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Formulation and Development of Herbal In-Situ Sustained Release Gel for Otitis Media

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ABSTRACT:
The purpose of this study was to highlight the potential of methanolic extract of Eclipta Alba to develop in-situ sustained release otic gel for the treatment of Otitis media. Otitis Media is a medical condition that affects middle ear majorly in young children. Primarily it is categorized into Acute Otitis Media and Chronic Otitis Media. Eclipta Alba. commonly known as Bringraj has been used traditionally for hair related purposes. However it has proven antimicrobial activity against Otitis media causing bacteria. In following experiment, a herbal in-situ thermosensitive gel was prepared by utilizing poloxamer 407 and poloxamer 188. The optimized batch C2 which had 20%W/V poloxmer 407 and 15% w/v poloxamer 188 were found to be having the satisfactory release profile of almost 70% in 5.5 hours. Other evaluation parameters like viscosity, gel strength and pH were found satisfactory in formulation.

I. INTRODUCTION

Otitis Media: A common medical disease known as otitis media impacts the middle ear, it being the area behind the eardrum wherein sound waves are delivered to the inner ear. Although it can impact everyone regardless of age, this illness is most common in young children. Otitis media can take on an array of forms, all of which have unique symptoms and treatment plan.Acute otitis media (AOM), chronic otitis media with effusion (OME), and chronic suppurative otitis media are still the three main kinds of otitis media (CSOM) (1) I.Acute Otitis Media (AOM II. Chronic Otitis Media with Effusion (OME. III. Chronic Suppurative Otitis Medium (CSOM**)**

Causes of Otitis Media : Otitis media is a disease which is characterized by accumulation of fluid and inflammation occuring in the middle ear. Otitis media can come in three primary forms, each with a unique reason.

I) Acute Otitis Media (AOM), especially in youngsters. It is brought on by bacterial or viral infections, which induce swelling and fluid accumulation in the middle ear (6).

- **Bacterial Causes:** Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis represent the most prevalent organisms to produce AOM. This Eustachian tube, particularly attaches to middle ear to throat's backside, enabling these microorganisms to travel from of the respiratory tract to the middle ear. Infants under the age of 2 and people who have impaired immune systems are more vulnerable to contract bacterial illnesses (7)
- **Viral Causes:** Bacterial infections, including bronchial syncytial virus (RSV), adenovirus, and influenza, also could contribute into AOM. Your Eustachian tube may have become enlarged and inflamed as a response of infections, causing it to be harder for middle ear fluid to drain. This may result in fluid accumulation and a higher risk of bacterial infections (8).

II) Chronic Otitis Media with Effusion (OME) is a type of otitis media called chronic otitis media with effusion (OME) is distinguished by fluid becoming persistent in the middle ear for quite a prolonged time frame, frequently longer than 3 months. OME is not usually followed by soreness or a temp, but it can culminate in hearing impairment and other problems.

- **Allergic Causes:** Allergies can cause swelling and inflammation in the Eustachian tube and nasal passages, which can lead to OME. This could make it harder for fluid to exit the middle ear, which might result in fluid accumulation.
- **Anatomical Causes:** OME risk might be increased by anatomical anomalies such a cleft palate or Down syndrome. Certain diseases

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may alter the ear's physical makeup and make it more challenging for fluid to flow normally.

- **Eustachian Tube Dysfunction:** The Eustachian tube might get clogged or stop working correctly in the case of eustachian tube dysfunction. This can raise the chance of getting OME and cause a buildup of fluid in the middle ear.[C] Chronic Suppurative Otitis Media (CSOM)

III)**Chronic suppurative otitis media (CSOM)** is a type of otitis media recognized by an inflammation and fluid drainage from the middle ear. It's caused by bacterial infections, and it can lead to hearing loss and other complications if remained untreated.

- **Bacterial Causes:** Pseudomonas aeruginosa, Staphylococcus aureus, and Proteus mirabilis are the microorganisms that cause CSOM. Through the Eustachian tube, these microbes may invade the middle ear, generating drainage and irritation.
- **Other Causes:** Trauma to the ear, such as from a foreign item or injury, or long-term exposure to irritants like cigarette smoke can also result in CSOM. In addition, immune system-affecting disorders like HIV/AIDS or chemotherapy might raise the likelihood of acquiring CSOM. (9).

