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MICROSPHERES FOR TOPICAL DELIVERY IN FUNGAL DISEASES: A REVIEW ON EFFICIENT SMALL CARRIER

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ABSTRACT

Microspheres are typically free flowing material having particle size ranging from 1-1000 µm comprise of drug and varieties of polymers in matrix or encapsulated form. Microspheres are multiparticulate carriers which are fabricated to achieve prolonged and controlled delivery of drugs with minimal side effects and improving patient compliance. Microspheres administrated by topical route, can avoid pre systemic metabolism, reduce side effects and improve the therapeutic activity of drug. This carrier delivery system offers numerous benefits over conventional dosage forms that lead to significant improvement in drug bioavailability. This review article mainly focuses on the basic concepts of microspheres along with their types, methods and materials of preparation along with latest advances of microspheres in topical delivery.

Keywords: Tiny carriers, Microspheres, Topical drug delivery, Fungal diseases, bioavailability

INTRODUCTION

Topical Drug Delivery System

Topical drug delivery may be defined as the direct application of an active medicament containing formulation for treating cutaneous disorder. The topical drug delivery system is generally used where other administration routes such as oral, sublingual, rectal, parenteral, etc., are inappropriate for the successful drug delivery.

Conventional topical formulations such as ointments, creams, lotions and emulgel

provide better storage stability, good spreadability, enhanced drug loading capacity, controlled drug release and easily removable from skin, if water soluble base is used **[1]**.

a) Factors affecting topical drug absorption:

- Application site
- Physical properties of stratum corneum such as thickness and integrity.
- Penetrability of the membrane
- Skin hydration
- Molecule size
- Formulation pH
- Amount of drug metabolism through skin flora
- Depot of drug in skin
- Blood flow variation in the skin

b) Merits of topical drug delivery system:[2]

- Avoid Pre systemic metabolism
- Steady infusion of a drug can be achieved by topical medication over a prolonged period of time.
- Reduction in side effects
- Gastric and intestinal fluids interference is avoided.
- Controlled drug plasma level can be maintained for an extended period of time.
- Improved patient compliance
- Drugs with shorter biological half-life and poor oral bioavailability are ideal candidates for topical delivery.
- Improve patient compliance.
- Ease in administration with reduction in pain.

c) Demerits of topical drug delivery system:[3]

- Probability of local irritation at the site of application.
- Formulation excipients may cause certain unwanted responses such as itching, redness, local oedema, etc.
- Permeation inability may occur with large molecules so ideal candidate should have size below 800-1000 Daltons.
- Variability in skin barrier function in different sites of same person.

FUNGAL INFECTION

Fungi usually make their homes in moist areas of the body where skin surfaces meet: between the toes, in the genital area, and under the breasts. Common fungal skin infections are caused by yeasts (such as Candida or Malassezia furfur) or dermatophytes, such as Epidermophyton, Microsporum, and Trichophyton. Many such fungi live only in the topmost layer of the epidermis (stratum corneum) and do not penetrate deeper. Obese people are more likely to get these infections because they

have excessive skinfolds, especially if the skin within a skinfold becomes irritated and broken down (intertrigo). People with diabetes tend to be more susceptible to fungal infections as well.

A different type of fungal skin infection arises as follows:

1. Athlete's foot (Tinea pedis)
2. Nail infection (Tinea unguium)
3. Ringworm of the body (Tinea corporis)
4. Ringworm of the groin (Tinea cruris)
5. Ringworm of the scalp (Tineacapitis)

Candida infections of the skin respond well to a range of antifungals available in cream, powder, or solution formulations. Useful antifungals for Candidiasis are azole drugs (econazole, clotrimazole, ketoconazole, and miconazole). Other antifungal agents, not suitable for dermatophytosis, are the topical forms of the polyene antifungal drugs, such as nystatin, amphotericin B, and natamycin. Generally, superficial infections due to Candida of the skin and mucous membranes respond well to these treatments.

