ANTIFUNGAL GEL: FOR DIFFERENT ROUTES OF ADMINISTRATION AND DIFFERENT DRUG DELIVERY SYSTEM

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ABSTRACT

Gel formulation could be improved the dermatomycoses are the most widespread superficial fungal infection among human beings. Different formulations and routes are used for the treatment of fungal diseases; among them topical, oral, vaginal and ophthalmic routes are most convenient, effective and highly patient’s acceptability. Topical application has many advantages over the conventional and injectable dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayer composition and without pain full. Most of antifungal drugs have lots of side effects such as stomach and intestine problems, kidney problem may occurred, especially upon oral administration, so topical application of the drug we can avoid these side effects. Topical gels are intended for skin application or to certain mucosal surfaces for local action as well as systemic action or percutaneous penetration of medicament or for their emollient or protective action. Gels are evaluated by following parameters such as pH, homogeneity, drug content, viscosity, spreadability, extrudability, skin irritation studies, in vitro release, ex vivo permeation study, in vivo study and Stability study.

Key words: Antifungal gel, topical, oral, vaginal, ophthalmic, liposome, noisome, ethosome, microsphere.

INTRODUCTION

Now a day’s transdermal drug delivery systems are a consistent source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of antifungal drug delivery (i.e. oral, intravenous). Because of the Skin particularly the stratum corneum, provides a barrier for the penetration of the majority of the substances. Gels are semisolid formulations, which have an external solvent phase, may be hydrophilic or hydrophobic in nature, Recent studies have reported other types of gels for dermal drug application, such as niosomal gels, liposomal gel, erythrosomal gel, microsphere gel. Topical, buccal, vaginal and ophthalmic provides a promising site for local effect as well as systemic drug delivery because of its smooth large surface area, rich blood supply, avoidance of the first pass effect, relatively high permeability to many antifungal drugs and self-insertion. The currently available formulations, such as creams, foams, gels, irrigations, tablets, have some limitations, such as leakage, less stability, messiness and relatively low residence time owing to the self-cleaning action of the vaginal tract, eye, and buccal cavity and often require multiple daily doses to ensure the desired therapeutic effect. This review aims to introduce the latest trends in transdermal drug delivery via topical, buccal, vaginal and ophthalmic routes and to provide insight into the latest gel types (niosomal gels, liposomal gel, erythrosomal gel, microsphere gel) as well as recent technologies for topical and transdermal drug delivery.

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Different routes of administration of antifungal gel
Topical routes of administration
Buccal routes of administration
Vaginal routes of administration
Ophthalmic routes of administration

Topical routes of administration
Topical preparations are formulae which are applied directly to an external body surface by spreading, rubbing, spraying or instillation. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects (Helal et al., 2012). Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations (Niyaz B, 2011).

Uses
Used in the treatment of a variety of dermatological skin infections like tinea and candidal infections of the skin.

Buccal routes of administration
Buccal routes have been used to deliver drugs such as certain antifungal drugs that are subjected to first-pass metabolism. The fluoride rinses and gels used in some oral care regimens are used primarily for antibacterial activity against gingival plaque; they are not used expressly for the prevention of dental caries. Candidal prophylaxis usually includes nystatin rinses or clotrimazole troches. If patients have a very dry mouth, troches are not as effective because they do not dissolve well in a dry environment. Amphotericin-B rinses also are occasionally used in place of nystatin. Fluconazole may be used for candidal prophylaxis or for treatment of suspected candidiasis.

USES
Oral gel is used to treat fungal infections in the mouth, throat and gastrointestinal tract, such as oral candidiasis (thrush) caused by the yeast candida; as well as to prevent spread of infection (Anonymous 1)

Vaginal routes of administration
Vaginal delivery is an important route of drug administration for both local and systemic diseases. The vaginal route has some advantages due to its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs and self-insertion. The traditional commercial preparations, such as creams, foams, gels 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. The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems in order to retain drugs for treating largely local conditions, or for use in contraception. In particular, protection against sexually-transmitted diseases is critical. To prolong the residence time in the vaginal cavity, bioadhesive therapeutic systems have been developed in the form of semi-solid and solid dosage forms (Fusun A, 2009).

