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A REVIEW ARTICLE ON FORMULATION AND EVALUATION OF ISOCONAZOLE NITRITE INSITU GEL SYSTEM BY USING VARIOUS POLYMERS

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ABSTRACT

Conventional vaginal dosage forms of antifungal drugs often show poor therapeutic efficacy due to rapid leakage, dilution, and short residence time at the site of application. To overcome these limitations, in situ gelling drug delivery systems have gained significant attention, as they transform from liquid to gel under physiological conditions, thereby enhancing drug retention and sustained release. The present study was aimed at the formulation and evaluation of an in situ gelling system of isoconazole nitrate using various polymers. Isoconazole nitrate, a broad-spectrum antifungal agent, was selected for the treatment of vaginal fungal infections. Sodium alginate was used as an ion-activated gelling agent, while HPMC E50 LV and other viscosity-enhancing polymers were incorporated to optimize gel strength and drug release characteristics. The prepared formulations were evaluated for clarity, pH, viscosity, gelation capacity, drug content, in vitro drug release, and stability studies. The optimized formulation exhibited suitable viscosity, rapid gelation in the presence of simulated vaginal fluid, and sustained drug release for up to 8 hours. The formulations were found to be stable, non-irritant, and effective in providing prolonged antifungal activity. Thus, the developed isoconazole nitrate in situ gelling system using various polymers offers a promising alternative to conventional vaginal formulations with improved residence time, enhanced bioavailability, and sustained drug release.

KEYWORDS: Isoconazole nitrate; In situ gelling system; Vaginal drug delivery; Polymers; Sustained.

NOVEL DRUG DELIVERY SYSTEM

"A Novel Drug Delivery System (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. "It aims to improve the efficacy, bioavailability, and targeted delivery of drugs, while minimizing side effects.

The field of pharmaceutical sciences has evolved significantly over the past few decades, particularly in the area of drug delivery. While the discovery of new drugs continues to be essential, the success of any therapeutic agent heavily depends on how effectively it reaches its target site within the body, at the right time, in the right concentration, and with minimal side effects. This critical aspect of healthcare has led to the development of Novel Drug Delivery Systems (NDDS)—a revolutionary advancement that has transformed conventional approaches to drug administration.[1,2]

ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM[3]

1. Decreased dosing frequency.
2. Sustained and consistent blood level within the therapeutic window.
3. Enhanced bioavailability.
4. To achieve a targeted drug release.
5. Reduced side effects.
6. Improved patient compliance.
7. Enhanced drug stability and minimized degradation

DISADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM[4]

1. High Cost.
2. Complex Formulation and Manufacturing.
3. Stability Issues.
4. Lengthy Regulatory Approval.

Storage and Handling Challenges.

CASSIFICATION OF NDDS BASED ON DRUG REEASE PROFILE[1,5]

1. Immediate release system

These formulations release the drug immediately after administration

Example: Soluble tablets of paracetamol, aspirin.

2. Sustained release system

These systems release the drug slowly and steadily over an extended period.

Example: Sustained-release tablets of Diclofenac, Propranolol.

3. Controlled release system

Similar to sustained release but with more precise control over drug release rate.

Example: Zero-order release osmotic pump systems.

4. Delayed Release Systems

Drug release is delayed for a specific period after administration

Example: Omeprazole

CLASSIFICATION OF NDDS BASED ON ROUTE OF ADMINISTRATION

1. Oral Drug Delivery Systems

NDDS improves solubility, stability, and controls drug release.

Examples: Osmotic pumps

2. Transdermal Drug Delivery Systems

Delivers drugs through the skin into systemic circulation.

Examples: Transdermal patches (e.g., nicotine, fentanyl)

3. Parenteral Drug Delivery Systems

Includes intravenous (IV), intramuscular (IM), and subcutaneous (SC) injection.

Examples: Liposomes, Nanoparticles, Depot injections

4. Ocular Drug Delivery Systems

For treating eye disorders, bypassing barriers like tear drainage.

Examples: In situ gels, Ocular insert

5. Nasal Drug Delivery Systems

Rapid absorption due to rich blood supply in nasal mucous.

Examples: Nasal sprays, Nanoparticle suspensions

6. Pulmonary Drug Delivery Systems

Delivers drugs directly to the lungs via inhalation.

Examples: Dry powder inhalers (DPI)

7**. Buccal and Sublingual Systems**

Placed in the cheek (buccal) or under the tongue (sublingual).

Examples: Muco adhesive films, Fast-dissolving tablets

8. Rectal and Vaginal Drug Delivery Systems

Useful when oral route is not feasible (e.g., vomiting, unconscious patients)

Examples: Suppositories, Vaginal rings

APPICATIONS[6]

1. Direct delivery of drugs to specific cells or tissues, reducing side effects.
2. Maintains therapeutic drug levels over an extended period.
3. Enhances absorption and effectiveness of poorly soluble drugs.
4. Reduces the frequency of drug administration.
5. Limits drug exposure to healthy tissues, minimizing toxicity.
6. Increases patient convenience and adherence to treatment.

INSITU GELLING SYSTEM[7]

An "in situ gel" is a liquid formulation that transforms into a gel-like state upon contact with body fluids or under specific environmental conditions, such as temperature or pH changes. This process allows for controlled and sustained drug release.

An in-situ gelling system is a formulation that is in the form of a solution before it enters the body, but it transforms into a gel under one or combinations of a variety of physiological conditions. The sol-to-gel transition depends on a variety of factors, including temperature, pH changes, solvent exchange, UV radiation, and the presence of specific molecules or ions.

