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REVIEW ON TOPICAL LIPOSOMAL GEL OF KETOCONAZOLE

Sunil Yadav*, Ajay Bilandi, Mahesh Kumar Kataria
Seth GL Bihani SD College of Technical Education Sri Ganganagar

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For Correspondence:

Sunil Yadav

Seth GL Bihani SD College of Technical Education Sri Ganganagar

E-mail:

sunilkamalyadav@gmail.com

ABSTRACT

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. There are various skin infections caused by fungus. An antifungal medication is a pharmaceutical fungicide used to treat mycoses such as athlete's foot ringworm, candidasis. Antifungal works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effect on host. kitoconazole is an imidazoles antifungal derivative and used for the treatment of local and systemic fungal infection. When administered orally, ketoconazole is best absorbed at highly acidic levels, so antacids or other causes of decreased stomach acid levels will lower the drug's absorption. Absorption can be increased by taking it with an acidic beverage, such as cola. Ketoconazole is very lipophilic and tends to accumulate in fatty tissues.

INTRODUCTION

Ketoconazole having broad spectrum activity against systemic and superficial mycoses. It is readily but incompletely absorbed after oral dosing and it varies among individuals. Common side effects associated with Ketoconazole therapy include mild burning at the application site, severe allergic reactions, blisters, irritation, pain or redness.[1]. Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infections of skin are one of the common dermatological problems. Among the topical formulations a wide choice for the treatment from solid dosage to semisolid doses forms and to liquid dosage formulation the transparent gels have widely accepted in both cosmetics and pharmaceuticals.[2]. A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route. It is freely soluble in dichloromethane; soluble in chloroform and in methanol; sparingly soluble in ethanol (95%); practically insoluble in water and ether.[3]There are various medicated products that are applied to the skin. Such products are referred as topical or dermatological products. There are various Hydrophilic polymers such as carbopol 940, hydroxypropyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system. Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation[4].

Topical delivery

It is necessary to understand the anatomy, physiology and physiological properties of the skin. Microscopically skin is composed of three histological layers: epidermis, Dermis and Hypodermis (subcutaneous layer). The epidermis is 0.1 -1.5 mm thick. It is further divided into five parts: stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum, the epidermis forms the pigment melanin. The squamous cell layer is the thickest layer of epidermis and helps to move certain substances in and out of the body. Nerve endings are responsible for the sense of touch. The hypodermis also known as subcutaneous tissue is the deepest layer of skin which acts as an insulator conserving body heat and as a shock absorber protecting internal organ from injury. It also stores fat[5]. The blood vessels, nerves, lymph vessels and hair follicles also cross linking through these layers. The barrier properties of intact skin limit the permeability of wide variety of substance including pharmaceutical active agent. The drug release from all gelling agents through standard cellophane membrane was evaluated using Franz diffusion cell[6].

Topical route of administration:

Drug molecules contact at skin surface with cellular debris, microorganisms and other materials which effect permeation. The applied medicinal substances follow three pathways:

- Through hair follicles
- Across continuous stratum corneum
- Via sweat duct

This route of drug delivery has gained popularity because it avoids first pass metabolism, gastrointestinal irritation and metabolic degradation associated with oral administration. The pathway of drug movement through this layer is believed to be mainly transcellular. Although the paracellular pathways becomes important for small molecular weight compound[4].Being a diffusion barrier the stratum corneum also serves as a reservoir for compound such as corticosteroids, grisofulvin and many other drugs. Upon reaching the subcutaneous tissue there is evidence that some drugs e.g. Like thyroxin estradiol and corticosteroids remain in this layer for an extended period of time or for prolonged release of drugs..Fungal infections are very common and can be topical as well as systemic. Treatment of fungal infection includes medicines like fluconazole, miconazole, ketoconazole, clotrimazole and grisofulvin[7].

