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Development of Organo gel for Tulsi oil

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Abstract: This study aim to develop an Organo gel for Tulsi oil obtained from specie of Ocimum sanctum Linn used for the treatment of candidiasis. Therapeutic potential of the tulsi oil extracted from fresh leaves of Ocimum sanctum L. has been found to be largely due to Eugenol which is a major constituent of the essential oil a phenolic compound (l-hydroxy-2-methoxy-4- allylbenzene). Candidiasis is a fungal infection caused by an overgrowth of a type of yeast that lives on body (Candida albicans). A candidiasis infection often appears on skin, vagina or mouth. Along with antifungal activity tulsi oil exhibits therapeutic potentials such as expectorant, analgesic, anticancer, antiemetic, diaphoretic, antidiabetic, antifertility, hepatoprotective, hypotensive and antistress agents and have been used by traditional medical practitioners, it is also used in treatment of fever, bronchitis, arthritis, convulsions Formulating tulsi oil as organo gel helps in physical and chemical stability of tulsi oil with better and prolonged activity.

***Keywords*- Candidiasis, Organo gel, Tulsi oil**

INTRODUCTION TO ORGANO GEL [1]

Organo gel

Organo gels are highly self-structured system, which are isotopic, thermoreversible, semirigid system formed by peculiar kinds of small organic molecules. They are efficiently self-assembled into a three-dimensional network of nanoscale measurement thereby a turning a liquid into gel. As a result, the interlacing three-dimensional scaffold structure of the dispersed phase's solvated macromolecule particles limits the dispersing medium's mobility.

Organogel does not create a semisolid state when left in a standing position because it is made up of twisted strands of macromolecules. The molecules are bound together by stronger types of vander waals forces so as to form crystalline amorphous region throughout the entire system**.**

Recently, spans have been demonstrated to offer a very promising topical drug delivery vehicle, namely organogel, when combined with certain additional chemicals. Organogel are thermodynamically stable, clear, viscoelastic, biocompatible and isotropic gels composed of phospholipids, appropriate organic solvent and a polar solvent. The formation of three-dimensional networks in the organogel is the result of transition at micellar level in a low viscous network liquid consisting of span cause micelles in non-polar organic liquid. After the addition of water, these spherical reverse micellar forms of lipid aggregates twine on to form elongated tubular micelles, and then entangle to create a temporal three-dimensional network in the bulk solution. However, the transparency and optical isotropy of the organo gel remain is maintained. Because of this, these systems are also referred to as living or equilibrium polymers, worm-like or thread-like micelles, or polymer-like micelles.

Advantages of Organo gel[2]

1. Not necessary to add penetration enhancer hence less harmful, not produce irritation.
2. Moisture insensitive.
3. Organic nature hence less resistance to the microbial contamination
4. Provide a variety of opportunities with various physicochemical characteristics in order to be incorporated.
5. Easy to handle.
6. Cost reduction due to fewer ingredients required.
7. Longer shelf life.
8. Thermoreversibility.

The rationale of Organo gel as topical drug delivery[3]

Amongst the various types of topical dosage forms, gels are gaining importance as relatively effective topical dosage forms. A gel can be described as the cross-linked material that retains a large amount of solvent inside its medium and if the solvent retained is organic one, such material is known as organo gel. Traditionally, organo gel type systems are applied topically when the active agent is oil soluble or, if we need sustained release of the drug in the deep skin layers. Organo gels show diverse physicochemical properties like thermoreversibility, ability to incorporate all types of drug molecules, controlled release, increased resistance to microbial contamination etc.

MECHANISM OF GEL PERMEATION INTO SKIN[4]

There are two potential pathways for gel penetration into the skin have been postulated.

1.Gel permeation into the skin occurs by diffusion through lipid intercellular matrix in stratum corneum.

2.Gel provides a slight disorganization of the skin allowing the permeation of the gel and the active drug through the stratum corneum.

