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Spermicidal activity-structure relationship of nonoxynol oligomers: physicochemical basis

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Abstract

Oligomers of nonoxynol-9 were isolated and purified using a preparative HPLC technique. The various oligomers obtained possess the same nonylphenol base, but vary in the length of poly(ethylene oxide) chain and thus have different physicochemical characteristics. The partitioning of these oligomers into human sperm and vaginal mucosa was performed. While the partitioning of the oligomers into human sperm was observed to follow a bell-shaped pattern, the vaginal mucosa partitioning showed a dome-shaped pattern. The permeation across the vaginal mucosa excised from the sheep was also studied for selected oligomers and the rate of vaginal permeation was found to follow zero-order kinetics, which varied with the number of ethylene oxide units in the oligomers studied. The vaginal permeabilities calculated for all the oligomers studied were observed to be a linear function of their partition coefficients. It is interesting to note that as the number of ethylene oxide units increased, both the spermicidal activity and the vaginal permeability increased proportionally, reaching a peak with a poly(ethylene oxide) chain having 8–10 ethylene oxide units, and then decreased as the chain length increased further. The observations substantiate the role of hydrophilic-lipophilic balance in the activity-structure relationship of nonoxynol-9 oligomers.

Keywords: Nonoxynol-9; Oligomer; Permeation; Partitioning; Spermicide

1. Introduction

Nonoxynol-9 is a nonionic surfactant that has been widely used as a spermicidal agent, by virtue of its ability to solubilize biological membranes, for more than forty years. Surfactants interact with both lipid and protein constituents, conceptually functioning as a wedge and compromising the natural orientation of the membrane components (Helenius and Simons, 1975). The efficiency of solubilization is dependent upon the type and concentration of surfactant (Chapvil et al., 1980).

By nature of its synthesis, nonoxynol-9 exists as a mixture of a homologous series of oligomers containing a 9-carbon alkyl chain and a poly(ethylene oxide) chain of varying lengths (Fig. 1). These oligomers follow a Poisson distribution and the ethylene oxide number for the major oligomer fraction yields the product nomenclature, i.e.,

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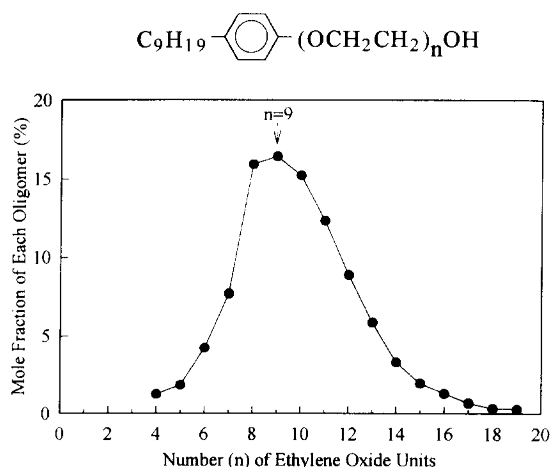

Fig. 1. Chemical structure of nonoxynol-9 and the Poisson distribution of its various oligomers in one commercial batch.

nonoxynol-9 has nine units of ethylene oxide as its major oligomer.

A small amount of research has been reported in the literature involving the in vitro characterization of select nonoxynol analogs (Igepal CO series). Evaluation over a series of nonoxynol compounds with ethylene oxide numbers of 1.5, 4, 9, 20, 30, 50 and 100 indicated that the nonoxynol-9 compound is the most effective on the inhibition of spermatozoal motility and is also highly cytotoxic (Chapvil et al., 1980). Employing a modified transmembrane migration model, the spermicidal activities of nonoxynol-5, -9, and -15 were compared. The results suggested that nonoxynol-5 and -9 have similar spermicidal potency, which is greater than nonoxynol-15 (Gadd and Curtis-Prior, 1988). Until recently, all the investigations had only used the commercially available compounds which are heterogeneous in nature. Nonoxynol-9 has been isolated into selected molecular weight fractions with differing units of ethylene oxide (n) for a more detailed assessment of spermicidal activity (Walter et al., 1991). The results suggested that medium-molecular-weight fractions (n = 6–8) possess a greater effect on sperm motility than the high-molecular-weight fractions (n = 11–13), with the least effect seen in the low-molecular-weight fractions (n = 1–4). Therefore, the activity of these oligomer fractions was shown to differ with the variation in the length of poly(ethylene oxide) chain. However, a quantitative assessment of the structure-activity of nonoxynol-9 could not be accomplished until the isolation of the individual oligomers in a highly purified form.

