Formulation and *In Vitro* Evaluation of Anti-Infective Dry Foams

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Abstract □ To improve local therapeutic techniques for the massively burned patient, the concept of topical films was utilized to formulate a hydrophilic dry foam. An amphoteric surfactant, sorbitol solution, dextran, and water were selected as components for the dosage form. The release of therapeutic agents *in vitro* from medicated dry foam formulations was compared with that of corresponding ointment bases utilizing a modified agar diffusion method. When using *Pseudomonas aeruginosa* as the test bacteria, these tests showed that silver nitrate and silver sulfadiazine produced significantly larger zones of inhibition when used as the dry foam rather than as the ointment. Mafenide acetate and gentamicin sulfate produced equivalent release rates from both the dry foam and the ointment, while nitrofurazone was without effect.

Keyphrases □ Anti-infectives—formulation and *in vitro* evaluation of dry foams □ Topical films, dry hydrophilic—formulation and *in vitro* evaluation of anti-infective dry foams □ Dosage forms—formulation and *in vitro* evaluation of anti-infective dry foams

Local therapy for the massively burned patient usually includes the application of medicated ointments and dressings to minimize and eradicate *Pseudomonas* infection (1). As this approach to local therapy for denuded areas may present problems regarding application and removal techniques, the purpose of this study was to formulate a topical dosage form that may be applied to denuded areas of the skin without inunction. By using the concept of topical films and dressings, an aerated, hydrophilic dry film was formulated which is highly water soluble, flexible, nontoxic, and adherent to intact and abraded areas of the skin.

Because local drug action is dependent upon the rate of release of a drug from its vehicle (2), *in vitro* studies were performed to compare the release of medicaments from dry films with that of ointments. Therapeutic agents effective against *Pseudomonas* were selected for study (3).

EXPERIMENTAL

Formulation of Dry Films—Dextran[1], 4 g, was dissolved in 19 ml of water at a temperature of 70–75° on a water bath. To this solution were added 2 ml of sorbitol solution USP and 0.05 ml of an amphoteric surfactant[2]. The entire solution was whipped for 10 min with an electric beater, and the resultant foam was cast on a Teflon-coated surface to a depth of 2–3 mm and dried at 40–45° for 20–30 min.

After drying, the moisture content of the dry foam was determined using a moisture balance[3]. Average values for these measurements approximated 10%. In addition, the liquefaction time of the dry foam was ascertained; 2.5 cm^2 of the dry foam liquefied in 0.1 ml of water at ambient temperatures in 20 sec.

Batches of the dry foam formulation were prepared containing each of the following therapeutic agents in the concentration listed: 8.5% mafenide as the acetate[4], 0.2% nitrofurazone[5], 0.1% gentamicin as the sulfate[6], 0.5% silver nitrate, and 1, 2, and 3% silver sulfadiazine. According to the method of Fox (4, 5), silver sulfadiazine was prepared by dissolving 27 g of sodium sulfadiazine[7] and 17 g of silver nitrate, each in 50 ml of water. The solutions were mixed, and the precipitate was collected, washed, and dried to constant weight at 50–60°.

***In Vitro* Evaluation**—Because *Pseudomonas aeruginosa* has been frequently implicated as the causative bacteria in burn wound sepsis, a modified microbiological agar diffusion test (6) was utilized to compare the effectiveness of the dry foam with ointments as a vehicle for selected agents active against this bacterium. The *in vitro* drug release rates of the medicated dry foam preparations were compared with the corresponding commercially available ointment formulations, namely, mafenide cream, nitrofurazone cream, and gentamicin cream. Although not commercially available, 0.5% silver nitrate in an oil-in-water ointment base[8] and 1, 2, and 3% silver sulfadiazine in an oil-in-water ointment base[8] were prepared extemporaneously and utilized in this study.

After autoclaving sufficient quantities of Bacto Antibiotic Medium 2[9] at 121° and 15 psi for 25 min, approximately 20 ml was poured into 100 × 15-mm sterile, disposable petri dishes. Upon congealing, 0.1 ml of Bacto Antibiotic Medium 3[9] containing an overnight inoculum of *Ps. aeruginosa* (ATCC 9721) was spread onto the agar medium with the aid of a sterile, L-shaped glass rod. Each of 15 penicylinders was filled with approximately 0.3 g of the ointment formulation under investigation, placed upon the seeded agar, and incubated overnight at 37°. Penicylinders filled with the nonmedicated ointment served as the control. Zones of inhibition were measured after 24 hr with an antibiotic zone reader[10].

The corresponding medicated dry foam formulations were evaluated in a similar manner. However, rather than utilizing penicylinders, 15 disks of each medicated dry foam were prepared, each with a diameter of 7 mm, approximately equal to the diameter of the penicylinders. Nonmedicated dry foam disks were also prepared and evaluated as the dry foam control.

The results of the *in vitro* determinations are listed in Table I.