Uses
This medication is used to treat certain types of bacterial infections in the vagina. It may help to decrease itching, discharge and other symptoms. Vandazole (metronidazole) is a vaginal gel used to treat bacterial vaginosis in women who are not pregnant. Vandazole is for vaginal use only and should not be put in the eyes, mouth or on the skin. The use of other vaginal products and vaginal intercourse should be avoided during treatment with vandazole.

Ophthalmic routes of administration
In last few decades, significant attention has been focused on development of controlled and sustained drug delivery systems. The unique structure of the eye restricts the entry of drug molecules at the site of action. Drug delivery to the eye can be broadly classified into anterior and posterior segments. Conventional systems such as eye drops, suspensions, and ointments cannot be considered optimal in the treatment of vision, threatening ocular diseases (Gaudana R, 2009 and Lang JC, 1995). Among them the extensive research has been carried in designing of polymeric drug delivery systems. The development of in situ gel systems has received considerable attention. Ocular in situ gels are the delivery system, which can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes (Kumar S, 1994).

In situ gels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. In situ gel-forming
ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel–sol) and pseudoplastic behavior to minimize interference with blinking.

Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye which, upon exposure to physiological conditions, changes to the gel phase, thus increasing the pre-corneal residence time of the delivery system and enhancing ocular bioavailability.

Gel systems are better retained in the eye than conventional eye drops and are better tolerated by patients than inserts and ointments. Like ointments, gels are also difficult to administer for some patients. In this respect in situ gels are interesting since these are conveniently dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence. The sol-gel-sol transition occurs as a result of chemical and physical change induced by the physiological environment. Here we described the in situ ophthalmic gels were prepared by the pH triggered method, pH triggered in-situ gelling system are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in conjunctival cul-de-sac (Padma PJ, 2010).

**Uses**

Ophthalmic in-situ gel generally more comfortable than insoluble or soluble insertion and less blurred vision as compared to ointment. Increased bioavailability due to increased pre-corneal residence time decreased naso-lacrimal drainage of the drug which causes undesirable side effects arising due to systemic absorption of the drug through naso-lacrimal duct is reduced. Drug effect is prolonged hence frequent instillation of drug is not required. The principle advantage of this formulation is the possibility of administering accurate and reproducible quantities, in contrast to already gelled formulations and moreover promoting pre-corneal retention (Katariya DC, 2012).

**Different drug delivery system of antifungal gel**

| A. Liposomal drug delivery system |
| B. Niosomal drug delivery system |
| C. Ethosomal drug delivery system |
| D. Microsphere drug delivery system |

**Liposomes**

Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shell(s) consisting of lipids arranged in a bi-layer configuration (Argan N, 2012).

**Preparation method of liposome**

Aqueous liposomal dispersions were prepared by conventional lipid film hydration method. Different weight ratios of phospholipids, cholesterol and drug were weight and dissolved in chloroform in 250 ml round bottom flask. A thin film was formed on evaporating organic solvent under vacuum in rotator evaporator at 35-40°C. Subsequently the flask was kept overnight under vacuum to ensure the complete removal of residual solvent. The dry lipid film was hydrated with 15 ml of phosphate buffer solution (pH 7.4) at a temperature of 40±2°C. The dispersion was left undistributed at room temperature for 2-3 hour to allow complete swelling of the lipid film and hence to obtain vesicular dispersion (Arcadio C, 1995).

**Preparation method of liposomal gel**

Gel was made as a vehicle for incorporation of antifungal liposome for topical delivery. Carbopol 934 (1 g) was dispersed in de-mineralized water (88 ml) by continuous stirring for 45 minutes. Then propylene glycol 10 ml was added and the mixture was neutralized by drop wise addition of 10% sodium hydroxide. Mixing was continued until a transparent gel appeared, while the amount of base was adjusted to achieve a gel with pH 6.5 (Argan N, 2012 and Chonn R, 1995).

**Advantages**

1. Precipitation at the injection site and in the blood circulation can be prevented.
2. Phospholipids are one of the few solubilizes that are well tolerated intravenously.
3. Provide selective passive targeting to tumor tissues.
4. Increase safety and therapeutic index.
5. Increase stability via encapsulation.
6. Site avoidance effect.

