous, but readily liquefied when placed on a water bath, and it was then incorporated into the remaining liquid official ointment to make a total of 100 Gm.

The resulting preparation was darker and considerably stiffer than the official ointment. For this reason further modification of the official ointment by the addition of increased concentrations of the neutralized carboxypolymethylene compound was not attempted. Products of methods *1* and *2* were evaluated. The 0.5% formulation prepared by trituration of dry unneutralized carboxypolymethylene compound into the official ointment was

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[1] Marketed as Carbowax 4000 by Union Carbide Corp., New York, N. Y.

[2] Marketed as Carbopol 934 by B. F. Goodrich Chemical Co., Cleveland, Ohio.

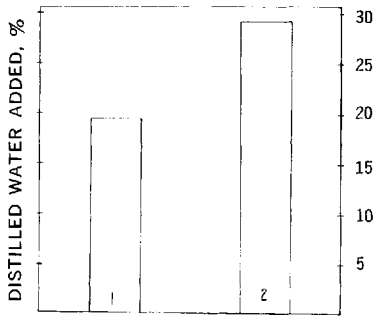

Fig. 1.—Comparison of absorption of water by PEG ointment U.S.P. (*1*); PEG ointment U.S.P. with 0.5% of dry unneutralized carboxypolymethylene compound (*2*).

selected as the most cosmetic in texture and appearance.

Hydrophilic Properties.—The official ointment and that modified with 0.5% of carboxypolymethylene compound were tested for hydrophilic capacity. Distilled water was added dropwise with trituration from a calibrated dropper to samples of each ointment until the point of flow was reached. Standardized point of flow was attempted in each instance by the delivery of a specified volume of the sample in a specified time from the same container.

After the initial hydration, the ointments thickened on standing. When this occurred, water was again added to the ointments in the same manner until they did not change consistency on standing for 30 days. Results of the initial hydration are shown in Fig. 1.

Relative consistency of the ointments was determined by the use of a rheostat connected to an electrically driven stirring device. The blades of the latter were submerged in the ointment under standardized conditions. The electrical power was slowly increased and the rheostat reading was taken at the first perceptible indication of the ointment's yield to the blades of the stirring device. Repeated experimental determinations gave values that differed within acceptable limits.

After the initial hydration, the samples of polyethylene glycol U.S.P. XVI containing an average of 19.6% of distilled water regained their original consistency in an average of 5.5 days on standing in tightly closed containers at room temperature. When compared to samples of the modified ointment containing the same amount of distilled water, the latter regained their original consistency in an average of 1 day. Distilled water was again added to the samples of the official ointment containing 19.6% of distilled water until each reached the point of flow. This time an average of 10.4% water/sample was required making a total of 30% of distilled water that was added. After standing 30 days, thickening occurred to a very slight degree.

The samples of the ointment modified by the addition of 0.5% of carboxypolymethylene compound, that contained an average of 29% water when initially hydrated to the point of flow, were stored in the same manner for 30 days. They thickened considerably but did not regain their original consistency.

Using fresh samples of the modified ointment, distilled water was added to each sample to the point of flow. This was repeated using the same samples until, on standing 30 days, these preparations did not thicken. A total of 34% water was required.

Evaluation as Vehicles for Yellow Mercuric Oxide.—The official and the modified ointments were tested to determine their relative effectiveness as bases for yellow mercuric oxide. One per cent of the latter was incorporated into samples of each

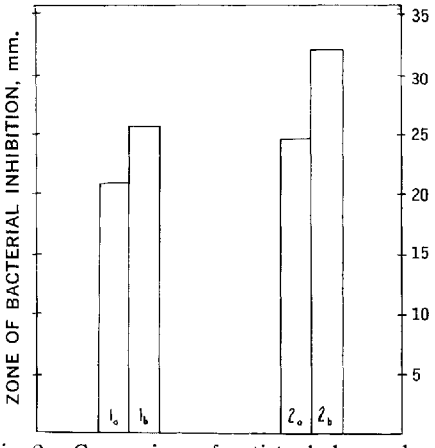

Fig. 2.—Comparison of antistaphylococcal activity. Key: 1_a, PEG ointment U.S.P. with mercuric oxide, 1%; 1_b, PEG dry unneutralized carboxypolymethylene compound ointment with mercuric oxide, 1%; 2_a, PEG ointment U.S.P. with potassium penicillin G, 1000 u./Gm.; 2_b, PEG dry unneutralized carboxypolymethylene compound ointment with potassium penicillin G, 1000 u./Gm.