MICROSPHERES

Microspheres are tiny spherical particles with diameters ranges 10-1000 μm. Microspheres have tremendous properties in significant enhancement of drug bioavailability and reducing it side effects. The main advantage of applying Microsphere as drugs delivery system is the controlled release of medicament. Microspheres are used for retarding the drug release from dosage forms, reduced the adverse effects and increased the patient compliance. Microspheres can be made using a variety of ways including emulsification technique with single or double solvent evaporation, spray drying method, phase separation technique and so on.

In general, two types of microspheres are exists in place: (i) Microcapsules and (ii) Micrometrics

Microcapsules are cavities of micron size, where entrapped substance is distinctly surrounded by a capsule wall where micrometrics are solid carriers in which entrapped substance is dispersed throughout the matrix. Solid biodegradable Microspheres have the potential for the sustained and controlled release of drug. They are made up of polymeric, waxy or other protective materials **[4].**

a) Merits of Microspheres

Microspheres have tremendous advantages over conventional delivery systems **[5]**.

- Tiny micron particle size of microspheres leads improvement in aqueous solubility followed by significant enhancement in bioavailability, especially for poorly water-soluble molecules.

- Drug-polymer matrix in microspheres maintains prolonged and controlled drug plasma levels that prevents drug bursting in systemic circulation.
- Improves patient compliance by reducing dose, frequency and dose related toxicity.
- Drug stability and release can be amended due to morphology of microspheres.
- Effective protein delivery can be possible by microspheres carriers system as it protect the drug molecule as of enzymatic and photolytic metabolism.
- Occurrence of adverse drug reactions may be reduced due to improved drug therapeutic response.
- The unpleasant taste of liquid medicaments can be masked by fabricating in these tiny particles.
- Frequent invasive processes for implantation can be avoided by manufacturing microspheres of biodegradable polymers.

b) Demerits of microspheres

Microspheres have certain drawbacks as under: **[6]**

- The manufacturing and material cost is relatively high.
- It is challenging to make batch to batch reproducibility.
- Occasionally, the stability of encapsulating drug is quite tough to be maintained due to various process parameters such as change in pH, temperature alteration, stirring speed, time, addition of solvent and evaporation.
- The environmental impact due to various chemical reactions leads to degradation of products.

CATEGORIES OF MICROSPHERES:

Based on the applicability and the properties of excipients used in microspheres, it is categorised in different classes.

- Bioadhesive microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Mucoadhesive microspheres
- Polymeric microspheres

(i) Biodegradable polymeric microspheres

(ii) Synthetic polymeric microspheres

a) Bioadhesive microspheres

The term bioadhesion can be defined as bonding of the entity to the mucus membrane. Bioadhesion principle is used to enhance residence time of formulation with the mucus for the prolonged release of medication. Bioadhesive microspheres are collectively developed for the improvement of drug performance. The special category

of polymers is utilized for the fabrication of bioadhesive microspheres. Such type of microspheres is manufactured for varieties of mucosal membrane such as nasal, buccal, rectal, ocular, etc. Enhancements in drug absorption along with controlled release of medication are the important outcomes of bioadhesive microspheres. This comprises significant improvement in drug bioavailability with lesser dosing frequency and improves patient compliance **[7]**.

b) Magnetic microspheres

Magnetic microspheres have tremendous achievements in the field of drug targeting. Such type of novel carrier is utilized for the deposition of medicament to a diseased site. This carrier receives responses from the externally applied magnetic field and deposit at one place inside the body that enhance the capability of drug to be remained at diseased site for the longer period of time, and thereafter shows its maximum therapeutic efficiency **[8]**.