Routes of Skin Permeation

The structure of skin shows number of diffusional pores like hair follicles, sweat glands, and intracellular spaces etc. which help in the absorption.

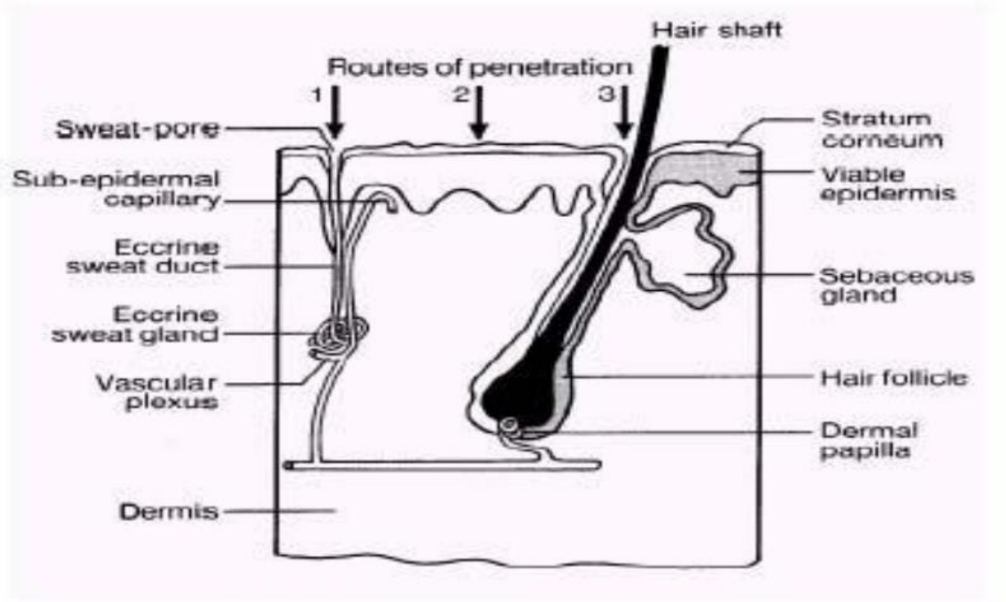

figure1: routes of skin permeation

Skin as Permeability Barrier

The skin itself is a crucial component in transdermal medication delivery systems. It acts as permeability barrier against the transdermal absorption of various chemicals and biological agents. Like all other epithelial systems of the body, the prime function of the skin is to keep water and other vital substances in the skin and restrict the entry of foreign substances.

A) Stratum Corneum as a Permeability Barrier

The stratum corneum is a wall-like structure with proteins and lipids. Stratum corneum has less water content as compared to other skin components. It is 10 μm thick and is the most important barrier. It has been proved experimentally that the permeability of water and other substances was enhanced after the stratum corneum was stripped out layer by layer by employing a cellophane tape. The lipid matrix, especially keratin-phospholipids complex of the stratum corneum, plays a significant role in determining the permeability of substances across the skin.

Once the dosage form is applied topically, the transdermal penetration can be visualized as a composite of a series of following steps as:

i) Adsorption of penetrant molecule on to the surface layer of stratum corneum.

ii) Diffusion through stratum corneum and through viable epidermis.

The final step involves passage through papillary dermis into the microcirculation. The capillaries and layers of live tissue are reasonably permeable, and the peripheral circulation is fast enough.

Hence permeation through stratum corneum acts as the rate- limiting step in the permeability of most of the substances.

B) Function of skin

Skin performs varied functions such as providing mechanical and protective function by acting as a microbiological barrier, Chemical barrier, Radiation barrier which plays a key role in hindering the absorption through skin.

Factors Affecting Organo gel [5]

Polar Solvent

An increase in the cross-sectional area of the lecithin polar region, where the solvent is placed, may be related to the effect of polar solvents introduced into spherical lecithin micelles.