LIPOSOMAL GEL:

Liposomes are microscopic vesicles composed of a bilayer of phospholipids or any similar amphipathic lipids. They are defined as "Liposome is simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule." Various amphipathic molecules have been used to form liposome. The drug molecules can either be encapsulated in aqueous space or intercalated into the lipid bilayer[8]. They can encapsulate and effectively deliver both hydrophilic and lipophilic substances and may be used as a nontoxic vehicle for insoluble drugs. Liposome as a microstructure consists of one or more concentric spheres of lipid bilayer separated by water or aqueous buffer compartments. Liposomes are microscopic vesicular structures consisting of one or more concentric spheres of lipid bilayers, enclosing aqueous compartments[9]. Liposomes have many of the requirements for good drug delivery systems as they are relatively nontoxic and biodegradable. They have been found to be useful carriers for both hydrophilic and hydrophobic drugs. Liposomal encapsulation of a drug can dramatically alter the pharmacokinetic properties of a drug, targeting the drug to particular organs and/or enhance the efficacy of the encapsulated drug. The formulation of an appropriate liposomal system as a carrier for a given drug is dependent on the type of the lipid used and the method of preparation. According to their size they are known as small unilamellar vesicles

(SUV) or large unilamellar vesicles (LUV). If more bilayers are present they are referred to as multilamellar vesicles (MLV)[10].Drug candidates for liposomal encapsulation are those that have potent pharmacological activity and are either highly lipid or water soluble. If a drug is water soluble, it will be encapsulated within the aqueous compartment and its concentration in the liposomal product will depend on the volume of the entrapped water and the solubility of that drug in the encapsulated water. They are usually applied to the skin as liquids or gels[11]. Skin has been considered as an alternative route for local and systemic treatment. Topical dosage forms provide relatively consistent drug levels for prolonged periods and avoid gastric irritation, as well as the other typical side effects of oral NSAID administration[12]. Considering the all above mentioned, liposome vesicles embedded into a suitable gel matrix, could be attractive candidates for the use as drug delivery vehicles for transdermal application of ketoconazole. Liposomes also facilitate intracellular delivery via fusion with the plasma membrane, receptor-mediated endocytosis and phagocytosis[13].

The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing an interpenetrated by liquid. The inorganic particles form a three dimensional structure. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into the continuous phase.

CLASSIFICATION OF GEL

BASE	TYPE	EXAMPLE
Based on colloidal	Two phase system Single phase system	thixotropic-forming semisolids. natural or synthetic polymer
Based on nature of solvent used	Hydro gel Organic gels Xerogels	Bentonite magma,gelatin polomer gel Plastibase,aerosol gel Tragacanth ribbons, cyclodextrin
Based on Rheological properties	Plastic gel Pseudo plastic gel Thixotropic gel	Bingham bodies. Sodium aginate, NA CMC Kaolin, bentonite and agar.
Based on physical nature	Elastic gel Rigid gels	Alginate and Carbapol. In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.
Bases or gel forming polymers	Natural polymers Semi synthetic Synthetic	Proteins like collagen, gelatin cellulose derivatives, Carbomer carbopol 940, carbopol 934

[14] Ketoconazole is a selective, irreversible inhibitor of Type B monoamine oxidase is a drug used for the treatment of early-stage Parkinson's disease, depression and senile dementia. Presently ketoconazole is available only in the form of tablet with dose of 10mg twice a day. Following oral administration bioavailability of this drug is very low due to different path of metabolism. Because of prominent first pass effect and their tendency to inhibit monoamine oxidase in gut, alternative route of administration is developed. Also upon oral administration due to the primary metabolites of L-amphetamine and L-methamphetamine, Ketoconazole shares many side effects seen with these sympathomimetic stimulants. Minor side effects such as dizziness, dry mouth, and difficulty falling or staying asleep, muscle pain, rash, nausea and constipation have been seen. Thus bioavailability problems associated with oral administration generate interest of designing novel drug delivery system of Ketoconazole with an alternative route of administration. Transdermal delivery of drugs provides advantages over conventional oral administration[11]. The benefit of transdermal systems includes improved patient compliance, convenience and elimination of hepatic first pass effect[15]. Nevertheless, most drugs are not applicable to this mode of administration due to the excellent barrier properties of the skin. Molecules must first penetrate the stratum corneum, the outer horny layer of the skin. The molecule then penetrates the viable epidermis before passing into the papillary dermis and through the capillary walls into systemic circulation. It is the stratum corneum, a complex structure of compact keratinized cell layers that presents the rate limiting step and the greatest barrier to absorption of transdermally administered drugs. it's melting point is 148^0 -152^0.it is not less then 99 percent and not more then 101 percent[3]. Loss of drying in dry it in came 80^0 for 4 hours. It loss not more then 0.5 percent of highest.residue on ignition not more then 0.1 percent from 2.0 gm[16]. (A) The determine by infrared absorption spectrophotometry(2,4,6).compare the spectrum with that obtained with ketoconazole RS or with the reference spectrum of ketoconazole. (B) In the test for related substances, the principal spot in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference(a)[17].

