Spermicidal Agents: A Comprehensive Review

Arjun*, Chandan CK, and Shwetha K

Department of Pharmaceutics, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, MSR Nagar, MSRIT Post, Bengaluru, India

***Corresponding author**
Arjun
M S Ramaiah University of Applied Sciences,
MSR Nagar, MSRIT Post, Bengaluru-560054, INDIA

Abstract

Background: Incidences of unintended pregnancies all around the globe are one of the major causes of population explosion, abortions, decline of reproductive health, crisis and poverty prevalent in underdeveloped and developing countries. Several contraceptive methods are described in the medical literature as alternatives to avoid unplanned pregnancy. These approaches include different compounds from various chemical classes, of various action mechanisms and with different levels of effectiveness. Barrier methods, for example, consist of the use of substances that prevent fertilization of the ovum by sperm by establishing physical or chemical barriers [1]. Old texts, like the Kahun Papyrus and works by Soranus, hint at early use of acidic and plant-based contraceptives. Modern contraceptives includes synthetic, natural, microbial and repurposed agents that have spermicidal activity [2].

Methods: The review conducted through a comprehensive literature search using databases such as PubMed, ScienceDirect, Scopus, and Google Scholar. Key search terms included *"spermicides," "vaginal contraceptives," "nonoxynol-9," "natural spermicides."* Studies were selected based on relevance, scientific rigor, and novelty. Our studies include data in *in vitro* assays (e.g., Sander-Cramer assay), mucosal irritation tests (e.g., slug mucosal irritation), and historical and modern clinical investigations into spermicidal mechanisms, efficacy, and safety.

Results: Spermicides are considered as an effective way to prevent contraception. Synthetic compounds like Nonoxynol-9 and Benzalkonium Chloride, natural products like neem oil, curcumin, and gossypol act through various mechanism to disrupt sperm membranes, alter ph, nhibiting acrosin, or inducing oxidative stress to act as spermicides. While they do provide advantages such as sperm immobilization, issues like mucosal irritation and limited protection against STIs remain. Emerging research highlights the potential of innovative spermicides that combine both contraceptive and antimicrobial actions with very little side effects or toxic effects.

Conclusion: While Nonoxynol-9 has been the mainstay, its mucosal toxicity demands alternatives. There is an urgent need for next-generation spermicides that are safe, non-toxic, and effective at both sperm immobilization and pathogen inactivation while having minimal side-effects.

KEYWORDS Spermicides; Detergents; Nonoxynol-9; N-9; Microbicides; New spermicide compounds

Introduction

One of the main causes of the global population expansion, abortions, decline in reproductive health, crisis, and poverty that are common in undeveloped and developing nations is the prevalence of unwanted pregnancies. The medical literature lists a number of contraceptive methods as possibilities to prevent unintended pregnancies. Different substances from different chemical classes, with diverse modes of action and varying degrees of efficacy, are included in these techniques. For instance, barrier approaches involve the use of chemicals that create chemical or physical barriers that stop sperm from fertilizing the ovum [1]

Vaginal spermicides, including creams, gels and foaming aerosols are examples of chemical barriers [3].

Contraception is the act of preventing pregnancy. This can be a device, a medication, a procedure or a behaviour. Vaginal contraceptives allow a woman control of her reproductive health and affords the woman the ability to be an active participant in her family planning. The prevention of unintended pregnancies helps to lower maternal ill-health and the number of pregnancy-related deaths. Delaying pregnancies in young girls who are at increased risk of health problems from early childbearing, and preventing pregnancies among older women who also face increased risks, are important health benefits of family planning [4].

There is a need for a new generation of spermicides because they have to act as a spermicide without causing or causing less side effects. The advent of the use of alternative contraceptive methods such as Oral Contraceptive Pills (OCP) and (Intrauterine Devices) IUDs keeps increasing due to side effects experienced. Since vaginal microbicides would be used many times over many years, the best one should be safe and not harm genital cells. It also needs to be cheap, made from easy to find stuff, and work well with many drugs to stop different STDs like HIV-1. Spermicides that will have a non- irritative, non-detergent, and water-soluble feature are very important with an added feature of effectiveness in combating STIs without harming vaginal flora. Infection with pathogens such as Chlamydia trachomatis continues to lead to outcomes of pelvic inflammatory disease and sterility. Although the traditional choice was Nonoxynol-9, which had spermicidal and microbicidal activity, this surfactant spermicide increases the risk of STI; therefore, research has been focused on providing effective, nondetergent spermicides that overcome these deficits and offer additional protection in use alone or with condoms [5].