Non-aqueous Solvent

As long as the non-aqueous solvent totally substitutes the water in the bacterial cellulose hydrogel without changing its structure, there aren't any special restrictions.

Phase Transition Temperature (PTT)

It provides information on the characteristics of the microstructures that make up the gelling cross-linked network. Accurate and sensitive methods for determining PTT include high sensitivity differential scanning calorimetry and hot stage microscopy.

Salt Addition

Salting out is the process by which salt draws out some of the water that hydrates the polymer, promoting the creation of additional intermolecular secondary bonds.

Temperature

The degree of hydration is decreased and gelation takes place if the temperature is lowered once the gel is in the solution. It is frequently impossible to liquefy gel that results from chemical cross-linking through dilution or temperature changes.

Surfactants

Gel characteristics can be varied by adjusting the proportion and concentration of the surfactant.

I. MATERIALS AND METHODS:

2.1 Raw material Collection: Tulsi oil extracted from specie of Ocimum sanctum Linn were procured from a local Ayurvedic store.

II. PREFORMULATION STUDIES

2.1. Characterization of Tulsi Oil

2.1.1. FTIR Spectroscopy of Eugenol

The identification of Eugenol was carried out using FTIR (Bruker). FTIR spectra of Eugenol was determined by KBr press pellet technique using Bruker FTIR over a range of 4000-400cm $^{-1}$. The characteristic peaks of the functional groups were interpreted and compared with reported IR spectrum of Eugenol.

2.1.2. Boiling Point Determination

The boiling point of Tulsi oil was determined by capillary method. The boiling point of Tulsi oil was determined for the determination of any impurity. The obtained result was compared with the reported data.

2.1.3. Ultraviolet-Visible (UV-Visible) spectroscopy

The UV system consisted of a Jasco V-630 UV-visible spectrophotometer with 10mm quartz cuvettes were used for determination of λ max and construction of calibration curve.

2.1.3.1. Determination of maximum wavelength

a) Determination of max in Methanol

The standard solution of Eugenol marker was prepared in methanol. The prepared solution was scanned between in the range of 400-200 nm.

b) Determination of max in Phosphate Buffer (pH 7.4)

The standard solution of Eugenol marker was prepared in Phosphate Buffer (pH 7.4). The prepared solution was scanned between in the range of 400-200 nm.

2.1.3.2. Construction of Calibration curve

Stock solution of Eugenol was prepared using methanol and phosphate buffer (pH7.4) as a solvent. Dilutions were made in the range of 0.2 to 1 µg/ml in phosphate buffer (pH 7.4) and 0.02 to 0.1 µg/ml in methanol. The absorbance of resulting solutions was measured against blank.

III. FORMULATION STUDIES

3.1. Selection of Surfactant

About 300 mg of each surfactant and 300 mg of tulsi oil taken in a vial. This mixture heated and cyclomixed. From this mixture, take 150 mg and add to 50 ml distilled water. The ease of emulsion formulation was monitored by noting the number flask inversion required to produce clear and uniform emulsion. Various combinations were evaluated for % transmittance at 638.2 nm by UV visible spectrometer using distilled water as blank.

3.2. Selection of Co-surfactant

The surfactant mixture was prepared by mixing 200 mg of Tween 80 surfactant and 100 mg of each cosurfactant with 300 mg of tulsi oil to assess relative efficiency of the cosurfactant to improve the emulsification ability of selected surfactant and to check number of flask inversion. The oil-S-mix mixture at each ratio was slowly titrated with distilled water. The addition of distilled water was carried out with at room temperature until a micro emulsion was formed.

