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Review Article

REVIEW ON FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES FOR VAGINAL APPLICATION

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ABSTRACT

Vaginal drug administration can improve prophylaxis and treatment of many conditions affecting the female reproductive tract, which includes fungal and bacterial infections, sexually transmitted diseases and cancer also. This is the best route for the administration of proteins, peptides, and also other therapeutic drugs like macro-molecules. For the administration of drugs like contraceptives, steroids, metronidazole, anti-retroviral, vaginal drug delivery is the most preferable route. However, achieving sufficient drug concentration in the vagina can be challenging because of its low permeability. The benefits of the vaginal drug delivery system are it increases the bioavailability, least systemic side effects; easiness of use and self-medication is possible. However vaginal drug delivery system is considered as a less effective route because of the unfortunate absorption of drugs across the vaginal epithelium. The traditional commercial preparations, such as creams, foams, gels, irrigations and tablets, are known to reside in the vaginal cavity for a relatively short period of time owing to the self-cleaning action of the vaginal tract and often require multiple daily doses to ensure the desired therapeutic effect. With the rapidly developing field of nanotechnology, the use of specifically designed carrier systems such as Nanoparticle-based drug delivery has been proven an excellent choice for vaginal application to overcome the challenges associated with the low permeability.

Keywords: Vaginal drug delivery, Drug absorption, Low Permeability, Factors affecting, Vaginal dosage forms, Solid lipid nanoparticles, Drug release

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INTRODUCTION

Introduction to vaginal drug delivery

Vaginal drug delivery is a novel drug delivery which acts as a local as well as systemic action based on the disease condition and drug characteristics it can be used for long-term treatment with possibility of low side effects. These systems are traditionally used to deliver contraceptives and drugs to treat vaginal infection. A formulation is given by this route as vaginal tablets, powders, cream, inserts, pessaries, douches, gel etc. The advantages of vaginal drug delivery are given below

- Achieve rapid drug absorption and quick on set of action [1].
- Avoids first pass metabolism.
- High vascularisation.
- Vaginal bio-availability of smaller drug molecules is good [2].
- Possibility of self-medication.
- Low systemic side effects.
- Non-invasive delivery.
- Convenient route for prolonged dosing.
- Avoid enzymatic deactivation in gastrointestinal tract (GIT).

Disadvantages

- Cultural sensitivity.
- Personal hygiene.
- Gender specificity.
- Local irritation.
- Sometimes the drug is leaked from the vagina.

Applications

- ✓ Drug administration by this route is useful for vaginal immunization.
- ✓ For the delivery of hormones this route is effective.
- ✓ This route is very effective for treating local fungal infections.
- ✓ This route of drug administration is useful for vaginal immunization.
- ✓ Useful for treating HIV infections [3].

Anotomy of vagina

Human vagina is a thin-walled, slightly S-shaped fibro muscular collapsible tube between 6 and 10 cm long extending from cervix of the uterus [4]. It consists of three layers which are epithelial layer, muscular coat and the tunica adventia. Surface of the vagina composed of legion folds, which are called rugae. Rugae provide dispensability, support and an increased surface area to the vaginal wall. Blood vessels supply blood to the vagina, which includes plexus of arteries extending from the internal iliac artery, uterine, middle rectal and internal pudental arteries [5]. Human vaginal fluid may contain enzyme, proteins, carbohydrates, amino acids, alcohols, enzyme inhibitors, ketones and aromatic compounds [6]. The pH of vaginal fluid is maintained in between 3.8 and 4.2 by lactobacillus acidophilus which is produced by the lactic acid, which acts as a buffer in the vagina [7]. Structure of the female reproductive system observed in the following (fig. 1).

Pathological conditions of vagina

The infection or inflammation of the vagina is known "vaginitis." The most common kind's viginitis are

- Bacterial vaginosis
- Candida or "yeast" infection
- Chlamydia
- Gonorrhea
- Trichomoniasis
- Viral vaginitis

Among all, vaginal yeast infections are very common of vaginitis, happening to over 1 million women in each year. A type of vaginitis, a vaginal yeast infection, is caused by a specific type of yeast called *candida*. *Candida vulvovaginitis* is a common problem that may affect mostly in adult women at least once in their lifetime. Approximately 80% of yeast infections are caused due to *candida albicans* and also other candida species which includes *candida glabrata* and *candida tropicalis,* which causes other infections [9]. A symptom of recurrent candida vaginitis is due to hypersensitivity reaction rather than invasive infection. This hypersensitivity reaction is associated with increasing vaginal secretion [10]. Candidiasis can be shown in the following (fig. 2).

