IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

REVOLUTIONIZING SINUSITIS RELIEF: MICROEMULSION-BASED NASAL SPRAY - FORMULATION, EVALUATION, AND OPTIMIZATION

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Abstract:Sinusitis is a prevalent inflammatory condition affecting the paranasal sinuses, causing discomfort and reduced quality of life for millions of individuals worldwide. Nasal sprays have emerged as a promising delivery system for sinusitis treatment due to their localized action and improved drug bioavailability. In this study, we aimed to develop a microemulsion-based nasal spray formulation using Basil oil, Eucalyptus oil, and Rosemary oil as the active components for the treatment of sinusitis.The microemulsion formulation was prepared by combining the selected oils with a suitable surfactant, co-surfactant, and an aqueous phase. The selection of Basil oil, Eucalyptus oil, and Rosemary oil was based on their known therapeutic properties in alleviating sinusitis symptoms. Various ratios of the oils were screened to determine the optimal combination that provided the desired characteristics, such as stability, droplet size, and drug release properties.The prepared microemulsion-based nasal spray formulation was evaluated for its physicochemical properties, including pH, viscosity, droplet size, and drug content. In vitro drug release studies were conducted using a modified Franz diffusion cell to assess the release profile of the active components from the nasal spray formulation. The optimized formulation was further subjected to stability testing, including physical appearance, pH, viscosity, and drug content analysis, over a three-month period.The results indicated that the developed microemulsion-based nasal spray formulation using Basil oil, Eucalyptus oil, and Rosemary oil as the active components exhibited favorable physicochemical properties, such as a small droplet size, low viscosity, and uniform drug content. In vitro drug release studies demonstrated sustained release profiles, which are crucial for prolonged therapeutic effects. Stability testing revealed that the optimized formulation remained stable, with no significant changes observed in its physical appearance, pH, viscosity, or drug content during the storage period.In conclusion, the development of a microemulsion-based nasal spray formulation utilizing Basil oil, Eucalyptus oil, and Rosemary oil as the active components presents a promising approach for enhancing drug delivery and efficacy in sinusitis treatment. The optimized formulation displayed desirable physicochemical properties, sustained drug release, and long-term stability. Future in vivo studies are warranted to evaluate the therapeutic effectiveness and safety of this microemulsion-based nasal spray for clinical applications in sinusitis treatment.

Index Terms **- Microemulsion, Sinusitis, Essential oils, Nasal Spray.**

I. INTRODUCTION

Sinus, in anatomy, a hollow, cavity, recess, or pocket; a large channel containing blood; a suppurating tract; or a cavity within a bone. The sinuses are small cavities in the skull that are normally filled with air. They make mucus, which helps keep the nasal passages clear of allergens and pollutants. Two types of sinus, the blood-filled and the air-filled sinuses, are discussed below. (1)

1.1 Introduction of Microemulsion

Microemulsions are stable transparent dispersions of water and oil (mixture of various hydrocarbons and olefins) and surfactant. They are prepared by simple mixing of the components and do not require specific preparation conditions. There are three kinds of microemulsions: oil dispersed in water (o/w), water dispersed in oil (w/o), and bicontinuous. The presence of o/w droplets is likely to be a characteristic of microemulsions where the amount of oil is low. In contrast, the existence of w/o droplets is a characteristic of microemulsions where the water fraction is low. Droplet diameter varies in the range of 10–140 nm. Bicontinuous microemulsions may result where the amounts of water and oil are equal. Microemulsion concept was introduced in the early 1940s by Hoar and Schulman who developed a clear single-phase compound using titration of a milky emulsion with a medium-chain alcohol. Schulman and coworkers subsequently coined the term "microemulsion." Microemulsions have been utilized in several disciplines like fuels, detergents, agrochemicals, food, cosmetics, and pharmaceutics.

1.2 Introduction of Drug

Composition Of Aromatic Essential Oils:

1.2.1 Introduction of Basil oil

Basil oil used mainly for the treatment of nausea is very popular in Europe, Central Asia, India and Southeast Asia. Some of its health benefits are: Antioxidant and antimicrobial: Since basil oil is a strong antioxidant and antimicrobial agent it acts as a natural remedy for sinusitis and congestion. Cures sinus problems: Basil oil is used for the treatment of sinus infections and also as a cold and influenza reliever. Cineole controls airway mucus hyper secretion and asthma via anti-inflammatory cytokine inhibition. (2)

1.2.2 Introduction of Eucalyptus oil

Eucalyptus tree native in Australia is used for the extraction of eucalyptus oil (from the leaves of the tree). It is useful in many ways such as: Treatment of sinus infections: Eucalyptus oil is used as an organic method to cure sinus infections. It is very efficient in unclogging the nasal passage. Air purifier: Eucalyptus oil helps in killing germs and bacteria thus acting as an air cleanser. Along with this, its antiseptic and deodorant nature helps to get rid of airborne irritants that cause sinus inflammation.