3.3. Construction of Pseudo-Ternary Phase Diagram

Using the titration method, pseudo-ternary phase diagrams were created to identify the gelling zone and explore the feasibility of creating an organogel with various Tulsi oil compositions (Tween 80 and Span 80, respectively) and water. These five combinations were made using the chosen ratios of two surfactants, namely span80 and tween80, which were 1:1, 1:2, 1:3, 2:1, and 3:1 was prepared and plotted with pseudo ternary phase diagram by using Chemix school software v3.6

3.4. Method of preparation of Organo gel [5]

After being taken in the necessary concentration, span 80 and tween 80 were thoroughly combined in proportion together with Tulsi oil, carbopol 934 was added to the surfactant mixture to create a gelling agent, and it was then left to agitate on a magnetic stirrer for 30 minutes, thus mentioned mixture was agitated at 50 rpm. Then, using a burette, a certain concentration of water was added to the fore said solution drop by drop. The mixture mentioned above was supplemented with methyl and propyl paraben. Finally, pH was adjusted to 6 to 7 using 0.1 N NaOH. homogeneous, creamy organogel was produced.

3.5. Optimization of Organo gel

Various formulations of organogel containing Tulsi oil were prepared with different concentration of gelling agent and optimized based on evaluation parameters and subjecting the formulations to freeze thaw cycle.

Table 1: optimization of organogel

Sr. No.	Ingredients and properties (%w/w)	F1	F2
1	Tulsi oil (active ingredient)	20	20
2	Carbopol-934 (gelling agent)	0.5	0.5
3	Tween 80 (emulsifying agent)	30	40
4	Span 80 (emulsifying agent)	30	40
5	Methylparaben (preservative)	0.03	0.03
6	Propylparaben (preservative)	0.01	0.01
7	Purified water (aqueous vehicle)	20	0
8	NaOH (0.1N)	q. s	q. s

3.6. Evaluation of Organo gel [6]

Appearance: Organo gel was tested visually for appearance to identify the presence of any aggregates.

Colour: colour of the Organo gel was observed visually

Odor: odor was observed by smelling the Organo gel directly.

Consistency: consistency was checked visually.

Homogeneity: Organo gel was checked visually to identify any non-homogeneity.

Oily feel: oily feel was checked by spreading on skin surface and by washing with tap water.

Grittiness: Organo gel was checked for grittiness by spreading on skin surface.

Phase separation: Organo gel was observed visually for phase separation.

Spreadability study: Spreadability denotes the extent of area to which the Organo gel readily spreads on application to skin or the affected part. The bioavailability efficiency of an Organo gel formulation also depends on its spreading value. The Spreadability was expressed in terms of time in seconds taken by two slides to slip off from the Organo gel which was placed in between the slides, under certain load. Lesser the time taken for separation of the two slides, better the Spreadability.

Extrudability test: The Organo gel formulation was filled into collapsible aluminium tube and sealed by crimping the end. The tubes were pressed to extrude the material and the extrudability of the Organo gel was checked.

Determination of pH: Five gram of Organo gel was dissolved in 45 mL of distilled water and then the pH was determined by using digital pH meter

IV. RESULT AND DECISION:

4.1. Characterization of Tulsi Oil

4.1.1. FTIR Spectroscopy of Eugenol

The pure drug spectrum showed the characteristic stretching's similar to the data reported in literature.