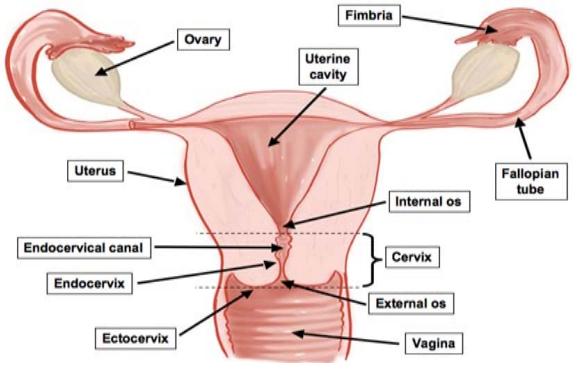

Fig. 1: Structure of female reproductive system [8]

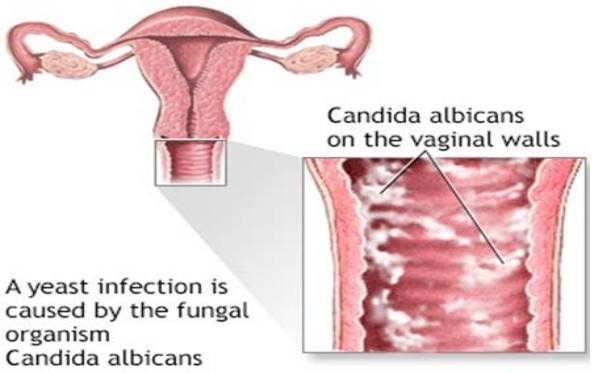

Fig. 2: Diagrammatic representation of candidiasis [11]

Symptoms of vaginal infection

- Itching and irritation in the vagina and vulva.
- Redness and swelling of the vulva.
- Watery vaginal discharge.
- Vaginal rash.
- Vaginal pain and soreness.
- Burning sensation during urination

Diagnosis

The combination of symptoms and the sample of the discharge will tell what type of yeast infection one can have and help to determine the best way to treat the infection [12]. For the diagnosis of candidal vaginitis, we can prepare hyphae on the potassium hydroxide wet mount preparation. For preparing wet mount slide, a large amount of discharge may needed. To diagnosis of yeast pH less than 4.5 are recommended. Diagnosis results can be noted in the following table (table 1).

Table 1: Diagnosis of vaginal infection

Infection	Symptoms	Physical examination	Discharge	Odour	pH	Diagnosis	Reference
Yeast infection	Pruritus	Flssures, labial rash	Thick, white to yellow	Absent	<4.5	KOH wet prep+hyphae	[12]
Bacterial vaginisis	Variable		Thin, white to gray	Present	>4.5	Clinical criteria, 3 of 4 g stain	[12]
Trichomonas infection	Pruritus	Strawberry cervix	Green, watery	Present or Absent	>4.5	NS wet prep+trichomonads	[12]

Treatment

Treatment for vaginal infections will depend on what's causing your infection. For example:

- Metronidazole tablets, cream, or gel, or clindamycin cream or gel may be prescribed for a bacterial infection.
- Antifungal creams or suppositories may be prescribed for a yeast infection.
- Metronidazole or tinidazole tablets may be prescribed for trichomoniasis.
- Estrogen creams or tablets may be prescribed for vaginal atrophy.

Vaginal route of drug absorption

Drugs can be administered into the vagina by two ways, namely

- Intra-vaginal
- Trans-vaginal

Absorption of drugs through vaginal route occurs in two steps are

1. Drug dissolution in lumen
2. Membrane penetration

Factors affecting drug absorption

Drugs transport through the vaginal membrane which takes place in three major distinct ways, namely

1) Trans-cellular transport
2) Para-cellular transport
3) Vesicular transport

The amount of drug concentration after intra-vaginal administration depends on physiological factors and physicochemical factors.

Physiological factors

- Rate of change in epithelial layer thickness.
- Cyclic changes.
- Changes in hormonal level.
- Vaginal fluid volume.
- Vaginal pH alteration.

Physicochemical factors

- Ionization.
- Molecular weight.
- Surface area.
- Chemical nature.

