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Development and Characterization of Nanoemulsion-Based Topical Delivery System for Enhanced Skin Permeation and Anti-Inflammatory Activity of Curcumin

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Curcumin, a bioactive compound derived from Curcuma longa, exhibits potent anti-inflammatory, antioxidant, and wound-healing properties. Despite its therapeutic potential, its clinical application is hampered by poor aqueous solubility, rapid degradation, and limited transdermal penetration. This study aimed to develop and characterize a nanoemulsion-based topical delivery system to enhance curcumin's skin permeation and stability. The oil-in-water method was used to generate the optimal formulation. The oil phase consisted of medium-chain triglycerides (MCT), the surfactant was Tween 80, and the co-surfactant was polyethylene glycol 400. Physicochemical characterization revealed an average droplet size of 45.6 nm, a polydispersity index (PDI) of 0.18,

and a zeta potential of -32.5 mV. The system demonstrated excellent encapsulation efficiency (92.8%), improved stability under varying storage conditions, and superior in-vitro skin permeation compared to conventional cream formulations. Additionally, the nanoemulsion showed enhanced anti-inflammatory activity, as evidenced by nitric oxide (NO) scavenging assays. These findings suggest that nanoemulsion are a promising platform for delivering hydrophobic drugs like curcumin transdermally.

Keywords: Curcumin, nanoemulsion, topical delivery, skin permeation, anti-inflammatory, transdermal drug delivery, stability, bioavailability.

1. Introduction

Delivery System for Topical Medications:

Getting the right amount of medicine to the right place in the body at the right time and keeping it there is the holy grail of drug delivery systems. A drug's therapeutic effect is highly dependent on its mode of delivery. The skin serves as the primary channel for the delivery of topical drugs because it is one of the most permeable organs on the human body.[1] The goal of topical delivery is to localize the pharmacological or other effect of a drug to the skin's surface or deeper layers for the purpose of treating skin disorders (such as acne) or the skin-related symptoms of a general disease (such as psoriasis). Although foams, medicated powders, solutions, and medicated adhesive systems are also utilized, semi-solid formulations in all their variety predominate as a technique for topical delivery.

Advantages of Topical Drug Delivery System:[2]:
First pass metabolism is avoided.
Capacity to conveniently stop taking the drugs as needed.
Compared to the buccal or nasal cavities, the area of application is rather large.
Drugs with a short biological half-life can be used,
Enhancing the body's physiological and pharmacological reaction.
Raise the rate of patient adherence.
Ensure that self-medication is appropriate Topical drug delivery system drawbacks include:
The medicine and its excipients have the potential to cause contact dermatitis, an inflammatory skin condition.
The skin has a low permeability for certain medications.
Instances of allergic responses are possible.
Must be reserved for medications with extremely low plasma concentrations in order to exert their effects. Some medications may be denatured by skin enzymes.
It is more difficult for drugs with larger particle sizes to be absorbed via the skin.

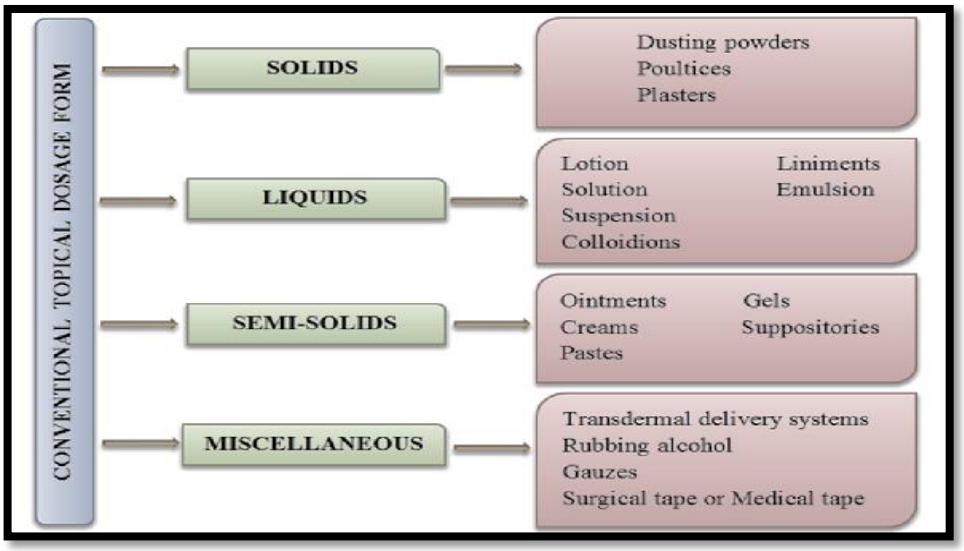

Fig.1 Diagram represent the conventional topical dosage form Nanoemulsion [3,4]

