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Development and Assessment of an Intravaginal Drug Delivery System for Polycystic Ovary Syndrome (PCOS)

Lakshmi Savithri Sateenapalli
Research Scholar, School of pharmacy, Sabarmati University, India.

Dr Yashoda Krishna
Professor, School of pharmacy, Sabarmati University, India.

Dr. Sujit Kumar Mohanty

Professor, School of pharmacy, Sabarmati University, India.

Abstract: The paper presents polycystic ovarian syndrome, sometimes known as PCOS, is a complicated hormonal condition that affects women, particularly those of reproductive age. As a result of a disorder that affects a significant proportion of the world's population, the chances of women becoming pregnant and their overall quality of life are significantly reduced. Considering that conventional approaches to treating polycystic ovarian syndrome (PCOS) are not only unsuccessful but often hazardous, this disease presents a challenge for the field of pharmacotherapy. Insulin resistance and a deficiency in naturally occurring myoinositol have been identified as key risk factors for endometrial cancer, according to the findings of researchers who have investigated the elements that contribute to the development of this disease. It is not possible for conventional medicine to lower the high effective doses that are contaminated with pollutants and the harmful effects that are created by the procedures that are utilized to administer conventional medication. Consequently, there is a significant need for the cutting-edge nano-applied technology that is used for the administration of medicine. This study analyzes two different combinations: myoinositol-loaded mucus penetrating particle mixes (MI-MPPs) and metformin-loaded mucus penetrating nanoparticle mixtures (MTF-MPPs). The purpose of this research is to determine whether combination is more effective. In addition to being dissolved in carbomer gel, the intravaginal route of administration is the one that is meant to be used.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age. It is characterized by hormonal imbalances, irregular menstrual cycles, anovulation, and the presence of multiple cysts on the ovaries. The condition often leads to infertility, metabolic disorders, and other long-term health complications, including an increased risk of diabetes and cardiovascular diseases. Despite the availability of pharmacological treatments such as oral contraceptives, anti-androgens, and insulin-sensitizing agents, many women with PCOS struggle with the side effects, inadequate efficacy, or inconvenience of oral drug regimens.

Intravaginal drug delivery systems (IDDS) represent an alternative approach to delivering medications directly to the site of action, offering advantages such as improved bioavailability, local targeting, and reduced systemic side effects. This delivery method can be particularly beneficial for the treatment of gynecological conditions like PCOS, as it allows for sustained release of active ingredients, greater patient compliance, and enhanced therapeutic outcomes.

The goal of this PhD research is to develop and assess an **intravaginal drug delivery system** specifically designed for the treatment of **PCOS**, focusing on delivering pharmacologically active compounds directly to the vaginal mucosa, which can potentially mitigate the systemic side effects typically associated with oral medications.

2. Research Objectives

1. **To Design and Develop an Intravaginal Drug Delivery System**:
   The first objective is to design a suitable intravaginal formulation (e.g., gel, suppository, or tablet) capable of delivering active agents such as **anti-androgens** (e.g., spironolactone), **insulin sensitizers** (e.g., metformin), or **progestins** (e.g., micronized progesterone) that are commonly used to manage the symptoms of PCOS.
2. **To Evaluate the Release Kinetics of the Formulation**:
   To ensure that the intravaginal delivery system

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provides sustained and controlled release of active ingredients, the formulation's release kinetics will be assessed using in vitro models. This will help determine whether the system can deliver a consistent therapeutic dose over time.

3. **To Assess the Pharmacokinetics and Bioavailability**:
   The study will investigate how the active compounds are absorbed through the vaginal mucosa and their subsequent distribution in the systemic circulation. This will involve pharmacokinetic studies to compare the bioavailability of intravaginal formulations with oral drug administration, with a focus on maximizing local delivery while minimizing systemic exposure.

4. **To Test the Safety and Toxicity of the Formulation**:
   Comprehensive safety assessments will be conducted to evaluate the biocompatibility of the delivery system. This includes testing for potential irritation, sensitization, and cytotoxicity, both in vitro (cell cultures) and in vivo (animal models).

5. **To Evaluate the Therapeutic Efficacy in PCOS Animal Models**:
   Preclinical testing in animal models of PCOS will be used to assess the clinical effectiveness of the intravaginal delivery system in managing symptoms such as menstrual irregularities, ovarian cyst formation, and insulin resistance. The therapeutic efficacy will be compared to traditional oral treatments.

