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Development of nanoemulsion based gel for the treatment of balanitis infection

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ABSTRACT

One of the most recent innovations in the Novel Drug Delivery System (NDDS) is nanoemulsion gel, which allows for the dual controlled release of an emulsion and a gel for topical application. When an emulsion is integrated into a gel, its stability is strengthened. It is challenging to conceptualize as a topical delivery. The goal of the current study was to create and improve the Clotrimazole nanoemulsion gel using different quantities of polymers such as Carbopol 934 and HPMC. The generated nanoemulsion gels were assessed for physical appearance, measurement of pH, viscosity, spreadability, drug content, and in vitro diffusion investigations as part of the Preformulation studies utilizing Fourier Transform Infrared (FTIR) research.Studies on the release of drugs in vitro were done for up to 8 hours. F6 exhibits better releasing property than any other formulations. F6was therefore shown to be the best formulation overall. When compared to formulations including Carbopol 934, F6 with low concentrations of HPMC polymer had greater releasing properties. Therefore, it was proposed that the Clotrimazole nanoemulsion gel might be superior to alternative topical drug delivery systems for integrating hydrophobic medicines and possessing improved activity and stability.

Keywords: Nanoemulsion gel, FTIR, HPMC, In-vitro diffusion studies, Carbopol 934.

INTRODUCTION

Balanitis infection-Inflammation of the penis tip is referred to as balanitis. At any age, it can happen(1). Thrush infection, bacterial infections, sexually transmitted infections, skin irritation, and certain skin diseases are a few of the causes. The balanitis infection usually clears with the treatment(2). Boys under the age of four who are also men who have not had circumcision are frequently affected. Balanitis affects roughly one in 25 boys and one in 30 uncircumcised men at some point in their lives(3). It rarely occurs in men who have undergone circumcision. According to data from meta-analyses, circumcised men have a 68 percent lower prevalence of balanitis than uncircumcised men do(1), and those who have the condition are at a 3.8-fold higher risk of developing penile cancer(4). The Symptoms of the infection are pain and irritation on the head of the penis, redness, swelling, and itching under the four skins(5).

Nanoemulsion sare a brand-new type of drug delivery technology that enable the regulated or sustained release of genetic material, pharmaceuticals, and biologically active substances(6). A dispersion called a nanoemulsion consists of an aqueous phase, a surfactant, and an oil(7). Oil-in-water (O/W) and water-in-oil (W/O) nanoemulsions are the dispersion of two immiscible liquids stabilised with the help of a suitable surfactant. Nano-emulsions are described as emulsion systems with a milky appearance and a size range of 50 to 200 nm (transparent) or up to 500 nm(8).Many research teams around the world have recently concentrated on creating biocompatible nanoscale systems for the efficient encapsulation, preservation, and transport of delicate bioactive substances(9). Fine oil-in-water dispersions with droplets ranging in size from 20 to 500 nm make up nanoemulsions. Nanoemulsions, which are typically spherical, are a collection of dispersed particles utilised in cosmetics, diagnostics, pharmacological therapies, and biotechnologies. They are also employed for pharmaceuticals and biomedical assistance(10).

Table 1: Comparison of the different properties of emulsions

Properties	Emulsion	Nanoemulsion	Microemulsion
Diameter Range	100nm-100µm	50-200nm	2-50nm
Shape	Spherical	Spherical	Spherical
Methods of preparation	High and low energy methods	High and low energy methods	High and low energy methods(11)(12)

Gel is a condensed mass that contains and interpenetrates a liquid. It is a solid or semisolid system made up of at least two components(13). To ensure the best cutaneous and percutaneous medication administration, gels are utilised. They can prevent problems with gastrointestinal medication absorption brought on by gastrointestinal acidity(14). Gels have the ability to prevent drug interactions and enzymatic activity with meals and beverages. When oral administration of a drug is not appropriate, gels can be used in its place(15). They can prevent the first-pass effect, or the first passage of a drug through the body. After gastrointestinal absorption, they evade systemic and portal circulation. Because the liver is bypassed, enzymes in the liver cannot degrade gels(16).

