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Nano-based Drug Delivery Systems; Recent Developments and Future Prospects

7 OCTOBER 2023

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INDIAN PHARMACEUTICAL ASSOCIATION

JOURNAL OF INNOVATIONS IN APPLIED PHARMACEUTICAL SCIENCES

JIAPS
JOURNAL OF INNOVATIONS IN APPLIED PHARMACEUTICAL SCIENCES
ISSN: 2455 - 5177

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JOURNAL OF INNOVATIONS IN APPLIED PHARMACEUTICAL SCIENCES

National Conference on Nano-based Drug Delivery Systems; Recent Developments and Future Prospects conducted By Nirmala College of Pharmacy, Muvattupuzha, in association with Indian Pharmaceutical Association on 7 October 2023

RESEARCH ARTICLE(S)

Online ISSN:2455-5177

CODEN (CAS-USA): JIAPAW

Impact Factor: 5.832

Journal Archived in

PORTICO

KEYWORDS

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Journal of Innovations in Applied Pharmaceutical Science [JIAPS]

Content available at: www.saap.org.in ISSN: 2455-5177

DESIGN AND CHARACTERISATION OF TOPICAL EMULGEL CONTAINING NEEM OIL FOR ITS ANTIDANDRUFF PROPERTIES

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Article History

Received: 07-10-2023
Revised: 28-10-2023
Accepted: 12-10-2023

Keywords: Neem oil, Malassezia, Neem oil emulgel, zone of inhibition.

Abstract

Emulgel is a novel drug delivery system for controlled release of drug. It is suitable for the dual release of drugs. This study focuses on the development and characterization of topical emulgel containing neem oil for its anti-dandruff properties. Neem oil is emulsified using suitable surfactant in the ratio 4:2:1 and the prepared emulsion is incorporated with Carbopol gel base in ratio1:1. A total of 5 formulations were prepared using the polymer carbopol-934. Topical emulgel of neem oil was formulated and subjected to evaluation studies such as organoleptic properties, pH, Viscosity, Spreadibility, Invitro diffusion studies, Accelerated stability studies using ultracentrifugation, SEM analysis and Invitro antifungal properties. Formulation F5 subjected to in vitro oil diffusion study had shown a total release of 65.27% after 8 hours. Korsmeyer-Peppa's plot had shown that the mechanism of diffusion was non-fickian. Emulgel of neem oil shown zone of inhibition on invitro antifungal study using Candida albicans as fungi. Formulation F5 show highest zone of inhibition of 12mm as compared to other formulations. It was concluded that, formulation of neem oil as a semi solid dual release control emulgel formulation with a time dependant oil diffusion, also add up all the advantage of a semisolid dosage compared to liquids with optimum Spreadibility, stability, aesthetic appearance, adherence to the affected scalp area and with pH that is similar scalp.

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https://doi.org/10.37022/jiaps.v8i3-S.508

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Introduction

Topical drug delivery can be defined as the delivery of drug containing formulation to the skin to treat cutaneous disorder directly with the intent of confining the pharmacological or other effect of the drug to the surface of the skin. Topical drug delivery system has the advantage of neglecting the first pass metabolism and topical formulation can be prepared as solid, semisolid, and liquid dosage form. Once applied, a topical formulation must interact with the skin environment, which can influence the rate of the release of the compounds to achieve adequate skin absorption. The formulation must allow for optimal penetration of the drug into the skin, a complex tissue. Dandruff is a chronic scalp condition characterized by scaling, itching and redness of the scalp. It occurs when scalp sheds epidermal cells in large clump [1, 2]. Neem tree ***(Azadirachta indica)*** a fast-growing tree belongs to family '***Meliaceae***.' Neem oil is a fixed oil pressed from fruits and seeds of neem. Neem oil can be used in medicines due to its anti-inflammatory, hypoglycaemic, anti-pyretic, anti-fungal, antibacterial, spermicidal, diuretic, and anti-ulcer properties. The major crude bitter principle extracted from neem oil is Nimbidin, which exhibit several of biological activities. Emulsions are colloidal dispersions consisting of 2 immiscible liquids (either oil or water) in which one i.e., dispersed, or discontinuous phase is distributed uniformly throughout the dispersion medium or continuous phase which are stabilized by the addition of suitable numberof emulsifiers (surfactants) [3]. Gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. 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 in the continuous phase, randomly coiled in the flexible chains [4-7]. When gel and emulsion are used in combined form the dosage form are referred as Emulgel. Emulgel have emerged as one of the most interesting topical delivery systems as it has dual release control system i.e., gel and emulsion. Rationale of emulgel as a Topical drug delivery system is that many widely used topical

agents like ointments, creams lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing and they also exhibit the problem of stability. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. In spite many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So, to overcome this limitation an emulsion-based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels. The pattern of release of drug from them is dual release i.e., release of drug from emulsion into gel matrix then release of drug from gel matrix to the site of application [8].

