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FORMULATION OF A FOAMING VAGINAL TABLET AND SUPPOSITORY

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ABSTRACT

Formulations for a foaming, spermicidal vaginal tablet and a foaming, spermicidal suppository are presented. Some pharmaceutical characteristics peculiar to both dosage forms were measured. A simple method is suggested for the evaluation of the quantity and collapse resistance of the foam.

INTRODUCTION

Recently effort has been directed to contraceptive products. In the individual family planned parenthood frequently protects the health of the mother and improves the care of the children. In the United States the trend toward self care is having an impact on nonprescription contraceptive use. In the third world nations there is a need for contraceptive dosage forms that are readily self-administered, inexpensive and relatively efficient.

Vaginal contraceptives contain a spermicide and are designed to hold the spermicide within the vagina and primarily against the cervix. The FDA Advisory Panel on Nonprescription Contraceptives considers menfegol, nonoxynol-9 and octoxynol as safe and

effective spermicides (Category I) (1). The majority of vaginal contraceptives contain nonoxynol-9.

Vaginal creams and jellies tend to be messy, provide lubrication and are easily removed if they are water soluble. Jellies tend to spread unevenly in the vagina. Foam-producing dosage forms are preferred as excessive lubrication and leakage from the vagina are minimal, and the foam adheres to the vaginal walls and tenaciously covers the cervical os. Aerosol dispensers have the disadvantage that they are bulky, and the user cannot tell when the dispenser is almost empty. Thus, the foaming suppository and vaginal tablet appear to be useful dosage forms as they are convenient to use, portable and the user knows how many units remain. The foaming vaginal contraceptive is designed so that when inserted high into the vagina within 10 minutes it will have formed a mechanically strong foam that will block the cervical opening for an hour. If properly employed with a condom, the efficiency of the combination rivals that of the oral contraceptives.

EXPERIMENTAL

Materials. Nonoxynol-9 (Ipegal CO-630) was donated by GAF Corporation, Wayne, N.J. Microcrystalline cellulose, anhydrous citric acid, hydrous lactose, magnesium stearate, polyethylene glycols, colloidal silicon dioxide, sodium bicarbonate, sodium lauryl sulfate and sodium starch glycolate were USP/NF grade.

Preparation of Tablets. Tablets containing 50 mg of nonoxynol-9 were prepared using a single punch tablet press fitted with flat-faced, bevelled edge punches having a diameter of 12.7 mm. The formulation was:

	mg/tab
Nonoxynol-9	50
Colloidal silicon dioxide	32
Hydrous lactose	316
Microcrystalline cellulose	79
Anhydrous citric acid	125
Sodium bicarbonate	142
Sodium starch glycolate	50
Sodium lauryl sulfate	5
Magnesium sterate	6

The collodial silicon dioxide was wetted with 50% alcohol. The nonoxynol-9 was dissolved in 50% alcohol. The solution was added to the colloidal silicon dioxide in a planetary mixer and blended until uniform. The mass was passed through a 12-mesh screen fitted in an oscillating granulator. The wet granules were dried overnight in an air oven at 55-60°C. The dried granulation was passed through a 30-mesh screen and placed into a V-blender. The citric acid, lactose and microcrystalline cellulose were added to the V-blender and blended for 10 minutes. The sodium bicarbonate and sodium starch glycolate were added to the V-blender and blended for 10 minutes. The sodium lauryl sulfate and magnesium stearate were added to the V-blender. The complete formulation was blended for 5 minutes. The granulation was compressed into tablets.

Preparation of Suppositories. The formulation for the suppositories prepared by the fusion method was:

	mg/supp
Nonoxynol-9	100
Microcrystalline cellulose	100
Sodium lauryl sulfate	10
Anhydrous citric acid	103.5
Sodium bicarbonate	86.25
Polyethylene glycol 6000	840
Polyethylene glycol 400	1070

The polyethylene glycols were fused at 70°C. The nonoxynol-9 and the microcrystalline cellulose were uniformily blended in a

planetary mixer, and then added to the fused polyethylene glycols. The sodium lauryl sulfate, citric acid and sodium bicarbonate were added to the fused mixture. The complete formulation was stirred gently for 10 minutes at 70°C. The mass was poured into room temperature aluminum molds. After congealing, the suppositories were removed from the molds and packaged in cardboard boxes with dividers.