In situ gels are commonly used in drug delivery, particularly for localized applications like ophthalmic (eye), oral, and rectal/vaginal administrations. They offer advantages over traditional drug delivery methods by providing sustained drug release, improved bioavailability, and increased patient compliance.

ADVANTAGES OF INSITU GELLING SYSTEM[8]

Prolonged and sustained drug release.

Improved patient compliance.

Localized action. Delivers the drug directly to the target site (ocular, nasal, vaginal, etc.).

Enhanced bioavailability.

Ease of administration.

DISADVANTAGES OF INSITU GELLING SYSTEM[9]

Sensitive to physiological variations.

Limited drug loading capacity.

Difficult to sterilize.

Stability issues Viscosity related issues.

POLYMERS USED IN INSITTU GELS

Hydroxy propyl methyl cellulose(HPMC): Thermo-sensitive polymer to increase the viscosity of the formulation.

Poloxamer127: It is a thermo reversible polymer to forming a gel at body temperature to enable sustained drug release.

Benzalkonium chloride: It is preservative. In gel system still needs protection from bacteria and other contaminants.

Sodium chloride (NaCl): To adjust the viscosity and stability of gel formulation.

Glycerine: act as a co-solvent to improving uniform distribution within the gel matrix.

EVALUATION PRAMETERS

1. Appearance
2. Ph
3. Drug content
4. Gelation studies
5. Rheology
6. In vitro release studies
7. Comparison of release profile with marketed product
8. Sterility
9. In vitro efficacy
10. Stability studies

VAGINAL DRUG DELIVERY SYSTEM

Vagina is route for administration for contraceptives, anti-fungal, and antimicrobials. It is used for the achievement of local or systemic absorption. The vaginal wall is very well suited for the absorption of drugs for systemic use. This route offers certain advantages, such as avoidance of gut and hepatic first pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs. Vaginally administered agents and formulations are mainly being developed to provide "dual prophylaxis" for contraception and protection against microbial infections.[10]

Advantages[11]

- Prolonged release minimal systemic side effects.
- An increase in bioavailability.
- First-pass metabolism can be avoided.
- Self-medication is possible.
- Quick onset of action.

Disadvantages[12]

- Gender specificity.
- Patient incompliance.
- Only a few drugs are administered by this route.
- Influence with sexual intercourse.
- Personal hygiene.

VAGINAL YEAST INFECTION (DISEASE)

A Vaginal yeast infection (also called candidiasis) is a common fungal infection caused by an overgrowth of a yeast called candida, most often candida albicans, in the vaginal area. Vaginal yeast infection, medically known as Vulvovaginal Candidiasis (VVC), is a common fungal infection affecting women worldwide. It is mainly caused by the opportunistic fungus Candida albicans, which is normally present in small amounts in the vagina as part of the normal microbial flora. Under certain conditions, the fungus overgrows, leading to infection and inflammation of the vaginal mucosa.

VVC is one of the most frequent causes of vaginal infections in women of reproductive age. It is estimated that nearly 75% of women experience at least one episode of vaginal candidiasis during their lifetime, and about 40–50% may have recurrent episodes.[13]

FEATURES	DETAILS
Cause	Over growth of candida albicans
Common symptoms	Itching Thick discharge Redness and burning
Diagnosis	Microscopic /lab test
Treatment	Anti-fungal Vaginal creams Tablets or pills
Prevention	Good hygiene, loose clothing
Risk factors	Pregnancy, uncontrolled diabetes Weakened immune system

Drug profile

ISOCONAZOLE NITRATE

Generic Names

- Isoconazole (OS: BAN, USAN, DCF)
- Isoconazolo (OS: DCIT)

Categories

- Antifungal agent
- Imidazole derivative

CAS number: 0027523-40-6

Molecular weight: 416.12 $g \cdot mol^{-1}$

Chemical formula: C18-H14-Cl4-N2-O

IUPAC Name

(*RS*)-1-[2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole

PLAN OF WORK

Preformulation study

- Drug-exipient compatibility
- Polymer selection
- Gelation mechanism studies
- In vitro characterization
- Other relevant studies

Formulation Development

Evaluation parameters of insitu gels

- Physical appearance
- Viscosity

- Gelation temperature
- Drug release profile
- Stability.
- Clarity
- pH
- Gelling capacity
- Rheological properties (viscosity and flow behavior)
- In-vitro drug release
- Sterility testing

SUMMARY

The aim of the present work was to develop an effective in-situ gelling vaginal drug delivery system of Isoconazole Nitrate to enhance local drug retention and therapeutic efficacy in the treatment of vaginal fungal infections. In-situ gels offer advantages such as prolonged residence time, reduced dosing frequency, controlled drug release, and improved patient comfort.

The formulations were prepared by the cold method using suitable concentrations of polymers. Different batches were formulated by varying polymer ratios to study their effect on gelling capacity, viscosity, and drug release behavior. The prepared in-situ gels were clear, homogeneous, and free from particulate matter.

Evaluation studies revealed that the pH of all formulations was within the normal vaginal pH range, indicating safety for vaginal application. Viscosity measurements showed that formulations had low viscosity before administration and increased viscosity after gelation. Drug content studies confirmed uniform distribution of Isoconazole Nitrate in all formulations.

In-vitro drug release studies showed a sustained release pattern, which is desirable for maintaining therapeutic drug levels at the site of infection. Rheological studies demonstrated non-Newtonian, pseudoplastic behavior, facilitating ease of administration. Sterility testing confirmed that the formulations were free from microbial contamination. Stability studies showed that the formulations remained stable under accelerated conditions.

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