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FORMULATION AND CHARACTERIZATION OF KETOPROFEN LOADED GUGGULOSOMAL GEL FOR THE TREATMENT OF INFLAMMATION IN RHEUMATOID ARTHRITIS

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ABSTRACT

This study investigated the topical anti-inflammatory promise of a ketoprofen-loaded guggulosomal vesicular system intended for the management of rheumatoid arthritis. Six batches (FF1-FF6) of nanovesicles were assembled through lipid film hydration, holding the drug load constant while the lipid composition was varied, and the chosen dispersion was then loaded into a Carbopol 934 gel base. Vesicle size, zeta potential, drug entrapment and surface morphology were profiled by dynamic light scattering, scanning and transmission electron microscopy (SEM, TEM), and Fourier transform infrared (FTIR) spectroscopy. *In vitro* drug release across the gels was traced on a modified Franz diffusion assembly, while pH, viscosity, spreadability, extrudability, homogeneity, drug content and entrapment efficiency (EE%) were recorded. The ATR-FTIR profile of the loaded vesicles preserved every characteristic peak attributable to the guggulosomes. The chosen batch yielded spherical particles of 462.6 nm with a PDI of 0.256 and a surface charge of -6.01 mV. Across the panel of batches, EE spanned 34.32 ± 1.716 to 75.96 ± 3.798 with vesicle dimensions of 75.14 to 173 nm; viscosity readings fell between 6392 ± 319.6 and 1175 ± 58.75 with extrudability rated good; drug content reached 96.27 ± 0.962 for the optimised batch alongside acceptable appearance and elegance on homogeneity inspection; pH lay within 5.9 to 6.8 and spreadability covered 1365 ± 0.445 to 20.84 ± 0.239. Cumulative release between 69.98% and 89% was achieved over 24 hours, pointing to enhanced sustained-release behaviour. Taken together, the findings support the ketoprofen guggulosomal gel as a candidate platform for prolonged and regulated topical delivery.

KEYWORDS: Guggulosomes, Gel, Rheumatoid arthritis, Inflammation, Ketoprofen.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-standing inflammatory autoimmune condition that develops once immune control over the synovial joint membrane breaks down.[1,2] Chronic synovial inflammation is the disease hallmark, and with time it progressively damages articular cartilage and subchondral bone, leading to permanent joint deformity. Inflammation within the joint is initiated when autoreactive T cells, primed in peripheral lymphoid tissues, migrate chemotactically into the synovium. Once present, they create a pro-inflammatory milieu that draws fibroblasts, neutrophils and macrophages into the joint cavity, and the collective action of these cells, in concert with mediators such as prostaglandins, proteolytic enzymes, cytokines and osteoclastogenic signals, sustains the synovitis along with the cartilage and bone breakdown.[3,4,5] Treatment strategies for RA are therefore directed mainly at the suppression of pro-inflammatory mediators such as thrombin, TNFα and IL-1β. Failure to intervene early carries a substantial risk of disability and mortality, whereas timely recognition together with appropriate therapy curtails impairment and lowers the rates of both disability and death. Drug therapy draws on several classes, namely NSAIDs, biologics and disease-modifying antirheumatic drugs (DMARDs). Within the propionic acid NSAIDs, ketoprofen delivers analgesic and antipyretic effects by inhibiting prostaglandin (PG) biosynthesis; since PGs are the chief drivers of the inflammatory symptoms associated with arthritis, this blockade relieves both pain and inflammation.[6] In clinical practice, ketoprofen is prescribed for fever, inflammation, dysmenorrhoea, osteoarthritis, rheumatoid arthritis and general pain relief. Since PGs act as hormone-like signalling molecules that propagate inflammation, suppressing their levels helps to dampen oedema. Its use, however, has been associated with a heightened risk of cardiovascular incidents such as myocardial infarction and stroke.[7,8] This risk rises with frequent dosing at elevated levels. Additional adverse effects include the emergence or aggravation of hypertension, respiratory discomfort, urticaria and other hypersensitivity reactions, while the wider class of anti-RA medications can produce myelosuppression, stomatitis, alopecia, pulmonary complications such as pneumonitis, hepatic and renal impairment, and gastrointestinal disturbance. Tolerance to anti-RA therapy is also reported in clinical practice, and conventional tablets and capsules continue to dominate the available dosage form options.[9] Topical and parenteral preparations have likewise been used as alternative routes. Parenteral delivery, although capable of nearly full bioavailability, offers little scope for adjusting or halting drug release after administration. Solid dosage forms exhibit the same shortcoming, generating the familiar peak-trough swings in plasma concentration. Holding a steady-state plasma level is especially troublesome for narrow-therapeutic-window molecules, and compliance problems compound the difficulty when short half-life drugs require multiple daily doses. Collectively, the drawbacks of traditional formulations, such as inter-dose variability, high dose demand and inadequate patient adherence, reduce efficacy and contribute

