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DEVELOPMENT AND IN-VITRO CHRATERIZATION OF CUBOSOMAL GEL FOR TOPICAL DELIVERY OF CELECOXIB FOR TREATMENT OF RHEUMATOID ARTHRITIS.

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INTRODUCTION

- **RHEUMATOID ARTHRITIS:** Rheumatoid Arthritis (RA) is auto immune disorder causes inflammation

in joints resulting pain & deformity in wrist, fingers and ankles. This disease arises in women more than men at any age. The manifestation of disease includes redness, inflammation. [1] Early diagnosis is important for improvement of symptoms but quite difficult to detect at early age as it depends upon gathering clinical information & history of patient. There is no permanent therapy to treat rheumatoid arthritis.

For complete suppression of disease symptoms, rheumatologist need to observe activity constantly and correctly to adjust treatment schedule. From last 20 years, Disease modifying anti-rheumatoid drugs (DMARDs) has gained much attention because of their effectiveness and can efficiently reduce the activity of disease and considerably decrease the joint deformity. In current therapies DMARDS are rarely implemented for the treatment of disease. Several new biological DMARDS such as anti-CD20 antibody, TNF inhibitors etc. With increase in the number of drugs and treatment options available, the long term disease remission is not achieved in many cases and thus new therapeutic options are still needed.[2,3]

The reason of occurring the rheumatoid arthritis is not clear till date, it is supposed that the disease occurs due to various genetic and environment factors. The disease causes the inflammation and thickening of the joint which occurs due to the immature system of the body directly attacking the joints. The disease may also result in low blood cell count, inflammation nearby the lungs and heart. [3]

Figure 1.1: Image showing Inflammation of joints

Epidemiology of RA

In 2015 rheumatoid arthritis affect 24.5 million cases. [4] The annual incidence of RA is approximately 40 cases per 10,000 populations and the incidence rate was increasing 1% in each year. The chances of occurring the disease in the women are 2.5 higher than the men, mainly occurs in the middle age.

In women disease occurs in the age between 40-50 years whereas in case of men disease occurs in the later stage

In 1990, disease results in 28,000 whereas in 2013 the disease causes 38,000 deaths and in 2010 the disease causes 49,000 deaths worldwide.[5] RA is a type of chronic disease and there are chances of remission of the disease.

Clinical Presentation: Chronic inflammation causes the cardiovascular disease which further leads to the death of individual suffering from RA. Treatment with the various biological agents (drugs) may decrease the risk of cardiovascular disease Lung disease may also be the complications in the treatment of RA The disease evaluates from the minimum damage to the destruction of the joints causing bony erosion leads to damage in the cartilage. Cartilage damage cause more non-reversible disability as compared to the bone damage. [6]

Diagnosis: Early diagnosis of disease helps to prevent 90% of joint damage. It is important to identify early symptoms of patient which helps to identify and treatment of patient. Early identification involves assessment of joints and serologic test to determine presence of antibodies.[7]

Cubosomes: Cubosomes are colloidal dispersion by the use of appropriate stabilizers of twisted, curved bicontinuous cubic phase lyotropic fluid crystals, formed by the combination of certain amphiphiles like glyceryl monooleate with the appropriate hydration and temperature conditions. Amphiphile concentration and temperature require an additional freedom to be given to lyotropic liquid crystals in various structures such as micellularcubics (I1), hexagonal (HI), lamellar crystals (Lα) and bicontinuous cubic phases (QI).[8,9] The amphiphiles are simpler to form reverse phases like reverse hexagonal (HII) than single-chain amphiphiles with

two hydrocarbon chains in their hydrophobic unit. Cubosomes encompass structure similar to honey comb structure of 100-500nm range in size. Cubosomes and polymeric micelle are structurally similar and used in various drug delivery application.[10]

Lyotropic gels maintain the same cubic shape and are slightly more sensitive to the surface area and less viscous in the heterogeneity of the bulk cubic level nanostructured gels. In contrast to liposomes dispersing the lamellar liquid crystalline level, the inner structure of Cubosomes provides a considerably higher membrane surface area for the loading of active molecules. Cubosomes as drug delivery system have various advantages:[11]