Varies types of such carriers are utilized in pharmaceutical applications such as Therapeutic magnetic microspheres and Diagnostic magnetic microspheres. The effective delivery of drugs for liver tumour is possible by therapeutic magnetic microspheres. Targeting of Proteins and peptides types of molecules can be also delivered through such novel carrier **[9]**. The medicament can be either encapsulated into the matrix or conjugated on microsphere surface, thereafter the medicament will be delivered after reaching to the target site **[10]**.

c) Floating microspheres

The principle of floating technology is based on the fact that the formulation has lesser bulk density than the gastric fluid and therefore leftovers buoyant in stomach irrespective gastric emptying time. Consequently, carrier releases the medicament at sustained and controlled rate for the desired period of time in the stomach. This leads to prolonged therapeutic effect with minimal chances of dose dumping. Many drugs such as antihypertensive drugs, proton pump inhibitors, etc. are delivered successfully with this technology **[11].**

d) Radioactive microspheres

Radioactive microspheres are of great importance in case of treatment of cancer. Such microspheres are targeted discriminatory to the affected tumour tissue and thereby prevent the serious adverse reactions to the non-tumorous tissues. Usually, this type of microspheres is administered by parenteral route to the systemic circulation for the prevention of development of tumour that enables the removal of tumour nodes. Different classes of radioactive microspheres such as α, β

and γ emitters are available for effective treatment of cancer **[12].**

e) Mucoadhesive microspheres

Mucoadhesive microspheres are designed to offer the potentials of localized along with systemic controlled drug release by sticking to the mucosal tissues of various cavities such as gastrointestinal tract, nasal cavity, eye, urinary tract, etc.

These microspheres are fabricated either exclusively with mucoadhesive polymer or coated from outer side with such adhesive polymer. Such material may enhance the intimate contact and improves the absorption followed by significant increment in bioavailability. The definite targeting of drug to the absorption site is achieved by attaching special moieties on the surface of the microspheres. [13]

f) Polymeric microspheres

Polymeric microspheres are categorized as follows:

- Biodegradable polymeric microspheres

Naturally accessible polymers are frequently utilized for the virtue of their biocompatibility, biodegradability and bioadhesiveness. Such polymers have ability for high degree of swelling that enhances the intimate contact with membrane which leads to controlled release of medicament. The concentration of polymer has more impact on the release pattern of formulation **[14].**

- Synthetic polymeric microspheres

The physicochemical properties of polymer can be modified synthetically. The laboratory synthesized polymers have superior capabilities for showing effective delivery of drug. They are proved to be safe and biocompatible for use. However, the shortfall of this kind of formulation is having potential risk that may leads to organ damage **[15].**

MATERIALS FOR MICROSPHERES

The important backbone for the preparation of microspheres to show its excellence is a type and property of polymers. There are two categories of polymers frequently used in fabrication of microspheres: (i) Synthetic Polymers and (ii) Natural polymers

- Synthetic polymers are classified into two types.

1) Non-biodegradable polymers

Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

2) Biodegradable polymers

Lactides, Glycolides and co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

- Naturally available polymers are obtained from different sources such as proteins (Albumin, Gelatin and Collagen), carbohydrates (Starch, Agarose, Carrageenan and Chitosan) and chemically modified carbohydrates (Poly dextran and Poly starch) **[16].**

TECHNIQUES FOR FABRICATION OF MICROSPHERES

The techniques utilized to prepare microspheres have major impact on various physicochemical properties and performance of dosage form. The ideal method should meet following needs.

1. The method should be suitable to incorporate maximum amount of drug.
2. The formulation should have good stability throughout the shelf life.
3. The method shall produce microspheres of narrow particle size range and shall be easily dispersible in aqueous solvent for injection.
4. The prepared micron size particles shall show controlled release of drug over large span of time.
5. The particles shall have compatibility with a biological environment.