❖ Development from the existing drug molecule, through the conventional drug dosage form to a new system of drug delivery, can improve the drug active substance characteristics significantly in view of compliance acceptability by the patient, safety and efficacy.

Conventional vaginal dosage forms

- Tablets and suppositories
- Creams and gels
- Vaginal rings

Vaginal tablets and suppositories

Plenty of vaginal medications are available in the form of tablets or suppositories. These vaginal formulations are designed to melt in the vaginal cavity and release the drug for prolonged time. Vaginal suppositories are dissolved in inside the body, it will shows in the (fig. 3) and they can deliver the medication, which are inserted in the form of solids. These are generally available in rod, conical or wedge-shaped [14].

Limitations

- o Mucosal irritation.
- o Manufacturing cost is high.
- o Patient incompliance [15].

Fig. 3: Vaginal suppository [16]

Creams and gels

For the topical delivery of contraceptives and anti-bacterial drugs, formulations may develop in the form of creams and gels. They can also be used for reducing vaginal irritation and other sexual problems. The use of creams and gels in vaginal formulations should be non-toxic and non-irritant to the mucous membrane [17]. One of the vaginal creams shown in the (fig. 4).

Limitations

✓ Messy to apply.

✓ Uncomfortable.

✓ Sometimes feel embarrassing when they leak into the undergarments.

Fig. 4: Vaginal cream [18]

Vaginal rings

These are circular ring-type drug delivery devices designed to release the drug in a controlled manner after insertion into the vagina. Vaginal rings are approximately 5.5 cm in diameter with a traverse segment diameter of 4-9 mm. To achieve constant release of a drug from vaginal ring [19].

- Sandwich type
- Reservoir types of rings are developed.

Sandwich device

It consists of a slender drug-containing film present below the surface of the ring and sited between a non-medicated central core and a non-medicated external band.

In reservoir device

The drug is immersed in a central core, which is then surrounded by a drug-free layer. The rate of drug release may alter by changing the core diameter or thickness of the non-medicated coating. Silicon devices are frequently used for making vaginal rings. Ring make up by ethylene vinyl acetate, which is clinically accepted due to their greater flexibility [20]. The only available contraceptive vaginal ring is the Nuvaring R. the ring is given below in the (fig. 5).

Dis-advantages

- Vomiting and nausea.
- Bleeding between periods.
- Causing of breast tenderness.

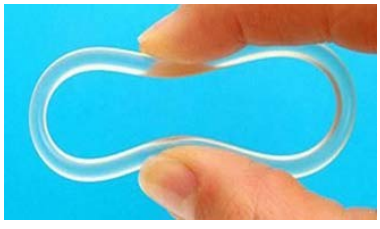

Fig. 5: Vaginal ring [21]

❖ Most vaginal dosage forms can be self-administered with minimal interference. However, these dosage forms have multiple limitations which includes.

- Inadequate spreading of drugs over vaginal surface.
- Low drug penetration to the submucosal layer.
- Possibility of leakage.

❖ Moreover, vaginal drug delivery has demonstrated inter-individual variations in the extent and rate of drug absorption such as vaginal pH, microbial flora, cervical mucus and cyclic changes during menstruation.

❖ To overcome these drawbacks, several novel approaches have been developed for efficient vaginal drug delivery.

Novel concepts in vaginal drug delivery

Vaginal drug formulations (VDFs) are made of several functional qualities. Novel vaginal drug delivery systems (NVDDS) are developed and designed with desirable qualities like distribution, bio-adhesion, retention and release characteristics. The conventional VDFs such as suppositories, creams, gels, foams can meet some but not all of these requirements, which can be achieved by the use of

- Bio-adhesive and
- Novel Nanoparticulate systems

Bio-adhesives

Conventional vaginal formulations having the disadvantage of low retention to the vaginal epithelium and leakage may occur so inconvenience may develop, to overcome these problems bio-adhesive drug delivery systems are designed to develop. These formulations are capable of delivering the drug for an extended period of time with a predictable rate.

❖ Mucosal surface properties play an important role in influencing bio-distribution and retention. To overcome all these limitations, there is need to develop novel drug delivery systems on the basis of nanotechnologies to increase drug physical stability and bioactivity, reduce toxicity and enhance patient compliance.

❖ Nano-systems such as liposomes, nanoparticles and micelles could be exploited to improve local vaginal drug delivery.