to toxicity and unwanted drug reactions, weakening the value of present pharmacotherapy.[10] To overcome these constraints, and acknowledging that classical approaches for herbal drug administration are frequently suboptimal, a variety of advanced delivery platforms have been engineered to prolong release, reduce drug breakdown and raise bioavailability.[11] At present, drug molecules are frequently encapsulated within carriers like liposomes, ethosomes, metallic nanoparticles and polymeric systems for controlled release. Nanosized carriers stand out among these owing to their high specific surface area, better solubility, improved bioavailability, greater stability, and capacity to deliver drugs in a regulated and site-targeted manner.[12]

Building on recent reports and the rationale outlined above, the present study set out to formulate and characterise a ketoprofen-loaded guggulosome and a corresponding guggulosomal gel intended for managing the inflammation associated with rheumatoid arthritis.

MATERIALS AND METHODS

MATERIALS

All chemicals and reagents used in this study were of analytical grade.

METHODOLOGY

Purification of Guggul: As a major ingredient of many herbal and semi-synthetic dosage forms, guggul must first be purified before formulation. Ayurveda assigns particular weight to processing procedures that can alter the potency and quality of such drugs. Classical Ayurvedic texts such as Bhaishajyaratnavali list multiple Shodhana (purification) protocols for Guggul that rely on different processing media.[13]

Swedana (Hot Immersion) method:

Crude guggul sourced from Commiphora Mukul was purified by the swedana hot water immersion technique, which is intended to enhance therapeutic activity while ridding the resin of foreign matter. Purification proceeded in two phases: surface contaminants such as adhered debris and dried leaves were first removed manually, and the cleaned guggul was then placed in a muslin pouch and left overnight in a beaker of hot water taken in excess of the guggul volume.[14,15] The next day the pouch residue was discarded and the soaking water was gently heated at a low temperature (50-60^{0}C) under continuous stirring to protect the volatile oils and other heat-sensitive constituents. When the volume reached half its original value, the mixture was filtered while still hot to prevent solidification on cooling, and the soft residue obtained was dried under sunlight. The purified guggul was finally triturated with a small quantity of ghee or butter.

Identification:

A 5 g portion of crushed material was added to 100 ml of hot water in a conical flask and mixed thoroughly with a glass rod or mechanical shaker; appearance of a milky emulsion was taken as a positive identification of guggul.[16]

Preformulation Studies:

Preformulation work forms the foundation of pharmaceutical development; collecting physicochemical data that establish identity, purity, performance and quality of the drug substance precedes the design of any dosage form and guides subsequent formulation decisions.[17,18]

Organoleptic properties:

Visual inspection of ketoprofen along with taste and odour evaluation were carried out and compared against the specifications listed in the British Pharmacopoeia (2008).