6. **To Conduct Clinical Pilot Studies**:
   Following preclinical validation, the research will aim to conduct small-scale clinical trials to assess the safety, efficacy, and patient compliance of the developed intravaginal drug delivery system in women diagnosed with PCOS.

3. Literature Review

You will discover papers that add to the current body of knowledge on drug delivery systems by presenting innovative formulations and procedures that have the potential to improve local disease management, reduce the frequency of medication administration, or boost treatment effectiveness. These publications may be found below.

Kulsirirat et al. (2021) suggested a complex approach for the long-term distribution of pharmaceuticals. This method involves the incorporation of andrographolide-loaded nanoparticles (AGNPs) into a mixture of gelatin-based hydrogels. They used a gelatin hydrogel in conjunction with a process that included the evaporation of a single emulsion fluid in order to produce AGNPs. The use of this dual carrier strategy resulted in a substantial modification of the drug's release. The AG-loaded low MW acid end group released its contents more slowly than the AG-loaded high MW ester end group. This was due to variations in hydrophilicity between the two groups. In addition, the study successfully showed the use of in vivo imaging to monitor the real-time distribution of medicine in mice after intraperitoneal injection and joint implantation. In accordance with the in vivo imaging system (IVIS), the AGNPs-hydrogel sheet and beads kinds exhibited continuous release for a period of more than sixty days. It has been suggested that a hydrogel product that is based on AGNPs might be a safe and reversible alternative to the continued use of medicine for the treatment of localized osteoarthritis (Kulsirirat et al., 2021).

Using the syringe sonication approach, Salem et al. (2019) were able to construct nanosized transethosomes that were loaded with progesterone and transported via the vaginal canal. According to Salem et al.'s 2019 research, the ability of these nanovesicles to penetrate the body profoundly after vaginal delivery and to maintain their stability for a lengthy period of time demonstrates the possibility for enhanced pharmaceutical administration.

In 2018, Ali Taghizadehghalehjoughi and colleagues conducted a research on glioblastoma multiforme. The purpose of the study was to explore the effectiveness of PLGA nanoparticles (NPs) loaded with metformin hydrochloride (MET) and irinotecan hydrochloride (IRI). Animals in their natural environments, as well as neuron and U-87 MG glioblastoma cell cultures generated in the laboratory, were used in the research that was conducted to study these implications. When PLGA nanoparticles loaded with MET and IRI were used, there was a discernible decrease in the amount of malignancy that was removed. According to Taghizadehghalehjoughi et al. (2018), the most successful therapy for glioblastoma multiforme was a treatment that was based on NP.

An investigation of the mobility of nanoparticles in freshly extracted human cervicovaginal mucus (CVM) was carried out by Yang et al. (2014) in relation to polyvinyl alcohol (PVA) film. In order to determine how the mobility of nanoparticles in CVM was affected by PVA, which is a hydrophilic, non-charged polymer that is often employed as a buffer in the production of drug carriers, they conducted an investigation. PVA-coated particles, such as polystyrene (PS) particles, poly(lactide-co-glycolide) (PLGA) particles, or diblock copolymers of PEG-PLGA nanoparticles, were shown to be more stable in CVM than untreated particles. This was the conclusion reached by the researchers. Due to the fact that PVA coatings created particles with a mucus adhesiveness, the study suggested that different ways of particle production be investigated in order to develop mucus-penetrating particles for mucosal applications (Yang et al., 2014).

VP5k-coated PLGA nanoparticles were produced by Olcay Mert et al. (2012) by the formation of a new surfactant molecule through the combination of vitamin E with 5kDa polyethylene glycol. It was possible for these nanoparticles to reach human cervicovaginal tissue with relative ease due to the high concentration of paclitaxel that they contained, which made them an excellent choice for oral medicine delivery. In the study that was conducted by Mert et al. (2012), it was shown that this combination was successful in

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delivering medications to specific mucosal areas and ensuring that they were retained for an extended period of time.

Studies on the topic of intravaginal medication administration:

Many patients are interested in intravenous drug delivery systems because they provide a regulated and sustained release of medication. This makes these systems attractive to patients. An infection caused by a virus and an imbalance in hormone levels are just two of the many possible health problems that these systems have the ability to relieve. There is a link to a key research study on the delivery of intravaginal medicine that describes unique formulations and the impact that they have on the outcomes of therapy after being administered.