The objective of this study is to isolate and purify the various oligomer components of nonoxynol-9, so their physicochemical properties could be determined and a quantitative relationship of spermicidal activity to these properties could be assessed.

2. Material and methods

2.1. Chemicals

The pharmaceutical grade of nonoxynol-9 (CO-630SP) was obtained as a sample from Rhône-Poulenc (Cranbury, NJ). All other HPLC grade solvents and chemicals were purchased from Fisher Scientific (Fair Lawn, NJ). Deuterated acetone was obtained from Aldrich Chemical Co. (Milwaukee, WI).

2.2. Oligomer isolation

Analytical HPLC

An analytical HPLC method was established for the measurement of peak purity and subsequent quantitation of in vitro experimental results. Modifications were made and adapted for these studies based on procedures established for determination of alkylphenol ethoxylates in river water (Kubeck and Naylor, 1990). A Microsorb Cyano (5 μm; 4.6 mm (i.d.) × 25 cm) column (Rainin, Woburn, MA) was used with an HP 1050 HPLC system (Hewlett Packard, Wilmington, DE). Nonoxynol-9 and its various oligomers were dissolved in tetrahydrofuran and injected at a volume of 20 μl. The gradient schedule is given in Table 1. The two mobile phases used consisted of tetrahydrofuran: hexane (20:80 (v/v)) as mobile phase A and water: 2-propanol (10:90 (v/v)) as mobile phase B. A Hewlett Packard 1046A fluorescence detector was set at an excitation and emission wavelength of 229 and 310 nm, respec-

Table 1
Gradient schedule for separation of nonoxynol-9 oligomers

Time (min)	Flow rate (ml/min)	Mobile phase	
		% A [a]	% B [b]
Start	1.0	99	1
1.5	1.0	97	3
30	1.0	58	42
31	2.0	99	1
35	1.0	99	1

[a] Tetrahydrofuran/hexane (20:80).
[b] Water/2-propanol (10:90).

tively. The signals were processed through an HP 3396A integrator. The quantitation of the oligomers in each of the experiments was performed using serial dilutions of nonoxynol-9 as the standards. Oligomer concentrations in nonoxynol-9 were equal to their peak height percentages multiplied by the total nonoxynol-9 concentration.

2.3. Preparative HPLC

A preparative HPLC ensemble (Gilson Medical Electronics, Middleton, WI) was used for oligomer separation and collection. The analytical procedure similar to that reported in the literature (Walter and Digenis, 1991) was scaled up for these purposes. A preparative Dynamax CN column (8 μm; 21.4 mm (i.d.) × 25 cm; Rainin, Woburn, MA) was employed. Nonoxynol-9 in tetrahydrofuran, at a concentration of 250 mg/ml, was injected via a 1 ml injection loop at full capacity. The same mobile phases used with the analytical HPLC were used here. Controlled by Gilson's Software 712 System Controller, a linear gradient from 1 to 42% mobile phase B was run at a constant flow rate of 21.4 ml/min for a period of 25 min. From a UV detector signal at 280 nm, an automated Gilson FC04 fraction collector was implemented in the isolation of oligomer peaks. The eluted fractions were evaporated under a stream of nitrogen (Organomation, Northborough, MA), consolidated and reconstituted with tetrahydrofuran for evaluation of purity by analytical HPLC outlined above. For the peaks that resulted in peak height percentages less than 90% purity, a second elution was executed.

2.4. Identification

The identity of the collected oligomers was determined by ^{1}H-NMR spectroscopy (Black et al., 1989; Walter and Digenis, 1991). Samples were dissolved in acetone-d_6 and analyzed using a Gemini NMR Spectrophotometer (Varian, Palo Alto, CA).