Definition

Spermicides are chemical barrier contraceptives that operate both physically, by forming a mechanical barrier interfering with sperm movement, and biochemically, by immobilising or destroying sperm that have been blocked.

History

An ancient Egyptian document called Kahun Papyrus is considered as first document to record the evidences of spermicide usage in those days. In Kahun Papyrus, a pessary prepared using crocodile dung and fermented dough has been prescribed as spermicidal contraceptive approach. It is also mentioned that the low acidic pH of the dung might be responsible for its spermicidal effect [2]. Fertility regulations were first documented in the Egyptian Papyrus (1550 BC) and the Kahun Papyrus (1850 BC), which used lint, honey, and acacia leaves as spermicides [7]. Ground dates, acacia tree bark, and honey were used as a pessary, according to the Egyptian Papyrus (1550 BC). Women in medieval Europe utilized rue and lily roots to avoid getting pregnant. In the English ruins of Dudley Castle, the oldest animal-gut condom, which dates to 1640, was found. Lemon juice is still used as a topically applied spermicide in some religious communities. Queen Anne's lace, sometimes referred to as wild carrot seed, has been used as a contraceptive method since Hippocrates [7].

While the decades since have welcomed many new contraceptive technologies, like the intravaginal ring or contraceptive implant, only the copper IUD and on-demand barrier methods offer reversible non-hormonal contraception. Furthermore, a significant lack of male-controlled options currently prevents men from accessing highly efficacious, yet reversible, control over their reproduction [8]. While investigative male hormonal contraceptives using testosterone and its synthetic analogues have been developed and reached clinical trials, none have obtained FDA approval [9].

Ideal properties of Spermicides:

- Non-irritant to mucous membrane
- Irreversibly produce immobilization of sperms
- Onset of action should be rapid once comes in contact with sperms
- No adverse effects on developing foetus
- No local or systemic toxicity on repeated exposure to medicament
- Should be absorbed systemically as it is intended only for local action
- Should possess anti-microbial properties
- Should be stable and effective during drastic pH change

Chemical classification of spermicide:

1) **Natural spermicides:** Hederagenin derivatives,Gossypol, Acaciasides A and B, Allitridium, Curcumin, Salannin, Mi-Saponin A, 14-Deoxy andrographolide, Asiatic acid etc [11]
2)

3) Synthetic spermicides:

a) Non-ionic surfactants- octoxynol and nonoxynol
b) Zidovudine derivatives
c) Vanadocenes
d) Carbodithionate and carbamodithionate derivatives
e) Disulphide esters of carbothioic acid
f) Indole derivatives
g) Carbaldehydes
h) Quinoline derivatives
i) Gel microemulsions
j) Parabens
k) 7-Membered oxazaquinolinium salts
l) Furo[3,2-h] quinolinium salts [11]

Table 1: Chemical Classification

a) Based on chemical classes:

Sl. No	Classification	Type	Mechanism of action	Examples
1)	Synthetic Products	Chemically synthesised spermicides	Damage sperm cell membranes, disrupts movement, which leads to loss of membrane strength, inability to move, and eventually cell death, stopping fertilization.	Benzalkonium chloride, Nonoxynol-9, Octoxynol
2)	Bactericidal Agents	Broad-spectrum spermicides. Acts on both the sperms and bacterial pathogens.	Interfere with sperm cell membranes and frequent administration can cause irritation to the vaginal flora.	Nonoxynol-9, Octoxynol
3)	Natural Compounds	Plant based agents with spermicidal effect	Damages the sperm cell membrane and further disrupts the mitochondrial functions, hence the sperm movement and viability is reduced.	Neem, curcumin, β-caryophyllene
4)	Sulfhydryl Binding Agents	Acts on the sulfhydryl groups.	inhibits enzyme activity essential for sperm motility. Acts by forming mercaptides by binding with sulphydryl group	Thimerosal, mercuric compounds.

