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Review Article

A REVIEW ON ADVANCES IN THE DEVELOPMENT OF SPERMICIDES LOADED VAGINAL DRUG DELIVERY SYSTEM: STATE OF THE ART

MENNA M. ABDELLATIF[1], MOAZ A. ELTABEEB[1*], MOHAMED A. EL-NABARAWI[2], MAHMOUD H. TEAIMA[2]

[1]Department of Industrial Pharmacy, College of Pharmaceutical Sciences and Drug Manufacturing, Misr University for Science and Technology, Giza, Egypt, [2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University
Email: moaz.eltabib@must.edu.eg

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ABSTRACT

Spermicides are bio-actives that might immobilize/kill the sperm in the vaginal tissues inducing contraception in the female genitalia. To inhibit sperm viability, the spermicidal drug might have to inhibit the penetration of sperm through the cervical tube of the uterus as well as attack sperm present in the vaginal walls. There are several classes of spermicidal agents, such as bactericides, sulfhydryl binding agents, natural compounds, and synthetic products. There are several classes of spermicidal agents that are widely reported. Spermicides could be available in different dosage forms as foams, gels, creams, films, sponges, and nanofibers. Available pharmaceutical spermicides showed particular importance for production on a large scale due to the continuous need for contraception. The upscaling of a process can be performed using a quality by design approach to ensure the achievement of the similarity principle between lab-scale and industrial scale. In addition, risk evaluation is performed to recognize all high-risk factors that can negatively affect the product to build the design space. Furthermore, the knowledge of the critical quality attributes enables the selection of the appropriate settings on a larger scale to establish a product of good quality and good packaging.

Keywords: Vaginal drug delivery, Spermicides, Critical quality attributes (CQAs), High throughput production

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INTRODUCTION

The history of contraception started with a concept that was close to the use of barrier techniques. Followers of this idea suggested the utilization of vinegar, lemon juice, and pessaries enclosing citric or lactic acid and Vaseline. Unfortunately, none of these techniques were effective, but the spermicides were fabricated and utilized widely [1]. Spermicides are fabricated in several pharmaceutical forms, like foams, gels, pessaries, creams, tablets, capsules, films, and sponges. Spermicides might be utilized coupled with other techniques such as condoms, diaphragms, and intrauterine contraceptive devices based on contraception awareness [2].

MATERIALS AND METHODS

This review article was oriented to explore the advanced developments in spermicides loaded vaginal drug delivery systems and mention the critical quality attributes that should be regarded during their scaling up.

Search strategy

Data was collected from three international databases, including PubMed, Research Gate, and Google Scholar, up to 2020. The search keywords used were vaginal drug delivery, spermicides, critical quality attributes (CQAs), and high throughput production.

Vaginal spermicide types

Bactericides/Surfactants

The integrity of the sperm membrane and its constituents are the main aspects of sperm viability. Any change occurs in the fatty constituents of membranes and proteins, resulting in a change in fluidity that might have an impact on sperm's quality [3]. Bactericides might interact with constituents in the sperm and might prevent sperm motion. For instance, benzalkonium chloride, which is a cationic surface-active agent, and sodium docusate which is an anionic surface-active agent, are employed as vaginal spermicides. Nonoxynol-9 has good spermicidal effects due to its impact on the lipotropic membrane of sperm [4]. Amphora, which was identified as Acidform, is a spermicidal drug with FDA consent as a lubricating agent for the vagina, which kills and immobilizes sperms by keeping the vaginal environment acidic (pH<5, for several hours) with no irritation. In addition, the great adhesion of amphora to the vagina membrane and the cervix might decrease the infiltration and consequently preserve its action for several hours. It has been recommended that amphora might be a good substitute for nonoxynol-9 as a contraceptive [5].

Membrane stabilizing agents

Membrane stabilizing drugs such as carbamazepine, quinidine, disopyramide, lidocaine, diltiazem, verapamil, and propranolol hydrochloride were all reported to inhibit the motility of spermatozoa *in vitro* [6]. These drugs immobilize sperm by acting on its membrane in a manner analogous to local anesthetics.