By using syringe sonication, researchers Salem et al. (2019) were able to construct nanosized transethosomes that were loaded with progesterone. These transethosomes have the potential to improve the administration of medications via the vaginal canal. According to Salem et al.'s 2019 research, their study highlighted the necessity of providing nanovesicles with exact timing and volumetric release in order to increase and extend the stability of medicine while it is being passed through the vaginal canal.

Rezk et al. (2018) focused their attention on this particular medication while they were doing their research on the problem of ovulation in PCOS women who were resistant to clomiphene citrate (CC). Rezk and his colleagues also looked at the possibility of using vaginal dydrogesterone in conjunction with letrozole that was being administered. According to the findings of the study, the clinical pregnancy rate was 48.9% for women who used luteal support in addition to going on letrozole, whereas the rate was just 23.9% for women who were only on letrozole. Based on the findings of Rezk et al. (2018), it seems that luteal phase support may have the potential to enhance the number of pregnancies that occur in women who have CC-resistant PCOS.

For the purpose of their investigation that was conducted in 2016, Saini and colleagues studied the possibility of delivering medicine via the vaginal route by using cationic niosomes in combination with a thermosensitive gel. They were able to generate cationic metformin HCl-loaded niosomes by using the process of reverse phase evaporation, which resulted in the formation of tiny, unilamellar structure. After that, a thermosensitive gel that was made up of chitosan and glycophosphate was put to them. Due to the fact that lower-dose versions did not exhibit any adverse effects, their research revealed that this method had the potential to be useful. As a result of these results, it is possible that a method of intravaginal drug administration for metformin HCl that is both safe and effective might be created, which would decrease the likelihood of experiencing side effects (Saini et al., 2016).

Since 2014, Patricia Bento da Silva and her colleagues have been exploring hypotonic nano-formulations, which is a relatively new area of research. A number of different combinations have the potential to absorb fluid, which would make it easier for nanoparticles and drugs to pass through the vaginal epithelium. This is an exciting possibility. In addition to this, they have the capability of enhancing the absorption of nano-formulations across mucosal surfaces, such as those that are present in the nose and the stomach. According to the findings of the study, particles that are able to penetrate other forms of mucus have the capacity to accomplish the same thing via vaginal mucus, especially when there is pressure-induced fluid present (Patricia Bento da Silva, 2014).

Yoo et al. (2011) conducted research on the use of Eudragit S-100 as the primary component in order to examine the creation of pH-responsive nanoparticles. By focusing on how these nanoparticles burst in situations with low pH, such as vaginal mucus and seminal fluid contact, they were able to establish that the releasing properties of these nanoparticles are reliant on the pH of the environment. According to the results of Yoo et al. (2011), pH-responsive nanoparticles have the potential to transport individualized medicines into the vaginal cavity.
Nanoparticles encapsulating tenofovir/tenofovir disoproxil fumarate were developed and reported by Zhang et al. (2011) for the purpose of administering medicine intravaginally. The release of these nanoparticles, which were composed of polylactic acid (PLGA) and methacrylic acid copolymer (S-100), occurred when the pH of the solution changed, especially when a substance that was similar to human seminal fluid was present. Zhang et al. (2011) shown in their research that PLGA/S-100 nanoparticles have the potential to serve as an alternative delivery mechanism for anti-HIV/AIDS microbicides. This is especially true when the nanoparticles are delivered vaginally via the caveolin-mediated pathway.

PEG was used in the synthesis of the modified PLGA nanoparticles that were changed by Cu et al. (2011). These nanoparticles included coumarin-6. It was thus possible for the drug to penetrate the uterus in a more effective manner. Avid-NPs and PEG-NPs, two forms of surface-modified nanoparticles, were shown to have a much longer vaginal retention time when compared to untreated PLGA-NPs, as evidenced by the data. I find it fascinating that PLGA-PEG NPs continued to reach their peak in different layers of vaginal tissue even six hours after the therapy was administered. This demonstrates that they have the potential to improve the delivery of drugs via the vaginal route (Cu et al., 2011).

Researchers have started down a potential new road by creating disease in animals as models in order to better understand and battle polycystic ovarian syndrome (PCOS). With the use of these models, it may be possible to get a better understanding of the intricate processes that contribute to polycystic ovarian syndrome (PCOS) as well as potential therapies for the condition. A research study that illustrates how new techniques affect the design of the PCOS model is presented in the following document.