2.5. Spermicidal activity

Assessment of the spermicidal activity of various nonoxynol-9 oligomers was conducted using a flow cytometer-based method developed previously (Yu et al., 1995). Briefly, 6-carboxyfluorescein diacetate ((CFDA), Sigma Chemical Co., St. Louis, MO) was added to a sperm sample to make a final concentration of 5 μM and incubated at 35°C for 15 min. Aliquots (100 μl each) of the labeled sperm were then pipetted into tubes each containing a purified oligomer of nonoxynol-9 (ranging from 60 to 100 μg/ml) in 400 μl of potassium phosphate buffer (pH 7.4). After an exposure time of 15 min., propidium iodide ((PI), Sigma Chemical Co., St. Louis, MO) was added to each oligomer solution to make a final concentration of 10 μM. Samples were analyzed for viable (CFDA, green fluorescence) and dead/dying (PI, red fluorescence) sperm using a flow cytometer. The spermicidal activity was calculated as a percentage of the dead/dying sperm to the total number of sperm.

2.6. Partitioning

Sperm

The partitioning into human sperm was determined for oligomers with ethylene oxide numbers of 4, 6, 9, 12 and 16. Oligomer solutions were each diluted with potassium phosphate buffer (pH 7.5) to concentrations ranging from 2.5 to 4 μg/ml. The sperm partitioning studies were run at low concentrations to avoid disruption of the sperm membrane. Semen samples were obtained from a single donor for each oligomer partition-

ing study. Each experiment was run at least 3 days apart to allow for the donor's sperm count to regenerate. The semen samples were washed with Ham's F10 media (Gibco, Grand Island, NY) and brought to a volume of 1 ml with the Ham's media. The sperm was washed by adding 2 ml of media to the liquefied semen, agitated and then centrifuged at $300 \times g$ for 10 min. The supernatant was removed and the process repeated once more. The number of sperm was determined by a computer-assisted semen analyzer ((CASA); Cryo Resources, New York, NY). Prior to the sperm count measurements, appropriate dilutions were made when necessary to remain within the counting capacity of the CASA.

For the partitioning study, the sperm suspension (ranging from 140 to 320 million sperm/ml) was lightly vortexed and aliquots (0.33 ml each) were placed in three test tubes to give sperm concentrations of 47-107 million sperm per test tube. Then an oligomer solution (2.5 ml) was added to the test tubes which were shaken at 37°C until the last sample was taken. Samples (200 μl each) were taken at 2, 5, 10, 15, 30, 45, 60 and 90 min and analyzed by HPLC. Before each sampling, the test tubes were centrifuged at 1000 rpm for 2 min. After sampling, the tubes were vortexed lightly. The partition coefficient was calculated from the ratio of the concentration in the sperm over the concentration in the solution. To determine the partitioning of each oligomer into the sperm, Eq. 1 was used and a sperm volume of 46.3 μm^3 (Brotherton, 1975) was used for calculations.

$$K_{\text{sperm}} = \frac{\left[A_s/(N_s \cdot 46.3\,\mu\text{m}^3)\right]}{C_{\text{soln}}} \quad (1)$$

where K_{sperm} is the partition coefficient, A_s denotes the amount of oligomer taken up into the sperm, N_s is the number of sperm and C_{soln} represents the solution concentration. A_s is obtained from the difference in solution concentration before and after the partitioning study.

2.7. Mucosa

For the determination of oligomer partitioning into lamb mucosa, the vaginal mucosa isolated was pinned to a dissecting board and small circular discs (0.95 cm in diameter) were cut using a hole punching device. Each circular disc was measured for thickness and weight. The partitioning characteristic was determined for oligomers with ethylene oxide numbers of 4, 6, 8, 10, 12, 14 and 16. The circular mucosal discs were immersed in various oligomer solutions, at a concentration of approx. 50 μg/ml, and shaken at a constant oscillation speed in a shaking water bath at 37°C. Samples (200 μl each) were taken, in triplicate, at 2, 6, 12, 24, 36 and 48 h. The samples were evaporated to dryness and reconstituted with tetrahydrofuran and the concentrations in the samples were analyzed by HPLC.