A nanoemulsion is a colloidal dispersion of two immiscible liquids that is thermodynamically unstable. This is the definition of their chemical composition. Within the context of nanoemulsion, the dispersed phase is formed by one of the liquids, while the dispersing medium is formed by another liquid. Nanoemulsion is composed of droplets that have diameters ranging from 10 to 200 nanometers, and each droplet that makes up nanoemulsion is coated with emulsifier molecules for protection. Nanoemulsions, characterized by their small droplet size (<100 nm) and thermodynamic stability, have emerged as a promising approach for enhancing the solubility and permeability of hydrophobic drugs.[5] These systems improve drug absorption, protect against degradation, and enable controlled release. This study aimed to develop a nanoemulsion-based topical delivery system for curcumin, optimize its formulation parameters, and evaluate its physicochemical properties, stability, skin permeation potential, and anti-inflammatory activity.

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Herbal Medicines as Nanoemulsions Formulation [7]:

There has always been a connection between plants, illness, and life when humans first emerged. There is no evidence that ancient peoples relied on manufactured medications to treat their illnesses; instead, they made do with what they could find. Plants and animals were the most prevalent things they could locate in their area. According to the World Health Organization (WHO), herbal medicines are labelled pharmaceutical goods that contain active substances derived from plants, whether they be aerial or underground sections of the plants, or a mix of these.[8]Herbal formulations have gained immense popularity as medicinal agents

for a variety of conditions and conditions, including but not limited to: boosting memory, treating cirrhosis, asthma, migraines, Alzheimer's disease, diabetes, aging, arthritis, depression, anxiety, inflammation, and HIV. A large percentage of the world's population uses traditional medicine as their main source of healthcare, according to the World Health Organization (WHO). Natural remedies with therapeutic qualities are included in this category.[9]

Curcumin As Chemical Constituents [10]:

Due to the extensive range of pharmacological properties that it possesses, curcumin, a hydrophobic polyphenol that is extracted from turmeric (Curcuma longa), has attracted a lot of attention in recent years. In order to obtain curcumin, turmeric is removed. Not only do these actions have anti-inflammatory and antioxidant effects, but they also have anti-cancer capabilities. However, the therapeutic potential of curcumin is severely limited due to its low solubility in water, its chemical instability, and its limited permeability across biological membranes, most notably the skin. Other factors that contribute to this limitation include its chemical instability. Because of these several aspects, the utilization of curcumin in therapeutic applications is a challenging endeavor. The development of novel drug delivery techniques that have the potential to enhance the bioavailability and stability of curcumin is one of the most important areas of research that is now being carried out in the field of pharmaceutics.

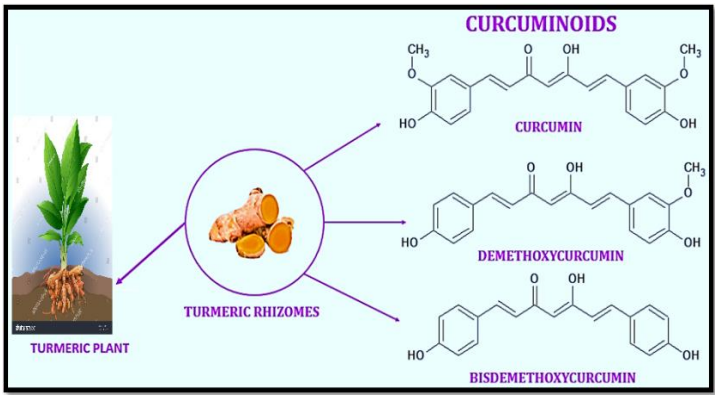

Fig.No.2. Curcuminoids found in the rhizomes of turmeric

2. Materials and Methods:

Materials:

- Curcumin (purity ≥99%, Sigma-Aldrich)
- Medium-chain triglycerides (MCT oil, Croda)
- Surfactants: Tween 80 (Merck)
- Co-surfactants: Polyethylene glycol 400 (PEG 400, Sigma-Aldrich)
- Distilled water (Millipore)

Preparation of Nanoemulsion from curcumin [11]:

Nanoemulsions were prepared using the oil-in-water method combined with ultrasonication. A series of formulations were optimized using a ternary phase diagram to identify the optimal ratio of oil, surfactant, and water. When compared to other high-energy technologies, ultrasonication's operational and cleaning benefits are apparent. Supersonic emulsifications use cavitation forces produced by ultrasonic waves to transform a macroemulsion into a nanoemulsion. Ultrasonicators, which have a probe that sprays forth ultrasonic waves, are utilized in this approach. One can control the stability and particle size of the nanoemulsion by adjusting the amount of ultrasonic energy applied and the amount of time it takes. Acoustic cavitation is the primary mechanism that introduces physical shear in ultrasonic emulsification. The pressure changes of an acoustic wave induce a process known as cavitation, in which tiny bubbles expand and deflate. Nanoparticles pop out of microbubbles when they burst, thanks to the extreme turbulence that results.