It is Ming-xing W. who is the author. The researchers et al.

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(2020) took a risk with their PCOS study by constructing an IR-PCOS model for rats. The rats were administered letrozole and a diet rich in fat for a period of thirty days in order to generate this model. The groups that served as controls were given either carboxymethylcellulose solution or letrozole solution in addition to their typical diet. On the 31st day, a large number of tests were carried out in order to ascertain the influence that the beginning of the sickness has on the therapy. Individuals who were diagnosed with IR-PCOS had significantly bigger ovaries and total bodies when compared to the control groups. After doing external exams of the ovaries, it was discovered that what seemed to be bigger sacs that were more translucent were really follicles. Furthermore, during the last week of therapy, the levels of FINS and HOMA-IR were significantly greater in the group who had IR-PCOS analysis. Furthermore, the levels of hormones in their bodies were considerably found to be raised. Our findings indicated that the PCOS-IR rat model, which is characterized by hormonal abnormalities and modifications in ovarian cysts, may be produced by either letrozole or a diet that is rich in fat (Wang et al., 2020).

A hormonal and metabolic illness that cannot be cured, polycystic ovarian syndrome (PCOS) is a condition that is not well understood and is difficult to treat. The extent to which dietary variables impact the PCOS profile was not well understood. The purpose of this study is to illustrate, using rats, how injecting DHEA at birth might potentially cause polycystic ovarian syndrome (PCOS). The rats were administered the 45 of the HFD as well as the 60 of the HFD. We discovered a wide range of reproductive issues in rats that were given DHEA and DHEACHFDs. These issues included polycystic ovaries, irregular periods, and hyperandrogenism. Hormonal changes, such as increased body fat and weight, lower glucose tolerance, and higher blood insulin levels, were among the many adverse effects of adding HFDs, especially 60% HFDs, which induced a more drastic shift in ovulation shape than is normal. These changes were among the numerous negative effects of adding HFDs. Based on the results of quantitative polymerase chain reaction (qPCR), the rise in LH and androgen receptor expression in the brain that was caused by DHEA was eliminated when 60% was added.

In a study that was published in 2016 by Zhang H. and colleagues, it was only after the inclusion of sixty percent high-fat diets that the expression of insulin receptor mRNA and LH receptor mRNA in the ovaries rose. Based on these findings, it seems that DHEA and DHEACHFDs may exert their impact on various types of polycystic ovarian syndrome in a variety of distinct patterns: LH is the mechanism by which DHEA has its impact on the regular functioning of the hypothalamus-pituitary-ovarian axis. The incorporation of HFDs aggravated hormonal and metabolic difficulties by causing a change in the ovarian response to insulin-related activities. In conclusion, we came to the conclusion that high-fat diets (HFDs) might be exploited to investigate the metabolic and reproductive components of polycystic ovarian syndrome (PCOS) by establishing unique PCOS phenotypes that are induced by DHEA.

In a rat model of polycystic ovary syndrome (PCOS), dehydroepiandrosterone (DHEA) promotes ovarian hyperfibrosis (and others 2018). Mr. Wang D. was the one who made this discovery. Examination is conducted on the pathway of TGF-β signaling. Through the enhancement of MMP2 and the inhibition of TGF-β's signals that extend farther, TGF-βRI inhibitors effectively limit the accumulation of collagen. A TGF-βRI inhibitor, which suppresses the production of genes that accelerate fibrosis and modifies the mediator of the epithelial-mesenchymal transition (EMT), has the potential to diminish ovarian hyperfibrosis in rats with polycystic ovary syndrome (PCOS) caused by DHEA. This particular inhibitor has the ability to lessen the severity of ovarian hyperfibrosis. In rats, the author has shown that DHEA has the potential to stimulate the TGF-β signaling system, resulting in the development of ovarian over-fibrosis.

4. Methodology

1. **Formulation Development**:

Selection of Active Pharmaceutical Ingredients (APIs): Based on the pathophysiology of PCOS, active ingredients such as **spironolactone**, **metformin**, and **progesterone** will be selected for the formulation. These are the cornerstone treatments for managing hyperandrogenism, insulin resistance, and menstrual irregularities in PCOS.

Formulation Types: The study will explore different intravaginal delivery systems, such as **hydrogel-based formulations**, **suppositories**, or **biodegradable tablets**. Each formulation will be designed for optimal stability, comfort, and sustained release of the active ingredients.