Melting point determination:

The melting point of ketoprofen was recorded on a digital melting point apparatus, using a small amount of drug packed into a single-end-sealed capillary tube along with a calibrated thermometer. The reported value represents the average of three independent measurements.[19,20]

Solubility of drug:

For each test solvent, 10 ml was dispensed into a test tube and one teaspoonful of ketoprofen was added with constant stirring; complete dispersion of the solute was taken as evidence of dissolution, and the resulting solutions were quantified by UV spectrophotometry.[21]

Partition Coefficient:

The octanol-water partition coefficient (KOW), an index of a molecule's hydrophilic or lipophilic tendency, was measured for ketoprofen by the conventional shake-flask method employing n-octanol and water as the two phases.[2]

Ultraviolet Absorption maxima (λ max):

Three ketoprofen solutions were prepared independently in phosphate buffer (pH 7.4), chloroform and distilled water, then scanned between 254 and 300 nm on a JASCO V-670 UV-Visible spectrophotometer with phosphate buffer as the blank reference.[23,24]

Preparation of ketoprofen loaded guggulosomes:

Guggulosomes were fabricated through the lipid film hydration technique.[25] Different proportions of guggul lipid, phosphatidylcholine and cholesterol were processed in a chloroform/water system. Weighed guggul lipid was first dissolved in 10 ml of distilled water under magnetic stirring at 700 rpm. Separately, ketoprofen, cholesterol and phosphatidylcholine were taken up in chloroform, and the organic phase was evaporated to lay down a thin lipid film on the inner wall of the flask. The guggul lipid aqueous phase was then introduced for film hydration, and the system was stirred at 200 rpm for 1 hour at 25^0C; the volume was made up to 20 ml with distilled water, and the resulting dispersion was probe-sonicated for 15 minutes to yield a uniform preparation

Table 1: Formulation Table of ketoprofen loaded guggulosome

Ingredient	FF1	FF2	FF3	FF4	FF5	FF6
Drug:Guggul:soya Lecithin	1:1:1	1:1:1.5	1:1:2	1:2:1.5	1:2:1.5	1:2:2
Cholesterol(mg)	100	100	100	100	100	100
Chloroform(ml)	10	10	10	10	10	10
Dis. water (ml)	20	20	20	20	20	20

Incorporation of prepared guggulosomes into Carbopol gel:

The topical vehicle was constructed on a Carbopol 934 base. A 1% w/v dispersion of Carbopol 934 was hydrated for one hour in a minimal water volume and then stirred to complete dissolution in distilled water. To this matrix, 6 ml of the ketoprofen-guggul-loaded guggulosomal suspension was introduced dropwise with constant stirring at 700 rpm at 30°C.[26] Triethanolamine was added to adjust the gel to a neutral state, the dispersion was kept overnight to release any trapped air, and glycerin, acting as a humectant to support skin hydration and assist cutaneous drug penetration, was blended into the final guggulosomal gel. The completed product was held in an air-tight container until further use.

Physiochemical Characterization of guggulosomes and guggulosomal gel:

Attenuated Total Reflectance FTIR(ATIR- FTIR):

Possible interaction between drug and excipients was screened by FTIR on a Jasco FT-IR 6100 (Japan) instrument; samples were held at room temperature for one month before scanning. The KBr pellet technique was used to record spectra for the pure drug, the loaded guggulosomes, and the individual excipients comprising guggul (GL), cholesterol (CHL) and soya-lecithin (SL). For each measurement, 32 scans were averaged at 4 cm-1 resolution over the 400-4000 cm-1 region.[27]

PDI and Zeta Potential:

Particle size and zeta potential of the optimised guggulosome dispersion were determined by dynamic light scattering on a Malvern Zeta master (UK). Samples diluted in Millipore water were analysed at a 90° scattering angle and 25 °C using a medium viscosity of 0.8872 and refractive index of 1.330; size distribution width was expressed as the PDI. Zeta potential was acquired on a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) by combined laser Doppler velocimetry and phase analysis light scattering (PALS), with each measurement run in triplicate.