The partition coefficient was calculated from the ratio of the concentration in the mucosa (C_m) over the concentration in solution (C_s). C_m was calculated according to the following equation:

$$(C_s^i - C_s^f) \times V_s \div \frac{W_m}{D} \quad (2)$$

where C_s^i and C_s^f are the initial and final concentrations of an oligomer in solution, respectively, V_s denotes the volume of solution, W_m is the initial weight of the mucosa and D represents the density of the lamb vaginal mucosa determined as a mean value of 25 mucosa samples.

2.8. Permeation

Lamb vaginal mucosa was obtained from a local slaughterhouse. The whole vagina including the cervix, bladder and a portion of the rectum was removed from a freshly killed lamb. The vagina was cut open and the extraneous fat and tissue removed (Kabadi and Chien, 1984)

Vaginal permeation kinetics studies were conducted in the hydrodynamically well-calibrated Valia-Chien permeation cells (Crown Glass, Somerville, NJ). This apparatus consists of two half-cells, in mirror image, each holding a solution volume of 3.5 ml. The solution in the half-cells was maintained at 37°C by circulating thermostated water through the water jacket. The vaginal mucosa was cut into small squares and mounted between the two half-cells leaving a mucosa area of 0.64 cm^2 exposed for permeation

The serosal side of the mucosa was mounted toward the receptor half-cell while the mucosal side faced the donor half-cell. The saturated solution of nonoxynol-9 or its various oligomers in phosphate buffer was placed in the donor solution compartment, while the receptor solution compartment held blank phosphate buffer (pH 7.4). Experiments were each run in triplicate over a period of 24 h with samples (200 μl each) taken from the receptor solution at 1.5, 3.5, 5, 7, 8.5, 10.5, 12.5, 15, 21 and 24 h. Following each sampling, 200 μl of fresh buffer was added into the receptor compartment to maintain the constant volume of 3.5 ml. The samples were evaporated to dryness and reconstituted with tetrahydrofuran for HPLC assay.

3. Results and discussion

3.1. Oligomers

The purity of the oligomers was maintained above 90% with one elution (Table 2), except the oligomers with ethylene oxide numbers of 4, 14 and 16 which required two elutions for satisfactory results. Although oligomer 4 did not reach the same level of purity, only two elutions were made since repeated attempts for purification of this minor oligomer did not lead to improved purity, but resulted in the lose of a significant quantity with each purification step. Since the gradient HPLC technique adequately separated each oligomer from its impurities, it was possible to determine individual oligomer concentrations using the nonoxynol-9 standards.

Table 2
Purity of nonoxynol-9 oligomers determined as a percentage of the cumulative peak heights

Oligomers (ethylene oxide number)	Purity (%)
4	65.4 [a]
6	99.1
8	99.0
9	98.8
10	97.5
12	92.3
14	90.1 [a]
16	89.7 [a]

[a] Purity after two elutions

Table 3
Ratio of the NMR integration values of the ethylene oxide hydrogens to the aromatic hydrogens to identify the ethylene oxide number in nonoxynol-9 oliogmers

Integration value		Ratio [a]	Ethylene oxide number [b] (n)
δ 4.4–3.4	δ 7.2–6.7		
42.8	7.1	6.0	6
45.4	6.3	7.2	7
38.6	4.3	9.0	9
46.4	3.5	13.3	13

[a] Ratio of integration value at δ 4.4–3.4 (for the ethylene oxide protons) over the value at δ 7.2–6.7 (for aromatic protons).
[b] Number of ethylene oxide units in the oligomer.

The identification of the isolated oligomers was accomplished using NMR. It has been shown that the oligomers follow a natural numerical progression, in which the number of ethylene oxide units can be identified by NMR (Black et al., 1989; Walter and Digenis, 1991). The ratio of the integral of the ethylene oxide protons to the integral of the aromatic protons, each numbering four, were used to determine the ethylene oxide number. The integration values and ratios of a selection of oligomers are listed in Table 3. The oligomers were found to fall into the defined sequence described by Walter and Digenis (1991) and the remaining oligomers were identified accordingly.