Cineole controls airway mucus hyper secretion and asthma via anti-inflammatory cytokine inhibition. (3)

1.2.3 Introduction of Rosemary Oil

Rosemary oil is extracted from the flowering part of the Rosemary plant through steam distillation. Its usefulness can be seen in:

Boosting of the immune system: Rosemary oil contains antioxidants which help in stimulating our immune system. A strong immune system helps in fighting sinus infections. Treatment of Respiratory ailments: The scent of Rosemary oil has been seen to be very efficient in removing throat and nasal congestion thereby relieving the body from colds, flu, and many sinus problems.

Cineole controls airway mucus hyper secretion and asthma via anti-inflammatory cytokine inhibition. (4)

II. METHODOLOGY

2.1 Materials:

Basil oil, Rosemary oil and Eucalyptus oil was bought from Relief Aroma Oils, Bombay, Iso Propyle Myristate, Oleic Acid, Castor Oil, Span 80, Tween 80, Iso Propyle Alcohol, PEG400, Methanol, Butan-1-Ol, Double Distilled Water.

2.2 Methods:

2.2.1 Preparation of Pseudo Ternary Phase Diagram:

Pseudo-ternary phase diagrams were constructed to determine the region into which maximum amount of ME formation takes place.Surfactant and cosurfactant mixture (Smix) were mixed in different ratios (1:1,

1:2 and 2:1) to obtain three different ternary phase diagrams. For each phase diagram, oil and Smix were mixed at ambient temperature in nine different ratios starting from 1:9, 2:8, 3:7 up to 9:1 (% w/w). To these various mixtures of oil and Smix, distilled water was added dropwise under continuous stirring until formation of transparent oil in water (O/W) ME takes place. After equilibrium, samples were observed visually for being clear or turbid. Phase diagrams were plotted using Ternaryplot.com software. (8)

2.2.2 Preparation of Microemulsion:
Drug loaded microemulsions will be prepared by dissolving drug (10%) in oil (isopropyl myristate) and surfactant (Tween 80)/cosurfactant (butanol) mixture with vigorous stirring at room temperature using composition of selected formulas until the transparent microemulsions were produced. These drug-loaded microemulsions will be allowed to equilibrate with gentle magnetic stirring for 15 minutes. Then various formulated microemulsions were passed through Whatman filter paper (no. 40).(6)

2.2.3 Design of Experiment
In design of experiment have taken Quality Target Product Profile (QTPP) And Critical Quality Attribute (CQAs), Critical Quality Attribute (CQAs) Analysis, Pre formulation and formulation attributes, In process (Equipment) Attribute, Post process attribute Of Microemulsion Based Nasal Spray. In design of experiment, we have taken central composite design with three independent variable (oil, Smix, Water), and dependent variable and response (Globule size) (9).

2.2.4 Evaluation test
Globule Size: Globule size of microemulsion is measured by using dynamic light scattering (zetasizer, marlven).
Zeta Potential: Zeta potential of microemulsion is measured by using dynamic light scattering (zetasizer, marlven).
PDI: PDI of microemulsion is measured by using dynamic light scattering (zetasizer, marlven).
Viscosity: Viscosity of microemulsion is measured by using dynamic light scattering (zetasizer, marlven).
Nasal Skin Irritation Study: Pieces of freshly excised sheep nasal mucosa with a thickness of 0.2 mm were exposed to CBZ ME for 2 h followed by thorough rinsing with PBS pH 6.4. In two other different sets of experiments isopropyl alcohol (a strong mucociliary toxin) and PBS pH 6.4 were used instead of CBZ ME for arriving at a comparative analysis of the extent of damage caused by the preparation. These pieces of mucosa were fixed in paraffin blocks and fine sections were taken that were stained by eosin andhematoxylin. The prepared slides were examined with an optical microscope (Olympus, Model BX10, Japan) and photomicrographs (magnification 400) were taken. (8,10)

III. RESEARCH AND DISCUSSION:

3.1 Pseudo ternary phase diagram

According to the ternary phase diagram the ratio of Smix 1:2 having good microemulsion region. In that the microemulsion is stable.