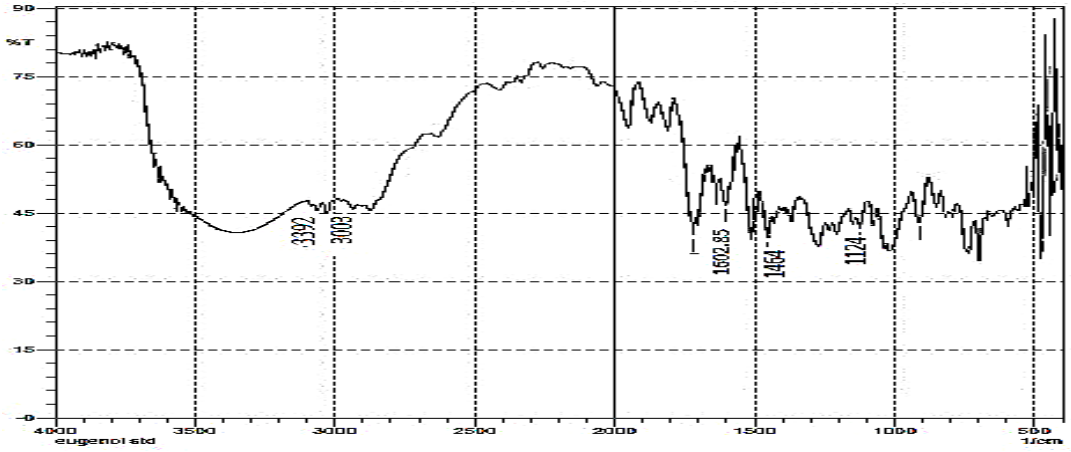

Figure 2: FTIR Spectrum of eugenol

Table 1: Functional groups detected by eugenol

Reported wave number (cm-2)	Observed wave number (cm-2)	Functional groups
3000-2850	3003	C-H alkanes (stretch)
1600 and 1475	1602.85	C=C aromatic(stretch)
1300-1000	1124	C-O ether (stretch)
1465	1464	CH2 alkane (bend)
3400-3200	3392	-OH (stretch)

4.1.2. Boiling Point Determination

The boiling point of Tulsi oil was found to be in range of 254°C which is in the range of reported boiling point as per literature survey.

4.1.3. Ultraviolet-Visible (UV-Visible) spectroscopy

4.1.3.1. Determination of maximum wavelength

a) Determination of λ max in Methanol

Eugenol solution was examined in the range of 400- 200 nm and 0.1 ppm solution of Eugenol in methanol showed absorption maxima at 281 nm.

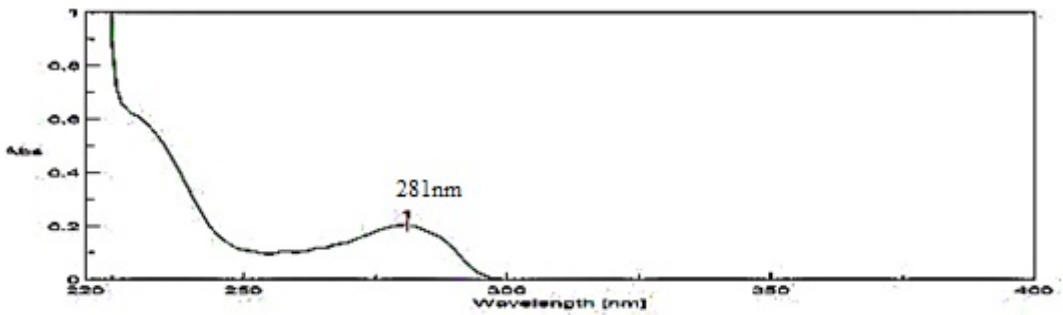

Figure3: Determination of λ max (in methanol)

b) Determination of λ max in Phosphate Buffer (pH 7.4)

Eugenol solution was examined in the range of 400- 200 nm in phosphate buffer pH 7.4 showed absorption maxima at 281nm.

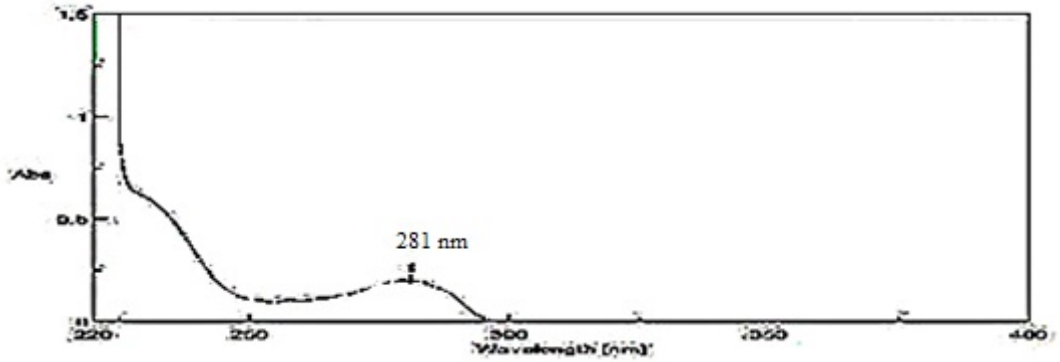

figure 4: Determination of λ max in Phosphate Buffer (pH 7.4)