MATERIALS AND METHODS

Clotrimazole was purchased from Varav Biogenesis Pvt. Ltd. (Kala Amb,Himachal Pradesh), Carbopol 934, Liquid paraffin purchased from QualiChem's, HPMC from Otto Chemie, and the span 80, propylene glycol, Benzoic acid purchased from Loba Chemie.

Methodology

Preformulation studies

Organoleptic properties (API)- The identification of Clotrimazole was done by checking the physical appearance i.e., color, odor, and state. It was recorded and kept as a reference for comparing with the other batches during formulations.

Melting point- The capillary method was used to ascertain the drug's melting point. The capillary tube was sealed at one end and filled with clotrimazole up to about two millimetres from the closed end before being placed inside the digital melting point device. The drug's melting point is the temperature at which it starts to melt. The drug's melting point was regarded as the average of three values. A capillary tube containing 2–10 mg of the medication was precisely weighed, put in the apparatus at room temperature, and the temperature of the instrument was gradually raised.The range of temperature at which the drug initiated started to melt and the temperature at which the drug was melted was noted down.

Partition coefficient when a material is placed in an environment consisting of an organic and aqueous phase, it gets distributed into two phases. The relative quantities that get distributed are expressed in the form of a ratio known as partition co-efficient, Partition coefficient of fluconazole was calculated by using the following formula:

$$\text{Partition coefficient} = \frac{\textit{concentration of drug in organic phase}}{\textit{concentration of drug in aqueous phase}}$$

The partition coefficient of RAS between n-Octanol & water was determined by a slight modification of the "shake Flask Method", at room temperature. An excess amount of API was added toa 100 ml mixture of n-Octanol and water (1:1). The system was prepared in triplicate and was shaken gently in the separating funnel for 24 hours for achieving equilibrium. Then the two phases were separated and the concentration of API in each phase was determined by UV spectroscopy and the partition coefficient was calculated using the equation.

Solubility studies- Solubility of clotrimazole determined in different oils, surfactants, and co-surfactant. Clotrimazole was added in excess to oils, surfactants, and co-surfactant and stir them. Solubility of Clotrimazole was determined in different media i.e., 0.1NHCL, Water, Ethanol, Methanol, PBS pH 6.8, pH 4.0 by the "Shake Flask Method". The solubility of Clotrimazole in various solvents was determined by dissolving an excess amount of the drug in 3ml of each of the selected solvents in 5ml capacity stoppered vials separately. Each glass vial was then mixed for 10 minutes using a vortex mixer. The mixture vials were then kept at 37 ±1.0°C in a shaker bath for 48 hours to get equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 5000rpm for 5 min to spear the undissolved drug. The supernatant was taken and filtered through a 0.45m membrane filter. The concentration of API was determined in each solvent by UV spectrophotometer by scanning from 200-400nm.

Determination of absorption maxima- Methanol was selected as the ideal solvent for spectrophotometric analysis of Clotrimazole. The UV spectrum is generally recorded as a plot of absorbance versus wavelength.A double beam UV-visible spectrophotometer was used to determine the λmax of the drug. A stock solution of the drug in methanol was prepared. The sample was then diluted with methanol to obtain the result and the resulting solution was scanned in the range of 200-400 nm to determine the λmax of the drug.

Preparation of standard calibration curve- A stock solution of 100µg/ml was prepared by dissolving 50µg/ml of Clotrimazole in a 500 ml volumetric flask and making the volume up to the mark with the same solvent. Various aliquots of working stocks solution were transferred to the different volumetric flasks to prepare various alternate

clear working standard dilutions of 20, 40, 60, 80, and 100µg/ml, and volume was made up to mark with methanol.The calibration curve was prepared from these dilutions against a clear blank by taking the absorbance of the prepared standard dilutions at an absorbance of 263nm.