- **IN-SITU GELS**

In-situ gels are a special kind of drug delivery technology made to transform from a liquid to a gel in the body. Since these gels can increase the bioavailability and therapeutic effectiveness of medications by lengthening their residence duration at the site of application, they have attracted increased interest as a viable alternative for drug delivery. Topical, ocular, nasal, and injectable administration are only some of the options for in-situ gels' many potential modes of administration (18). In-situ gels provide various benefits over conventional drug delivery techniques. For instance, they can lengthen the time between medication administrations, lessen drug waste, and reduce the number of times a medicine must be administered. Furthermore, in-situ gels can lessen the pain associated with numerous injections, hence increasing patient compliance (14).

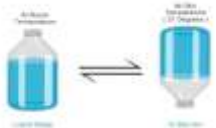

Figure No 1 Thermo sensitive In-situ Gel

The characteristics of in-situ gels are affected by a number of variables, such as the polymer utilised, the pH of the surrounding environment, and the temperature. For the gel to have the correct viscosity, gelation duration, and drug release characteristics, the right polymer must be chosen. Another factor that can influence the gel's stability and how quickly the medicine is released is the surrounding environment's pH. The rate of gelation, gel viscosity, and drug release kinetics can all be affected by temperature [(2)]

Merits of in-situ gel over conventional drug delivery system

- Poor bioavailability
- Localized drug delivery:
- Short half-life
- Difficulty in achieving sustained release

Bhringraj (Eclipta Alba) : Bhringraj is a medicinal herb used in Ayurvedic medicine for its therapeutic properties. Bhringraj is Eclipta alba. Asteraceae, it grows in India, Nepal, and Brazil. Bhringraj is an annual or perennial herb plant. It grows to a metre and has small daisy-like blooms. Bhringraj is an anti-inflammatory, antioxidant, antibacterial, hepatoprotective, and neuroprotective medicinal herb. Flavonoids, alkaloids, triterpenoids, polyacetylenes, and coumestans make Bhringraj medicinal. (23).

Figure No 2: Bhringraj (Eclipta Alba)

Classification of Bhringraj:

- Kingdom: Plantae
- Subkingdom: Tracheobionta
- Superdivision: Spermatophyta
- Division: Magnoliophyta
- Class: Magnoliopsida
- Subclass: Asteridae
- Order: Asterales
- Family: Asteraceae
- Genus: Eclipta
- Species: Eclipta alba

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Antimicrobial Properties of Eclipta Alba : Eclipta alba (Bhringraj) is effective against bacteria, fungus, and viruses. Commonly known as the plant. Bhringraj is its linguistic name. Bioactive substances in Eclipta alba may explain its antibacterial properties. Eclipta alba is Mediterranean-native. Wedelolactone, ecliptal, and demethylwedelolactone are instances of this group. Demethylwedelolactone is another bioactive compound that may be extracted from plants. This is demethylwedelolactone. Researchers found these chemicals in Eclipta alba samples. Wedelolactone prevents germ development by disrupting cell membranes or walls. It may induce these abnormalities. Wedelolactone and eclipta alba suppress microorganism growth (15).Eclipta alba fights bacteria, fungi, and viruses. These qualities help it fight pathogen infections. These traits may help the plant treat bacterial infections. It may prevent bacterial illnesses due to these traits. This antibiotic kills Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli. It also kills Candida albicans and Aspergillus niger. Eclipta alba possesses several antibacterial bioactive compounds. Wedelolactone, ecliptal, and demethylwedelolactone are examples. A few instances. These chemicals are antibacterial because they can destroy bacterial cell membranes and walls. This hinders organism growth and reproduction (25)

II. MATERIALS AND METHOD

Sr No	Materials	Use of Ingredient	Quantity Taken
1	Methanolic Extract Eclipta Alba	API	28mg/10ml
2	Kolliphor P407(Poloxamer 407)	Thermo sensitive Polymer	20%w/w
3	Kolliphor P188 (Poloxamer 188)	Gelling Agent	15%w/w
4	Water	Vehical	Q.S

Table.1 List of Materials

METHOD OF PREPARATION:-

Extraction of Eclipta Alba : The methanolic extract was obtained by adding 300 mL of methanol to a flask containing 50 g of dry powder. The mixture was agitated vigorously and subsequently left to settle in an area with reduced exposure to light for a duration of 5 days. Following this, the solution underwent filtration using Wattman filter paper, and the resulting filtrate was subsequently subjected to evaporation until complete dryness while being kept in a shaded location. The collected residues were subsequently dried.