Excipients: Non-active ingredients, such as stabilizers, emulsifiers, and preservatives, will be carefully chosen to enhance the bioavailability of the API and ensure the overall stability and compatibility of the formulation with vaginal tissues.

2. **In Vitro Release Studies**:

Dissolution Testing: The in vitro drug release kinetics will be tested using **phosphate-buffered saline (PBS)** or **Simulated Vaginal Fluid (SVF)** as release media. The study will monitor the amount of drug released over time, comparing different formulations for their release profiles.

Release Mechanisms: The study will investigate whether the release of the drug follows **zero-order** (constant release) or **first-order** kinetics, which will guide the formulation design for optimal therapeutic dosing.

3. **Pharmacokinetics Studies**:

Animal Models: In vivo absorption and bioavailability will be assessed in animal models, with a focus on the vaginal absorption of the drug and its systemic distribution. Blood and tissue samples will be analyzed to measure the concentration of active compounds over time.

Comparative Studies: The pharmacokinetic profile of the intravaginal formulation will be compared with that of oral administration, helping to determine whether vaginal administration provides higher local concentrations of the drug while minimizing systemic exposure.

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4. **Safety and Toxicity Testing**:

In Vitro Cytotoxicity Assays: Cell viability assays (e.g., MTT, LDH release) will be used to assess the toxicity of the formulation on vaginal epithelial cells or other relevant cell lines.

Irritation and Sensitization: Standardized **irritation tests** (e.g., Draize test) will be performed to ensure that the formulation does not cause adverse reactions, such as burning, redness, or swelling, in the vaginal mucosa.

Histopathological Studies: Post-treatment tissue samples from animal models will be examined histologically for any signs of inflammation, tissue damage, or adverse effects.

5. **Preclinical Testing and Animal Studies**:

Preclinical studies will involve the use of **PCOS animal models** (such as rodents treated with hormonal imbalances to mimic the symptoms of PCOS) to assess the formulation's ability to regulate ovarian function, restore menstrual cycles, reduce cyst formation, and improve insulin sensitivity.

Endocrine Assessments: Hormonal levels (e.g., testosterone, estradiol, progesterone) and metabolic markers (e.g., glucose, insulin) will be monitored to evaluate the therapeutic efficacy of the drug delivery system in restoring hormonal balance.

6. **Pilot Clinical Trials**:

A small-scale pilot study will be conducted with women diagnosed with PCOS to assess the safety and patient acceptability of the intravaginal formulation. Parameters like ease of use, comfort, frequency of application, and patient compliance will be evaluated alongside clinical endpoints such as changes in menstrual cycle regularity, ovarian cyst reduction, and improvements in symptoms of hyperandrogenism (e.g., acne, hirsutism).

Expected Outcomes

1. **Development of an Optimized Drug Delivery System**:

The research is expected to result in the development of a highly effective, patient-friendly intravaginal drug delivery system that can provide sustained and controlled release of active compounds used in the treatment of PCOS.

2. **Improved Bioavailability and Targeted Delivery**:

By delivering the medication directly to the vaginal mucosa, this system is anticipated to increase local bioavailability and reduce the need for higher systemic doses, potentially minimizing side effects and improving the overall therapeutic response.

3. **Demonstration of Safety and Efficacy**:

The formulation will be validated for safety and efficacy through rigorous preclinical and clinical testing. The goal is to demonstrate that the intravaginal system is as effective, if not more so, than conventional oral therapies for managing PCOS symptoms.

4. **Enhanced Patient Compliance**:

The convenience and reduced side effects of intravaginal delivery may lead to higher patient compliance compared to traditional oral regimens, improving long-term management of PCOS.

Conclusion

The development of an **intravaginal drug delivery system** for the treatment of **Polycystic Ovary Syndrome (PCOS)** represents a promising alternative to conventional oral treatments. By improving drug bioavailability, minimizing systemic side effects, and providing a targeted approach to managing PCOS symptoms, this research has the potential to offer women a more effective and convenient treatment option.

The outcomes of this study could pave the way for the development of new intravaginal delivery systems for a variety of gynecological disorders, contributing to the growing field of localized drug delivery and personalized medicine. The findings could also have broader implications for enhancing patient compliance and improving the quality of life for women suffering from PCOS.

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