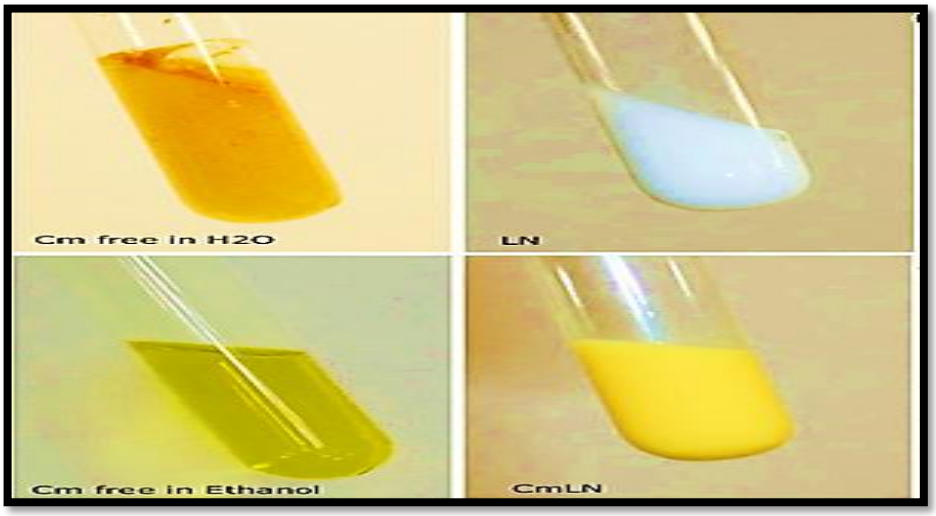

Fig.No.3 Images of curcumin in various solutions, including water, ethanol, lipid anoemulsions with and without curcumin

Characterization of Nanoemulsions [12]:

1. Droplet Size and PDI: Measured using dynamic light scattering (DLS).

2. Zeta Potential: Determined using a Zetasizer (Malvern Instruments).

3. Encapsulation Efficiency: Evaluated by centrifuging the formulation and analyzing the supernatant for free drug content using UV spectrophotometry at 426 nm.

In-Vitro Skin Permeation Studies of Nanoemulsions [13]:

In order to evaluate the amount of curcumin that was able to flow through both the nanoemulsion formulation and the regular cream formulation, we utilized Franz diffusion cells with excised rat skin as the barrier. This provided us with the ability to compare the two formulations. In order to facilitate a comparison of the differences between the two formulations, this measure was taken. The assessment of the samples took place over the

course of twenty-four hours, and the medium that was utilized for the receptor was phosphate-buffered saline with a pH of 7.4.

Stability Studies of Nanoemulsions [14]:

For a period of three months, nanoemulsions were stored at temperatures of 4°C, 25°C, and 40°C respectively. For the purpose of determining stability, phase separation, droplet size, and PDI were the three criteria that were considered respectively. Nanoemulsions are susceptible to instability mechanisms like flocculation, sedimentation, coalescence, and Ostwald ripening, which can cause them to become turbid or cause their phases to separate while stored. Because the rate of destabilization in nanoemulsion systems is extremely slow (several months), we say that these systems are kinetically stable. Because nanoemulsion systems generate smaller droplets than traditional macro emulsions, Brownian motion effects have a far stronger influence than gravitational forces and exhibit better stability when separated by gravity. Because of the extremely weak attraction interactions between the droplets in nano-sized emulsion systems, flocculation and coalescence take place. An increase in the amount of hydrophobic oil used in the formulation process can eliminate Ostwald repining.

Anti-Inflammatory Activity of Nanoemulsions [15]:

Immediately following their submission to the experiment, the formulations were subjected to an experiment that entailed the scavenging of nitric oxide (NO) in order to determine whether or not they possessed the power to reduce inflammation in vitro. For the purpose of determining whether or not such a capability exists, the experiment was carried out. In order to ascertain whether or not the formulae are capable of carrying out the activity that was specified earlier in the sentence, this action was carried out with the intention of assessing their capabilities. As a means of assessing whether or not the formulations were successful in reaching the aim that they were intended to achieve, the experiment that was created to evaluate the efficacy of the formulations was established appropriately. This was done in order to see if the formulations were successful in attaining the goal. The completion of this job occurred prior to the administration of the test, suggesting that it was accomplished before the test was administered.