Sulfhydryl binding agents

Anaerobic metabolism, sperm motion, and protection versus reactive oxygen free radicals are important for the survival of sperm, depending on the existence of free thiols. Therefore, sulfhydryl-binding drugs might interact with thiols present in sperm, producing lipid peroxidation, incomplete axonemal phosphorylation, and, subsequently, lack of viability and motility [7]. Sulfhydryl-binding drugs act through alkylation, oxidation, or formulation of mercaptides on sperm cells [8].

Natural products and their derivatives

Several natural materials have been considered to fabricate vaginal spermicides. Curcumin provides sperm immobilizing impact, in addition to the anti-HIV aspect [9]. Allitridum, an active substituent present in garlic, was inspected as a restraint to sperm motion *in vitro* [10]. This investigation illustrated an excellent spermicidal impact of allitridum at 7.5 mg/ml. Nisin (cationic peptide) is produced by bacteria, mainly *Streptococcus* and *Lactococcus* species. Nisin is recognized for its antibacterial and spermicidal action [11]. Vaginal application of nisin (200 µg) generated total inhibition of sperm motion. The continuous vaginal application of nisin for 14 d at 200 µg did not produce any changes in the vaginal tissues of rats [12]. Besides these natural substances, microorganisms are also described to decrease sperm motion by agglomeration or by excretion of extracellular materials. For example, *Staphylococcus aureus* illustrated a spermicidal impact. In a previous investigation, *Staphylococcus aureus* was entrapped in a Carbopol gel that emitted 80% of *Staphylococcus aureus* in 30 min, which might inhibit sperm in 20 s, at 200 µg/ml [13]. It seems that *Staphylococcus aureus*

displays a sperm-agglomerating aspect through binding to define receptors on sperm and alters the shape of sperm, producing agglomeration [14]. Several natural substances have been identified as spermicides. Tartaric acid produced the greatest spermicidal action among benzalkonium chloride, nonoxynol-9, and verapamil [15]. Moreover, another investigation inspected the spermicide potential of natural substances, such as pineapple, lemon, and apple juice [16]. Moreover, saponins [17], and tannins [18] have been studied as spermicidal substances.

Synthetic products

Bis (cyclopentadienyl) complexes of vanadium are spermicides that decrease sperm motion [19]. The capability of vanadium was described to be 400 times more than that of nonoxynol-9, and unlike nonoxynol-9, the sperm-inhibiting effect was not destructive to the vaginal walls [20]. Vanadium might be present as cationic or anionic, with several oxidation states varying from+1 to+5. Vanadium complexes having oxidation states+4 and+5 might produce reactive oxygen species that might decrease sperm motility at a low amount [21].

Pharmaceutical dosage forms of spermicides

Dosage form constituents and efficacy might be as crucial as the active constituent for the medicinal action of vaginal spermicides. Commercially available spermicides must negatively affect sperm motility and viability. Spermicidal dosage forms valid worldwide involve gels, creams, capsules, tablets, foams, pessaries, films, ointments, rings, douches, and tampons. The majority of spermicidal drugs have been available as gels, with the increasing need for substitute dosage forms such as films, tablets, and rings [23].

Nonoxynol-9 is the active constituent of various novel controlled vaginal dosage forms for birth control [24]. In an investigation developed by Lee *et al.*, a mucoadhesive gel was fabricated utilizing Carbopol 934P for controlled drug delivery of nonoxynol-9 [25]. In another investigation, a silicon vaginal ring containing nonoxynol-9 was suggested to assess the capability of the utilization of this ring to prohibit sexually transmitted diseases [26]. Propranolol hydrochloride was developed as a hollow type suppository using different hydrophilic (Polyethylene glycol) and lipophilic (Witepsol H 37) bases and proved its efficacy in humans [27]. Moreover, propranolol hydrochloride was developed as a film by solvent casting method using Eudragit RS PO and HPMC 15000, which showed good mucoadhesive properties to vaginal walls [28]. In addition, propranolol hydrochloride was developed as a gel using sodium alginate at 6.5% w/w and proved its mucoadhesive property toward vaginal walls that might sustain its spermicidal activity [29]. Other spermicides were developed as a contraceptive sponge which provides not one but a combination of three active spermicides (nonoxynol-9, benzalkonium chloride, and sodium cholate) [1].