**Disadvantages**

1. Production cost is high Leakage and fusion of encapsulated drug / molecules.
2. Sometimes phospholipids undergoes oxidation and hydrolysis like reaction
3. Short half-life
4. Low solubility
5. Fewer stables

**Niosome**

Niosome are very small vesicles (200-250 nm) non-ionic surfactant vesicles that have potential applications in the delivery of hydrophilic and hydrophobic drugs (Shatalebi MA, 2010). Niosome may be formed form a diverse
array of amphiphiles bearing sugar, polyoxyethylene, polyglycerol, crown ether and amino acid hydrophilic head groups and these amphiphiles typically possess one to two hydrophobic alkyl, perfluoroalkyl or steroidal groups. The self assembly of surfactants into noisome is governed not only by the nature of the surfactant but by the presence of membrane additives, the nature of the drug encapsulated and the actual method of preparation (Ijeoma F, 1998, naturalis lifetechnologies and Pharmainfo.net).

Preparation method of niosomes

Non-ionic surfactant, Span series (Span 20, 40, 60 and 80) was used to prepare niosomes by thin film hydration method in a rotary flask evaporator (Samar Mansour et.al, 2005). Surfactant and cholesterol were accurately weighed and dissolved in 15ml of Chloroform: Methanol (2:1 v/v) solvent mixture. Then it was vortexed in a round bottomed flask at temperature 60°C to remove the solvent under reduced pressure in the rotary flask evaporator at 150 rpm for 30-40 min. A thin layer or film formed inside the flask was the hydrated with aqueous phase containing the drug in 10ml of distilled water for 1h at temperature 60°C to obtain yellowish white dispersion of noisome (Mullaicharam A R and Murthy R S R, 2004). The resultant dispersion was then cooled in an ice bath, sonicated for 3min at 150v. Then the resultant noisome which was stored at 4°C in refrigerator (Naseem Charoo A et al., 2003) for further studies.

Preparation method of niosomal gel

Sufficient quantity of Carbopol 934 (1% w/w) was weighed and sprinkled onto warm distilled water with continuous stirring. The dispersion was allowed to hydrate for 1-2 hours. Other ingredients like Propylene Glycol (10% w/w) and Glycerol (30% w/w) were added subsequently to the aqueous dispersion with continuous stirring. A required quantity of antifungal drug (2% w/w) was added and properly dispersed. The dispersion was neutralized to pH 6 using 1% w/v of Sodium hydroxide solution and the final weight was adjusted with distilled water. The gel was sonicated for 15 minutes and kept overnight to remove air bubbles. Niosomal dispersion was then added to the hydrated gel with stirring (Vyas JA, 2011).

Advantages

1. The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.

2. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility.

3. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.

4. The vesicles may act as a depot, releasing the drug in a controlled manner.

5. They are osmotically active and stable, as well as they increase the stability of entrapped drug.

6. Handling and storage of surfactants requires no special conditions.

7. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

8. They can be made to reach the site of action by oral, parenterals as well as topical routes.

9. The surfactants are biodegradable, biocompatible and non-immunogenic.

10. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

Disadvantages

1. Physical instability.

2. Aggregation.

3. Fusion leaking of entrapped drug hydrolysis of encapsulated drug which limit the shelf life of the dispersion.

Ethosomes

Ethosomes were developed by Touitou et al., 1997, as additional novel lipid carriers composed of ethanol, phospholipids, and water. They are reported to improve the skin delivery of various drugs (Bendas R, 2007). Ethanol is an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Ethosomes are soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water. These soft vesicles represent novel vesicles carriers for enhanced delivery through the skin.

Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization. Therefore, when integrated into a vesicles membrane; it gives the vesicle the ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is
Mechanism of action of the ethosomal drug delivery system

A synergistic mechanism was suggested between ethanol, vesicles, and skin lipids (Touitou E, 2001). The enhanced delivery of actives using ethosomes over liposomes can be ascribed to an interaction between ethosomes and skin lipids. A possible mechanism for this interaction has been proposed. From Mechanism of Action of the ethosomal drug delivery System, it is thought that the first part of the mechanism is due to the ethanol effect, where ethanol interacts with the lipid molecules in the polar head group region resulting in a reduction in the transition temperature of the lipids in the stratum corneum, increasing their fluidity and decreasing the density of the lipid multilayer. This is followed by the ‘ethosome effect’ which includes lipid penetration and permeation by the opening of new pathways, due to the malleability and fusion of ethosomes with skin lipids, resulting in the release of the drug into the deep layers of the skin. Ethanol may also provide vesicles with soft flexible characteristics, which allow them to penetrate more easily into the deeper layers of the skin. The release of the drug in the deep layers of the skin and its transdermal absorption could then be the result of a fusion of ethosomes, with skin lipids and drug release at various points along the penetration pathway (Elsayed A, 2006).

Methods of preparation of ethosomes

The literature reports various methods for the preparation of ethosomes and some commonly used methods have been compiled in the proceeding text.

Hot Method

The drug is dissolved in a mixture of ethanol and propylene glycol and the mixture is added to the phospholipid dispersion in water at 40°C. After mixing for five minutes the preparation is sonicated at 4°C for three cycles of five minutes, with a rest of five minutes between each cycle, using the Probe Sonicator. The formulation is then homogenized at 15,000 psi pressure, in three cycles, using a high pressure homogenizer to get nano-sized ethosomes.

Cold Method

This is the most common and widely used method for ethosomal preparation. The phospholipids, drug, and other lipid materials are dissolved in ethanol, in a covered vessel, at room temperature, with vigorous stirring. The mixture is heated up to 30°C in a water bath. The water is heated to 30°C in separate vessel and added to the above mixture and then stirred for five minutes in a covered vessel. The vesicle size of the ethosomal formulation can be decreased if desired to extend using the sonication or extrusion. Finally the formulation must be properly stored under refrigeration.

Classic mechanical dispersion method

Soya phosphatidylcholine is dissolved in a mixture of chloroform: methanol (3:1) in round bottom flask. The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form of a thin lipid film on wall of the flask. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vaccum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the flask at suitable temperature (Dubey V, 2007 and Dubey V, 2007).

Classic method

The phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles (Jain S, 2007).

Preparation method of ethosomal gel

The specified amount of carbopol 934 (1.5%, 2.0%, 2. w/w) was slowly added in minimum amount of buffer and kept for an hour. Appropriate amount of optimized ethosomal-drug was incorporated to the swollen polymer with continuous stirring at 700 rpm in a closed vessel and maintained at temperature 30°C until homogeneous ethosomal gels were achieved. The pH was then adjusted to neutral using triethanolamine and stirred slowly.

Advantages of ethosomal drug delivery

1. Ethosomes enhance permeation of the drug through skin transdermal and dermal delivery.
2. Ethosomes are platforms for the delivery of large and diverse groups of drugs (peptides, protein molecules).
3. Ethosomal systems are much more efficient at delivering a fluorescent probe (quantum dots) to the skin in terms of quantity and depth.
4. Low risk profile, the technology has no large-scale drug development risk, as the toxicological profiles of the ethosome components are well documented in the scientific literature.
5. High patient compliance, the ethosomes are administered in a semisolid form (gel or cream), producing high patient compliance. In contrast, iontophoresis and phonophoresis are relatively complicated to use, which will affect patient compliance.
6. High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for the production of ethosomes.
7. The ethosomes system is passive, non-passive, and available for immediate commercialization.
8. Various applications in the pharmaceutical, veterinary, and cosmetic fields.

**Disadvantages of ethosomes**

1. Drugs that require high blood levels cannot be administered, limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.
3. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
4. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
5. Adhesive may not adhere well to all types of skin.
6. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
7. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
8. Loss of product during transfer from organic to water media.

**Microsphere**

Microspheres are free flowing polymeric micro particles loaded with biologically active drugs intended for providing constant and prolonged therapeutic effect thus reducing the dosing frequency and thereby improving the patient compliance. They not only used for prolonged release but also for targeting drug to specific site for minimizing the side effects (Martin A, 1996; Portero A; 2007, Singla AK, 2003 and Kataria S, 2011).

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 µm (Umamahesh B, 2011). The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs also known as micro-particles. It is the reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of antifungal drugs (Vijay Y, 2013).