Scanning Electron Microscopy(SEM):

The external morphology and three-dimensional appearance of the loaded guggulosomes were examined using SEM (Scanning Electron Microscope MA15 / 18, CARL ZEISS MICROSCOPY). Lyophilised material was fixed onto copper stubs with double-sided carbon tape, sputter-coated with platinum, and imaged at 20 kV over magnifications spanning 400x to 5000x (400x, 500x, 1000x, 1300x, 2000x, 2500x, 4000x and 5000x).[28]

Transmission Electron Microscopy (TEM):

Vesicle morphology and dimensions were further confirmed using transmission electron microscopy (Hitachi HT7700 Exalens, Japan) operated at 100 kV. A 5 µL droplet of the dispersion was placed on a 3 mm Formvar/carbon-coated copper grid, air-dried at room temperature, and subsequently transferred into the microscope for imaging.

In-vitro drug release:

Ketoprofen release from the guggulosomal gel was measured in a modified Franz diffusion cell as previously described; the diffusion tube carried a cellulose acetate membrane pre-soaked for 24 h, was clamped and immersed in a beaker of phosphate buffer (pH 6.8), and 1 g of the ketoprofen guggulosomal gel was loaded into the donor compartment with the assembly held at 37^0C in phosphate buffer pH 6.8. Receptor buffer (pH 6.8) was stirred at 500 rpm on a magnetic stirrer. Aliquots of 3 ml were sampled at 0, 1, 2, 8, 24 and 25 h, with an equal volume of fresh buffer replacing each withdrawal to keep the receptor volume constant. The collected aliquots were assayed at 254 nm against a phosphate buffer blank. Runs were conducted in triplicate and reported as Mean ± SD; cumulative drug release (%CDR) was then derived and plotted against time. [29]

Determination of drug content:

For drug content, 10 g of gel was dispersed in 100 ml of phosphate buffer (pH 6.8) under continuous shaking until fully dissolved, sonicated for 15 min, filtered, suitably diluted and read by UV spectrophotometry at 254 nm.

Determination of pH:

The pH of the ketoprofen-loaded guggulosomal gel was measured by dipping the calibrated electrode into the gel, allowing it to stabilise, and recording the value on a pH meter (Model-ECOSTRPHI, Maharashtra, India) operated at 25^0C. Determinations were carried out in triplicate.

Viscosity:

Each gel was assessed on a Brookfield viscometer fitted with an LV1 spindle, operated sequentially at 5, 10, 15, 20, 25 and 50 rpm after a 30-minute equilibration of the samples at 32 ± 1°C.

Determination of Spreadability:

For spreadability, 1 g of gel was placed between two plates of 20×20cm , with a 125 g upper plate; the spread diameter after one minute was noted and the spreadability calculated from the relationship below.

$$S = mt/l$$

Where,

S = Spreadability,

m = weight of upper slide,

I = length of the glass slide,

t = time.

Determination of Homogeneity:

Gel homogeneity was assessed by visual examination and through an elegance check. A (+) sign denoted satisfactory clarity and good elegance, whereas a (–) sign denoted lack of homogeneity and elegance.

Extrudability:

For extrudability, each gel was filled into a collapsible aluminium tube with the open end crimped, weighed, clamped between two glass slides, and a 500 g load was applied; after

opening the cap the extruded portion was collected and weighed, and the percentage extruded was rated as excellent (>90%), good (>80%) or fair (>70%).

Entrapment Efficiency(EE%):

Entrapment was estimated as the difference between the total drug initially incorporated and the unentrapped drug found in the supernatant after centrifugation. Ultracentrifugation of the loaded guggulosomes was carried out on a Remi instrument with a TLA-45 rotor at 10,000 rpm and 4^0C for 1 h. After vesicle separation, free drug in the supernatant was quantified by UV/Visible spectrophotometry at 369 nm, with measurements run in triplicate.[30] Vesicle-entrapped drug was then computed using the formula given below.

Entrapment Efficiency(EE %) = $W_{total\ ktf}$ - $W_{free\ ktf}$ / $W_{total\ ktf}$ ×100

RESULT AND DISSCUSSION

Pre-formulation studies

Organoleptic properties: Ketoprofen was observed as a colourless to white crystalline powder, odourless, with a bitter taste.

Melting point determination: The melting point of ketoprofen is 94ºC to 97ºC.