3.2. Spermicidal activity

The spermicidal activities of four oligomers (4, 8, 12 and 16) were evaluated at three concentration levels: 60, 65 and 100 μg/ml. Nonoxynol-9, as a mixture component, is an efficient spermicidal agent at 100 μg/ml. The individual oligomers were evaluated in concentrations of μg/ml rather than equimolar concentrations to observe their contribution to nonoxynol-9 as a whole. The results in Fig. 2 show that the greatest spermicidal activity has been consistently attained for the oligomer with 8 units of ethylene oxide (EO), followed sequentially by oligomers with EO of 12

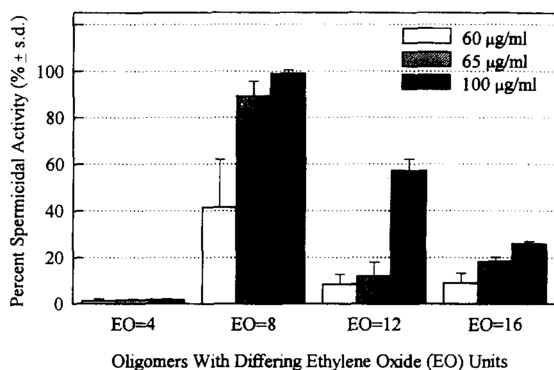

Fig. 2. Spermicidal activity of nonoxynol-9 oligomers 4, 8, 12 and 16 compared at three concentration levels (60, 65 and 100 μg/ml).

and 16, and lowest for oligomer with EO of 4. This trend resembles the bell-shaped partitioning characteristic of these oligomers onto the sperm (see section on 'partitioning'). The observation of the bell-shaped pattern suggests that the oligomers with a medium number of EO units would possess the greater activity than the oligomers with a higher or a lower EO unit, which is demonstrated in Fig. 3. The concentration of mixtures in Fig. 3 were made in the same proportions with respect to each other as each is found in nonoxynol-9. The results, which were generated at two critical concentrations (Yu et al., 1995), show that 100% spermicidal activity has been achieved with the combination of

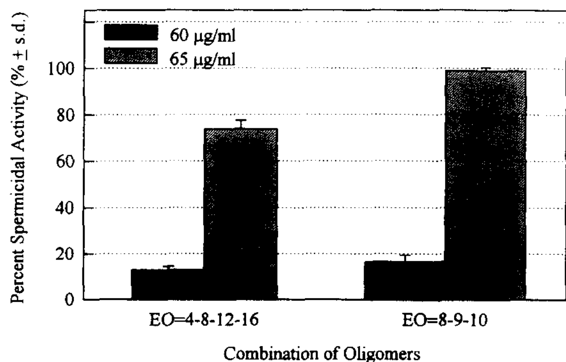

Fig. 3. Spermicidal activity for the combination of nonoxynol-9 oligomers with low and high numbers (4-8 and 12-16) of ethylene oxide (EO) units and with medium (8-10) EO units compared at the critical concentrations of 60 and 65 μg/ml.

oligomers with the medium numbers of EO units (i.e., EO = 8-10) at 65 μg/ml. Apparently, the oligomers with 8-10 EO units possess the greatest spermicidal potential, which show a bioequivalence to the spermicidal activity of nonoxynol-9. The observation suggests the spermicidal action of nonoxynol-9 is attributed to these medium oligomers, which constitute 42% (w/w) in a typical sample of nonoxynol-9.