Table 1: Advantages and disadvantages of spermicides

Advantages	Disadvantages	Reference
• Available over the counter	• Behave as cytotoxins	[1, 22]
• Cost less	• Might irritate vaginal tissues	[22]
• Safer than hormonal contraceptives	• Persistent utilization might change the normal vaginal flora	[1, 15]
• No systemic side effects	• Increase risk of urinary tract infection	[22]
• Easy to utilize	• Might cause messiness in intercourse	[1]
• Under the control of a woman	• Might cause a burning sensation	[1]
• Might enhance intercourse by their lubricating action	• Might irritate the genital organs of the male partner	[1, 22]
• Might produce protection against some sexually transmitted diseases	• Pregnancy with spermicides alone varies vastly	[1]

High throughput production of spermicides loaded vaginal drug delivery system

One criterion of an ideal spermicide-loaded vaginal drug delivery system is its capability to be scaled up at a low cost, which is of special importance for the continuous need for contraception. To successfully scale up a pharmaceutical product, the similarity principle should be adopted. This principle assumes that across all equipment and process scales equal ratios between for example, dimensions, forces, and temperature gradients must be achieved [30]. In practice, it is impossible to fully meet the requirements of similarity. Therefore, scale-up is a serious point of attention in drug development. The upscaling of a process can be performed by using a quality by design (QbD) method. QbD is a statistical experiment that maintains a good relationship among the process parameters [31]. The International Conference of Harmonization (ICH) and FDA confirmed the implementation of QbD in the pharmaceutical industrial field. In addition, regulatory authorities stipulate its application for agreement on the medicinal finished product Through QbD, the cruciality of the process parameters is determined. The knowledge of the critical parameters that contribute to the final product specifications (critical quality attributes (CQAs)) enables the selection of the appropriate settings on a larger scale. Normally, the initial assessment of CQAs is conducted on the lab-scale level since experiments at industrial scale batches are associated with high costs [32]. In addition, risk evaluation was performed to recognize all high-risk factors to build the design space. As stated in the (ICH) Q9 document, risk identification and risk analysis are two basic elements of risk evaluation. The first stage of the risk evaluation was to define all the potential risk factors which might have an impact on the quality of pharmaceutical products. A Fishbone diagram (Ishikawa) (fig. 1) was performed to determine the potential variables (risk factors) impacting the CQAs of several pharmaceutical products.