Method of Preparation for In Situ Gel:- The method of preparation involved sprinkling of Methanolic Extract of Eclipta Alba and stirring Poloxamer 407 and Poloxamer 188 in cold water at approximately 10°C and refrigerating for 24 hours. The resulting clear solution was evaluated for suitability in subsequent in-situ gel formulations. Table 1.3 shows the different composition of Poloxamer 407 and Poloxamer 188.

III. EVALUATION PARAMETER

- **Gelation Time:** The samples were tested at 37 ± 0.5°C to determine each batch's gelation time. A glass plate had been angled at 45 degrees and 100 microliters of gel were cautiously placed on it. The gelation time was determined by monitoring the transition of the gel to a semi-solid state. The aforementioned technique presents a direct and dependable methodology for ascertaining the gelation duration of diverse compositions.
- **Gelation Temperature:** In order to determine the gelling time of each otic formulation, a test tube was utilised. The test tube was filled with approximately 0.5ml of prepared formulations and kept on water-bath that was consistently maintained at a temperature of 37°±0.5°. The temperature of solution transitioning into a viscous gel was visually monitored and evaluated based on the duration required for gel formation and the subsequent collapse of the gel structure, with numerical grades being assigned to the gelation time. The aforementioned method offers a systematic and impartial approach to assess the duration of gelation in diverse otic preparations.
- **Visual Test / Clarity Test:** The Visual Test, also known as the Clarity Test, is a method used to evaluate the clarity of a product or material. A little amount of in-situ gel was

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placed in a transparent glass vial for a visual/clarity test. The gel formulation was then visually tested under normal light for particle matter and turbidity.

- **pH Test**.: Perform pH metre calibration in accordance with the manufacturer's guidelines, utilising standard buffer solutions with established pH values, such as pH 4.0 and pH 7.0. Retrieve a modest amount of the in-situ gel formulation and place it within a sanitised and moisture-free receptacle. Submerge the pH electrode of the pH metre into the sample gel, ensuring that the electrode is fully enveloped by the gel. It is recommended to wait for a brief period of time until the pH measurement reaches a steady state. And then, thoroughly cleanse the pH electrode utilising distilled water in order to eliminate any remaining gel.
- **Viscosity:** The Brookfield viscometer was utilised to ascertain the viscosity of the optimised batches. The study employed spindle number 64 to determine the viscosities pre-gelation (at 10°C) and post-gelation (at 37°C) at a consistent rotational velocity of 10 revolutions per minute.
- **Gel Strength:** The Bloom Test methodology was employed to evaluate the gel strength. A 5 mL syringe was utilised to contain the in-situ gel, which was subsequently allowed to settle until it achieved a gel state. Subsequently, a plunger was introduced into the syringe. Subsequently, a force equivalent to 100 grammes was exerted on the syringe, and the velocity of the plunger displacement was quantified in millimetres per second..
- **In-Vitro Drug Release:** The Franz diffusion cell used in the present investigation was a standard device commonly used for in-vitro diffusion experiments. It consisted of two compartments: the donor compartment and the recipient compartment. The donor compartment had a volume of approximately 2ml and was loaded with a gel containing 0.56mg/ml of Methanolic Extract. The gel was spread evenly on the membrane, which was placed on the top of the donor compartment. The membrane was made of a 0.45 µm semi-permeable material that allowed the diffusion of the extract into the recipient compartment. The recipient compartment was filled with distilled water and placed beneath the donor compartment. The entire apparatus was clamped together and placed on a magnetic stirrer to maintain a constant temperature of 37°C throughout the experiment. The diffusion experiments were carried out by extracting 2ml samples at 30-minute intervals for a duration of 7 hours, using an appropriate syringe. The samples were then diluted with distilled water and analyzed using UV spectrophotometry at a constant wavelength of 330nm. The absorbance values were used to determine the amount of extract that had diffused across the membrane into the recipient compartment at each time interval.

IV. RESULTS AND DISCUSSION

- **Methanolic Extraction and Yield Optimization of Eclipta Alba:** Methanolic extraction was done on 50g of Eclipta Alba plant material using 300ml of methanol and 2g of methanolic extract was obtained. The physical characteristics of the extract, including color and odor, were also analyzed. The resulting methanolic extract was dark brownish in color with a sour odor.

Figure No 3 the physical description of Methanolic Extract.

From the following formula, % yield was calculated

$$\% \text{ Yield} = \frac{\text{Weight of Yield}}{\text{Initial Weight of Sample}} \times 100$$

The % yield from methanolic extraction was found to be 4%.