The data in Fig. 2 and 3 demonstrate that there is a minimum concentration (65 μg/ml) that needs to be reached in order to achieve a substantial spermicidal activity. Generally, the action of a surface-active agent on biological membranes is dependent upon concentration (Jones, 1992) and has been shown to require a threshold concentration (Buttar et al., 1986). From the data from Fig. 3 and from work reported previously (Yu et al., 1995), the threshold concentration for nonoxynol-9 appears to be 65 μg/ml. It has been observed here and also noted by others (Sunamoto et al., 1983) that the spermicidal activity of surface-active agents occurs below their critical micelle concentrations (CMC). Oligomer 8 exhibited a CMC of 120 μg/ml, which is above its effective concentration of 65 μg/ml. The CMC values for the other oligomers were not determined. According to the product literature, nonoxynol-9 has a CMC of 205 μg/ml, also above its spermicidally effective concentration. This observation suggests that the oligomers could incorporate themselves, in their monomeric form, into the sperm plasma membrane when an adequate concentration surrounding the membrane surface has been reached. Aside from the concentration, the molecular structure and thus the physicochemical characteristic of the oligomers plays an important role in their respective potencies. Reports have suggested the relationship of membrane solubilization with hydrophilic-lipophilic balance (HLB) (Helenius and Simons, 1975). Nonionic surfactants have been shown to be the most effective on bacterial membranes at an HLB ranging from 12.4 to 13.5 (Umbreit and Strominger, 1973). Surfactants with higher HLB values have been reported to trigger the release of peripheral proteins without dissociation of the lamellar structure of the membrane (Brotherton, 1977). The

HLB values for a selection of oligomers have been determined (Table 4). The results indicate that the HLB values of the more potent oligomers (with EO = 8–10) are in similar range as the optimal range reported for the disruption of bacterial membranes. In addition, the partitioning characteristics of these oligomers determined in the next section also suggested the need to achieve a balance of the hydrophilicity and lipophilicity of these nonoxynol-9 oligomers.

3.3. Partitioning

With the attainment of equilibrium concentration in the solution, the amount of oligomer in the sperm or in the mucosa can be measured. Solution concentrations were adjusted for the quantity of solution removed for assay. Following this, the equilibrium concentrations of each nonoxynol oligomer in the sperm and in the mucosa could be calculated and the partition coefficient for each oligomer could be determined. After a series of preliminary studies, an optimal condition for sperm partitioning studies was found: the sperm count should be greater than 40 million sperm per test tube while the oligomer concentration should fall into the range of 2.5–4 μg/ml. In the sperm partitioning experiments conducted, the sperm counts in the range of 47 to 107 million sperm per test tube were used. Due to the sperm size and the total surface area, partitioning equilibrium was achieved rapidly. For

Table 4
Hydrophilic-lipophilic balance (HLB) of nonoxynol-9 oligomers

Oligomer	Molecular weight	HLB [a]
4	396.6	9.7
6	484.7	11.6
8	572.8	12.9
9	616.8	13.4
10	660.9	13.9
12	749.0	14.6
14	837.1	15.1
16	925.2	15.6

[a] Calculated from HLB = $E/5$, where E is the weight percent of ethylene oxide content in the oligomer.

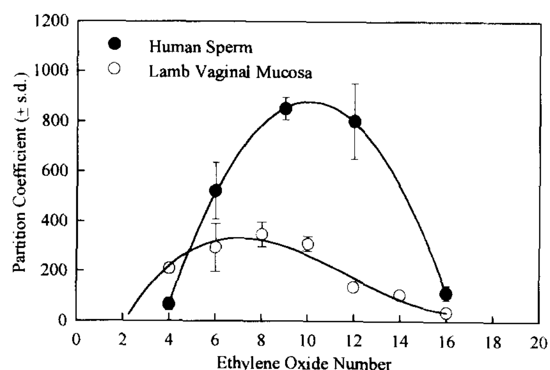

Fig. 4. Relationship between the partitioning behavior of a selection of nonoxynol-9 oligomers into human sperm (●) and lamb vaginal mucosa (○) and the ethylene oxide units in the oligomers.

calculation of the change in oligomer solution concentration, the equilibrium concentration was determined by using the mean value of all the data points after the zero time point.