Introduction to solid lipid nanoparticles (SLNs)

Nowadays, so many formulation approaches meet the nanotechnology for the preparation of Nanosized structures containing active pharmaceutical ingredient [24]. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. Solid lipid nanoparticles introduced in 1991, the structure was shown in (fig. 6) which is alternatives for traditional colloidal carriers such as emulsions, liposomes and polymeric micro nanoparticles [25]. The reasons for the increasing interest in the lipid-based system are

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipid excipients.

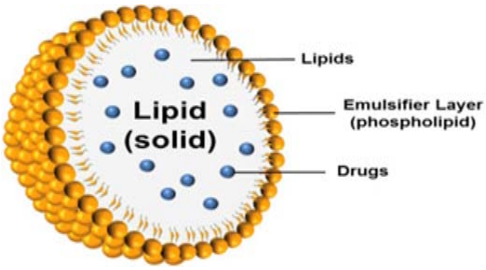

Fig. 6: Structure of solid lipid nanoparticles [26]

Advantages

1. Excellent biocompatibility.
2. No special solvents are required.
3. Long-term stability.
4. Possibility of controlled drug release and drug targeting.
5. Easy to manufacture [27].

Disadvantages

1. Particle growth.
2. Sometimes burst release.
3. Unpredictable gelation tendency [28].

Drug incorporation models

There are three drug incorporation models which describe drug release from SLN as shown in fig. 7 [29].

A) Homogenous matrix model

B) Drug enriched shell with a lipid core

C) Drug enriched core with lipid shell

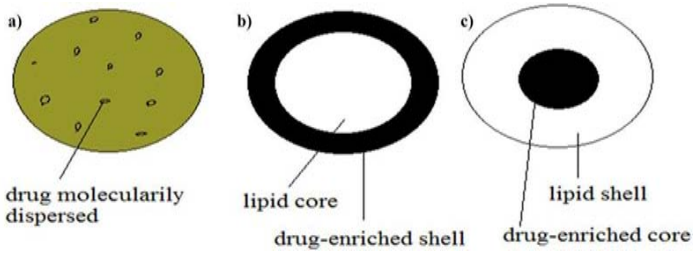

Fig. 7: Drug incorporation models [30]

Solid solution model

Drug is dispersed molecularly in the lipid matrix when solid lipid nanoparticles are prepared by cold homogenization method.

Drug-enriched shell model

A solid lipid core is formed on the basis of recrystallization temperature of lipid.

Drug-enriched core model

Cooling the nano-emulsion, which may leads the super saturation of drug which is dissolved in lipid melt it may lead recrystallization of lipid.

Composition

Ingredients

Lipids (ex: stearic acid).

Surfactants (ex: tweens).

Co-surfactants (ex: lecithin).

Others

Charge Modifiers (ex: stearyl amine).

Cryoprotectants (ex: trehalose).

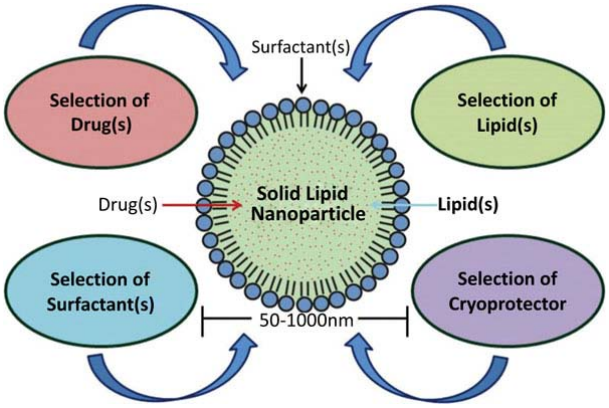

Fig. 7: A typical composition of solid lipid nanoparticles

Lipid

Lipids are the major components of SLNs. When formulating the SLNs the selection of proper lipid is essential. Selection of proper lipid for SLNs depends on the following factors [31].

- ✓ Ability to produce particles in the submicron range.
- ✓ Biodegradability.
- ✓ Biocompatibility and solubility upon storage.

Lipids can be classified on the basis of lipid matrix formed i.e., ordered, less ordered disordered matrices. Which are given in below (table 2)

Surfactant

Surfactants stabilize SLNs by decreasing the surface tension between water and lipids. The selection and concentration of surfactant depends on the lipid and the route of administration. Surfactants are divided into three categories based on their charge i.e.

- IONIC surfactant
- Non-ionic and
- Amphoteric surfactants.

