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ITRACONAZOL LOADED SOLID LIPID NANOPARTICLES TO IMPROVE ANTIFUNGAL EFFICIENCY

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ABSTRACT:-

Fungal infections pose a growing threat to human health and livelihood. Tinea capitis are the species of Dermatophytes group of fungi, which cause the fungal infection in the scalp known as scalp ringworm. Solid-lipid nanoparticles (SLNs) are an innovative group of nanosystems used to deliver medicine to their respective targets with better efficiency and bioavailability in contrast to classical formulations. SLNs are less noxious, have fewer adverse effects, have more biocompatibility, and have easy biodegradability. Lipophilic, hydrophilic and hydrophobic drugs can be loaded into SLNs, to enhance their physical and chemical stability in critical environments.

Nanoparticles have many properties that would make them useful antimycotic agents. Nanoparticles can facilitate efficient topical drug delivery by increased penetration, enhanced safety, efficacy and sustained and target release of the drug. Itraconazole a antifungal drug was formulated into drug delivery system aiming to treat opportunistics ringworm infection (Tinea capitis) that infect scalp.SLN increase the approach to enhance the permeability of Itraconazol through the skin. The used of Itraconazol loaded solid lipid nanoparticles considered a good alternative to control pathogenic fungi in humans. Different synthesis methods have been used to produce the SLNs, few of them are microemulsion dispersion method, homogenization, ultrasonication, melt emulsion sonication, and low temperature solidification method.
Characterization of SLNs includes particle size, zeta potential, drug loading and drug entrapment efficiency.

The objective of the review to evaluate Itraconazol loaded solid lipid nanoparticles to improve the therapeutic efficacy and reduction of toxicity of this broad spectrum antifungal agent. Entrapment efficiency of drug carrier and it's effect in physical parameter, drug release are reviewed. Important points in characterization and stability of SLNs are outlined. The study of the SLNs loaded with Itraconazol was the aim of these investigation. The drug molecules physiochemical and pharmacokinetic performance is constrained by the drug profile, poor solubility, toxicity, instability, incompatibility and poor penetration. The review submerizes the

basic of nanoparticles (SLN) with respect to drug delivery for better therapeutic effects of scalp ringworm infection.

KEY WORDS :-

Itraconazole, SLN, Fungal infections, High shear homogenization, Ultrasonication, Emulsion.

INTRODUCTION :-

DRUG DELIVERY SYSTEM

There are several troubles associated with drug depending upon their physicochemical and pharmacokinetic overall performance similar as bad solubility, toxin, lack of confidence, incompatibility and negative penetration(Patel et al., 2011). due to which, it necessary for the improvement of appropriate medication transport device to decorate the delivery of the medication accessibly. considering the truth, numerous traditional methods like micronization, precipitation, coating,use of surfactants and many others. are used to conquer the challenges, however some obstacles of those strategies edged to the exigency of latest vesicular structures(Pallavi etal., 2006). Thus, expansive sweats were made to increase and modify the vesicular medication transport structures to achieved dreams.

There have been several approaches and techniques are made to meet goals associated with the above referred to advanced drug delivery systems (Elnaggar etal., 2011). As entioning approximately the reaction astronomically, these systems are able of suggesting location for targeting, have offered safety from degradation of drugs, controlled drug release along side brilliance in numerous other features(Biju etal., 2006., Gangwar etal., 2012).

FUNGAL INFECTION:-

Fungal infections has been divided into two large groups that are systemic and superficial categons(Bennet etal., 2001). Serious skin diseases are produced from fungal species note as fungal infections. The name ringworm is because of the round marks at the skin, with flat centre's and raised border caused of fungus. The infection is also known as Tinea capitis, an infection which affects scalp and hair shafts creating small patches itchy and scaly.

