

Design and Development of an Antifungal Microsphere based Topical Formula for Treating Skin Problems

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Abstract: The main objective was to design diffusion controlled drug delivery system of antifungal drug in order to control or sustain the delivery of the drug and thereby reduce the gastrointestinal disturbances and dose related adverse effects like hepatic dysfunction and allergic reactions. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200 μ m. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release. Microspheres were prepared by optimizing various parameters and studying their effects on particle size as well as entrapment efficiency. Size of microspheres affects the rate of drug release. As size decreases, the surface area - to - volume ratio of the particle increases. Microspheres was prepared with aim to deliver the drug which passes through transdermal route as it provides quick onset of action when compared to oral route.

Keywords: Microsphere, Transdermal delivery, Fungal infection, controlled release, Topical formulation

1. Introduction

The present research has been undertaken with the aim to develop a topical gel formulation of antifungal microsphere. It is an imidazole derivative and used for the treatment of local and systemic fungal infection. The oral use of antifungal drug is not much recommended as it has many side effects.

Commercially Itraconazole topical microsphere based preparation are not available in the market, thus this formulation is made for better patient compliance and to reduce the dose of the drug and to avoid the side effects like liver damage and kidney damage.

Fungal infections

Fungi are responsible for fungal infections. Contagious fungi can cause certain infections. Although most fungal infections are not dangerous, some can be. You can contract a fungus by inhaling its spores or coming into touch with them. The skin may potentially be exposed to the spores. Some fungus can grow new offspring using spores. Infections with fungi may begin on the skin or in the lungs. You may be more susceptible to developing a fungus infection if you have a compromised immune system or are using medications (such as those used to treat cancer or organ transplants) that impair immunity.

Symptoms of Fungal Infections

Depending on the type of infection and the illness's location, different fungal infections may cause different symptoms.

- Irritation
- Scaly skin
- Redness
- Itching
- Swelling
- Blisters

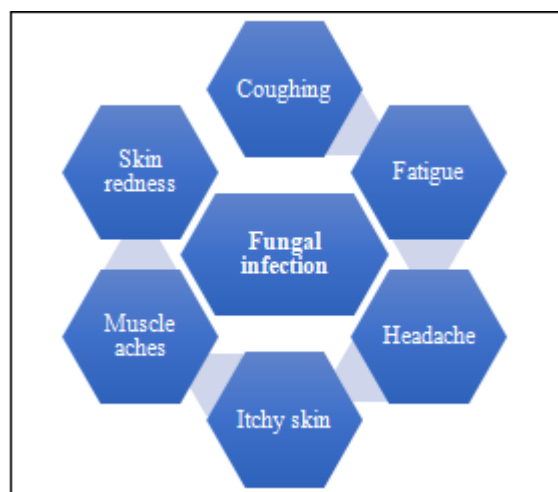


Figure 1: Symptoms of Fungal infection

Topical delivery system

The term "topical delivery system" describes a technique whereby the formulation is administered to the skin, eyes, nose, and vagina in order to treat local ailments. When a medicine is applied topically, it avoids the hepatic first pass metabolism, changes in stomach pH, and fluctuations in plasma levels that are typically experienced when a drug is delivered orally.

The local therapy of these disorders involves ongoing research on topical medicine delivery to the skin's surface. The majority of exogenous compounds (drugs/active moiety) exhibit resistance to permeability, which poses a significant design issue for topical drug delivery systems. Furthermore, it is challenging to create an effective topical delivery system since illness states affect skin's permeability and its barrier qualities.

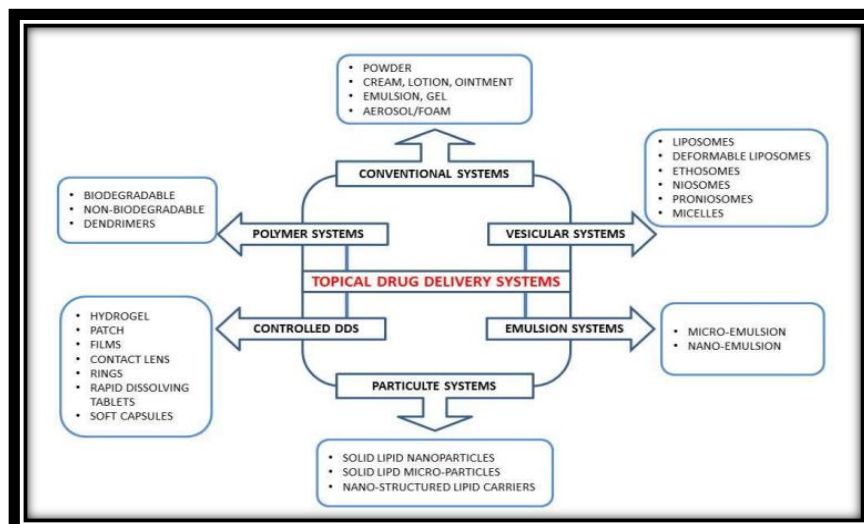


Figure 2: Topical delivery system

Benefits of the topical route of drug administration

- Alternative to Oral Medicine Administration
- Low Chance of Drug Abuse
- Minimal Chance of Digestive Issues
- Extremely Simple Administrative Procedure.
- Reducing Hospital Traffic

Microsphere

Small spherical shape particles known as microspheres range from 1 μ m to 1000 μ m in size. They are spherical, freely circulating particles made of biodegradable synthetic or protein polymers. Micromatrices and microcapsules are the two different forms of microspheres. Microparticles are another name for microspheres. Multitudinous organic and synthetic materials can be used to make microspheres. Microspheres are important for improve the absorption of traditional medications and reducing negative effects.