The following methods are used often for the preparation of microspheres.

a) Emulsion solvent evaporation technique

The emulsion solvent evaporation technique is widely used for the successful preparation of microspheres. The suitable organic solvent containing dissolved drug and polymer are dispersing into the aqueous medium containing suitable stabilizer such as polyvinyl chloride (PVP). The mixture is undergone stirring with specified period of time for the evaporation of organic phase. The resultant microsphere particles are collected by filtration, dried and desiccated at room temperature for 24 h **[15].**

b) Emulsion cross linking method

A previously heated aqueous solution containing a drug and polymer was dispersed drop wise into non aqueous solvent such as liquid paraffin with stirring at high speed for a specific period of time. This mixture results into w/o emulsion. The cross-linking agent (Glutaraldehyde) was added with constant stirring. The micro sized particles so obtained were filtered and washed a number of times with petroleum ether to get rid of oil. Finally, the washing was again carried out with organic solvent such as acetone to remove additional cross-linking agent. The microspheres thus prepared were dried at room temperature and stored **[17]**.

c) Coacervation / phase separation method

Drug to be encapsulated is dispersed in the aqueous solution of polymer (gelatin) followed by addition of incompatible solvent to induce coacervation. The suspended particles are encapsulated by coacervated gelatin droplets to form micro sized particles **[8]**.

d) Spray drying technique

This technique is used successfully for large scale production of microparticles.

The spray drying technique is an ultimate method as it produces the particles with specific quality standards such as polydispersivity in particle size, moisture content, density, and shape of particles. A mixture of suitable organic solvent containing drug and polymer is sprayed in the spray dryer environment for solidification of particles followed by quick evaporation of organic solvent. At the end, the particles are collected from the bottom of sprayer **[18]**.

e) Ionic gelation

An aqueous solution of polymer such as sodium alginate consisting of drug is stirred continuously to get complete solution. Aqueous solution is added to the solution containing Ca^{2+} /Al^{3+} and chitosan in acetic acid. Microparticles are then kept in original solution for gelling up to 24 h followed by filtration **[18]**.

f) Hydroxyl appetite (HAP) microspheres in sphere morphology

This method is utilized to prepare sphere shaped microspheres. In this technology, o/w emulsion prepared followed by evaporation of solvent. An o/w emulsion was first prepared by the addition of organic phase consisting of drug, polymer and HAP in to aqueous surfactant solution with constant stirring. Surfactant is providing strength to particles from preventing agglomerates. Solid micro particles are formed after evaporation of organic phase **[19]**.

RECENT ADVANTAGES OF MICROSPHERES FOR TOPICAL DELIVERY SYSTEM

Giannola G *et al* (2001) have developed a new formulation, in which vancomycin is entrapped into trehalose and hydroxyethylcellulose spherical matrices. Microspheres were produced by the solvent evaporation method. The entrapped drug was fully recovered following microspheres dissolution. Differential scanning calorimetry analyses proved that drug is existing in its amorphous form. The stabilizing effects of trehalose on vancomycin were evaluated even after long storage of microspheres. Calorimetric data indicated no decomposition of the entrapped drug. The vitro drug release study shows sustained release of formulation. The prepared new delivery system seems to have characteristics suitable for topical applications on extensive and purulent wounds **[20]**.

Rolland A *et al* (1993) have found that for the improvement in therapeutic index of adapalene, a fabrication of novel microspheres as particulate carrier is required for the development in the treatment of acne. The prepared narrow sized microspheres shown to target via follicular ducts but not penetrate through

the stratum corneum followed on topical delivery. Thus, minimal particle size is having important role in site specific delivery. In vitro release showed controlled and rapid release of microsphere loaded adapalene into artificial sebum at 37°C than in vivo sebum excretion in humans. To study the impact of formulation on dose and dosage form frequency, various formulations of drug loaded microspheres were studied in the rhino mouse model. In this model, topical formulations of drug loaded microspheres showed dose-related comedolytic activity. Additionally, 10 times lesser concentrated site-specific delivery of formulation (0.01%) showed similar pharmacological activity with the aqueous gel containing drug crystals (0.1%). The Follicular drug targeting by micron size particles showed significant therapeutic response in the treatment related with pilo sebaceous units **[21].**