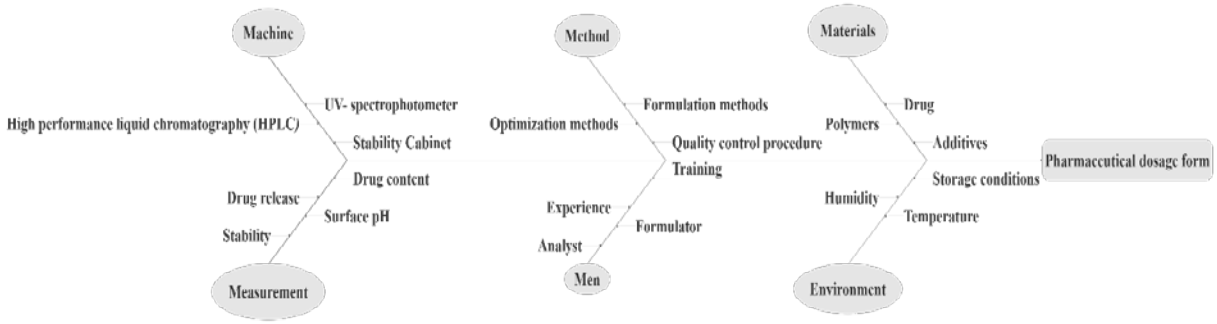

Fig. 1: Fishbone (Ishikawa) diagram for manufacturing a pharmaceutical product

At scaling up, another manufacturing equipment might be utilized as most development work has been produced on simple and small lab instruments. The instrument, which is regarded as economic, the simplest, efficient, and the ablest of formulating products with the required aspects, should be inspected based on the CQAs. The equipment size must be optimized, and the easiness of cleaning must be regarded. The production rate of pharmaceutical preparation depends on the immediate requirement and future market process. Scale-up and post-approval changes (SUPAC) system defines the pilot-scale batch for dosage forms as one-tenth of the full production or larger. The guidance categorizes changes in batch size post-approval into two levels, i.e., level I and level II. Level I changes include changes in the batch size up to and including a factor of 10 times the size of the pilot/batch, whereas level II changes encompass changes in the batch size beyond a factor of 10 times the size of the pilot/batch. Regardless of whether batch size changes fall in level I or II, certain conditions must be met for these post-approval changes to be applicable. These conditions are: The equipment employed to prepare the test batch must have the same design and operating principle, and batches are prepared following good manufacturing practices (GMP). Standard and controls employed for test and production batches, including formulation composition and manufacturing process, must be the same. Both levels I and II changes require a long-run stability study on one batch, which must be reported in the annual report. Level II changes in batch size require an additional 3 mo of accelerated stability study and dissolution profile studies on one batch, to be reported in changes being affected supplement [33]. To evaluate the manufacturing processes, validation must be done to ensure that there is no alternation in the formulation, quality of the constituents, and the instrument shape. Revalidation must be done to guarantee that alternations have not taken place [34]. Then the manufacturing procedures must have the following; weight sheet: the sheet in which the chemicals or active constituents for batch production must be stated. The process directions: must be accurate, mentioned in detail, and without confusion. Finally, the manufacturing protocol that was written by the operator illustrates several aspects such as addition rate, mixing time, mixing speed, cooling, and heating rates of the final product [35]. Hence, the next section of this review was provided to translate the outcomes of the lab-scale design for vaginal spermicides to industrial scale and to establish a product of good quality and elite packaging.

Semisolid vaginal dosage form (gel, cream, and ointment)

Vaginal semisolid preparations are commonly used to formulate microbicides and spermicides. These preparations are used to provide local and systemic effects [36]. Briefly, semisolid dosage formulation is composed of two phases; the external-continuous phase and the internal-discontinuous phase. Based on active substance solubility, it might be mixed into any of these two phases [37].

High throughput production of vaginal semisolid preparations

The manufacture of semisolid products is dependent on the dispersal of solid substances in the carrier media. The dispersion of aqueous polymers might demand various measures based on the scale where the product is fabricated. The aim is to meet the same set of CQAs no matter if 50 or 50,000 doses are being produced [23]. Several aspects should be considered during semisolid large production preparation, such as:

Material transfer rate

Transport of semisolid materials from the production tank to the filling tank is done via pipes with the help of pumps. Stimulation of flow happens through gravity, centrifugation, mechanical impulse, electromagnetic force, and displacement. Transfer of semisolids from holding tanks to the mixing or filling instrument is regarded as a problem. Any alternation in the shear stress or rate of shear or transfer rate might produce unstable final products. In addition, the particle size of the product might be increased through transfer. All these factors might be maintained in the up-scaling process as these obstacles are not observed in formulating at the lab-scale [37].

Mixing

Semisolid dosage forms are fabricated through admixing the aqueous and the oily phase in tanks with various shapes of impellers. To fabricate semisolids, agitator or shear mixers are utilized [38]. Agitator mixers such as sigma and planetary mixers while Shear mixers encompass colloidal and triple roller mills. While regarding the mixing of the discontinuous and continuous phase, we must evaluate the optimal degree of shear and the optimum admixing techniques and if the speed is enough to get a uniform semisolid at a large scale [39]. Creams need higher shear to get uniform dispersion. On the other hand, gel demands lower shear to maintain physical aspects such as viscosity. Therefore, admixing speed must be optimized at batch scale [40]. Other important considerations in the up-scaling of semisolid dosage forms encompass the admixing of two solutions at various pH at the same time to get a uniform solution. In this state, at the lab scale, the amounts are little and might be readily admixed. However, through up-scaling, the solution must be pumped and while the amount is large, the time required for pumping the whole solution will be larger [41]. Therefore, during the initial period pH might change when compared to the final pH when the whole solution is pumped. This change in pH might cause precipitation or particle size enlargement.