It is interesting to note that the relationship between the partition coefficient and the number of ethylene oxide units shows a bell-shaped pattern for human sperm partitioning, but a dome-shaped pattern for vaginal mucosa partitioning (Fig. 4). The relationships observed suggest the need to attain an optimal balance of the hydrophilicity and lipophilicity for the maximal partitioning of spermicidal agents. The bell-shaped pattern observed substantiates the spermicidal activity results of the nonoxynol oligomers, which demonstrated that the oligomers with 8–10 units of ethylene oxide have the maximal activity (Fig. 2 and 3). The similar relationship has also been reported for the vaginal bioelectric activity of nonoxynols (Sunamoto et al., 1984) and on the release of carboxyfluorescein from liposomes by a series of menfegol (a nonionic surfactant) analogs (Hwang et al., 1976). The change in potential difference across the rat vaginal epithelium produced by nonoxynol-9 was attributed to the ability of nonoxynol-9 to achieve effective concentrations in the lipid membrane to yield alterations in the short-circuit current and the resistance (Sunamoto et al., 1984). A comparison of the partition coefficient data of the lamb vaginal mu-

cosa and the sperm indicates that there is difference in the lengths of the poly(ethylene oxide) chain that achieve the maximal partitioning into the sperm and into the vaginal mucosa, which provides some insight into the spermicidal activity in the vaginal lumen. The rapid partitioning into the sperm and the lower magnitude of vaginal partitioning suggest that an effective spermicide concentration could be maintained within the lumen with minimal loss due to mucosal uptake.

3.4. Permeation

The permeation characteristics across the lamb vaginal mucosa was determined for oligomers 4, 6, 8, 12 and 14. Saturated donor concentrations were used for oligomers 4 (43.0 μg/ml), 6 (93.1 μg/ml) and 8 (275.0 μg/ml) while the total quantity collected for oligomers 12 (31.3 mg/ml) and 14 (62.4 mg/ml) were used. The donor concentration was determined by dilution and HPLC analysis. The vaginal permeability coefficient can be determined for each oligomer studied from the slope of the linear permeation profile. A plot of the permeability coefficients as a function of the ethylene oxide number in the oligomers shows a bell-shaped relationship (Fig. 5A). In the nonoxynol structure, the lipophilic alkyl chain confers the 'pushing' of the oligomer out of the water phase and the 'pulling' into the lipid phase (Levin, 1988), while the poly(ethylene oxide) chain counteracts the alkyl chain, making the oligomer prefer the aqueous phase. Similar to the dome-shaped pattern observed for mucosal partitioning, the permeability profile also suggests that nonoxynol molecules need to possess an adequate hydrophilicity to balance with the hydrophobicity in order to reach an optimal permeability.

Since the permeation across vaginal mucosa can occur by a lipoidal or aqueous pore pathway, it is important to examine the mechanism of permeation. To accomplish this, the vaginal permeability of various oligomers and their mucosal partition coefficients were compared. A strong linear correlation of the permeability with the partition coefficients is observed (Fig. 5B). This suggests the predominance of the lipoidal pathway for permeation of these oligomers. The same

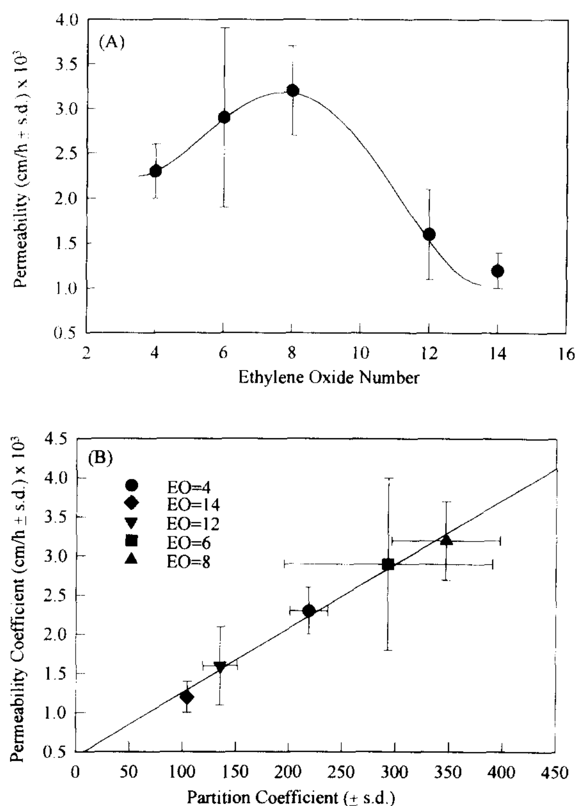

Fig. 5. Dependency of the permeability of selected nonoxynol-9 oligomers on (A) the number of ethylene oxide units and (B) vaginal partition coefficient.