PREPARATION METHODS FOR CUBOSOMES

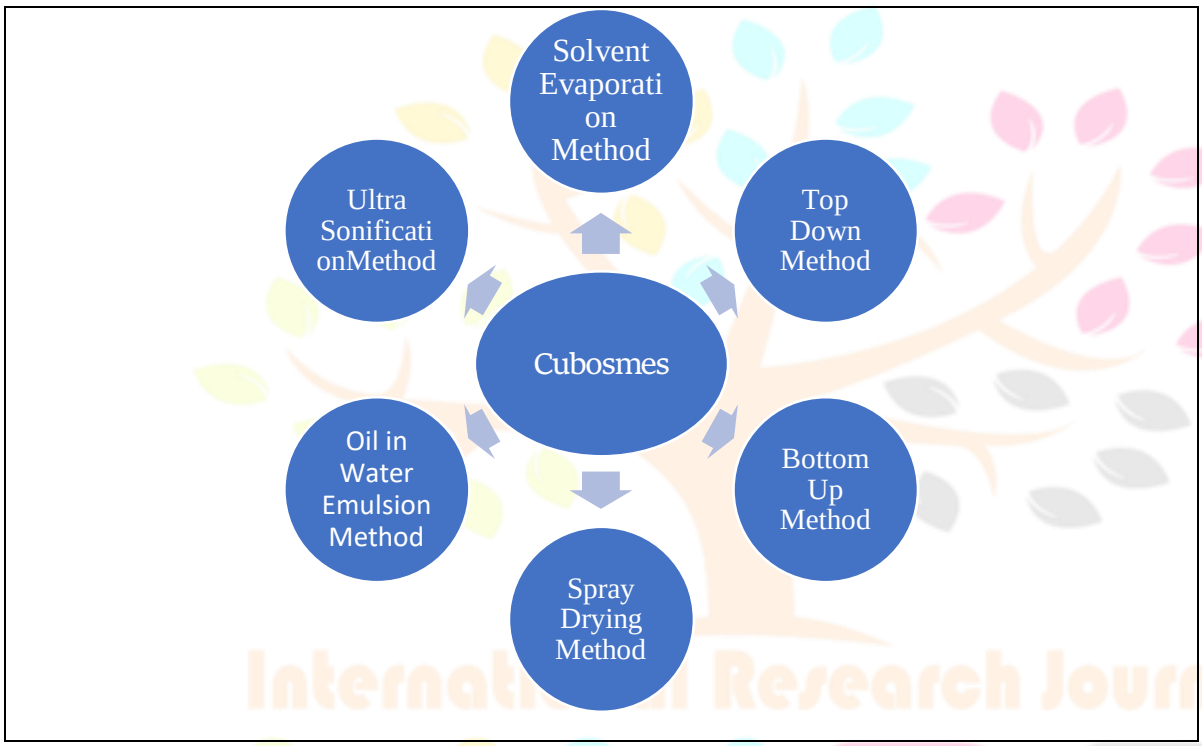

Figure 2.1: Image showing Preparation of Cubosmes

Method of Preparation:

- Top-down and bottom-up techniques are often utilised, and both require the use of an appropriate stabiliser to avoid Cubosome dispersion aggregation. Biocompatibility and optimal medication administration continue to be important targets.[12]

Top-down approach-

- The most common way for preparing Cubosomes. Cubosomes producing lipids are mixed with an appropriate stabiliser to generate viscous cubic lipids. Cubosomes are formed when viscous cubic phase is dispersed in aqueous solutions using a high energy and pressure homogenizer or sonication.[13]

Bottom-up approach-

- This is also known as solvent dilution. With minimum energy input, a mixture containing Cubosomes

producing lipids, stabilisers, and a hydrotrope is dispersed in surplus water. Hydrotrope is an important component in this process since it is used to dissolve water-insoluble lipids in order to produce precursors and prevent corrosion.

Dermatological Application-

In transdermal medication administration, the stratum corneum, or outermost layer of skin, acts as a barrier to topically administered drugs penetrating the skin.