- **Antibacterial Activity Of Methanolic Extract:** In this study, the methanolic extract of Eclipta alba was evaluated for its antimicrobial activity against two common bacteria, Staphylococcus aureus and Pseudomonas aeruginosa, which are known to cause otitis media. The extract was tested at different concentrations, ranging from 0.1 mg/mL to 3 mg/mL, and the results were found to be satisfactory. The minimum inhibitory concentration (MIC) was found to be 0.2 mg/ml. The agar well diffusion method was used to determine the antimicrobial activity of the extract against the tested bacteria. The results showed a dose-dependent activity of the

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extract against both bacteria, with higher concentrations showing greater inhibition. The findings of this study suggest that the methanolic extract of Eclipta alba has potential as an antimicrobial agent against Staphylococcus aureus and Pseudomonas aeruginosa

Figure No 5 Minimum Inhibitory Concentration

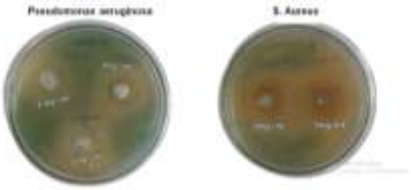

Figure 6 No Maximum Concentration Tested

Constraints

The process of creating optimized batches involved the utilization of Design Expert software, wherein a set of specific criteria were chosen as the guiding principles for the optimization procedure as mentioned in Table

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Concentration of Poloxamer 407	is in range	-1	+1	1	1	3
B:Concentration of Poloxamer 188	is equal to	-1	+1	1	1	3
Gelation Time	Minimize	6	10	1	1	3
Gelation Temperature	is in range	35	37	1	1	3
Name	**Goal**	**Lower Limit**	**Upper Limit**	**Lower Weight**	**Upper Weight**	**Importance**
A:Concentration of Poloxamer 407	is in range	-1	+1	1	1	3

Table No 2 Constraints for optimization

From the results obtained from DOE Trials, criteria for Optimized Batches were selected as mentioned in Figure 5and 6. The required gelation time range was 6-10 seconds and required gelation temperature was 35-37 ºC. Concentrations of both Poloxamer were kept in range of minimum to maximum.

- **Optimized Batches:** From the above constraints, 3 solutions were found that are mentioned in figure The Optimized Batches (C1, C2, and C3) were prepared and further evaluated.

Number	Concentration of Poloxamer 407	Concentration of Poloxamer 188	Gelation Time	Gelation Temperature	Desirability	
1	0	+1	6.000	35.600	1.000	Selected
2	-1	+1	6.000	35.600	1.000	
3	+1	+1	6.000	35.600	1.000	

Table No 3 Formulation Composition of Optimized Batches

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- **Gelation Time**

Batch	Gelation Time (Seconds)				
	Trial 1	Trial 2	Trial 3	Average (Seconds)	Std. Dev.
C1	10	11	10	10.33	0.57
C2	9	10	10	9.66	0.57
C3	11	12	9	10.66	1.52

Table No 4 Gelation Time of Optimized Batches

From the above results, it was found that Optimized Batches shows 9-10 seconds of gelation time which is sufficient and had no higher standard deviation in gelation time.

- **Gelation Temperature**

Batch	**Temp (ºC)**
C1	**36**
C2	**37**
C3	**37**

Table No 5 Gelation Temperature of optimized batches

From the above results, it was found that the Optimized Batches have gelation temperature similar to Otic temperature which let the formulation to convert into gel at target site.

- **pH**

Batch	**pH**	**Inference**
C1	7	Neutral
C2	8	Neutral
C3	7	Neutral

Table No 6 pH of Optimized Batches

pH levels of Optimized Batcheses were found to be neutral hence there will not be any irritation due to high or low pH of formulation at target site.

- **Viscosity**

Viscosity (cP)		
Batch	**Before Gelation**	**After Gelation**
C1	134	670
C2	167	863
C3	260	1233

Table No.7 Viscosity of Optimized Batches

The results showed that the viscosity values before gelation were 134, 167, and 260 cp for the C1, C2, and C3 batches, respectively. After gelation, the viscosity values increased significantly to 670, 863, and 1233 cp, indicating that gelation had occurred in all three batches. After gelation viscosity levels were sufficient enough to produce thin film at target site and avoid drop out from ear canal.

- **Gel Strength**

Gel Strength	
Batch	**mm/second**
C1	0.68
C2	0.34
C3	0.18

Table No .7 Gel Strength Evaluation of Optimized Batches

Based on the results obtained from the blood test using 100gms of weight and measuring gel strength in mm/seconds, it can be concluded that the gel strength decreases with increasing concentration of C1, C2 and C3 Batch. Specifically, the gel strength was found to be 0.68, 0.34, and 0.18 for C1, C2, and C3 Batch, respectively. These findings suggest that the concentration of C1, C2, and C3 Batch have a significant impact on the gel strength.