has been shown for rabbit vaginal mucosa with aliphatic alcohols (Hwang et al., 1976). The importance of the membrane lipids have been shown by the intracellular incorporation of nigrosin dye after treatment of the rat vaginal mucosa with nonoxynol-9 (Levin and Parker, 1987). It has also been demonstrated that more hydrophobic strains of lactobacilli are more susceptible to nonoxynol-9, while the more hydrophilic organisms are more resistant (Tomeczek et al., 1992).

3.5. Proposed mechanism of spermicidal action

The term 'spermicidal activity' is used in reference to cessation of sperm motility. Nonoxynol-9 disrupts the sperm plasma membrane which leads to the loss of motility and eventually to sperm death. While, the loss of motility is an indication

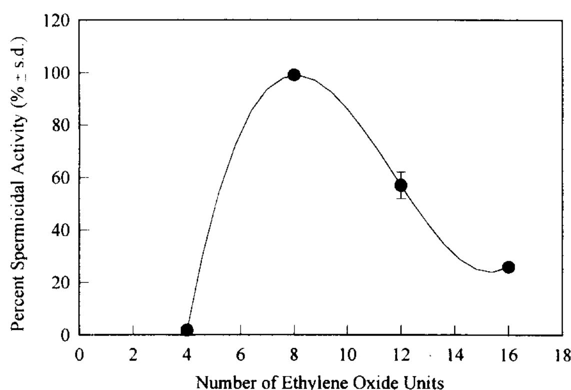

Fig. 6. Dependency of the spermicidal activity of selected nonoxynol-9 oligomers (100 μg/ml each) on the number of ethylene oxide units.

of reduced fertilization potential, biochemical processes may still be occurring and so the death of the sperm is not always immediate.

The spermicidal activities of various nonoxynol-9 oligomers show a bell-shaped dependency on the number of ethylene oxide units in the oligomers (Fig. 6). This relationship follows the same trend observed earlier with both the mucosal partitioning and vaginal permeability data. Since partitioning and permeability exhibited a linear relationship (Fig. 5B), the importance of membrane lipophilicity in achieving spermicidal activity is also suggested. A comparison of spermicidal activity and sperm partitioning exhibits a marked increase in spermicidal activity for those oligomers with high partition coefficients in a narrow range of 800–850. Again, the need to obtain a proper balance of hydrophilicity and lipophilicity in the nonoxynol oligomer for optimal activity is apparent.

4. Conclusion

Overall, it has been demonstrated that physicochemical characteristics of the oligomer plays a role in the determination of spermicidal effectiveness as well as the permeation properties across the vaginal mucosa. Previous findings which indicated the lack of correlation between the spermicidal activity of surfactants and their physicochemical properties was probably due to the use of these compounds in their heterogeneous forms (Furuse et al., 1983). In the present investigation, by isolating the individual oligomer components from nonoxynol-9, in highly purified form, their spermicidal activities could be determined and compared quantitatively and related well to their physicochemical properties. The prevailing potency of nonoxynol-9 over structurally related analogs (Yu et al., 1995) can be explained by the fact that 75% of the nonoxynol-9 compound contain those oligomers (oligomers 7–12) that are capable of partitioning into the sperm effectively. The general mechanism for the spermicidal action of nonoxynols was found to be a function of their physicochemical properties, including optimal lipophilicity, which are related to HLB values. An optimal range of HLB values is needed for maximal spermicidal activity. A critical concentration was observed for each particular oligomer.

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