Solubility of Ketoprofen:

Ketoprofen was found to be practically insoluble in water and hexane, while it dissolved freely in organic solvents such as ethanol, methanol, chloroform and acetone.

Table 2: Solubility of ketoprofen in different Solvent

SOLVENT	SOLUBILITY
Water	Practically insoluble
Ethanol	Freely soluble
Methanol	Freely soluble
Chloroform	Freely soluble
Acetone	Freely soluble
Ether	Soluble

Partition Coefficient:

The log P value obtained for ketoprofen indicated poor aqueous solubility with a clear preference for organic solvents, confirming that the molecule partitions more favourably into lipophilic phases than aqueous ones.

Calibration curve:

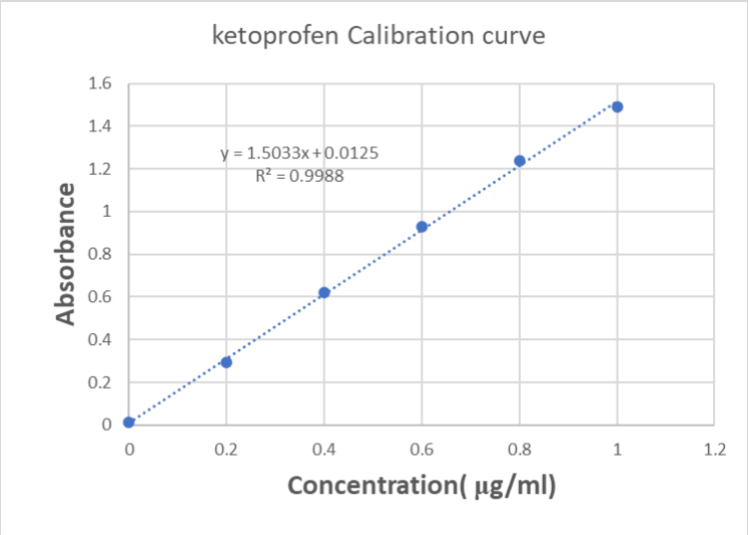

Fig. 1: Calibration curve of ketoprofen

Attenuated Total Reflectance FTIR (ATIR- FTIR):

To probe possible interactions between ketoprofen, the chosen excipients (guggul, cholesterol, soya-lecithin), and the optimised formulation, infrared spectra were collected over the 4000 cm^{-1} to 500cm^{-1} region. In the guggul spectrum a distinctive band at 3295.75 cm-1 was assigned to N-H stretching.