Apparatus. The bottom of a test tube with a 15.87 mm inside diameter was flattened using an oxygen torch. Employing pipets the length of the tube was calibrated in terms of volume. The calibrated tube was suspended from a ring stand in a constant temperature bath at 37 ± 0.1°C. A 1.0 g rubber cylinder with a diameter of 12.7 mm was cut from a rubber stopper. By means of an attached thread, which was aligned by two lengths of glass tubing, the weight could be gently lowered onto the surface of the foam (Figure 1). For tablets 2.0 ml and for suppositories 4.0 ml of distilled water at 37°C were pipetted into the tube. The dosage form was dropped into the tube, and the times were recorded for the foam to expand to various volumes (see Table 1). After 10 minutes the weight was placed on the surface of the foam, and the volume of the foam and time were recorded until the foam no longer supported the weight which then settled to the bottom of the tube.

Disintegration was conducted without disks in the USP disintegration apparatus. Dissolution was conducted in the USP dissolution apparatus 2 operating at 50 rpm using 500 ml of distilled water at 37°C. Samples were periodically withdrawn by

a filter-tipped pipet and analyzed spectrophotometrically at 276 nm for nonoxynol-9.

RESULTS AND DISCUSSION

Foaming Tablet. The average weight of 20 tablets was 818 mg, and the range was from 806 to 830 mg. The tablets met the specifications of the Weight Variation Test USP XX (2). As measured by a Schleuniger 2E hardness tester the average hardness of 20 tablets was 4.2 kp. With 6 tablets in the disintegration apparatus without disks the disintegration occurred within 3 minutes. The pH of 100 ml of distilled water in which one tablet had dissolved was 4.9, which approximates the clinically desired pH of the vaginal fluid. In the USP dissolution appratus 2 using 500 ml of distilled water at 37°C and a speed of 50 rpm the tablet dissolved within 4 minutes. In terms used to pharmaceutically characterize a tablet, the vaginal tablet appeared acceptable.

Clinically a copious and mechanically strong foam is required to form a protective barrier containing the spermicide over the cervical os. As a developmental tool to compare various formulations, the apparatus shown in Figure 1 was used to measure the volume of foam produced in 10 minutes, and then by use of a 1.0 g weight placed on the surface of the foam its resistance to collapse was determined. Six tablets were considered to be the minimum number to provide a valid test (3). The data are given in Table 1. the maximum volume (22 ml) of foam was attained at approximately 6 minutes after which the volume receded. When at 10 minutes the 1.0 g weight was placed on the surface of the foam, it required approximately 9 minutes before the foam had collapsed to the extent that the weight settled to the bottom of the tube.