Drug and excipients compatibility studies- Drug and excipients compatibility studies were conducted to determine the compatibility of the excipients with the drug for the preparation of formulation. Fourier transforms infrared (FTIR) analysis studies were conducted for studying the compatibility and to determine if there are any possible drug excipients interactions. The IR absorption of the Clotrimazole drug was taken in the range of 4000-450 cm-1 using the KBr disc method, with 1-2 mg of the substance to be examined and triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide. The quantities are usually sufficient to give a disc of 10-15 mm diameter and pellet of suitable intensity by hydraulic press. The scans were evaluated for the presence of principle peaks of the drug. The IR absorption of the Clotrimazole drug and HPMC, Carbopol 934, were taken in the range of 4000-450 cm-1 using the KBr disc method, with 1-2 mg of the substance to be examined and triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide. The quantities are usually sufficient to give a disc of 10-15 mm diameter and pellet of suitable intensity by hydraulic press. The scans were evaluated for the presence of principle peaks of the drug, Shifting and masking of drug peaks due presence of HPMC, Carbopol 934.

Preparation of Nano-emulsions- The aqueous phase of the Emulsion was prepared by dissolving Tween 80 in purified water. Preparation of Oil phase: Methyl Paraben was dissolved in propylene glycol whereas the drug was dissolved in methanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to75ºc. Then the oil phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

Characterization of Nano-emulsions

Physical appearance- The identification of nanoemulsion was done by checking the physical appearance i.e., color, odor, and state. It was recorded and kept as a reference for comparing with the other batches during formulations.

pH- The pH of nanoemulsion was determined by immersion of the electrode of the pH meter in the formulation at room temperature in triplicate which was previously calibrated with standard buffers of pH 4, 7, and 10.

Viscosity- The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 20 rpm using the spindle and the corresponding dial reading was noted.

Preparation of Nano-emulsion based gel- The gel bases were prepared by dispersing different concentrations of polymers in distilled water separately with constant stirring at a moderate speed using a mechanical shaker. The pH of all formulations was adjusted to 6-6.5 using Triethanolamine (TEA).

Characterization of Nano-emulsion based gel

Physical appearance- The identification of nanoemulsion gel was done by checking the physical appearance i.e., color, odor, and state. It was recorded and kept as a reference for comparing with the other batches during formulations.

pH- The pH of nanoemulsion gel was determined by immersion of the electrode of the pH meter in the formulation at room temperature in triplicate which was previously calibrated with standard buffers of pH 4, 7, and 10.

Spreadability- One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of the area to which gel readily spreads on application to the skin. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel which is placed in between the slides under the direction of a certain load, the lesser the time taken for separation of two slides, the better the spreadability.

It is calculated by using the formula:
S = M.L/T
Where M = Weight tied to upper slide
L = Length of glass slides
T = Time taken to separate the slides

Drug content-The drug content uniformity was determined for all the formulations by UV spectrophotometric method. A 500 mg of clotrimazole gel was taken and dissolved in 50 ml of methanol. The volumetric flask was kept

for 2 hours and stirred well to mix it properly and filtered. The drug content was measured spectrophotometrically at 263nm.

Viscosity- The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 20 rpm using the spindle and the corresponding dial reading was noted.

RESULT

Preformulation studies-
Organoleptic studies- Organoleptic properties of the drug (API) were found to be as per the I.P. monograph. The properties of the drug are found a white, odorless, and crystalline appearance.

Melting point- The Melting point of the drug is found to be 148±0.2ºC.

Partition coefficient - The partition coefficient of Clotrimazole in n-octanol and water mixture was shown in the tablebelow. Log P greater than one indicates that the drug is lipophilic, whereas those with partition coefficients less than one are indicative of a hydrophilic drug. The partition coefficient of the drug is found to be 4.56±0.32.