Cubosomes have bio adhesive qualities and can be employed in mucosal and topical drug delivery
Oral drug delivery systems are especially useful for poorly water-soluble medicines and medications with high molecular sizes.[15]

Because of their bio adhesive qualities, cubosomes aid in the absorption of orally given medicines.[16]

Table 1.1: Examples of applications of Cubosomes as Ocular Drug Delivery System

S.	S.NO	Loaded Drug	Oil Used	Stabilizer used	Pharmacological Uses	Conclusion
	1.	Dexamethasone	GGMO	Pol. 407	Anterior ocular Inflammation	Improve Preocular Retention time & bioavailability
	2.	Ibuprofen	GGMO	Pol. 407	NSAID for Ocular transformation	Improve trans corneal permeation
	3.	Ketorlac	GGMO	Pol. 407	NSAIDS used for itching eyes (seasonal allergies)	Prolong Prec corneal retention time
	4.	Timolol	GGMO	Pol. 407	Non selective beta blocker	Increase Corneal penetration
	5.	Cyclosprine A	GGMO	Pol. 407	Immuno-Suppressive agent used in treatment of immune related ocular disease	Low Ocular Irritation Improved Ocular bioavailability

Table 1.2: Example of Drug delivery utilizing Cubosomes formulation

S. No.	Loaded Drugs	Oil Used	Stabilizer Used	Pharmacological Uses	Conclusion
1.	Insulin	GMO	Pol. 407	Insulin Dependent Diabetes	Stable upon storage. Highly effective in Controlling Hyperglycaemia in reproducible manner
2.	Ibuprofen	PYT	Pol. 407	Non-steroidal, anti-inflammatory drug with analgesic action	Sustain delivery with increase in bioavailability
3.	Simvastatin	GMO	Pol. 407	Used to lower bad cholesterol and raise good cholesterol in blood	Enhance bioavailability when orally administered (simvastatin water insoluble)
4.	Amphotericin B	PYT	Pol. 407	Antifungal Drug	Enhance bioavailability, did not show nephrotoxicity

LITERATURE REVIEW

G. Leelaprakash *et al*., This work raises the possibility that an effective anti-inflammatory medicine could be developed using an ingredient from the plant Enicostemma axillare to treat conditions like cancer, neurological disorders, ageing, and inflammation. In the current study, anti-inflammatory activity is assessed using multiple Invitro methods, including the albumin denaturation assay, proteinase inhibition, membrane stabilisation, and anti-lipoxygenase activity at various concentrations. Standard medications included aspirin, diclofenac sodium, and indomethacin. The findings of the current investigation suggest that methanol extracts of Enicostemma axillare may have anti-inflammatory properties.

Loveleenpreet kaur *et al*., This study used polymers and permeation enhancers to increase the rate of medication penetration. The topical gel formulations have two distinct polymers, such as carbopol-940 and HPMC, in varying concentrations, and have also used permeation enhancers, such as seasam oil and oleic acid in varying concentrations, to speed up permeability through the skin. The formulations have undergone analysis based on factors like viscosity, homogeneity, extrudability, skin irritancy research, and pH determination. The highest drug permeability through the cellophane membrane was produced by the HPMC formulation as compared to Carbopol-940, according to an in-vitro drug release research. Due to permeability enhancers, two versions of the

meloxicam medication showed maximum release. Studies on skin irritation have not revealed any dermatological effects.

Zhinan M *et al.*, Triptolide has been studied for its anti-inflammatory, immunosuppressive, anti-fertility, and anti-neoplastic properties; however, due to its poor water solubility and its hazardous side effects, its clinical application is limited. Therefore, novel delivery systems for Triptolide, like solid lipid nanoparticles and microemulsion, were created in order to provide the drug and mitigate its drawbacks.

They discuss how to prepare and characterise a specialised delivery system for Triptolide in this article. They also assess the capability of transdermal distribution and the anti-inflammatory activity. As a result of solid lipid nanoparticle dispersions and micro-emulsions, Triptolide penetration into skin may be effectively aided.