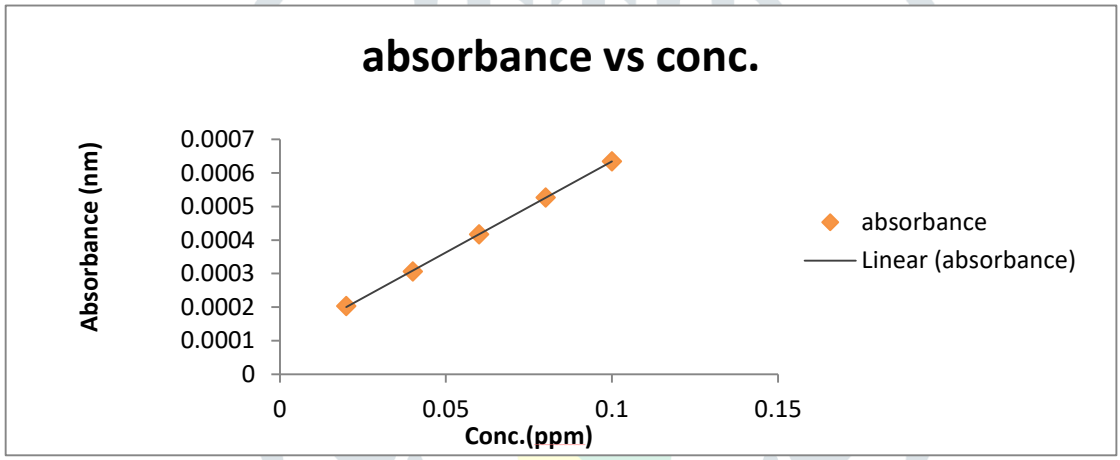

figure5: standard calibration curve of eugenol in methanol

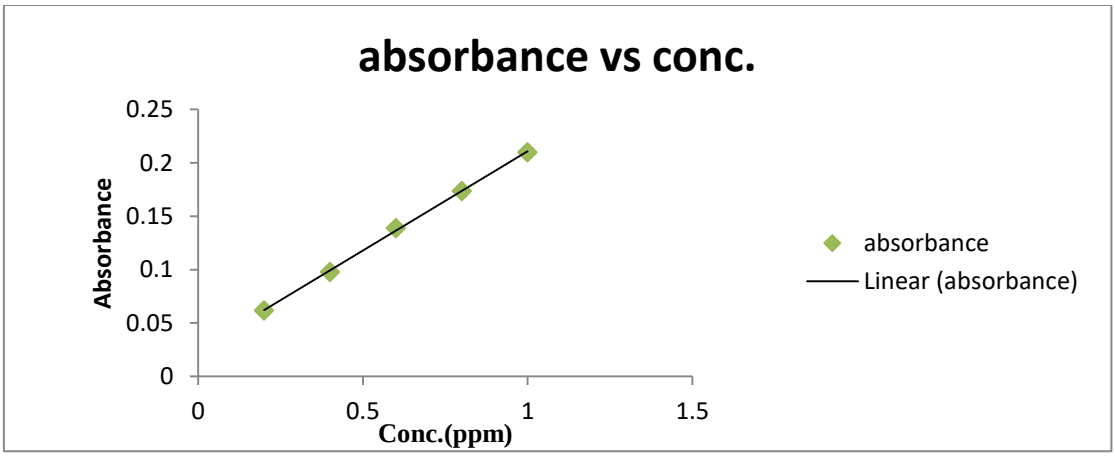

figure 6: standard calibration curve of eugenol in phosphate buffer (7.4)