Materials and methods

The investigation made use of a diverse range of chemicals, each contributing to specific aspects of the research. These chemicals and their respective sources are as follows: Neem oil wasobtained from leave N Relief, while Tween80, Carbopol935, Polyethylene glycol,Tri ethanol amine and Methyl paraben were sourced from nice chemicals. Mentha oil was provided by Vikas pharma.

Development of neem oil emulgel

Table 1: Formula used for the development of Neem oil emulgel

Ingredients (% w/w)	F1	F2	F3	F4	F5
Neem oil	57.14 ml	57.14 ml	57.14 ml	57.14 ml	57.14 ml
Tween 80	17ml	17ml	17ml	17ml	17ml
water	28.57 ml	28.57 ml	28.57 ml	28.57 ml	28.57 ml
Carbopol 935	1	1.5	2	2.5	3
Polyethyleneglycol	5ml	5ml	5ml	5ml	5ml
Triethanolamine	4	4	4	4	4
Methyl paraben	1	1	1	1	1
Mentha oil	1.2ml	1.2ml	1.2ml	1.2ml	1.2ml
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.

Formula used for the development of Neem oil emulgel:

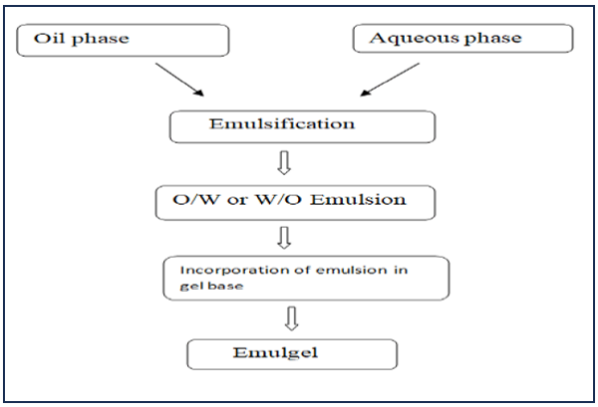

Figure1.Flowchart for Emulgel preparation

Preparation of gel base

The required amount of Carbopol was weighed and transferred to the solvent mixture containing water and PEG. The polymer was allowed to swell completely without constant stirring. After complete swelling, the solution was stirred continuously by mechanical stirrer and neutralized by the addition of the alkali TEA. At neutral pH the solution was converted to a gel with maximum viscosity.

Preparation of Neem oil emulsion

Measured quantity of neem oil was taken in beaker, aqueous phase with emulsifying agent (tween 80) and water was taken in another beaker. Both are heated to 70℃ Then the oil phase is added to aq. Phase with continuous stirring until a creamy emulsion is formed.

Preparation of Neem oil emulgel

The prepared gel is mixed with Neem oil emulsion in the ratio 1:1 using mechanical agitator. 5 different formulations F1, F2, F3, F4, F5 of varying concentration of gelling agent was prepared [9].

Evaluation

The parameters that are used for the evaluation of gels which includephysicochemical characteristics like determination of emulsion type, homogeneity, grittiness, colour, phase separation.Physicochemical evaluation data like ph, viscosity, Spreadibility, In-vitro Diffusion Studies Using the Pre-hydrated Cellophane Membrane.

Procedure

The in vitro diffusion studies of prepared emulgel were carried out in hollow tube diffusion cell using prehydrated cellophane membrane.100 ml of phosphate buffer of pH 7.4 was used as receptor compartment, and then 500mg of emulgel containing neem oil was spread uniformly on the membrane. The donor compartment was kept in contact with a receptor compartment. The solution on the receptor side was stirred by externally driven Teflon coated magnetic bars at pre-determined time intervals. Pipette out 5ml of solution from the receptor compartment and immediately replaced with the fresh 5ml phosphate buffer. The drug concentration on the receptor fluid was determined spectrophotometrically at 281 nm against appropriate blank.