Method of Preparation of Liposomal Gel

These are prepared by two step which are given in below

1. Preparation of gel

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing. Gels can be prepared by following methods.

1. Thermal changes

2. Flocculation
3. Chemical reaction

Thermal changes :

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g.: - Gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method[18].

Flocculation:

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g.: Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the colloidal and gelation doesn't occur[5].

Chemical reaction:

This is one of the widely used methods to grow a large number of crystals. The basis of the reaction method is the chemical reaction of the components used for the growth purpose. It has specially suited for growing crystals which are insoluble or partially soluble and those having thermal instabilities. There are two types of growth which can take place in the chemical reaction: one in which the growth takes place by the reaction of one component with the other and in the other with the reactior of one component impregnated in the gel medium. In this method the crystals grow inside the gel. The process is a highly controlled one because the reactants combine due to the diffusion of ions through fine pores. The reaction can be represented as[19]

$$AX+BY \rightarrow AY+BX$$

2. preparation of liposome gel

General methods of preparation

All the methods of preparing the liposomes involve four basic stages:

1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product[20].

REVIEW OF LITRATURE

Naazneen Surti, Umesh Upadhyay, Jaswandi Mehetre, Ankit Patel at 2014 Solubility of Ketoconazole was determined in different oil, surfactants and co-surfactant by dissolving an excess amount of drug in 5ml of oil,and other components. The samples were vortexed and kept for 72hr at 370C in a shaking water bath to facilitate the solubilization. The equilibrated samples were centrifuged at 3,000 rpm for 15 min to remove the undissolved Ketoconazole. The supernatant was taken and filtered through a 0.45µm membrane filter. The solubility of Ketoconazole was determined by analyzing the filtrate spectro photometrically after dilution with methanol at 222 nm. Optimum formulation of microemulsion base hydrogel showed higher drug release of 76.12% and higher flux of 75.78±0.06% at the end of 24hrs, with comparable in vitro antifungal activity as compared to marketed formulation[21].

Niyaz Basha, Kalyani Prakasam, Divakar Goli at 2014 Carbopol 934p (1, 2, 3, 4, 5% w/w) and purified water were taken in a beaker and allowed to soak for 24 h. To this required amount of drug (2 gm) was dispersed in water and then Carbopol 934p was then neutralized with sufficient quantity of Triethanolamine. Glycerine as moistening agent, methyl paraben and Propyl paraben as preservatives were added slowly with contineous gently stirring untill the homogenous gel was formed. Fluconazole is an imidazole derivative, used for the topical as well as systemic fungal infections. The bioavailability of fluconazole is 90%. In the present study, an attempt was made to formulate topical gel of fluconazole for efficient delivery of drug across the skin[4].

Doaa A. Helal, Dalia Abd El-Rhman, Sally A. Abdel-Halim, Mohamed A. El-Nabarawi at 2012 Fluconazole(1% w/w) was dissolved in a hot mixture containing propylene glycol (20% w/w) and glycerin (10% w/w) as moistening agent. Polyacrylic acid polymer (carbopol 940), cellulose polymers (HPMC, MC), polysaccharide polymer (Pectin) gel were prepared by dispersing the calculated amount of polymer in calculated amount of warm water with constant stirring using magnetic stirrer at a moderate speed. Then add the previous mixture containing the drug. The pH of carbopol gel was adjusted using TEA. While polymer undergoing transition (Pluronic) . 12-14 was dispersed slowly in cold water 4ºC with constant stirring according to cold technique15-16. Finally methyl and propyl paraben as preservatives were added slowly with continuous stirring until gel formation. The prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with an aluminum foil and were

kept in dark and cool place. Therefore, it was concluded that our formulae could be very promising topical alternative for the treatment of skin fungal infections. However, further preclinical and clinical studies are required[22].