In the preparation of SLNs, surfactants used are poloxamer 188, poloxamer 182, polysorbate 20, polysorbate 60, polysorbate 80, sodium cholate, sodium glycholate, soyabean lecithin, sorbitan trioleate.

Drug loading capacity of solid lipid nanoparticles

The drug loading capacity is related to the nature of the lipid and is generally expressed in terms of percentage. Drug loading capacity ranging from 1% to 50% some of the factors may affect on the drug-loading capacity of SLNs are

- ✓ Drug solubility in lipid melt.
- ✓ Miscibility of drug.
- ✓ Lipid melt.
- ✓ Structure of the lipid matrix and
- ✓ Polymeric state of the lipid.

Various drugs have been investigated as potential agents for incorporation into SLNs [32]. Some of the examples are timolol, pilocarpine, diazepam, cyclosporine, retinol, acyclovir, oxazepam. Hard fats have higher drug loading capacities because of their crystalline nature when compared with pure monoacid triglycerides [33].

Table 2: Commonly used lipids in the preparation of solid lipid nanoparticles

Lipids	Matrix arrangement	Examples	Reference
Triglycerides	Highly ordered	Trimyristin	[31]
Hard fat type	-	Witepsol W 35	[31]
Acylglycerol mixtures	Less ordered	Glyceryl monostearate	[31]

Challenges for formulation and delivery

Problems frequently occurring with many drugs are:

- Poor solubility
- Insufficient *in vitro* stability (shelf life)
- Too low bioavailability
- Too short *in vivo* stability (half-life)
- Strongside effect
- Need for targeted delivery
- Regulatory issues/hurdles
- Lack of large-scale production.

Drug release from solid lipid nanoparticles

The release of the entrapped drug from the SLNs is governed by the following principles:

o An inverse relationship exists between the release of the drug and the partition coefficient of the drug.

o Smaller particle size promotes higher surface area, thereby leading to higher drug release.

o Homogeneous dispersion of the drug in the lipid matrix causes slow release of the drug.

o Lipid crystallinity and high drug mobility lead to rapid release of the drug from the SLNs.

Various studies have been carried out on the effect of formulation parameters and process conditions regarding the release of drug from SLNs. one of the main problems with SLNs is the initial burst release of drug. The release of drugs in the form of burst from SLNs may depend on the particle size and surface area. SLNs incorporated with tetracaine and etomidate shows burst release with 100% release of the drug less than 1 min which is shown in (fig. 8).

Parameters that affect the release of drug from SLNs are temperature, amount of drug incorporated, lipid structure, drug structure, duration of production, processing equipment, lyophilisation process and sterilization process [34]. Among these, the two major parameters that influence the release of drug from solid lipid nanoparticles (SLNs) are temperature and the presence of surfactants.

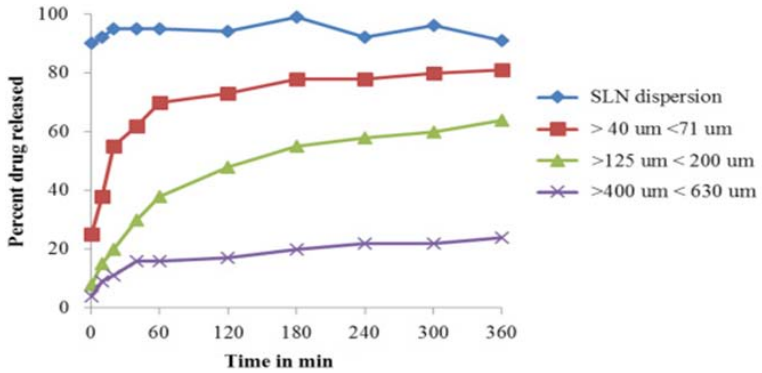

Fig. 8: Drug release profile of etomidate from SLNs and lipid microparticles of increasing particle size [35]

Influence of temperature

Investigation of drug release may prove that the highest burst release is observed at highest temperatures of production and also when hot homogenization is used as a method of production [36].

Influence of surfactants

The amount of surfactant or mixture of surfactant in the formulation also influence the burst release of drug from SLNs. at high surfactant concentration, the burst release of the drug is higher and at a lower concentration of surfactant, the burst release is lower.

Stability concerns of solid lipid nanoparticles

To the ideal drug delivery system, it must have the fallowing properties:

- Sufficient drug loading.
- Stable in environment conditions.
- Controlled and targeted release.
- Easy and inexpensive scale-up procedures.
- Selective for the site.
- Biodegradable, nontoxic and non-immunogenic.