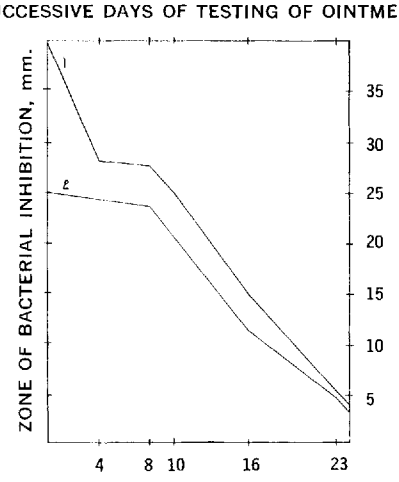

Fig. 3.—The rate of decline of potency of (*1*) PEG dry unneutralized carboxypolymethylene compound ointment with potassium penicillin G, 1000 u./Gm.; (*2*) PEG ointment U.S.P. with potassium penicillin G, 1000 u./Gm.

of the ointments by trituration until homogeneous composition was obtained. Aseptic techniques were observed.

A solution of nutrient agar in distilled water (2.3%) was prepared, autoclaved, and cooled to 45°. Each of 20-ml. samples of this solution was inoculated with 0.2 ml. of *S. aureus* PS 81 which had previously been incubated for 18 hr. at 37° in an aqueous solution of thioglycollate (1%). The 20-ml. samples were then poured into sterile Petri dishes and allowed to harden, after which 0.5 Gm. of the official ointment containing yellow mercuric oxide (1%) was placed in the center of the nutrient agar in each plate. This procedure was repeated using the modified ointment containing yellow mercuric oxide (1%).

These preparations were incubated at 37° and read after 48 hr. Bacterial inhibition zones were measured from the edge of the ointment to the edge of the zone of complete inhibition. Controls consisting of the nutrient agar, the official, and the modified ointments were prepared. They showed no zones of bacterial inhibition. Results are shown in Fig. 2.

Evaluation as Vehicles for Potassium Penicillin G.—Ointments of potassium penicillin G (1000 u./Gm.) were prepared using the official and the modified bases. The penicillin was incorporated into the bases by the same method used in the preparation of the mercuric oxide ointments.

Effectiveness of the two bases as vehicles for the penicillin was tested by the same method used for testing the yellow mercuric oxide ointments. Results are shown in Fig. 2.

Stability Studies.—The stability of potassium penicillin G in the official and in the modified bases was tested. The ointments, after preparation, were immediately stored in tightly closed containers at room temperature. Using *Staphylococcus* PS 81 as the test organism and the previously described media and techniques, the ointments were tested at 1, 4, 8, 10, 16, and 23-day intervals for potency of their contained penicillin. Results are shown in Fig. 3.

DISCUSSION AND CONCLUSIONS

Hydrophilic Capacity.—According to this investigation, the initial hydrophilic capacity of the official polyethylene glycol ointment (19.6%) is greater than that of 8–10% reported by the literature, and the addition of 0.5% of carboxypolymethylene compound increased this capacity to 29%.

However, a total of 30% water was added to the official ointment at successive times before it ceased to thicken when stored 30 days. When 29% water was initially added to the modified ointment, it thickened on standing, but did not regain the original consistency on standing for the same period of time. The addition of a total 34% of water was required before the modified base showed no change when stored for 30 days.

The changes that occurred in the consistency of the ointments on standing might be considered as thixotropic in nature. However, thixotropy is customarily demonstrated by a 2-phase system. Polyethylene glycol ointment is an organogel and thus exists as a 1-phase system (5).

It is important to note that total hydration (30%) of the official ointment and the initial hydration (29%) of the modified ointment were approximately the same. Also, the total hydration of the latter was 34%. It is probable that apparent increased hydration of the official ointment when carboxypolymethylene compound was added was predominately due to increased rate of hydration caused by the polymer.

Incomplete hydration (8–10%) could account for the observation by King and Sheffield (6) that "The polyethylene glycol ointments are not completely satisfactory cosmetically . . . ."