Stability—Preliminary studies were performed on replicate samples of medicated dry foams to determine the effect of varying levels of humidity and temperature upon stability. Mafenide and silver sulfadiazine dry foams were stored for 24 weeks in sealable, moistureproof, plastic bags[11]. Samples were stored at −5, 5, 25, 35, and 45° in a dark environment. Gross physical examination of the samples at weekly intervals indicated that the formulations will retain stability if packaging and storage conditions are designed to prevent moisture contact with the hydrophilic dry foams.

RESULTS AND DISCUSSION

To determine the effectiveness of the dry foam as a dosage form, a modified agar diffusion test was performed utilizing *Ps. aeruginosa* as the test bacteria. Mafenide, silver sulfadiazine, silver nitrate, gentamicin, and nitrofurazone were selected as typical topical antibacterials. The diameters of the zones of inhibition observed with the various medicated dry foam formulations were

[1] Sigma Dextran, A.M.W. 86,900, Sigma Chemical Co., St. Louis, Mo.
[2] Miranol 2MCA Modified, Miranol Chemical Co., Irvington, N.J.
[3] Cenco.
[4] Sulfamylon, Winthrop Laboratories, Division of Sterling Drug, Inc., New York, N.Y.
[5] Furacin, Eaton Laboratories, Division of The Norwich Pharmacal Co., Norwich, N.Y.
[6] Garamycin, Schering Corp., Bloomfield, N.J.
[7] Ruger Chemical Co., Irvington, N.J.
[8] Neobase Ointment, Burroughs Wellcome & Co., Research Triangle Park, N.C.
[9] Difco Laboratories, Detroit, Mich.
[10] Fisher-Lilly, Fisher Scientific Co., Pittsburgh, Pa.
[11] Zip-loc Plastic Bags, Dow Chemical Co., Midland, Mich.

Table I—*In Vitro* Microbiological Evaluation of Medicated Dry Foams

Formulation	Mean Diameter[a], Zone of Inhibition, mm	*SD*	Student *t* Test
0.5% silver nitrate dry foam	12.8	1.6	$p < 0.001$
0.5% silver nitrate ointment	9.3	1.2	
1% silver sulfadiazine dry foam	17.2	1.7	$p < 0.001$
1% silver sulfadiazine ointment	8.5	1.1	
2% silver sulfadiazine dry foam	16.6	2.1	$p < 0.001$
2% silver sulfadiazine ointment	9.7	0.9	
3% silver sulfadiazine dry foam	20.6	1.7	$p < 0.001$
3% silver sulfadiazine ointment	9.7	1.1	
8.5% mafenide dry foam	27.2	2.4	$p < 0.1 > 0.05$
8.5% mafenide ointment	25.9	1.0	
0.1% gentamicin dry foam	12.3	1.4	$p < 0.1 > 0.05$
0.1% gentamicin ointment[b]	13.6	1.6	
0.2% nitrofurazone dry foam[c]	—	—	—
0.2% nitrofurazone ointment[c]	—	—	—
Dry foam control[c]	—	—	—
Ointment control[c]	—	—	—

[a] Results listed are mean values for 15 determinations. [b] Gentamicin ointment liquefied at the incubation temperature. [c] No zones of inhibition were observed.

compared with those of the corresponding medicated ointments.

Mafenide was tested *in vitro* as the dry foam and also as the commercially available ointment. The mean diameter for 15 replicate determinations using mafenide dry foam measured 27.2 mm, while similar testing of the ointment formulation produced zones equal to 25.9 mm. Although the dry foam produced larger zones, a Student *t* test of these results suggested that a significant difference may not exist between the mean diameters of the zones of inhibition ($p < 0.1 > 0.05$). For this reason, it was assumed that the dry foam was as effective as the ointment when testing *in vitro* release of mafenide from these two dosage forms.

With respect to the silver sulfadiazine preparations, significance, as determined by the Student *t* test, could be assigned to the data obtained. That is, the mean diameter of the zones of inhibition was significantly larger for the dry foam formulation than for the corresponding ointment.

The mean diameters of the zones of inhibition measured 12.8 and 9.3 mm for the silver nitrate dry foam and the silver nitrate ointment, respectively. As was the case with silver sulfadiazine, the silver nitrate dry foam proved to be a better formulation *in vitro* than the corresponding ointment, as determined by the Student *t* test ($p < 0.001$).

In determining the *in vitro* effectiveness of the dry foam and ointment as a vehicle for 0.1% gentamicin, liquefaction of the ointment occurred during incubation. Due to the liquefaction and resultant flowing of the ointment onto the seeded agar plates, it is possible that exaggerated values were obtained. Nevertheless, zones were measured and evaluated. For the medicated dry foam, mean values of 12.3 mm were recorded, while values for the corresponding ointment equaled 13.6 mm. Since no statistically significant difference was noted between the means of the data obtained ($p < 0.1 > 0.05$), it was assumed that the dry foam and the ointment were equally effective as dosage forms for gentamicin.

The *in vitro* data indicated that drug release, as determined by the microbiological method, from the medicated dry foam formulations was at least as great as that from ointments. A medicated dry foam may be of value as a vehicle for topical use. The data obtained in this work indicated that the therapeutic concept of a medicated dry foam may be valid and should be subjected to clinical investigation at the earliest opportunity.

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