SLNs are more stable formulations than liposomes and they produce prolonged drug release with no sterilization problems, but some SLNs are prone to gelation after certain period of storage time this is avoided by changing the lipid composition and the use of stabilizing surfactant [37]. Various factors effect the stability of SLNs are given below

- Gelling tendency.
- Influence of shear force.
- Lipid concentration.
- Stability and storage conditions.
- Properties of the lipid.
- Influence of surface of the packing material.

Preparation techniques for solid lipid nanoparticles

The performance of SLNs depends on the method of preparation which may influences the particle size, drug loading capacity, drug release, drug stability etc [38].

1. High-pressure homogenization

a. Hot homogenization

b. Cold homogenization

2. Ultra-sonication or high-speed homogenization

a. Probe ultrasonication

b. Bath ultrasonication

3. Solvent emulsification-evaporation method
4. Supercritical fluid method
5. Micro emulsion-based method
6. Spray drying method
7. Double emulsion method
8. Precipitation technique
9. Film-ultrasound dispersion

The overall preparation method was given below (fig. 9) in the form of diagrammatic representation.

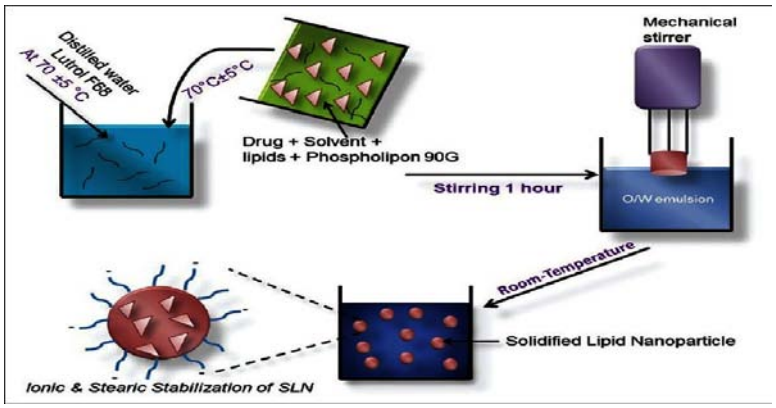

Fig. 9: Over all method of preparation of solid lipid nanoparticles (SLNs) [39]

Applications of solid lipid nanoparticles

- SLN as a potential new adjuvant for vaccines.
- SLNs in cancer chemotherapy.
- SLN in cosmetic and dermatological preparations.
- Solid lipid nanoparticles for delivering peptides and hormones.
- Solid lipid nanoparticles for targeted brain drug delivery.
- SLN as targeted carrier for anticancer drug to solid tumour [40, 41].

CONCLUSION

Still now, the vagina remains an underutilized route of drug delivery. Even though human vagina is used as a route for local action in the cervicovaginal region, but now it become a potential route for non-invasive, controlled transmucosal delivery of both local and systemically active compounds. Various therapeutically important drugs like insulin, calcitonin, sex hormones, and anti-retroviral drugs are administered through the vaginal route, but there is no success in their safe for these macromolecular drugs. Development of bio-adhesive vaginal formulations may introduce new vaginal formulations for both local and systemic delivery. Vaginal rings play a significant role in acceptable vaginal formulations. Several combinations of vaginal contraceptive rings show excellent contraceptive efficacy with minimal side effects. Here describe various types of fabrication and characterization techniques for the synthesis of solid lipid nanoparticles. SLNs shows improved skin permeation due to enhanced contact between drug and skin, which may results in large particle surface area and film formation. Controlled release nanoparticles result in reducing bacteria and fungi tolerance and decrease in the frequency of administration due to prolonged release of highly interpenetrated particles in the vaginal tissue and enhance the activity of drug, polymer, and oil-core. These nanoparticles are fast, reproducible and possess a high concentration in solids.

SEARCH CRITERIA

Solid lipid nanoparticles, vaginal drug delivery system, management of vaginitis, solid lipid nanoparticles for antifungal therapy, solid lipid nanoparticles as drug delivery system, composition of solid lipid nanoparticles, conventional dosage forms for vagina, novel concepts for vaginal drug delivery, advantages and disadvantages for solid lipid nanoparticles and vaginal drug delivery system.

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AUTHORS CONTRIBUTIONS

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

Declared none

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