Evaluation of Bases for Yellow Mercuric Oxide and Potassium Penicillin G.—Polyethylene glycol ointment U. S. P. XVI and its modified form containing 0.5% carboxypolymethylene compound were suitable bases for mercuric oxide (1%) and potassium penicillin G (1000 u./Gm.). When the anti-infective agents were added to the official and the modified bases and the finished preparations were tested, both produced zones of bacterial inhibition; however, the modified base was superior to the official base.

Controls of the official ointment and of the modified ointment containing 0.5% carboxypolymethylene compound did not demonstrate anti-infective activity. The polymer did not possess anti-infective activity in this instance, but when it was added to the official ointment containing mercuric oxide or penicillin, the anti-infective activity of the ointment was increased. These results suggest that increased anti-infective activity that occurred when the polymer was present was not due to the polymer alone but to direct relationship of the polymer to the anti-infective agent.

Thus, the superiority in regard to anti-infective activity of the modified base when compared to the official base could be due to the ability of the polymer to act as an emulsifying agent and in this manner increase the ratio of anti-infective/bacteria exposure.

Stability of Potassium Penicillin G in the Official and Modified Bases.—The PEG's have useful roles as vehicles for penicillins (7). However, there is difference of opinion concerning the effect of these compounds on the penicillins. Some investigators (8, 9) have reported that the presence of these compounds hastens the decomposition of the antibiotic, while others (10) have found it to be remarkably stable in PEG bases. In studying this problem, Ferlanto and Clymer (11) found that penicillin stability varies with the vehicle and with the particular salt used.

Numerous references are found in the literature in regard to the stability of penicillin in polyethylene glycol bases. However, none of these was concerned with the effect of carboxypolymethylene compound when present as a component of the polyethylene glycol base. It was decided to determine that effect.

According to the data of this investigation, the potency of the penicillin in the official and the modified bases when stored at room temperature declined to 18.3 and 13.5% of their original activity at the end of 23 days. This decline was fairly gradual and consistent except for the rapid decline of the penicillin potency of the modified base during the first 4 days. On further testing, this occurred again and remains unexplained.

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Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices II

Quantitation of Procedures

By SAURABH J. DESAI*, PARVINDER SINGH, ANTHONY P. SIMONELLI, and WILLIAM I. HIGUCHI

Recently a number of factors governing the rate of release of drug from plastic matrices were investigated. This study showed that while the experimental results were generally in agreement with Higuchi's relationship, they were not always quantitative. The present paper describes a refined experimental procedure for quantitatively studying the various factors. Matrix porosities are determined in two ways so that available and inaccessible pores can be differentiated. Diffusion coefficients are independently determined. The matrix tortuosity can now be quantitatively determined independently of the solid drug release rate data. In addition to these experimental refinements, the limitations of the theory are reviewed and some useful modifications proposed.

A PREVIOUS communication (1) discussed preliminary results on the investigation of the factors influencing drug release from solid drugs dispersed in inert matrices. An attempt was made in that study to compare experimental release rate data to the Higuchi relationship (2). While it was found that qualitative and semiquantitative comparisons between theory and data could easily be made, considerable difficulty was generally encountered when a quantitative test of the theory with data was attempted.

It was believed that much of the difficulty was due to the porosity and the tortuosity of the matrix not being independent of the other variables and changing from experiment to experiment. For example, these studies (1) showed that a small amount of surfactant in the solvent phase could markedly increase the release rate from the polyethylene plastic matrix. It was shown that this was not an increased solubility effect, and therefore, must be related to the porosity or tortuosity factors.

It has now become apparent that, in order to clearly understand the basic mechanisms involved, a more systematic study must be undertaken. Wherever possible, each of the parameters in the theory should be quantitated independently and then incorporated into the theory to see whether the equation accurately predicts the rate. Then when discrepancies occur, real or apparent, physical interpretations that are meaningful may be assigned.

The purpose of this paper is to present details of methods, both theoretical and experimental, designed for the quantitative physical evaluation of the various factors involved in drug release from nondisintegrating matrices. It will be shown that these techniques should permit the unambiguous interpretation of release rate data in most instances.

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THEORY

The basic Higuchi relationship (2) for the rate of diffusional release of drug incorporated as solid drug in an insoluble matrix, from one surface of the matrix, is