4.2. Selection of Surfactant

The Surfactant were compared for ease of emulsification of the Tulsi oil. selection of surfactant primarily based on their efficiency to spontaneously emulsify the selected oil. Surfactant such as Tween 20, Tween 60, Tween 80, Span 20 were tested it was observed out of 5 surfactants tested, Tween 80 have shown better emulsification ability with 94.8% Transmittance requiring 0 flask inversion for ease of emulsification thus Tween 80 selected as surfactant.

4.3 Selection of Co-surfactant

Addition of a cosurfactant to the surfactant containing formulation lowers the interfacial tension fluidizes the hydrocarbon region of the interfacial film, and decreases the bending stress of interface which improves the dispersibility and drug absorption from the formulation. Various cosurfactant such as PEG 400, span 20, span 80, Ethylene glycol was tested Out of 4 co- surfactant tested, span 80 have shown better emulsification ability with 95.2% Transmittance requiring zero flask inversion for ease of emulsification.

4.4. Construction of Pseudo-Ternary Phase Diagram[7]

In this study surfactant tween-80 and span 80 as co-surfactant used because previous studies have proven that the combination of both is the right choice to produce preparations with good physical characteristics and stability. The ratio of oil, surfactant, and co-surfactant in the microemulsion region was determined using a pseudo-ternary phase diagram. According to region obtained from pseudo ternary phase diagram, the ratio 1:1 gave more region as compare to the other four ratios, so 1:1 ratio of surfactant was selected for the preparation of the organogel.

Stability to Freeze thaw cycle

After subjecting the both formulations to Freeze thaw cycle F1 found to be stable to freeze thaw cycle having oil: Smix 1:3 ratio and surfactant and co-surfactant in the ratio of 1:1 have shown neither separation and nor color change. Thus oil: Smix ratio 1:3 and surfactant and co-surfactant in the ratio of 1:1 considered as optimized ratio for formulation. Additionally, due to presence of water, less viscous formulation was formed leads to less packed gel matrix which easily get breaked, thus contributes tohigher release of drug

4.6. Evaluation of Organogel

Table 2: evaluation of organo gel

Sr. no	Evaluation	F1	F2
1	**Appearance**	Opaque smooth	Opaque liquid
2	**Colour**	Off white - white	Off white - white
3	**Odour**	Pleasant	Pleasant
4	**Consistency**	Excellent	Poor
5	**Homogeneity**	+++	0
6	**Oily feel**	Absent	Absent
7	**Grittiness**	Absent	Absent
8	**Phase separation**	Absent	Present

9	**Spreadability**	+++	+
10	**Extrudability test**	Excellent	Poor
11	**Determination of PH**	5.55	4.57

4.7. Optimization of Organo gel

Table 3: optimized formula of organo gel

Sr. No.	Ingredients and properties (%w/w)	F1
1	Tulsi oil (active ingredient)	20
2	Carbopol-934 (gelling agent)	2
3	Tween 80 (emulsifying agent)	30
4	Span 80 (emulsifying agent)	30
5	Methylparaben (preservative)	0.03
6	Propylparaben (preservative)	0.01
7	Purified water (aqueous vehicle)	20

Conclusion: In this research, we have formulated tulsi oil organo gel loaded with Tween 80 and Span 80 as a emulsifying agent and Carbopol-934 as a gelling agent also presence of water causes less viscous formulation leads to less packed gel matrix which easily get breaked, contributing to higher release from formulation which can be used for the treatment of candidiasis. thus, several problems associated with Tulsi oil formulation can be overcome by preparing organogel which hold the oil in their 3-dimensional scaffold structure, helping in development of organogel formulation of Tulsi oil with improved stability and applications.

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