Calculation of percentage drug release:

% drug release = (concentration of drug in (mg) × volume of receptor compartment) × 100 Label claim (amount of drug in donor compartment).

Centrifugation Test

To perform the centrifugation test, 10 g of formulation was added in a tapered test tube. In centrifugation, the sample gel was subjected to a cycle of 3000 rpm for 30 minutes at room temperature. Centrifugation was performed with Model Centribio® 80-2B equipment [10].

SEM Analysis

Surface morphology observation was performed using JEOL JSM 6390. Samples are mounted with double sided Carbon tape on Aliminium stubs. All specimens were sputtered with thin layer of gold in auto fine coater JEOL JFC 1600 and the images were examined at an accelerating voltage of 10kv.

In-vitro Anti-fungal activity by Zone of Inhibition method

Procedure: Inoculum preparation: Transfer a loopful of culture from working stock slant to 5ml of YEPD broth and incubated at 25ºC for 24 hours or till getting a visible turbidity

equivalent to 0.5 MacFarland unit. Culture was inoculated on plate and allow the plate to dry for 5 minutes. Agar wells were prepared using sterile corn borer. 100µl sample (Direct) and 80% sample concentration prepared in DMSO were placed to the well using micropipette. Standard drug fluconazole 500 ppm and solvent control DMSO were also kept. Kept the plates for incubation at 25° C. After incubation, check the plates for zone of inhibition, measure the diameter (mm) of the zone. Record the results.

Preparation of Neem oil emulsion by fusion method

The o/w neem oil emulsion was prepared by fusion method in a beaker.

Preparation of Gel base using Carbopol 934

The gel bases were prepared by dispersing polymers of concentration 1.5%, 2%,2.5%,3%,3.5 %. The pH of all the formulations was adjusted to 6 - 6.5 using TEA. TEA was added as neutralising agent that when added dropwise to dispersion during mixing will form gel.

Preparation of Neem oil emulgel

The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring using mechanical stirrer to obtain the Neem oil Emulgel.

Organoleptic evaluation

Physical appearance

Table 2: Organoleptic properties

Formulation	Colour	Homogeneity	Grittiness	Phase separation
F1	White to cream in colour	Excellent	No grittiness	Slight separation
F2	White to cream in colour	Good	No grittiness	No separation
F3	White to cream in colour	Excellent	No grittiness	No separation
F4	White to cream in colour	Excellent	No grittiness	No separation
F5	Whiteto cream in colour	Good	No grittiness	No separation

Physiochemical evaluation data

Measurement of pH

pH values are around the pH of scalp which indicates that there are less chances of irritation due to variation in the pH of ormulation.

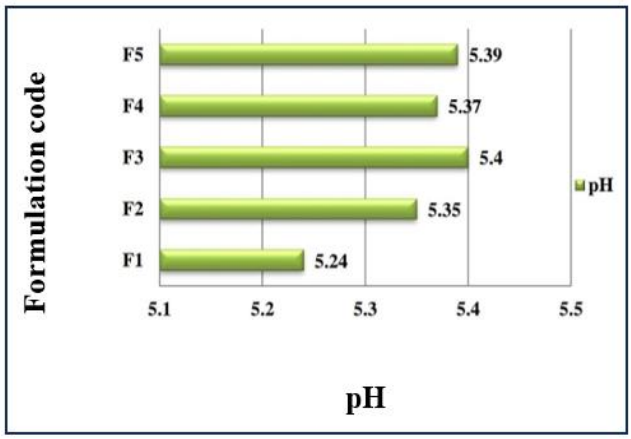

Figure2: pH of Different Formulations F1- F5

Measurement of viscosity

It shows a linear relationship of viscosity and the concentration of Carbopol 934. The formulation F5 shows maximum viscosity with a value of 21760 cP.

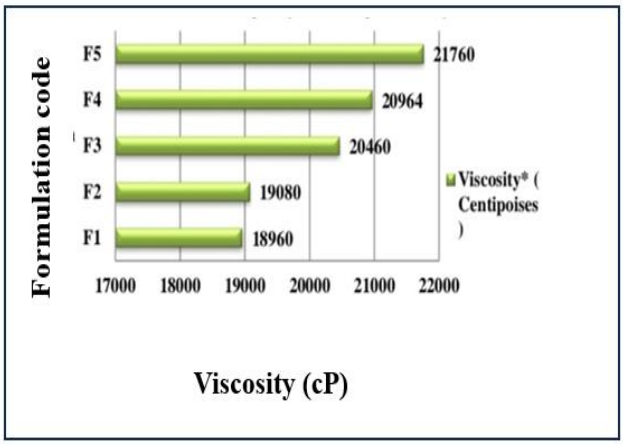

Figure3: Viscosities of Different Formulations F1- F5

Determination of Spreadibility by parallel plate method

As per the results obtained for Spreadibility it was found that the formulation F2 had shown maximum Spreadibility which shown to be decreased in a linear manner from as it goes to F2 to F5.