Solubility studies

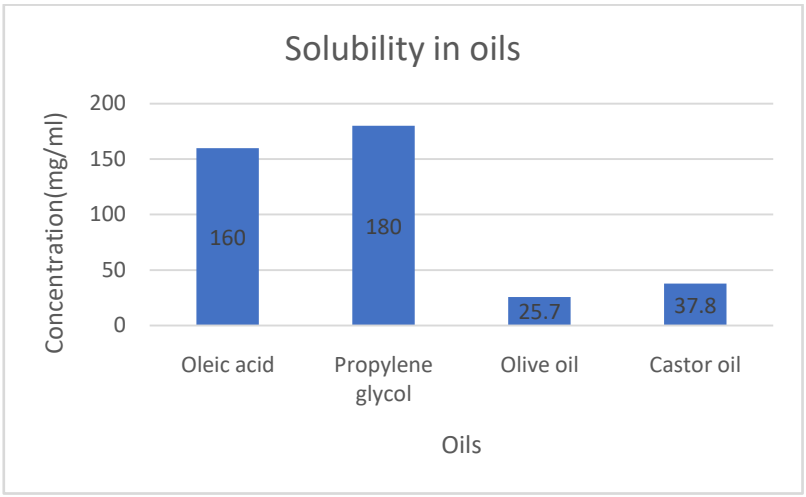

Fig.1: Solubility of Clotrimazole in different oils.

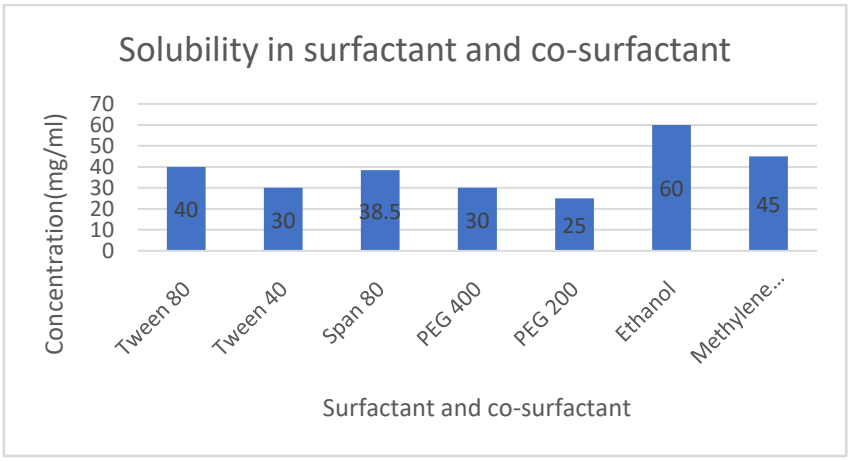

Fig.2: Solubility of Clotrimazole in different surfactants and co-surfactant

Determination of absorption maxima
On scanning between 200-400nm, the concentration of (µg/ml) of Clotrimazole displayed a maximum of 263nm indicating absorption maxima,