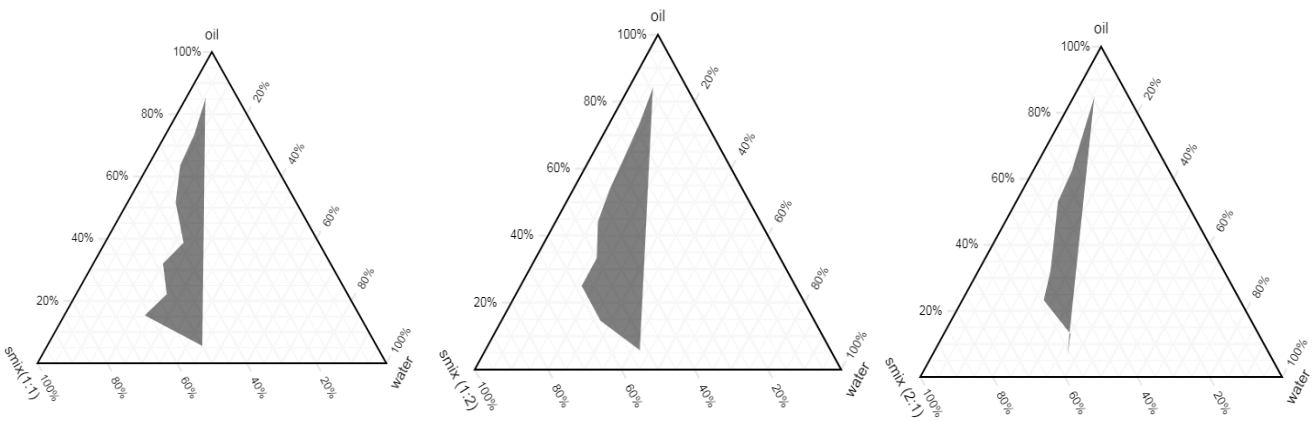

Figure 1: Pseudo ternary diagram

3.2 Design of Experiments

Quality Target Product Profile (QTPP) And Critical Quality Attribute (CQAs) Of Microemulsion Based Nasal Spray

Table 1: Quality Target Product Profile (QTPP) with their justification

Quality Target Product Profile (QTPP) with their justification.		
QTPP Elements	**Target**	**Justification**
Dosage Form	Microemulsion based Nasal Spray	Essential oil microemulsionhelps in the dermal drug delivery system.
Dosage Type	Rapid release	Quick onset of action of essential oils frommicroemulsion to enhancetherapeutic effects.
Dosage Strength	10%	Incorporated in a single formulation of ME
Route of Administration	Nasal	Good therapeutic effect
Drug Permeation	Determines the drug permeation through layers of skin.	Require to determine the amount of drugpermeating through the layers of skin.
Drug Retention	Required for treating sinusitis	Required for achieving higher drug level in the skinfor enhanced sinusitisaction.
Stability	At least 6 months at various temperature	To maintain therapeutic potential of the during.

Table 2: Critical Quality Attribute (CQAs) with their justification

Critical Quality Attribute (CQAs) with their justification.			
Quality Attribute of the drug product	**target**	**Is this CQA?**	**Justification**
Physical Attributes	0	No	Physical Attributes of the formulation werenotconsidered.
Color	Light yellow	Yes	Odor is not directly linked to efficacy andsafety.
Odor	Unpleasant	No	Odor is not directly linked to efficacy andsafety.
Appearance	Transparent	Yes	Microemulsion systems are generally transparent, thefactor is consideredcritical.
Globule Size	Less than 200 nm	Yes	Smaller globule size of ME will permeation drugs hencewasregarded as critical.
Percentage of nonionic surfactant	Higher amount but not cause toxic effect	Yes	Higher amount of surfactant which lowthe particle size.

Table 3: Critical Quality Attribute (CQAs) Analysis

Critical Quality Attribute (CQAs) Analysis		
Preprocess Attribute	**In process Attribute**	**Post Process**
Preformulation attribute	Magnetic stirrer equipment attribute	Packaging attribute
Formulation attribute	Evaluation equipment attribute	Storage and stability attribute

Table 4: Pre-Formulation and Formulation Attributes

Pre formulation and formulation attributes				
CQA parameter	**Iso-propyle myristate**	**Tween 80**	**Butan 1 ol**	**Formulation**
Physical Parameter	Non-critical	Non-critical	Non-critical	critical
Solubility	critical	critical	critical	critical
Compatibility Study	critical	critical	critical	critical
Viscosity		Non-critical	Non-critical	critical
Melting Point	Non-critical	Non-critical	Non-critical	Non-critical

Table 5: In process (Equipment) Attribute

In process (Equipment) Attribute					
CQA parameter	**Equipment**				
	Magnetic stirrer		**Evaluation equipment**		
			UVinstrument	**Centrifuge**	
	Time	**Speed**	**Dilution**	**Time**	**Speed**
Particle size	Critical	Critical	Non critical	Non critical	Non critical
Physical Appearance	Critical	Critical	Non critical	Critical	Critical
DrugContent	Critical	Critical	Critical	Non critical	Non critical
Drug Diffusion	Critical	Critical	Non critical	Critical	Critical

Table 6: Post Process Attribute

Post process attribute			
CQA	**Packaging parameter**	**Storage attribute**	**Stability attribute**
Dosage form	Critical	Critical	Critical
Appearance	Critical	Non critical	Critical
Particle size	Critical	Critical	Critical
Turbidity	Critical	Critical	Critical
Drug release	Non critical	Non critical	Critical

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