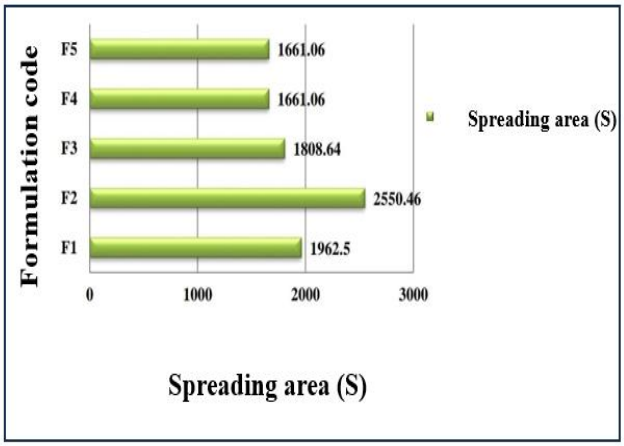

Figure 4: Spreading area of Different Formulations F1- F5

In-vitro diffusion study of formulation F5

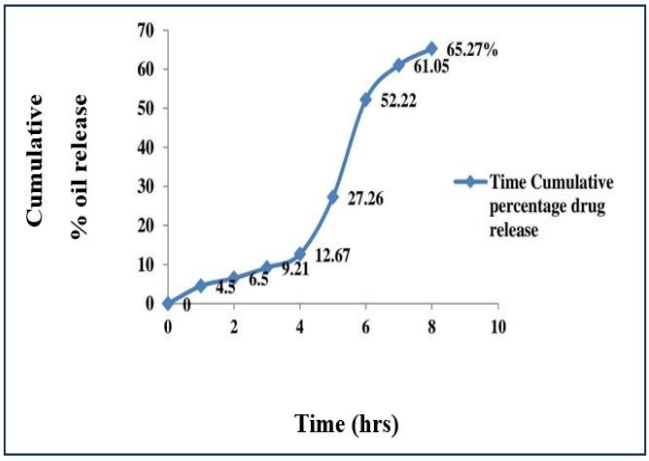

Figure 5: Cumulative percentage oil release of F5

It was observed that there was only a slight diffusion of oil through the membrane up to 4th hour. But was found to be increasing steadily after 5th hour and had released a total of 65.27% of oil from the formulation F5. The release was found to be satisfactory since the neem oil is supposed to be used as a topical anti dandruff preparation.

Determination of mechanism of release from Diffusion exponent (n) by Korsmeyer-Peppas plot.

A plot of log (time) Vs log (%CDR) yields slope n, i.e., Diffusion exponent

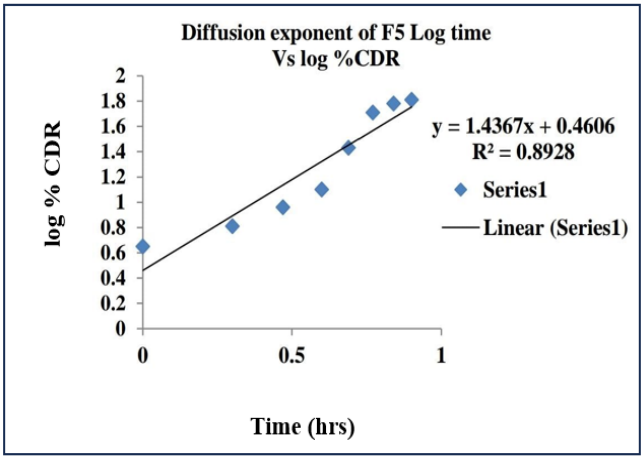

Figure 6: Diffusion exponent plot of F5

Accelerated stability study for phase separation using ultracentrifugation technique Ultracentrifugation was carried out at 2000 and 3000 rpm for emulgel shown no sign of phase separation

Scanning electron microscopy of Emulgel (F5)

The selected emulgel F5 was observed under Scanning electron microscope at different the value of diffusion exponent (n) for F5 was found to be 0.892 that indicates Anomalous non-Fickian diffusion of oil from emulgel. The mechanism indicates that the drug release is independent of concentration. Diffusion process in which the mean square displacement (MSD) of drug grows non linearly with time are referred to as Anomalous or non-Fickian i.e., the release pattern is irregular and is independent of drug concentration. magnifications (80X, 85X, 140X, 190X, 300X, 330X). Nearly spherical globules of emulsion were observed.