Table 2: Dual Action Spermicides

b) Dual action spermicides:

Sl.No	Classification	Mechanism	Examples
1)	Anti-Inflammatory and Bioadhesive	Adheres to the vaginal tissues, providing a sustained release of active ingredients.	Bioadhesive agents combined with anti-inflammatory compounds
2)	Plant-Based Formulations	Antimicrobial properties alongside spermicidal effects	Neem extract

3)	Microbicides	An agent that inhibits the replication of HIV and also considered to be an antiretroviral.	Dapivirine
4)	Combination Formulations	Disrupts the sperm cell membrane and antimicrobials prevent STDs.	Synthetic spermicides and antimicrobial agents

MECHANISM OF ACTION

- **Change in calcium balance**

Acrosome part of spermatozoa contains some digestive enzymes which helps in breaking down the thick outer wall of ovum and helps sperms to enter inside ovum leading to fusion of egg and sperm. Extracellular calcium is required to complete this fertilization process. Spermicides have been reported to act by blocking this calcium channel or by forming complex with calcium thereby completely suppressing the availability of extracellular calcium required for acrosomal reaction or by elevating intrasperm Ca^{2+} levels affecting sperm motility [11]

- **Change in pH level:**
HV has an acidic pH because of presence of natural microbiota namely lactobacilli. Various by-products such as lactic acid, lactacin, hydrogen peroxide are continuously released into HV by lactobacilli species. These by-products are responsible for maintaining acidic pH ranging from 3.5 – 5. This low acidic vaginal pH shields from numerous pathogens causing STD's including HIV. Slightly alkaline pH range (6.7-8.5) are required to maintain spermatozoa alive and motile. Therefore once semen enters the female reproductive tract, it neutralises the acids present there leading to increase in pH above 6 and thereby facilitating sperm motility. Spermicides act by maintaining the original pH of HV by interacting with the normal ejaculate. This process hinders the increase in vaginal pH resulting in the permanent loss of motility and death of spermatozoa. [11]
- **Sulfhydryl binding agents**
Spermatozoa undergoes maturation by converting thiols groups to disulphide bonds. Hence protein present in plasma membrane spermatozoa has increased concentration of disulphide bonds in it. Chemical agents possessing ability to bind with these sulphydryl group, exerts spermicidal action. Spermicides undergoes either oxidation or alkylation and denatures the protein structure thereby killing sperms. Some of the spermicidal agents also act by forming mercaptides by binding with sulphydryl groups. [11]

- **Evaluation of spermicidal agents**
Slug mucosal irritation test:
The Slug Mucosal Irritation test enables to estimate the irritation potential of a repeated treatment with bio-adhesive powder formulations on nasal and buccal mucosal tissue. Furthermore, the local tolerance of ocular minitablets can be evaluated by means of the Slug Mucosal Irritation test. There was an excellent agreement between the Slug Mucosal Irritation test and the in vivo data on local tolerance. Recently, the procedure of the Slug Mucosal Irritation test was optimised for local tolerance testing of semi-solid vaginal formulations. As no list of reference standards exists for local tolerance screening of vaginal formulations, the relevance of the test procedure was assessed by means of a few commercially available gels with published human data on vaginal tolerance. The vaginal gels could be classified into four irritation categories (non, mild, moderate, and severe) and the results of the mucosal irritation test were comparable to the available in vivo data. Although human data should be the final standard against which the relevance of an alternative test is assessed, comparing the available data was difficult. The studies differed with

respect to their purpose, frequency and duration of use, sample sizes, target populations, comparison products, rules regarding intercourse, the means and time points for assessing safety outcomes. [13]

Sander Cramer assay for sperm immobilization:

The spermicidal effect of VRP on human spermatozoa was assessed in vitro by a modified Sander-Cramer assay method (Sander and Cramer, 1941). Serial dilutions of VRP stock solution ranging from 50μM to 450 μM were prepared in RPS medium. An aliquot of prepared sperm suspension (5×107 sperm/ml) was mixed well with different concentrations of stock VRP solution at a ratio of 1:5 (v/v). A drop was immediately placed on a glass slide and quickly examined in an Axiovert 40 CFL inverted phase contrast microscope (Zeiss, Jena, Germany) at 400X magnification. The results were observed for 20 seconds and assessed for motile spermatozoa. The optimum dose was calculated as that in which the spermatozoa lost complete motility within 20 seconds following treatment with VRP [14].