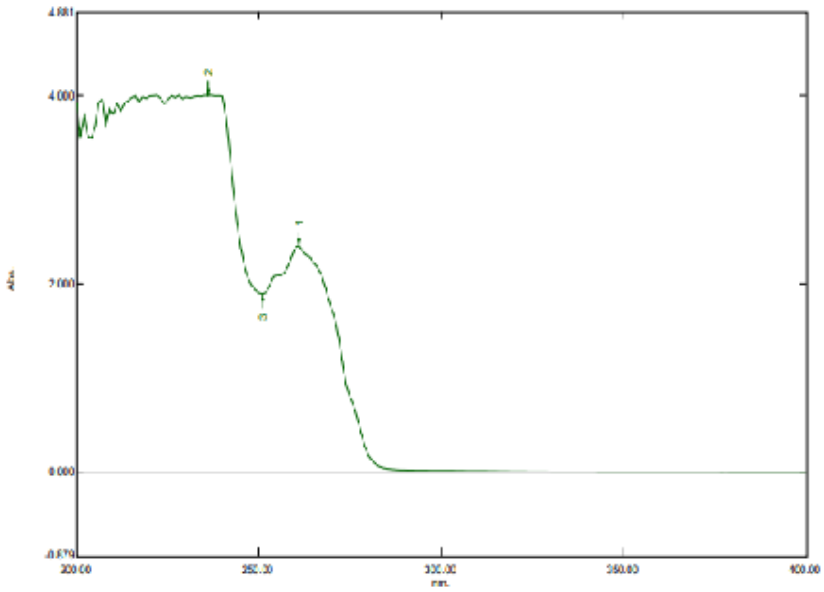

Fig.3: Graph of absorption maxima (λmax) of Clotrimazole in methanol

Preparation of standard calibration curve

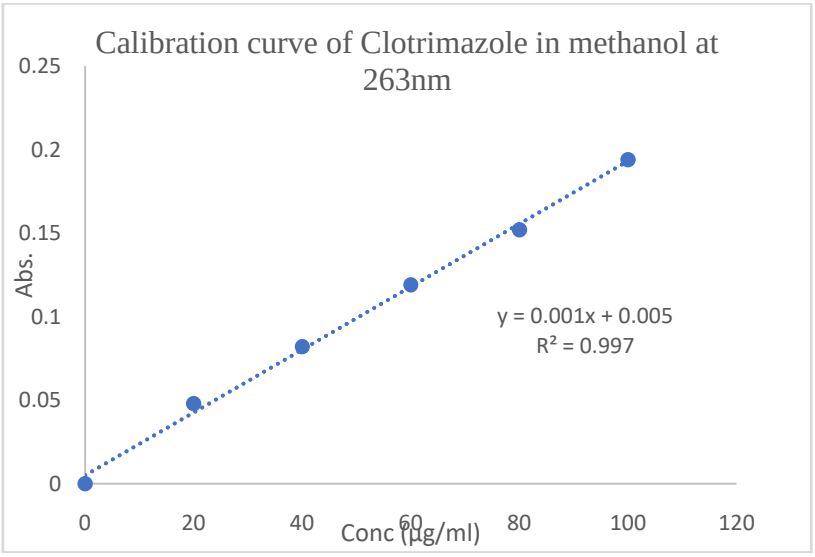

Fig.4: Graph of standard calibration curve between absorbance and concentration of Clotrimazole in methanol.

Drug and excipients compatibility studies

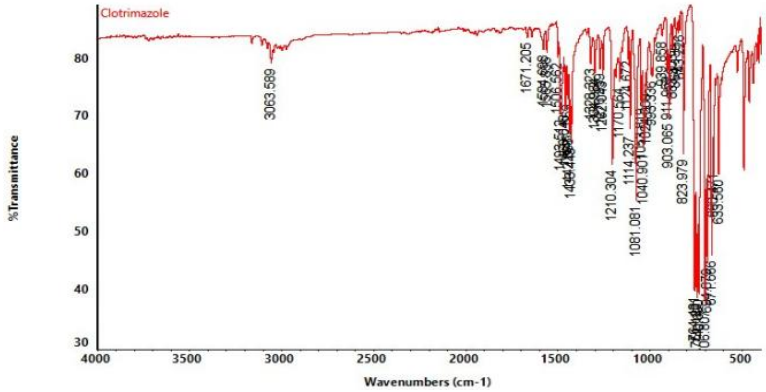

Fig.5: FTIR spectrum of Clotrimazole

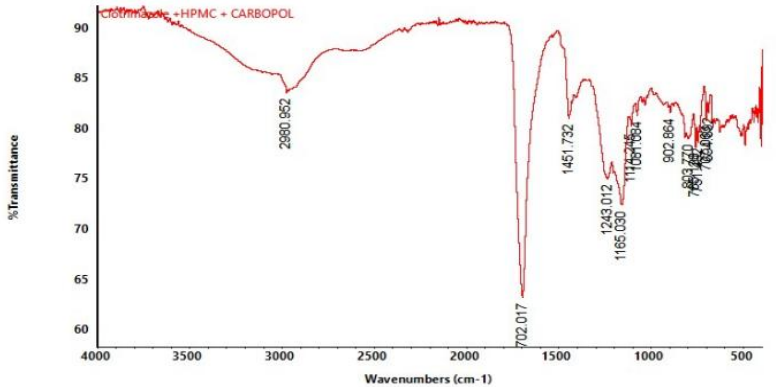

Fig.6: FTIR spectrum of Clotrimazole + HPMC + Carbopol 934

Characterization of Nano-emulsions

Physical appearance- The prepared nanoemulsion formulations were white, Odourless, preparation with a smooth, homogeneous appearance.

pH- The pH of optimized Clotrimazole loaded nanoemulsion was determined using a digital pH meter and was found to be 6.13±0.032which is favourable for tropical application because the pH of the skin is in the range of 5.5 to 7.0

Viscosity- The viscosity was measured at 10 rpm after 60 seconds. The viscosity of the nanoemulsion was obtained at 8129±0.19.