SB Shirsand, MS Para, D Nagendrakumar, KM Kanani, And D Keerthy at 2012 Niosomes gel with ketoconazole were prepared by a thin film hydration method using a lipid mixture consisting of surfactant (span 40, span 60 and tween 60) and CHO, at different specified ratios. Surfactant, CHO and drug were dissolved in 10 ml of chloroform. The lipid mixture was then transferred to a 100 ml round bottom flask, and the solvent was evaporated under reduced pressure at a temperature of 55-65°C, using a rotary flash evaporator until the formation of a thin lipid film. The formed film was hydrated with 20 ml of Phosphate buffer saline pH 7.4. The hydration was continued for 1 h, while the flask was kept rotating at 55-65°C in the rotary evaporator. The hydrated niosomes were sonicated for 20 min using a bath sonicator to obtain niosomal dispersion containing both free and entrapped drugs of varying size. The prepared Ketoconazole niosomes were evaluated for various parameters like particle size, shape, entrapment efficiency and *in vitro* drug release. Finally, the promising formulation was selected and then it was incorporated into the gel for topical uses[23].

Sanjeevani Desaia, Ajit Dokeb, John Disouzaa, Rajani Athawalec at 2011 Niosomal gel was prepared by adding niosomal dispersion (N7) in to suitable gel base like carbopol U21. Various batches of the gels were prepared using carbopol at varied concentrations (0.1%, 0.5%, 1% and 1.5%). Definite amount of polymer was sprinkled into the vortex created by stirring double distilled water and stirred for 25-30 min. Gelling was induced by neutralization using triethanolamine. Niosomal dispersion was then added to the hydrated gel with stirring. A conventional gel (1%) was prepared by adding small portions of gelling agent (Carbopol Ultrez 21) to the dispersion of the drug in water under stirring. After complete addition of the polymer, gelling was induced by neutralization using triethanolamine[24].

Rakesh P. Patel, Hardik H. Patel and Ashok H. Baria at 2009 As a vehicle for incorporation of liposomes for topical delivery, a carbopol gel was made. Carbopol 934 (1 g) was dispersed in distilled water (88 g) by stirring at 800 rpm for 60 minutes. Then, propylene glycol (10 g) was added and the mixture was neutralised by dropwise addition of triethanolamine. Mixing was continued until a transparent gel appeared, while the amount of the base was adjusted to achieve a gel with pH 5.5. The prepared LKG and PKG formulations were white viscous creamy preparations with a smooth and homogeneous appearance. They were easily spreadable with acceptable bioadhesion and fair mechanical properties[25].

Meiying Nig, Zhongwei Gu , Huaizhong Pan, Heming Yu & Kai Xiao at 2004 To study the effect of composition of the vesicles containing clotrimazole, a series of formulations containing different compositions with EP, sorbitan ester(span) and cholesterol were designed table 1. Conventional multilamellar vesicles (MLV) were prepared by thin lipid evaporation method. The formulations containing phospholipid or nonioninc surfactants,, cholesterol and DCP were resolved in ethanol, the desired volumes were added to a 100 ml round bottom flask, the flask was attached to a rotary evaporator (Buchi Rotavapor R 100, Switzerland) and the organic solvents were evaporated under reduced pressure at 150 rpm to form a thin, dry film on the wall of the flask. Any excess orgainic solvents were removed by leaving the flask in a desiccators under vacuum, overnight. The dried lipid film was hydrated when required with buffer phosphate buffered saline, PH 7.4 followed by vigorous shaking in an incubator at 30^0 C (for liposome) or 60^0C(niosomes) for about 60 min to form large multilamellar, and probe sonicating (prob sonicator, taijing autoscience company, china) for 2min to form the blank liposomes/noisome. Conventional, drug containing liposomes/noisome were prepared by adding drug (clotrimazole was dissolved in ethanol previously) to the surfactant mixture prior to evaporating the orgainic solvent. Fluconazole is an imidazole derivative, used for the topical as well as systemic fungal infections. The bioavailability of fluconazole is 90%. In the present study, an attempt was made to formulate topical gel of fluconazole for efficient delivery of drug across the skin[26].

EVALUATION OF GEL

- Physical appearance[8]
- Measurement of pH[7]
- Drug content
- Viscosity study
- Extrudability study
- Skin irritation studies
- Invitro study
- Stability[28]

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