Heating and cooling rates

Semisolid materials have the characteristic to melt at moderate temperature and solidify if cooled at room temperature. Semisolids might have a phase transition where melting absorbs heat while cooling emits heat. Cooling rates have a great impact on the initial and final uniformity of creams fabricated with fatty alcohol or nonionic polyoxyethylene surfactants. Abrupt cooling of emulsion creams might produce mobile emulsion that might form gel during storage [42].

Packaging of semisolid vaginal preparations

Semisolids could be loaded into collapsible tubes that are made up of aluminum and tin. In the case of collapsible aluminum tubes, there are chances of minimum contamination of the remaining portion of tube content because of the absence of suck back mechanism [43].

Vaginal films

Films are water-soluble polymers formed as thin sheets that transport drugs added locally through fluids present in the vagina. Films might impart some merits over other dosage forms as their film is small in size with no need for applicators which might generate a pharmaceutical product that is easier to utilize, transport and store at low cost. The solid formulation might augment product stability through decreasing degradation via oxidation or hydrolysis and by decreasing precipitation. Vaginal films have been inspected as delivery systems for antifungals and anti-bacterial. In a study, itraconazole was fabricated as a film for the management of vaginal candidiasis [44]. Further, films were fabricated enclosing clindamycin phosphate for the management of bacterial vaginosis [45]. Moreover, contraceptive films were commercially available that contain nonoxynol-9 [46].

High throughput production of vaginal films

Films are distinctive pharmaceutical forms as they mix two dosage forms in one formula: solid dosage forms and gels. The two major techniques utilized to fabricate films are hot-melt extrusion and solvent casting [47]. These techniques include the fabrication of a pre-mix with an increment of the drug; then the formed matrix is passed via a roller. Inventive manufacturing techniques such as printing or rolling have emerged. The printing technique is composed of printing the drug on a placebo film with distinct technologies [48]. There are general CQAs of the films that must be regarded during scale up as:

Physical strength

The product must have good mechanical aspects so it might be manufactured easily, handled, and packaged with no damage. The major aspects that should be considered: are elongation at breakage, tensile strength, and young's modulus. The suitable value for the mechanical strength might differ based on the polymer matrix and manufacturing technique [49]. A good balance must be established among these aspects. The film should be soft so it can be handled with no breakage but not too flexible that it might deform through

the packaging procedure. It should have sufficient strength so it might be removed from the pouch, rolled up after casting, and pealed from the release liner, but not too much that might be hard in the cutting procedure [48].

Appearance

The size and the morphology must be carefully monitored and opted based on the strength and site of application. This is very important for vaginal formulae that have a small space available for adhesion.

Drug release profile

The optimum drug release profile should be declared early in development, depending on the product profile. The most credible tests to assess this characteristic are the disintegration time and the dissolution profile. It is also crucial to regard that following FDA rules a fast disintegration time *in vitro* must be lower than 30 s [50].

Residual water content

The water content of the films is crucial and must be determined for every formula as it might impact film aspects. Further, it is important to evaluate and control the room conditions (temperature and humidity) throughout the production process, and a suitable primary packaging substance might be supplied to prevent water transfer between the product and the surrounding environment. An increment or diminish in water content might impart the mechanical aspects of the polymer matrix. The water might intervene inside the polymer chains serving as a plasticizer, so the lack of water content might result in brittle polymeric matrices and might participate in high polymeric chain links, making it hard for water permeation so that the disintegration time might be postponed. An increment of water uptake by the polymeric matrix might result in sticky films which might adhere to the patient fingers and/or packaging material. In addition, the free water in the film might harm the stability of the drug added and/or with the excipients [50].