Some common signs of scalp ringworm :

- The infection begins with excessive dandruff on many parts of the scalp. Signs and symptoms may be confused with psoriasis.
- The bald patches on scalp caused by few infections are mainly inflamed and scaly.
- In few cases, painful boils arise on the bald patches.
- In extreme cases, a huge' boggy' swelling arises on the bald portion of scalp, referred as kerion. This swelling is oozing and gentle and should be treated early.
- Within the case of severe infection, this could lead to high body temperature and glands present inside the neck can begin swell scalp.

SOURCES OF INFECTIONS

Dermatophyte group of fungi produced an infection known as scalp ringworm. The Geophilic organism live in soil, zoophile organisms (Microsporum Canis or Trichophyton verrucose) on animals (cattle) and anthropophilic organisms (T.Hondurans) on humans. T. Hondurans spreads directly from child to child.

ITRACONAZOL (ITZ): AN ANTIFUNGAL AGENT

Itraconazole is a artificial triazole antifungal agent. It slightly soluble in alcoholic agents and extremely soluble in methylene chloride. ITZ is fairly lipophilic in nature and insoluble in water with extremely basic nature, Pka value of 3.7 that is ionized at low pH value. It is a lipophilic antimycotic drug with three chiral centers. It is clinically used because the stereo isomeric combination(Prasuna etal., 2013).

It is active against broad spectrum of fungal species including Dermatophytes, Malassezia furfur, Candida species, Aspergillus and Histoplasma capsulatum. The capsule dosage form of drug used to treat fungal infections in lungs and fingernails. It liquid dosage form applicable to treat yeast infections in mouth and throat or of oesophagus (Prasuna et , 2013).

PROBLEM ASSOCIATED WITH ITRACONAZOL

Oral and parenteral administration of the drug is related to many side effects including headache, nausea, vomiting, diarrhea, dizziness, stomach upset, and muscle weakness. Itraconazole is also related to have a few uncommon effects like hepatotoxicity, liver failure with incersive doses and due to oral route of administration. In a few cases adverse drug reaction has also been arrived with oral capsules in clinical trails indicating Hepatobiliary disorders like hyperbilirubinemia(Rao et al., 2009). Also, invasive parenteral delivery leads to poor patient compliance. Hence, alternate of route of administration from oral to topical can serve the reason to overcome the route associated restrictions. Likewise, the less absorption of the drug via skin due to its hydrophilicity as in comparison to other drug of its category. Thus, secondly development of system with greater topical permeation by altering effective elements might be a challenge for study. Therefore, the primary aim of this review is to study Itraconazole containing solid lipid nanoparticles for efficient and fast delivery of drug to treat the scalp fungal infections quickly.

SOLID LIPID NANOPARTICLES(SLNs) :-

Preface of solid lipid nanoparticles(SLN) in 1991 offer an volition to the traditional carrier systems similar as emulsions, liposomes and polymeric micro and macro-particles (Ekambaram etal., 2011).SLNs are composed of a high melting point lipid as a solid core coated by aqueous surfactant and the drug used are typically of BCS category II and IV with solubility related issues(Neha etal., 2013). This system is sub- micron colloidal transporters (50-1000nm) self held of physiological lipid, dispersed in aqueous surfactant.

It has extensive advantages over traditional colloidal carrier system like lower size, larger surface area, effective drug loading and capacities.(Ekambaram et al., 2011). SLNs provided leading result to overcome the problems related with liquid-liquid system, the surface and structure is shown in fig.1(Ekambaram et al., 2011).

From the various testings, it has been found that the SLNs supports a better network formation and frame as compared to the fluid lipids. The use of SLNs as an matrix material for drug delivery remains very well considered as lipid pellets for oral drug delivery.(Example: Mucosolvan ® retard capsules)(Muller RH et al., 2000).