Characterization of Nano-emulsion based gel

Physical appearance- The prepared nanoemulsion based gel formulations were white, Odourless, creamy preparation with a smooth, homogeneous appearance with good consistency and without any gritty particles.

Comparison of pH, Spreadability, Drug content, and Viscosity

Formulation code	pH	Spreadibility	Drug content	Viscosity
F1	6.3±0.01	6±0.1	98.5±0.01	3337±0.13
F2	6.2±0.02	5.8±0.2	97.2±0.11	4528±0.15
F3	6.5±0.1	5.7±0.2	94.22±0.15	8129±0.19
F4	6.4±0.14	5.9±0.05	97.65±0.12	3529±0.12
F5	6.5±0.12	5.7±0.12	96.22±0.14	4693±0.10
F6	6.3±0.14	5.5±0.15	92.17±0.01	8232±0.12

In-vitro drug release-

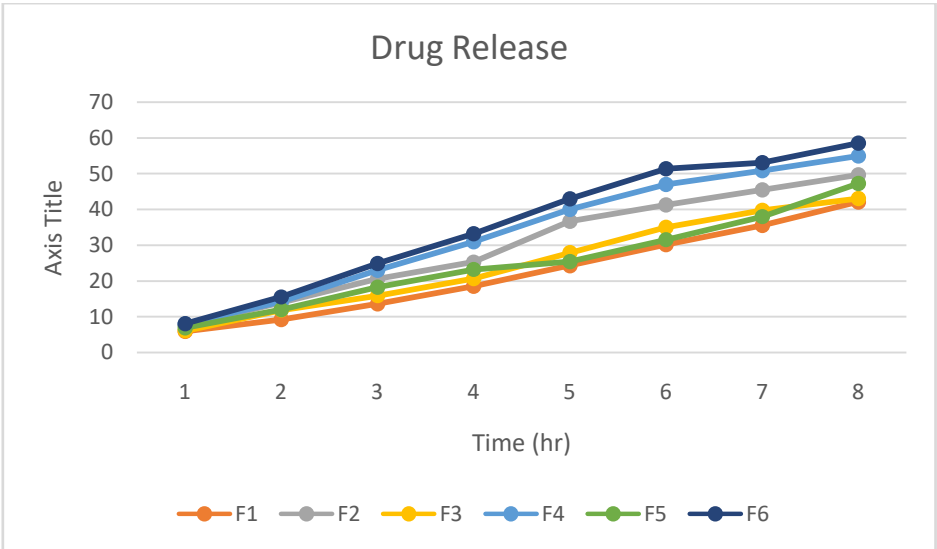

Fig.11: In-vitro drug release profile of different formulations.

CONCLUSION

Diseases of the male genitalia range from infectious lesions to inflammatory and neoplastic conditions, including many genital manifestations of more general skin diseases. Balanitis means inflammation of the head of the penis. The risk factors of balanitis disease are poor hygiene, sexually transmitted disease, diabetes, and the presence of foreskin. The main symptoms of the disease are redness, swelling, and itching under the four skins. Paraphimosis is a urologic emergency that can be occurring in uncircumcised males.

Polymers like Carbopol 934 and HPMC were used to create clotrimazole nanoemulsion gel formulations, and these formulations showed acceptable physical characteristics, viscosity, and drug release**.** HPMC-based nanoemulsion gel in its high concentration i.e., F6 proved to be the optimized formulation, since it showed the highest drug release i.e., 58.57 % in 8hrs. Nanoemulsion gel is therefore one of the greatest topical medication delivery systems and is particularly efficient for loading drugs.

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