Others

Additional attributes might be regarded as, adhesion tests and pH evaluation especially when the drug kinetics or stability relies on it. Further, the pH determination might be critical in the evaluation of mucus membranes irritability [50].

Packaging of vaginal films

Films might be packaged in single air-tight heat-sealed foil packages. Single-dose packages might offer a more stable product and averts fusion that might happen for some multidose packaging formats [43].

Vaginal tablets

The vaginal tablets available are composed of hormones, anti-infective bio-actives, and plant extracts. Commonly utilized drugs such as tablets include neomycin, clotrimazole, tenofovir, and povidone-iodine [23]. Tablets provide various merits such as portability, accurate dosing, easy storage, the possibility of manufacture at a large scale, and low cost. Tablets could be fabricated with additional aspects such as sustained release, bioadhesion, and rapid dispersal with the aid of some excipients. In addition, tablets could be utilized to inhibit leakage that could be linked with vaginal semisolid formulations [51].

High throughput production of vaginal tablets

Tablets are generated by compressing powder in a die through punches in a rotary tablet press. At this procedure, the tablet die rotates, and punches travel inside the die and compress the powder [52]. Therefore, the process of fabrication of tablets encompasses two steps: compaction and compression. In compaction flow, the behavior of powder in the blender or hopper might be expected by mathematical calculations, including dimensionless relations and it might be repeated [53]. Hopper angle relies on two factors: wall friction angle and internal friction of the substance. A suitable hopper angle is mandatory for mass flow and reflects the level of powder in the hopper or the diameter or height of the bin, particularly for minimal outlet size. At reduced normal pressure, the wall friction augments and if the outlet size is higher, it discharges and displays a mass flow manner. In addition, the mass flow of powder depends on conditions below the hopper as a throttled valve, a lip or other protrusion, or anything that might dose a zone of stationary powder into funnel flow, regardless of the hopper angle or surface finish [54]. The intense vibrations to which a blend is subjected during the tablet compression procedure might induce blend segregation in the tote (bin blender), overhead feeding system, or in the turret. Tableting scale-up is coupled with some problems; most of these obstacles are related to decreased compaction dwell period as die cracking and tablet defects happen and their effect must be determined early in scale-up. Common tablet defects that happen in scale-up are weight variation, high friability, picking, sticking, capping, mottling, lamination, double impression, chipping, etc. Another obstacle related to the scale-up of the filling/compression procedure is over-lubrication which is very common in types of equipment using force feeders particularly when magnesium stearate lubricant is utilized in the formulation that might over-lubricate the blend and affect tablet hardness and/or dissolution adversely. Plastic materials such as microcrystalline cellulose that deform primarily via plastic deformation are largely affected as they exhibit high strain rate sensitivity, and the impact of press speed is likely to be significant. Subsequently, plastic substances might warrant filling/compression at a lower speed to gain tablets of good hardness. The majority of these problems could be decreased by enhancing the compactability and flow aspects of the blend by selecting suitable binder and other excipients with suitable moisture levels and occasionally, it might be important to redesign the tote or feeding system. Adjustments in the depth of upper punch penetration to allow removal of air from the die cavity might be suitable for resolving some of these obstacles. Providing a pre-compression stage could decrease the migration of small dust particles and simultaneously augment the total dwell period. Press speed, punch pressure, and compression force should be part of the procedure fabrication, and the critical speed at which tablet defects exacerbate must be evaluated. The importance of suitable tooling cannot be overemphasized [33].

Fortunately, the geometric similarity is maintained on the scale-up of filling/tablet compression processes as the unit volume remains the same. However, compression force, rate of its application, and ejection force should be matched to facilitate scale-up. Further, the relationship between compression force and CQAs should be investigated during the development stage. For instance, the impact of force on hardness and friability and the hardness versus dissolution relationship should be studied. High ejection force may provide an alarm for potential capping, lamination, and other issues during scale-up [33].