Shweta Vashist *et al.*, The current study's primary objective was to create a proniosomal gel formulation for diclofenac sodium using a 32 factorial design. Different surfactant (span 60) and cholesterol concentrations were used to produce the proniosomes. The pH, vesicle size, viscosity, spreadability, entrapment efficiency, and ex-vivo drug permeation investigation of the produced proniosomal gel were characterised. There were zero order kinetics in the medication release profile. Utilising contour plots, expected vs. actual plots, and response surface plots, formulation was optimised. It was discovered that the optimised formulation included medium concentrations of span 60 (1350 mg) and cholesterol (250 mg). It was also done to examine the formulation's stability. Results indicate that proniosomal gel can improve Diclofenac distribution through skin and can increase

Kotta Kranthi Kumar et al., In addition to delivering drugs to the body, their study aims to increase patient compliance, and dispersible medications are no exception. The improvements in Diacerein cream formulation and evaluation that are intended to speed up the beginning of effect. Diacerein cream was created using the fusion method to cure psoriasis and reduce the whiteness of the patchy skin. The cream is created using a two-phase process. 90 percent of the oil phase melts before being transferred to the heated aqueous phase. The stiffener, emulsifier, antioxidant, and pH modifier are used in varied combinations to create the cream using the fusion technique. It is abundantly clear that physical and chemical characteristics like colour, pH, specific gravity, and first drug assay were present in both formulations.

Muhammad Razi Ullah Khan *et al*., In order to avoid the gastrointestinal toxicities connected with oral delivery, they tried to create a unique topical cream formulation of etoricoxib. They utilised a different combination of active component and excipients to prepare the cream from which they had taken a set concentration of etoricoxib (1%). In-vitro testing was done to determine the formulation cream's efficacy. This testing included stability tests, tube extrudability, spreadability, pH, viscosity and rheological properties, and drug

diffusion experiments. After cream formulations were tested in vitro, the formulation was assessed for a skin irritation and anti-inflammatory study. The results were positive, and the formulation containing etoricoxib (1%) showed the most pleasing outcomes across all parameters. It was suitable for topical use and its results are equivalent to those of other topical medications.

PURUSHOTHAM RAO K *et al.*, In the current work, an O/W emulsion-based cream was created utilising

salicylic acid as a model medicine because it is the most effective keratolytic agent for treating skin psoriasis. The cream also contained preservatives. A number of physiochemical criteria, including drug content, pH, spreadability, tube extrusion capability, viscosity, and IR studies, are applied to the formulation. The in-vitro drug release was tested against the commercial formulation in phosphate buffer (pH 7.4). According to ICH requirements, stability tests of the chosen formulation were also conducted at room temperature (30 C° & 40 C) for a six-month period. The chosen formulation was tested on healthy human volunteers, guinea pigs, and rabbits for 72 hours for primary cutaneous irritation.

AIM AND OBJECTIVES

EXPECTED RESEARCH

The stratum corneum, or outermost layer of skin, acts as a barrier to topically administered medications in transdermal medication delivery. Rheumatoid arthritis is a long-term inflammatory disease that affects more than just the joints. In some patients, the sickness can impair a variety of physiological systems, including the skin, eyes, lungs, heart, and blood vessels.

Rheumatoid arthritis is an autoimmune disease that occurs when your immune system mistakenly attacks your own body's tissues.

Rheumatoid arthritis, as opposed to osteoarthritis, attacks the lining of your joints, causing severe swelling that can eventually lead to bone erosion and joint deformity.

Rheumatoid arthritis's inflammation can potentially impair other parts of the body. Despite the fact that new medications have improved treatment, severe rheumatoid arthritis can still cause physical limitations.

PLAN OF WORK

A. Pre-formulation research

Drug identification

Physical appearance

Melting point

I.R. spectroscopy

UV spectroscopy

Solubility studies

Partition coefficient

Drug-excipient compatibility study

DSC-Calorimetric Technique-Solubility & Physical State of Drug in Complex

FTIR

B. Preparation and optimization of the formulation

C. Characterization of formulation.

Method of preparation of Cubosomes

Homogeneity

Spreadbility

Extrudability

In-Vitro Release using Franz diffusion cell

D. Results and Discussion

E. Compilation of statistical analysis data and submission of thesis.