Merits:

- Affordable and economical
- Does not interfere during intercourse process
- No systemic adverse effect is seen
- These are non-hormonal contraception
- Do not require a prescription
- Does not interfere with regular menstrual cycle
- Increases lubrication during intercourse
- When used effectively, can prevent unintended pregnancies
- When used in combination with any barrier, it gives protection against sexually transmitted diseases (STDs) including from Human Immuno Deficiency Virus (HIVs)

Demerits:

- It is for single time use unlike implants which can protect for years from unintended pregnancy
- These are not considered as an effective form of contraception when used alone
- Must remain in place after ejaculation in order to make sure that all sperm are killed
- Must be applied at the correct time, and reapplied with subsequent intercourse
- Does not provide protection against sexually transmitted diseases (STDs)
- Some spermicides due to repetitive usage results in irritations of mucous membrane which increases risk of vaginal infections, HIV etc.,
- They may ooze out of vagina making it less popular among patients
- Some spermicides increase the risk of urinary tract infection (UTI) in women, by destroying the normal microbial flora of the vagina

Formulations containing spermicidal agent

- new pharmaceutical form of benzalkonium chloride, the vaginal capsule , with are reference form, the pessary, in women habitually using a contraceptive method involving a spermicide. The results concerning the acceptability criteria show that the capsule form presents a number of advantages over the pessary form: a tendency towards less discomfort through immediate discharge (possibly as a result of the superior bioadhesive properties of the capsule due to its enhanced viscosity), greater ease of use and greater satisfaction expressed by the women's partners. The remaining criteria evaluated (discomfort due to delayed discharge, signs noted at the gynecological examination, subjective signs elicited during questioning) were comparable for the two forms and in both cases were of moderate intensity and frequency. [15]
- Surface active agents (i.e. detergents) were among the first compounds to be tested as microbicides. Their mechanism of action is believed to involve membrane disruption, causing damage in the phospholipid bilayer of target cells [57-58]. This disruption probably implies changes in the electrostatic potential at the membrane surface [59]. Another a possible mechanism of action more recently proposed for this class of compounds includes a possible toxic effect in the cell cytoplasm [60]. Surfactants insert their hydrophobic regions in the lipid bilayer and may then penetrate into the cell, quickly reaching equilibrium between the inner and extracellular space

[61]. Once the detergent gets into the cell it may interact with cytoplasmic components and change their activity, for example causing changes in protein synthesis or inducing cellular death through apoptotic mechanisms by activating caspases [62]. Possible targets for surfactants inside the cell include nucleic acids (evidently targeted by cationic detergents, as DNA and RNA are negatively charged polymers) [63]. Indeed, a few studies have noted surfactant-induced DNA fragmentation [64], while others have attempted to discriminate genotoxic actions (direct action on the DNA) from the extragenomic cytotoxic action (indirect effect, also eventually leading to DNA fragmentation and subsequent cell death [16]

- Laureth 9, and ethoxylated lauryl ether, is a light yellow, viscous liquid soluble in water. It was lethal to human spermatozoa within 20 seconds in a final concentration of 1:2000. It occurred most frequently with the commercially available vaginal cream which has had an acceptable seven-year market history. None of the 51 subjects challenged with the five preparations tested reacted with edema, vesiculation, eczematization, or pruritus indicative of sensitization. [17]

Emerging science and future of contraception:

Development of novel contraceptives which are effective and safe is on the horizon with a better understanding of reproductive biology. Since the 2004 Institute of Medicine report, where recommendations were made for initiating discussions with the pharmaceutical industry about the development of new and innovative contraceptive targets, based on the rapid expansion of new technologies, and the genomic and proteomic revolution (the “omics”), the pharmaceutical industry has jettisoned many contraception R&D programs. Prospects of innovative contraceptives for females and males (both hormonal and non-hormonal) have suffered a serious setback. The working group on contraception in the Scientific Vision Workshop on Reproduction convened by the National Institute of Child Health and Human Development (NICHD) recognized that the NICHD would now need to take the lead in contraceptive R&D and change the research paradigm in this field [18]

- Ideally research objectives in the field of contraception include the improvement of existing methods, their proper use with increased access to the users, and the development of new methods which would bring additional health benefits with the goal of improving willingness to use the method and compliance. Improvement of existing contraceptive methods includes working to improve their safety and acceptability; improving cycle control in users of hormonal contraception; developing approaches to improve adherence, convenience and access to contraceptives; developing ways to increase the use of long-acting, reversible contraceptives; understanding what non-contraceptive health benefits of contraceptives are valued by users, more effectively communicating those benefits, and developing additional benefits based on end-user desire; developing programs to increase successful contraceptive use in order to achieve actual efficacy. These strategies will ensure the most effective use of current contraceptive methods, while new contraceptives are developed. Remarkable progress in the field of genomics and proteomics has led to the development of animal models such as a transgenic mouse model, with a better understanding of the complex process of reproduction. Further, behavioural assessments/indicators that predict acceptability/successful use of new contraceptives should also be developed. [18]

- The integration of nanotechnologies into vaginal spermicides opens the way to unlimited opportunities and prospects for solving their shortcomings [19]. This combination offers the potential for developing a sustained-release vaginal spermicidal formulation that may improve user acceptability by being independent of coitus. In addition, sustained release from

nanocarriers could reduce transient peaks in drug concentration and avoid high local concentrations. Further, it may provide advantageous distribution of spermicides throughout the vaginal canal [20]. Vesicular nanocarriers can also improve spermicide permeability, stability, and targeting to the site of action [21].

Preparations

An excipient and a chemical agent with spermicidal qualities make up spermicides. Excipients can be found in the following forms: soluble film, cream, jelly, suppository, pill, or foam (aerosol). They obstruct sperm migration in the vagina by acting as an inert physical barrier. The ancient Greeks were aware that the active ingredient may be an acid, such as lactic, boric, tartaric, or acetic acid. Phenyl mercuric acetate (PMA), quinine compounds, ricinoleic acid, and its derivatives are examples of microbicidal (bactericidal) drugs that work by interfering with spermatozoa metabolism. The most widely used spermicides in recent decades have been surface active agents, or detergents. The main way they work is by dissolving the sperm wall. Among the detergents are p-methanylphenyl polyoxyethylene (8.8) ether (TS-88), methoxy polyoxyethylene glycol 550 laurate, and nonylphenoxy polyethoxy ethanol (nonoxynol-9 or N-9) [10].

Conclusion

Spermicides stay key in birth control plans, offering over the counter, female-led choices. However, commonly used types such as Nonoxynol-9 can cause mucosal irritation and don't offer much protection against STIs. This shows why we must make new, gentle, dual-role spermicides that prevent fertilization and keeps the vagina healthy. New ideas in natural products, microbial peptides, and repurposed drugs hold significant promise in creating next-generation spermicides that are both effective and well-tolerated.

References

1. Abbe, C.R., Page, S.T. and Arthi Thirumalai (2020). Male Contraception. *The Yale Journal of Biology and Medicine*, 93(4), p.603.
2. Abhijit Hazra, M.B. (2014). Insights of Spermicidal Research: An Update. *Journal of Fertilization: In Vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology*, 03(01).
3. Asif, M. (2013). A Review on Spermicidal Activities of Azadirachta indica. *Journal of Pharmacognosy and Phytochemistry*, 1(5).
4. Aubeny, E., Colau, J.C. And Nandeuil, A. (2000). Local Spermicidal Contraception: A Comparative Study Of The Acceptability And Safety Of A New Pharmaceutical Formulation Of Benzalkonium Chloride, The Vaginal Capsule, With A Reference Formulation, The Pessary. *The European Journal Of Contraception & Reproductive Health Care : The Official Journal Of The European Society Of Contraception*, 5(1), Pp.61–7.
5. Bansode, O.M., Sarao, M.S. and Cooper, D.B. (2023). *Contraception*. Pubmed.
6. Baptista, M. And Ramalho-Santos, J. (2009). Spermicides, Microbicides and Antiviral Agents: Recent Advances in the Development of Novel Multi-Functional Compounds. *Mini-Reviews in Medicinal Chemistry*, 9(13), pp.1556–1567.
7. Batár, I. (2010a). State-of-the-art of non-hormonal methods of contraception: II. Chemical barrier contraceptives. *The European Journal of Contraception & Reproductive Health Care*, 15(2), pp.89–95.