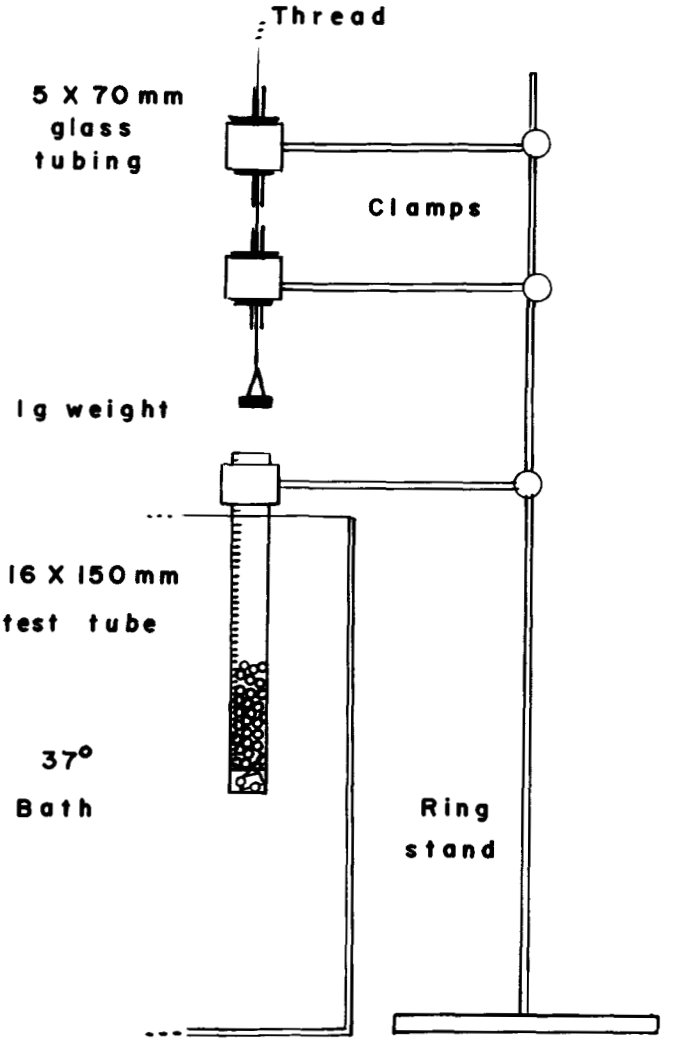

Figure 1. Apparatus for the evaluation of a foam.

Foaming Suppository. The average weight of 20 suppositories prepared using three molds was 2.42 g, and the range was from 2.30 to 2.54 g. The collapse or fracture load of 2.7 kg assured an adequate firmness for insertion (4). With 6 suppositories in the disintegration apparatus without disks no suppository existed after 20 minutes.

TABLE 1

Quantity and Collapse Resistance of Foam from a Vaginal Tablet

Volume of Foam, mL	Time[a], min
3.0	0.39 (0.04)[b]
5.5	0.60 (0.02)
8.0	0.93 (0.12)
10.5	1.44 (0.21)
13.0	2.00 (0.26)
15.5	2.57 (0.33)
18.0	3.42 (0.04)
20.5	4.60 (0.53)
22.0	5.82 (0.64)
15.5	8.20 (0.50)
13.0	9.06 (0.50)
8.0[c]	11.05 (0.66)
5.5	12.01 (0.86)
3.0	14.24 (1.06)
0	19.70 (2.90)

[a]average of 6 tablets
[b]standard deviation
[c]1.0 g weight placed on foam at 10 minutes

TABLE 2

Dissolution Profile of Nonoxynol-9 from a Spermicidal Suppository

Time, min	Percent Dissolved
3	28.0
6	36.0
9	64.8
12	81.2
15	93.5
18	97.8

TABLE 3

Quantity and Collapse Resistance of Foam from a Suppository

Volume of Foam, mL	Time,[a] min
1.0	2.91 (0.68)[b]
1.5	5.21 (0.42)
1.6	7.58 (1.91)
1.4	12.73 (1.91)
1.2	15.34 (2.28)
1.0	19.46 (1.07)
0	30.00[c]

[a]average of 6 suppositories

[b]standard deviation

[c]suppository residue average 44 mg

The pH of 100 ml of distilled water in which one suppository had dissolved was 4.2. In the USP dissolution apparatus 2 using 500 ml of distilled water at 37°C and a speed of 50 rpm, 90% of the nonoxynol-9 dissolved within 20 minutes. A typical result is shown in Table 2.

The maximum volume (1.6 ml) of foam was attained at approximately 8 minutes as shown in Table 3. At 30 minutes when the test was terminated approximately 98% of the suppository was dissolved. If at 10 minutes the 1.0 g weight was placed on the surface of the foam, it settled to the bottom of the tube within 5 seconds as the foam collapsed. These foam characteristics were compared to a

CONCLUSION

A formultion for a foaming spermicidal suppository and a foaming vaginal tablet are given. Their properties were evaluated

by standard methods and compared although the dosage forms are different. From the formulation viewpoint both appear to have acceptable pharmaceutical characteristics.

For most vaginal contraceptives it is directed that insertion occur at least 10 minutes prior to intercourse. Thus, it is logical to evaluate a product in terms of the quantity of foam produced and its collapse resistance at that time. A simple commercial effervescent suppository (Intercept^{TM}), which produced a foam processing a maximum volume of 1.0 ml at approximately 7 minutes and which did not support the 1.0 g weight. apparatus is suggested for this evaluation. In comparing an experimental and a commercial suppository to an experimental vaginal tablet, the tablet formulation produced approximately a tenfold greater volume of foam which collapsed less readily than the foam from the suppositories. From the developmental viewpoint the tablet formulation may be an acceptable candidate for clinical study.

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