In- vitro Antifungal study by Zone of inhibition method

Moreover, emulgel of neem oil shown zone of inhibition on In-vitro antifungal study using Candida albicans (NCIM 3102). Whereas neem oil used alone did not show a clear zone around the well which can be due to poor diffusion in nutrient media. Formulation F5 show highest ZOI of 12mm as compared to other formulation.

Table 3: Zone of inhibition produced by the Emulgel (F1-F5) and in 80% DMSO

Test Organism	Test Results- Zone of Inhibition							Test method
Candida albicans (NCIM 3102)	Sample (Direct)							Agar well diffusion method
	F1	F2	F3	F4	F5	Drug	Standarddrug	
	10 mm	10 mm	10 mm	10 mm	12 mm	No Zone	Fluconazole (500 ppm) 36mm	
	Sample 80% (In DMSO)							
	F1	F2	F3	F4	F5	Drug	Standarddrug	
	No Zone	No Zone	No Zone	No Zone	No Zone	No Zone	Fluconazole (500 ppm) 36mm	

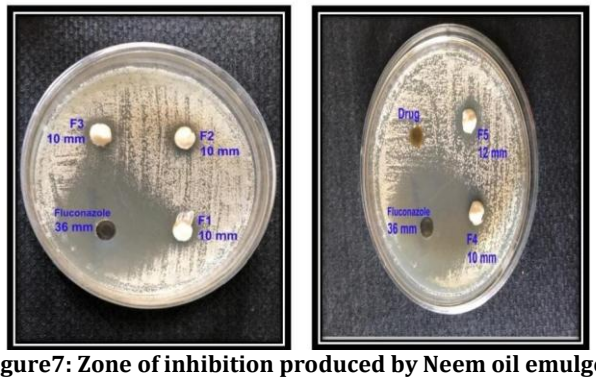

Figure7: Zone of inhibition produced by Neem oil emulgel

Summary and Conclusion

Topical emulgel of neem oil was formulated and subjected to evaluation studies such as organoleptic properties (colour, odour, homogeneity, and grittiness), pH, Viscosity, Spreadibility, Invitro diffusion studies and Invitro antifungal properties. The pH of all formulation was around to be 5 which is slightly acidic and around the normal pH of scalp 5.4. The viscosity was found to be increase with increase in Carbopol strength, formulation F5 show maximum viscosity. The Spreadibility increased with decrease in Carbopol

concentration. However, formulation F2 had shown more spreading coefficient. Emulgel shows more spreading than gels due to the presence of oil phase. Ultracentrifugation was carried out at 2000 and 3000 rpm for emulgel shown no signs of phase separation. Formulation F5 subjected to in vitro oil diffusion study had shown a total release of 65.27% after 8 hours. Kosmeyer Peppa's plot had shown that the mechanism of diffusion was non-fickian. Moreover, emulgel of neem oil shown zone of inhibition on invitro antifungal study using Candida albicans as fungi. Whereas neem oil used alone did not show a clear zone around the well which can be due to poor diffusion in nutrient media. Formulation F5 show highest zone of inhibition of 12mm as compared to other formulations.

From all the above results it was concluded that, formulation of neem oil as a semi solid dual release control emulgel formulation with a time dependant oil diffusion, also add up all the advantage of a semisolid dosage compared to liquids with optimum Spreadibility, stability, aesthetic appearance, adherence to the affected scalp area and with pH that is like scalp.

Acknowledgement

Iwould like to express my sincere gratitude towards Dr. DhanishJoseph associate professor. Department of pharmaceutics for his immense support and valuable suggestion for the project. I wish my humble regards and sincere thanks to department of pharmaceutics, management and colleagues who had directly or indirectly contributed for the completion of project.

Conflict of interest

Authors are declared that no conflict of interest

Funding

Funded by Nirmala College of pharmacy Muvattupuzha

Ethical consideration and inform consent

Not applicable

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