8. Batár, I. (2010b). State-of-the-art of non-hormonal methods of contraception: II. Chemical barrier contraceptives. *The European Journal of Contraception & Reproductive Health Care*, 15(2), pp.89–95.
9. Berberian, d.a., gorman, w.g., drobeck, h.p., coulston, f. And slighter, r.g. (1965). The toxicology and biological properties of laureth 9 (a polyoxyethylene lauryl ether), a new spermicidal agent. *Toxicology and applied pharmacology*, 7, pp.206–14.
10. Dhondt, M., Adriaens, E., Roey, J. And Remon, J. (2005). The Evaluation Of The Local Tolerance Of Vaginal Formulations Containing Dapivirine Using The Slug Mucosal Irritation Test And The Rabbit Vaginal Irritation Test. *European Journal Of Pharmaceutics And Biopharmaceutics*, 60(3), Pp.419–425.
11. Dias, d.a., urban, s. And roessner, u. (2012). A historical Overview of Natural Products in Drug Discovery. *Metabolites*, 2(2), pp.303–336.
12. Ghosh, P., Bhoumik, A., Saha, S., Mukherjee, S., Azmi, S., Ghosh, J.K. and Dungdung, S.R. (2017). Spermicidal efficacy of VRP, a synthetic cationic antimicrobial peptide, inducing apoptosis and membrane disruption. *Journal of Cellular Physiology*, 233(2), pp.1041–1050.
13. Horvath, S., Schreiber, C.A. and Sonalkar, S. (2018). *Contraception*.
14. Lech, M.M. (2002). Spermicides 2002: an overview. *The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception*, 7(3), pp.173–7.
15. Long, J.E., Lee, M.S. and Blithe, D.L. (2021). Update on novel hormonal and non-hormonal male contraceptive development. *The Journal of Clinical Endocrinology & Metabolism*, 106(6).
16. M., S., Panda, S.P., Buddha, S., Kumari, P.V.K. And Rao, Y.S. (2021). Proniosomes: A Vesicular Drug Delivery System. *International Journal Of Current Pharmaceutical Research*, Pp.32–36.
17. Nath, S., Nahar, L. And Sarker, S.D. (2020). Fertility regulating natural products. *Annual Reports in Medicinal Chemistry*, 55, pp.459–479.
18. Sitruk-Ware, R., Nath, A. And Mishell, D.R. (2013). Contraception technology: past, present and future. *Contraception*, 87(3), pp.319–330.
19. Vieira, O.V., Hartmann, D.O., Carla, Oberdoerfer, D., Baptista, M., Manuel, Almeida, L., João Ramalho-Santos and Vaz, C. (2008). Surfactants as Microbicides and Contraceptive Agents: A Systematic In Vitro Study. *Plos ONE*, 3(8), pp. e2913–e2913.
20. Whaley, K.J., Hanes, J., Shattock, R., Cone, R.A. and Friend, D.R. (2010). Novel Approaches to Vaginal Delivery and Safety of Microbicides: Biopharmaceuticals, Nanoparticles, and Vaccines. *Antiviral Research*, 88, pp. S55–S66.
21. Zimina, M., Babich, O., Prosekov, A., Sukhikh, S., Ivanova, S., Shevchenko, M. And Noskova, S. (2020). Overview of Global Trends in Classification, Methods of Preparation and Application of Bacteriocins. *Antibiotics*, 9(9), p.553.