**Preparation method of microspheres**

The literature reports various methods for the preparation of microsphere and some commonly used methods have been compiled in the proceeding text.

**Thermal cross-linking method**

Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of chitosan (2.5% w/v) maintaining a constant molar ratio between chitosan and citric acid (6.90 × 10⁻³ mol chitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25 mL of corn oil previously maintained at 0°C, with stirring for 2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120°C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried and sieved (I. Orienti, et al., 1996).

**Glutaraldehyde crosslinking method**

2.5% (w/v) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (w/v) Span 85 to form a water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a 3-blade propeller stirrer. A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% v/v) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C-80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde.
respectively. The microspheres were then finally dried in vacuum desiccators (B.C. Thanoo et al., 1992).

**Tripolyphosphate method**

Chitosan solution of 2.5% (w/v) concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5% or 10% (w/v) TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, then they were air dried (Bodmeier R, et al., 1989 and Shiraishi S et al., 1993).

**Emulsification and ionotropic gelation by NaOH method**

Dispersed phase consisting of 40 mL of 2% (v/v) aqueous acetic acid containing 2.5% (w/v) chitosan was added to the continuous phase consisting of hexane (250 mL) and 0.5% (w/v) Span 85 to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5 mL per min at 15-minute intervals. Stirring speed of 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried (Singla AV et al., 2003 and Ranga Rao KV et al., 1988).

**Ethylcellulose microspheres method**

A solution of ethylcellulose in acetone was added to liquid paraffin containing emulgent (Span 85) while stirring at a speed of 1500 rpm. The emulsion was stirred for 5 to 6 hours at 25°C to 30°C subsequently, a suitable amount of petroleum ether was added to the dispersion, filtered and dried at ambient temperature. The resultant microspheres were washed with water followed by petroleum ether to remove traces of liquid paraffin. The microspheres were desiccated under vacuum (Ranga Rao KV, et al.,1988).

**Spray drying method**

In spray drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions (Koff US et al., 1963).

**Solvent evaporation method**

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is dispersed in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made (Lim ST et al., 2000).

**Wet inversion method**

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyposphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres (Mi FL et al., 2000). Complex coacervation CS microparticles can also prepare by complex coacervation, sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by inter-ionic interaction between oppositely charged polymers solutions and KCl & CaCl₂ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying (Nishioaka Y et al., 1990 and Ohya Y et al., 1990).

**Hot melt microencapsulation method**

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil),
continuously stirred and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. polyanhydrides. Microspheres with diameter of 1-1000 µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed (Mathiowitz E et al., 1987).

**Preparation Method of Microsphere Gel**

Carbopol 934P (1 g) was dispersed in distilled water (88 g) in which glycerol (10 g) was previously added. Mixture was stirred until thickening occurred and neutralized by drop wise addition of 50% (w/w) triethanolamine. Mixing was continued until a transparent gel appeared.

**Advantages**

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

**Disadvantages**

Some of the disadvantages were found to be as follows

1. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
3. Differences in the release rate from one dose to another.

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**Fig 1. Application of topical Gel**

**Fig 2. Application of Buccal (Oral) Gel**

**Fig 3. Application of vaginal gel**

**Fig 4. Application of vaginal gel**

**Fig 5. Application of ophthalmic In-situ gel**

**Fig 6. Application of ophthalmic Gel**
Fig 7(a). Structure of liposome

Fig 7(b). Structure of liposome

Fig 8. Structure of Niosomes

Fig 9. Structure of Niosomes

Fig 9. Structure of Ethosomes

Fig 10. Structure of Hollow microsphere with microporous shell

Fig 11. Structure of Chitosan microsphere
CONCLUSION

During the last two decades, a lot of research work has been carried out on different drug delivery systems and different routes of administration of the drugs to overcome the problems associated with poor aqueous solubility of highly lipophilic drugs compound, adverse effect of the antifungal drugs, low bioavailability for the degradation of the drugs, low onset of therapeutic action due to local or systemic action of the drugs, high cost of the formulation and poor patients acceptability. From the industrial point of view topical, oral, vaginal and ophthalmic routes of administration and liposomal, niosomal, ethosomal and microsphere drug delivery system are most acceptable and safest for the commercial production.

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