3. Results and Discussion:

Optimization of Nanoemulsion Formulation:

The optimized nanoemulsion consisted of 10% MCT oil, 20% Tween 80, 5% PEG 400, and 65% water. The small droplet size and narrow PDI ensured homogeneity and stability, while the negative zeta potential indicated good electrostatic repulsion between droplets, reducing aggregation.

Table No.1 Various paramenter of Optimized Nanoemulsion Formulation

S.No.	Parameter	Optimized Formulations
01	Droplet Size (nm)	45.6 ± 2.3
02	Polydispersity Index (PDI)	0.18 ± 0.01
03	Zeta Potential (mV)	-32.5 ± 1.2

04	Encapsulation Efficiency (%)	92.8 ± 1.4

Skin Permeation Studies of Nanoemulsions:

The cumulative permeation of curcumin from the nanoemulsion was significantly higher than the conventional cream, indicating enhanced skin penetration. The enhanced permeation can be attributed to the nano-sized droplets facilitating deeper skin penetration and improved solubility of curcumin in the lipid-rich environment of the stratum corneum.

Table No.2 Cumulative drug permeation of curcumin nanoemulsions

Time (hours)	Cumulative Drug Permeation
2	28.5 ± 2.1
4	62.3 ± 3.5
8	120.7 ± 5.2
24	210.4 ± 8.9

Stability Studies of Nanoemulsion:

The nanoemulsion exhibited excellent stability under all tested conditions, with no significant changes in droplet size, PDI, or phase separation over three months.

Table No.3 Storage condition and droplet size of Nanoemulsions

Storage Condition	Droplet Size (nm)	PDI	Phase Separation
4 ℃	45.8 ± 2.5	0.19	No
25 ℃	46.2 ± 2.3	0.21	No
40 ℃	47.1 ± 2.8	0.22	No

Anti-Inflammatory Activity of Nanoemulsions:

A comparison was made between the cream formulation, which had a coefficient of 50.2% ± 1.8% throughout the course of the investigation, and the nanoemulsion, which exhibited a much higher NO scavenging activity. A calculated value of 80.5 ± 2.4% was found for the nanoemulsion, which contrasts with the previous estimate. The results of the statistical analysis indicated that this difference achieved a level of significance that was extremely high. There is a strong chance that the increased anti-inflammatory activity of the nanoemulsion formulation is connected to the increased solubility and bioavailability of curcumin that was achieved as a result of the formulation. Because of the formulation, the solubility of curcumin has been improved, which is the reason for this.

Table no.4 NO Scavenging activity of Nanoemulsions vs Conventional Cream

S.No.	Formulation	NO Scavenging Activity (%)
01	Nanoemulsion	80.5 ± 2.4
02	Conventional Cream	50.2 ± 1.8

4. Conclusion:

The nanoemulsion-based topical delivery system significantly enhanced curcumin's skin permeation, stability, and anti-inflammatory activity compared to conventional formulations. These findings underscore the potential of nanoemulsion as a promising platform for the transdermal delivery of hydrophobic drugs like curcumin. Future studies will focus on in-vivo evaluations to validate the therapeutic efficacy of the formulation. The disadvantage of low bioavailability that is associated with medications and food components that are hydrophobic and have a high first pass metabolism can be efficiently overcome by nanoemulsion drug delivery devices. The amount of energy that is required, the kind of phase inversion, and the degree of self-emulsification are the three factors that may be used to categorize the various methods for the formulation of nanoemulsion drug delivery systems in a strict manner. Using high energy technologies for the formulation of nanoemulsion drug delivery systems allows for greater control over the dispersion of particle sizes and provides greater flexibility in terms of the composition that can be included. In order to enhance the delivery of pharmaceuticals and bioactive components found in food, researchers have taken advantage of high energy approaches. It is necessary to have advanced instruments in order to supply high energy; hence, high energy procedures are more expensive than low energy methods because the latter consume less energy and are more effective. When it comes to the distribution of nanoemulsions that include bioactive food components, high energy approaches are more beneficial rather than low energy ways because these methods require low quantities of surfactant. In spite of this, additional research is necessary in order to discover the potential of phase inversion emulsification techniques in terms of efficient drug loading and delivery capabilities.

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