Virmani T *et al* (2018) have reviewed important aspects of microspheres as new drug carrier in pharmaceutical industries. In last decades, newer techniques and innovation have played important role in the improvement of health all over the globe. The drawbacks of conventional techniques such as lower bioavailability, toxicity, adverse side effects and poor efficacy of medicament can be significantly altered by the use of novel technologies. Among all newer carriers, microspheres have shown tremendous impact as far the sustained and controlled release is concerned. Microspheres showed impactful applications in pharmaceutical field as it may administer by many routes such as topical, oral. Parenteral, etc. Radioactive labelled microspheres have shown major medicinal importance for the treatment of disease with labelled isotope tagging. Fluorescent microspheres have remarkable contribution for membrane-based technology flow cytometry, cell biology, fluorescent linked immuno sorbent assay **[22]**.

Rai SY *et al* (2016) have prepared microsphere and shown the impact of process parameters such as drug-polymer ratio, amount of surfactant and stirring speed on dependent parameters such as particle size and entrapment efficiency. A statistical tool was used for characterization and optimization of formulation. A three-level factorial Box Behnken design was used for optimizing of Microspheres by utilizing emulsion solvent evaporation method containing Clotrimazole as drug model and Eudragit S100 as polymer. The optimized formulation showed 35.6 µm particle size and 83.3%, entrapment efficiency. The formulation of microsphere-based cream showed a controlled release pattern **[23]**.

Bansal H *et al* (2011) have studied that the improved therapeutic efficacy of drug molecules can be achieved by designing controlled drug carriers over the convention systems. Microsphere as a novel carriers shown enhanced impact in drug performance due to its sizes lesser than 200 µm, spherical shape and controlled release. The performance of drug molecule encapsulated in microspheres is depending on independent parameters such as type of raw materials, preparation method or process parameters used. This article emphasis on delivery of optimal amount of drug molecule to the specific site / tissue at given course of time with lesser toxicity and side effects. This article also emphasis on the use of biodegradable polymers in fabrication of microspheres for the controlled drug delivery **[24].**

Kumar JR *et al* (2014) have aimed to develop ketoconazole loaded microsphere gel for topical delivery in the treatment of fungal infections. The optimized formulation showed maximum encapsulation of antifungal drug with controlled drug release up to 12 h. The formulation is also reducing percutaneous absorption on administration to the skin. The optimized formulation showed particle size in range of 30-120µm while gel showed viscosity in the range of 6999 to 18596 cps. The formulation has shown good mucoadhesion force (26.72 dynes/cm^2) with notable spreadability (4.44 gm.cm/sec), which are the prime importance for any topical formulation **[25]**.

Albertini B *et al* (2009) have aimed to design Econazole nitrate loaded mucoadhesive microparticles as an innovative vaginal delivery system to increase the drug antifungal action. Microparticles of lipid–hydrophilic matrix (Gelucire® 53/10) and mucoadhesive polymers (chitosan, sodium carboxy methylcellulose and poloxamers - Lutrol® F68 and F127) were prepared by spray-congealing technique. Optimize formulation showed particle size from 100–355 µm with significant impact on solubility, mucoadhesive strength and in vitro bioavailability enhancement for poorly soluble drug. The microparticulate formulation showed inhibition influence on the growth of C. albicans. It can be concluded that mucoadhesive microparticles can be utilized effectively in the treatment for vaginal candidiasis with reduced frequency of administration **[26]**.

CONCLUSION

It can be concluded from above review that the microspheres are better choice of drug carrier for topical delivery of antifungal drugs. An application of microspheres has tremendous impact on therapeutic

efficiency of drug molecule in terms of improvement in solubility, absorption, followed by bioavailability. With the aim to reduce side effects, avoidance of first pass metabolism and maximizing the antifungal drug activity, microspheres can be successfully utilized for site specific delivery via topical route. Topical delivery of microspheres improves patients' compliance by reducing administration of lesser amount of dose and frequency. These features of microspheres impart the acceptability for their usage or the maximizing the therapeutic behaviour of drugs.

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