Packaging of vaginal tablets

Tablets might be packed in either strip or blister packages. In a strip package, the contents are sealed in a packet. The package is made up of two layers of film. A strip contains many pockets and each pocket contains a single dose of medicament. While in a blister pack, the package is made up of a base layer (Polyvinyl chloride layer) with cavities that contain the pharmaceutical product. This type of package provides greater protection than a strip package. The lid is made up of aluminum or paper foil. The package is sealed by combining lid and base utilizing heat and pressure [43].

Vaginal sponge

The vaginal sponge is a barrier technique that appears to be as efficient as a diaphragm with vaginal contraceptives. This disposable polyurethane sponge encloses the spermicidal drug nonoxynol-9. The Protectaid sponge contains 3 spermicides with a polydimethylsiloxane dispersing substance; the spermicides are nonoxynol-9, sodium cholate, and benzalkonium chloride. Additionally, sodium cholate produces antiviral action, whilst the other two bio-actives supply antimicrobial action with decreased vaginal irritation [1].

Vaginal ring

The vaginal ring is a circular ring-type drug delivery device; after insertion into the vagina, it releases the medication in a controlled pattern [55]. Ring design, the solubility of the drug in the elastomer,

and the molecular weight of the drug are regarded as CQAs for the liberation behavior of the drug. Very large emission rates might be achieved by utilizing a great drug amount at the ring. Moderately large emission rates might be accomplished through coating a ring. If an even small emission rate is required, the drug might be constricted to a small diameter at the core of the ring [56].

Electrospun nanofibers for vaginal delivery

They are a solid dosage form with several polymers that might be fabricated, and they have been discovered as a new technique for vaginal delivery. Fibers might be produced into various geometries (tubes, sheets, coatings), and fictitious dosage forms have been described for vaginal administration of fibers that are comparable to vaginal films or cervical barrier tools [57].

High throughput production of vaginal nanofibers

On the lab scale, small measures of polymer matrix are electrospun utilizing a single needle electrode, voltage generator, syringe pump, and metal collector. Formats utilized for electrospinning scale-up enclose multi-nozzle, centrifuge-based, and free surfaces, and they have been described to augment production from 0.1–1 g/h (single needle) to up to 6.5 kg/h (multi-nozzle). The NS-1WS500U (Elmarco, Inc.) is the only commercially valid production-scale electrospinning tool that utilizes the same techniques as the available manufacturing equipment, which is crucial for process transferring. In types of equipment use free surface electrospinning, a high voltage is performed via a wire or a rotating metal drum electrode. By using the wire electrode, a moving carriage adds a polymer matrix onto the wire. The polymer coating undertakes a Plateau–Rayleigh instability, forming several charged droplets on the wire. Various electrospinning jets emerge at the same time from these droplets, resulting in a large sheet of fibers gathered on a negatively charged parallel electrode. This system might operate much higher measures of solution than single needle electrode systems and has been described to generate 200 g of fibers/h, with the capability for larger production by mixing several units in series [58].

Future trends of spermicides

The integration of nanotechnologies into vaginal spermicides opens the way to unlimited opportunities and prospects for solving their shortcomings [59]. 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 [60]. Vesicular nanocarriers can also improve spermicide permeability, stability, and targeting to the site of action [61].

CONCLUSION

Recently, attention has been increased toward the large production of spermicides such as gels, foams, pessaries, sponges, and rings due to the continuous need for contraception. Some major obstacles might be taken into consideration regarding the spermicides loaded in various dosage forms during manufacturing, development, and marketing. Through the development, the critical quality attributes must be established to prohibit uncontrolled issues. Despite the complexity of the formulation and procedure, a deep knowledge of the system might be enough to control and surpass some inevitable and unpredictable proceedings. This review has come across a range of technologies that may be applied to scale up the production of spermicides. Eventually, it is critical to combine the manufacturing techniques along with the chosen spermicidal substance to acquire customer approval as convenient pharmaceutical forms.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare that there is no conflict of interest regarding the publications of this paper.

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