Microspheres play a crucial role to improve bioavailability of traditional drugs and minimizing side effects. The main advantage of applying microspheres as drugs delivery system is the controlled release of the drug substances.

Microspheres can be made by a variety of ways including emulsification technique with single or double solvent evaporation system, spray - dry technique or phase separation technique. Microspheres can be prepared by dissolving the starting materials in volatile solvents and then dispersing them in another solvent which is not miscible with the previous. Later complete evaporation of the last solvent will produce a fine powder called microspheres which is soluble in water.

Advantages of microspheres

- Reducing the size of the particles to improve a drug's low solubility.
- Offer a consistent and long - lasting therapeutic impact.
- Maintain a steady medication concentration in the blood, boosting the compliance with patents.
- Reduce toxicity and dosage.
- They are excellent for drug distribution because they prevent enzymatic and photolytic cleavage of the medication.

- Compared to big polymer implants, biodegradable microspheres offer the benefit of not requiring surgery for installation or removal.
- A delivery with controlled release utilizing biodegradable microspheres to regulate medication release rates reduce hazardous side effects and eliminates the hassle of frequent injections.

Disadvantage:

- The cost is more.
- Reproducibility is less.
- Degradation of product.
- Polymer may produce toxic effect

Method of preparation of microspheres

Single emulsion technique: Various Carbohydrates and Proteins are mainly prepared by this technique. In this technique, natural polymers are first dissolved in aqueous medium and then dispersed in non - aqueous medium (oil phase) followed with next step crosslinking of dispersed globule which can be performed by 2 methods:

- **By Heat:** Addition of dispersion into heated oil, but this method is not suitable for thermolabile drugs.
- **By Chemical Cross - linking Agent:** Using glutaraldehyde, formaldehyde, acid chloride etc. as cross - linking agent. Chemical cross - linking suffers the disadvantage of excessive exposure

Double emulsion technique: In preparation microsphere of Double emulsion method involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is exposed then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). The results in the formation of a

double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH - RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction

Spray drying technique: In this technique, the polymer is dissolved in volatile organic solvent like dichloromethane, acetone etc. and then drug (solid form) is dispersed in polymer solution under high speed homogenization. Dispersion is then atomized in the hot air stream, and atomization lead to the formation of small droplets from which solvent evaporates instantaneously; leading to formation of microsphere in a size range of 1 - 100 μm . Prepared micro particles are separated by hot air by the help of cyclone separator and solvent traces is removed by vacuum drying.

Phase separation coacervation technique: Phase separation method is mainly designed for preparing the reservoir type of the system. This method is used to encapsulate water soluble drugs e. g. peptides, proteins and some of preparations having matrix type particular, when the drug is hydrophobic in nature e. g. steroids. The process is based on the principal of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the coacervates. The coacervation can be brought about by the addition of the third component to the system which results in the formation of the two phases, one rich in polymer, while other not, i. e. depleted of the polymer. There are various methods which are effectively employed for coacervates phase separation. The methods are based on the salt addition, on - solvent addition, addition of the incompatible polymer.

Solvent evaporation technique: This is one of the earliest methods of microsphere manufacture. The polymer and drug must be soluble in an organic solvent, frequently methylene chloride. The solution containing the polymer and the drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvent and leave the solid polymer-drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension.

Evaluation of Microsphere

Drug polymer interaction (FTIR) study: FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer. The drug and potassium bromide were mixed and pellets were prepared by compressing the powders at 100 kg/cm² for 1 min on KBR - press and the spectra were scanned in the wave number range of 4000 - 400 cm^{-1} . FTIR study was carried out on drug, physical mixture of drug and polymer, drug loaded microspheres.

Surface morphology (SEM): Scanning electron microscopy has been used to determine particle size, surface morphology and texture. SEM studies were carried out by using scanning microscope. Dry microspheres were placed

on an electron microscope stub covered with a black adhesive tape and observed under microscope after applying vacuum. Picture of microspheres were taken by random scanning of the stub.

Antifungal activity: Antifungal activity of the final formulation was checked by cup - plate method. A definite volume of the *Candida albicans* suspension (inoculum) was poured into the sterilized dextrose agar media cooled at 40° and mixed thoroughly. About 20 ml of this medium was poured aseptically in the petriplates and kept to solidify. The surface of the agar plates was pierced using a sterile cork bottles. Standard solution of Itraconazole, optimized batch of microsphere cream and conventional cream having same strength was filled in the prepared wells. After that it was incubated at 28° for 24 h. The fungal growth was observed and the zone of inhibition was measured using antibiotic zone reader.

Isoelectric point: The micro - electrophoresis is an apparatus used to measure the electrophoresis mobility of microsphere from which isoelectric point can be determined.

Dissolution apparatus: Standard USP or BP dissolution apparatus have been used to study in vitro release profile using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100 - 500 ml and speed of rotation from 50 - 100rpm.

Application of Microsphere:

- Vaccine drug delivery
- Oral drug delivery
- Buccal drug delivery
- Gastrointestinal drug delivery
- Nasal drug delivery
- Improvement of flow properties
- Taste and odour masking
- Protection of the drug from the environment

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