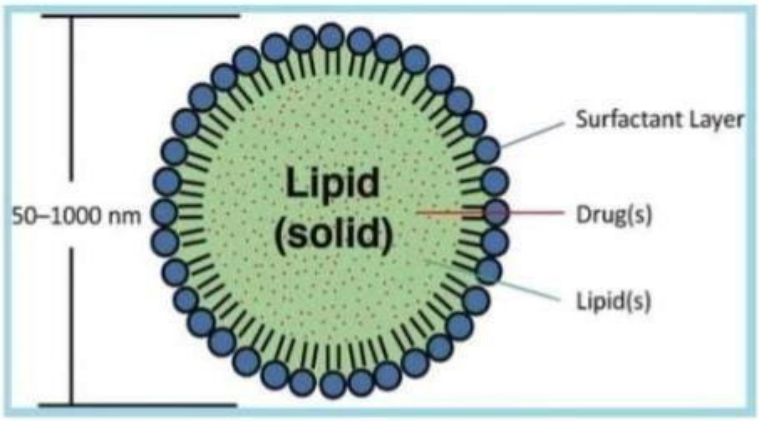

Fig.1. Structure of Solid Lipid Nanoparticles

Mainly lipid consists of triglycerides, partial glycerides, fatty acids, hard fat & waxes. Lipid matrix is made from physiological lipids, it reduces the risk of severe and long term toxicity. The use of solid lipid instead of liquid lipid is reduce the release kinetics of encapsulated drugs and to enhance stability.

Surfactants are added in order to stabilize the system. These are used as emulsifier to form o/w type emulsion and stabilizer for SLNs spreading and their highest effect by mostly the route of administration (Neha et al.,2013). SLNs provide all the benefits of polymeric nanoparticles, fat emulsions and liposomes. The diagrammatic representation of particulate drug transporters such as emulsions and liposomes are compared with SLNs in fg.2.(Ekambaram et al., 2011).

ADVANTAGES OF SLNs

(S. Mukherjee et al., 2009; Wolfgang Mehnart and Karsten Mader., 2001)

• SLNs are used for targeted and control drug release systems.

• They gives better biocompatibility due to the lipid content.

• They provide increased stability to the medications.

• Enhanced bioavailability of entrapped bioactive mixtures have been reported.

• Essentially stress-free to be produced than biopolymeric nanoparticles.

• Does not require specific solvents for formulation.

DISADVANTAGES OF SLNs

(Melik et al., 2007)

• Particle growth which may lead to stability issues.

• Sometime burst release is offered.

APPLICATIONS OF SLNs

(Indu et al., 2008)

• Can provide controlled drug release and drug targeting.

• Offers increased drug stability.

• Ability to offer high drug payload.

• No bio-toxicity of the carrier has been reported till date, which state that it is biologically safe.

• Potentiality for incorporation of lipophilic and hydrophilic drugs.

• No issues with admire to large scale production and sterilization has been described.

• The system can offer elevated bioavailability of entrapped bioactive compound.

METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES :-

(Antoni et al., 2007)

HIGH SHEAR HOMOGZENISATION (HPH)

The process of homogenization entails impulse of a fluid with high pressure a (100– 2000 bar) throughout a defined opening (in microns).The fluid accelerate on quick separation to high speed(over one thousand Km/ h). Due to this high shear stretch and cavitation strings upset the particles depressed to the submicron radius. For the maximum part 5-10 % lipid substance is used however in a few other studies 40 % lipid content has also been studied (Ekambaram et al., 2011).

The high pressure homogenization is done with two methods they are

• hot homogenization

•Cold homogenization

ULTRASONICATION / HIGH SPEED HOMOGENISATION

To create a smaller particle size, a mixture of both ultrasonication and high-speed homogenization are required (Vivek et al., 2007). During this process shear stress can be decreased but has some disadvantages such as potential metal adulteration, physical instability such as particle development during storage. Therefore during preparation probe sonicator or bath sonicator are used (Neha et al., 2013).

SOLVENT EMULSIFICATION – DIFFUSION METHOD

Voiding of heat is main advantage of this process. (Ekambaram et al., 2011). The lipid is generally liquefied in the organic phase in water bath at 50 °C and an acidic aqueous phase is used to adjust the zeta potential to form coacervation of SLNs, and then informal collections by centrifugation. SLN (diameter, 30-100nm) suspension is produced and the entire dispersed system then centrifuged and resuspended in distilled water (Neha et al., 2013).