- **In-Vitro Diffusion Test** : The present investigation involved carrying out of in-vitro diffusion experiments using a Franz diffusion cell. A gel with a concentration of 0.56mg/ml of Methanolic Extract was loaded into the donor compartment, with a volume of approximately 2ml. The recipient compartment was filled with distilled water. Samples of 2ml were extracted at 30-minute intervals for a duration of 7 hours utilising an appropriate syringe. For In-vitro diffusion studies, the following parameters were used. Samples were

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observed in UV Spectrophotometer at 330nm fixed wavelength.

Semi Permeable Membrane Size	0.45 µm
Receptor Medium	Water
Volume	25ml
Circulating Temperature	37° ± 0.5
Time Interval	30 Minutes
Wavelength	330nm

Table No.8 Parameters for In-Vitro diffusion

Figure 7 In-Vitro Diffusion using Franz diffusion cell

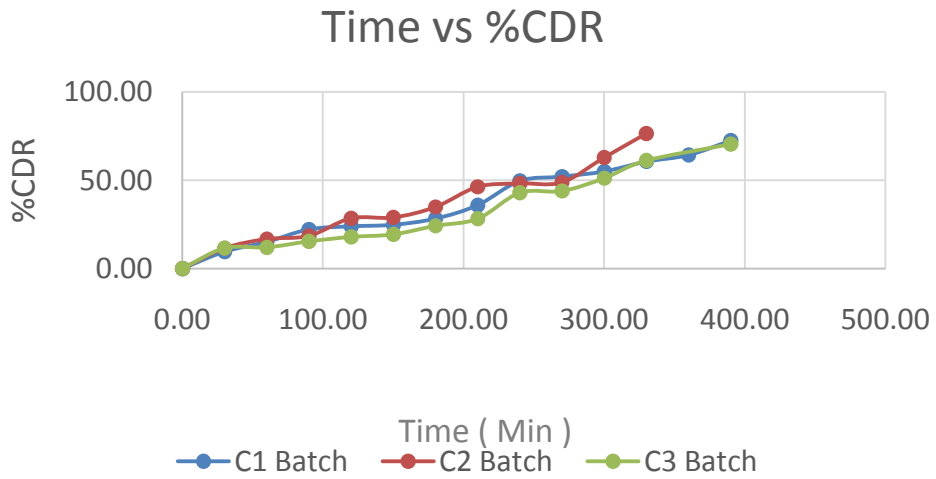

Figure No.8 %Cumulative Drug Release of Optimized Batches

The results of the in-vitro diffusion studies indicate that the release profile of the drug from the different batches (C1, C2, and C3) of the tested formulation is influenced by the concentrations of the poloxamer 407 and 188. Specifically, C2 Batch, which had the least amount of poloxamer as compared to C1 and C3 Batch, showed a more rapid release of approximately 70% of the drug within 330 min, whereas C1 and C3 Batch showed a similar drug release of approximately 70% at 390 min. These findings suggest that adjusting the concentration of the poloxamer may allow for the modulation of the drug release profile, which may be useful in optimizing the therapeutic effect of the formulation.

V. CONCLUSION:

In this study, a novel herbal in-situ gel formulation for the treatment of otitis media was successfully developed and optimized using Design of Experiment. The methanolic extract of Eclipta Alba showed potent antimicrobial activity against S. Aureus and P. Aeruginosa, with a minimal inhibitory concentration of 0.2 mg/ml, indicating its potential as an effective agent against these pathogens responsible for otitis media.The optimized batch (C2) containing 20% W/V Poloxamer 407 and 15% W/V Poloxamer 188 exhibited the most promising drug release profile, with a release rate of almost 70% in 5.5 hours. This improved drug release profile compared to other batches may be attributed to the lower concentration of the polymer, which facilitated faster drug diffusion through the gel matrix. The gel's rheological properties, including viscosity, gel strength, and pH, were found were found to be satisfactory for topical administration.Overall, this study highlights the potential of Eclipta Alba's methanolic extract for developing in-situ gels for the treatment of otitis media, offering a promising alternative to conventional treatment options. Furthermore, future investigations could explore the synergistic effects of this extract with other herbal compounds while optimizing the active

ingredient's concentration to further enhance the formulation's efficacy and safty profile.

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