METHOD BASED ON MICREEMULSION

Microemulsions are two-phase systems that contain an internal and an external phase (e.g o/w microemulsion). In this process, continuous mixing is ensured and optically transparent mixture is obtained at 65-70°C, which is logically low melting fatty acid (e.g. stearic acid), emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. Isolation of hot microemulsions is carried out in ice water (2-3°C) while stirring. Preparation of a solid product (tablets, pellets) by granulation process by using the SLNs dispersion can be done, but too much water is needs to removed in case of low particle content. High temperature gradients facilitate rapid lipid representation and reduce aggregation. Because of the dilution step; the probable lipid content is significantly smaller compared to HPH-based preparations (Vyas et al., 2002).

METHOD BASED ON DOUBLE EMULSION

The warm w/o/w double microemulsion can be created using two steps. Initially, w/o microemulsion is prepared by adding an aqueous solution that contains a drug in combination with a molten lipid, a surfactant, and of the co-surfactant at temperature slightly above the melting point of lipid to obtain pure system. In next step, the microemulsion that was formed earlier as w/o is added to a combination of water, surfactant and co-surfactant to achieve clear w/o/w system. SLN can be created by dispersing warm micro-double emulsions in ice and then washing away with dispersion medium by the ultrafiltration process. If SLN is to be formed, the emulsion must growing for few minutes (because they have their own instabilities caused by oil phase and layer's on surface of internal droplets) the time between arrangements of a reasonable double microemulsion and its dropping into a cold aqueous medium that can be possible to achieved (Chakraborty et al., 2009).

SPRAY DRYING METHOD

It is an alternative, cheap and less expensive method to the lyophilization procedure. This indicate the use of a lipid with a melting point higher than 700 °C. The best results were found with SLN absorption of 1% in trehalose solution in water or 20% trehalose in a combination of ethanol and water. For the protection of colloidal particles size during spray drying carbohydrates and low lipid content are added. (Helgason et al., 2009).

FILM ULTRASOUND DISPERSION TECHNIQUE

The drug and lipid are then placed in suitable organic solution organic solutions, afterward resting, replacement and disappearance of organic solutions, the lipid film is formed, then an aqueous solution is added containing the emulsion. Using ultrasound with probe to diffuser at earlier, SLN with minute and uniform particle size is formed (Locksley et al., 2009).

INFLUENCE OF EXCIPIENTS:-

FORMULATION VARIABLES EFFECTS ON PARTICLE SIZE

Particle size has a significant effect on the physical and biostability of lipid particles and drug release rate of loaded drug. Therefore, we need to measure the size of SLNs within appropriate range. Microstructured systems such as liposomes, nanospheres, and nanoparticles must show the distribution of fine particles in the submicron size range of less than 1μm determination of colloidal particles (Alaa et al., 2010). The particle size of lipid nanoparticles are affected by various parameters like, composition of formulation such as surfactant/surfactant mixtures, properties of lipids and drug contained production methods and conditions such as time, temperature, pressure, cycle number, equipment, sterilization and lyophilization. Large particle size are obtained at lower processing temperature. Hot homogenization technique generally yields lower, particle sizes below 500 nm, and a narrower particle size distribution compared to cold homogenization. The particle size as well as polydispersity index (PI) values are reported to decrease with increasing homogenization pressures up to 1500 bar and number of cycles (3–7 cycles) (Helgason et al.,2009).

EFFECTS OF LIPID

Using the hot homogenization method, it has been described that with high melting lipid, average particle size of solid lipid nanoparticles begins to increase. While others critical parameter for nanoparticle preparation will be different for different lipids. This Parameters include lipid hydrophilicity (influence of self-emulsifying properties of lipids, shape and its surface area) and the velocity of lipid crystallization (Robhash et al., 2009). Increase in lipid content by more than 5-10% results in larger particle size and increase particle size distribution in most formations.

EFFECT OF EMULSIFIER

The concentration of surface active agents/mixture affects the particle size of solid lipid nanoparticles. The above study revealed that higher the surfactant/lipid ratio the lower the particle size. Surface active agents acts by reducing the surface tension between the particles, therefore, increasing the surface area (Behzad et al., 2010).

DRUG INCORPORATION AND LOADING CAPACITY:-

Average particle size, entrapment efficiency and size distribution of SLNs vary with types of lipid (triglycerides, fatty acids, steroids, waxes, etc.), emulsifying agents (anionic, cationic, nonionic) and preparation methods etc. (Yingchao et al., 2006).

FACTORS DETERMINING THE LOADING CAPACITY OF THE DRUG IN THE LIPID ARE

•Solubility of lipids in dissolved state.

•Incompatibility of drug and lipid in its dissolved state.

•Physical and chemical structure of solid lipid matrix.

•Polymorphic nature of lipids.

STORAGE STABILITY OF SLNs:-

Physical properties of SLNs formulations in storage for longer periods evaluated by observing changes in zeta potential, drug content, particle size, its appearance and viscosity of formulation with function of time. Other parameters such as temperature and light appear to be essential partners for long-term stability. Zeta potential Should be greater than 60mV for stable dispersion.

•4 °C - The most favorable storage temperature.

•20°C - Long-term storage did not result in drug-loaded SLN aggregation or drug loss.

•50 °C- Rapid growth of particles at this temperature.

STERILIZATION OF SOLID LIPID NANOPARTICLES:-

SLN should be suitable for intravenous and ocular administration. High temperature during sterilization autoclaving causes o/w hot emulsion results changes in the size of hot nanodroplets (Yang et al., 1999). But on slow cooling SLNs are reformed, but some nanodroplets produce large size SLNs to avoid this problem It is washed before sterilization and a small amount of surfactant and co-surfactant is used in hot system (Wong et al., 2006).

CONCLUSION:-

Ringworm, candidiasis and unique forms of leishmaniasis are a type of fungal infections which might be very commonplace everywhere in the global. Many people suffer from numerous fungal infections and take medicinal drug for treatment. So, to keep away from the side consequences of oral dosage shape and to improve the efficacy and efficiency of conventional topical dosage form, novel SLNs machine become evolved. Itraconazole turned into decided on as a version drug. The characterization of Itraconazole become analysed by melting point analysis. The solubility analysis and partition coefficient turned into studied to make certain the nature of drug.

The look at suggests the element statistics on the proportion entrapment efficiency and percentage permeability. SLNs are a new and rising drug transport method used to deliver pills to their respective targeted sites, that blessings us inside the shape of improved performance and solubility of many classical and latent antifungal marketers. In contrast to bases and automobiles used for older antifungal arrangements, Itraconazol loaded SLNs are normally seemed as biocompatible and without problems decomposable and feature little cell toxicity to mammalian cells additionally, they also showed the excellent loading quantity for hydrophilic in addition to hydrophobic pills. SLNs additionally increase the bioavailability of lipophilic tablets and shield tablets against harsh environmental conditions and have greater bodily stability.

SLNs have shown promising responses in antifungal drug delivery. Although they've positive limitations; as an example, in developing SLNs that are intended for parenteral management ought to be sterilized, and upon sterilization, they can lose physical and chemical balance. but, it must be saved in mind that the physical and chemical balance of any drug components should now not be compromised, so inside the case of SLNs, sterilization impacts the stability in addition, sterilization via gamma radiation fosters the era of free radicals that might make chemical modification- tions in the SLNs, even as sterilization through warmth can boom the particle length and render the bodily stability of the system.Lipid molecules occasionally go through structural alterations which result in decreasing lipid layer company for the duration of drug loading, as the drug gets integrated

between lipid layers. Lastly, further research need to consciousness at the feasibility of formulating pills with SLNs to decorate their motion and reduce antimicrobial resistance.

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