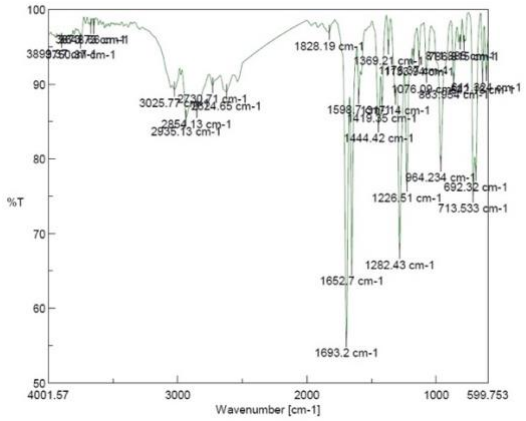

Fig. 2: FTIR Spectra of Ketoprofen drug

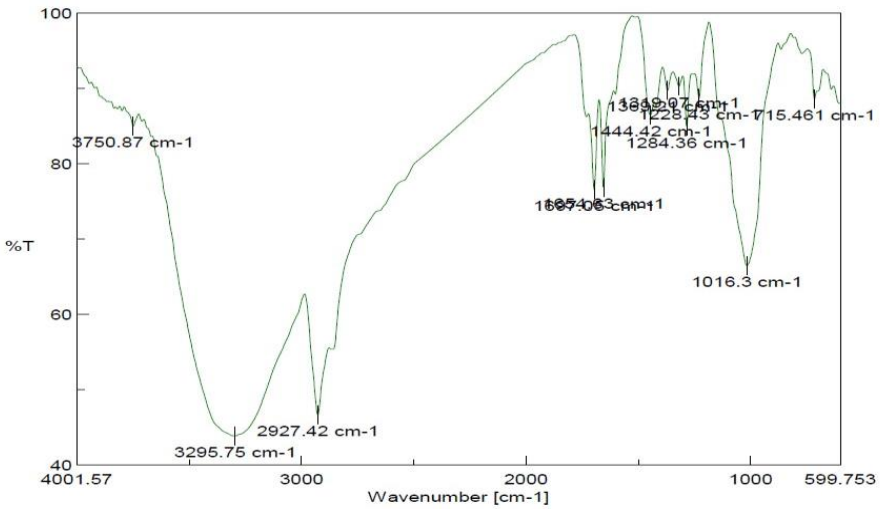

Fig. 3: FTIR Spectra of Guggul

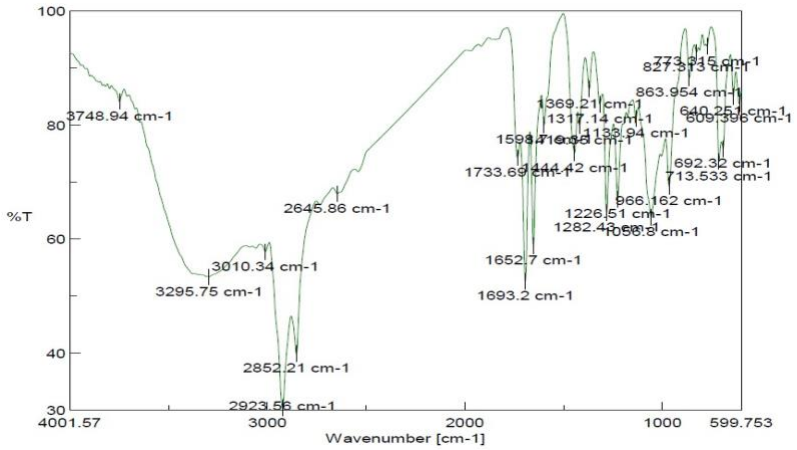

Fig. 4: FTIR Spectra of Optimized final formulation (FF2)

The accompanying figures depict the ATR-FTIR fingerprints obtained for pure ketoprofen, guggul, cholesterol and the loaded guggulosomes, all of which featured broad absorption envelopes. Infrared scans of the pure drug and the excipients were collected across the 100-4000 cm-. Carbonyl stretching of the drug was located at 1693 cm^{-1} , assigned to C = O stretching; additional bands appeared at 1228 cm^{-1} (C─O stretching), 2854 cm^{-1} (C─H stretching), 713 cm^{-1} (C─O─H bending), 964.234 cm^{-1} (CH3 rocking), 1076.09 cm^{-1} (C-CH3 rocking), 3025.77 cm-

[1](C─H stretching), 1369.21 cm^{-1} (C─C─H deformation), 863.954 cm^{-1} (C─O─H bending), 692.32 cm^{-1} (C─H bending) and 1414.42 cm^{-1} (C─C stretching) [30] [35] . When the optimised formulation was scanned over the identical window, all of these vibrational features were retained within a closely matched region, indicating preservation of the drug's chemical environment in the vesicular system.

PDI and Zeta Potential:

DLS analysis returned the vesicle size and polydispersity index (PDI) for each batch. FF2, which combined 400 mg guggul lipid with 300 mg cholesterol at a constant 150 mg drug load, recorded a mean particle size of 426.7 ± 1.13 with PDI 0.256 ± 0.23 and was therefore selected as the optimised batch; its dimensions are well suited for topical use. The dataset further showed that higher cholesterol levels enlarged the negative surface charge on the guggulosomes, contributing to greater colloidal stability. The data confirm that FF2 represents the most stable batch among the lipid film hydration formulations.

Scanning Electron Microscopy(SEM):

SEM imaging revealed the surface morphology and three-dimensional features of the guggulosomes. Representative SEM micrographs of the drug-loaded FF2 batch (below) show that the vesicles produced by lipid film hydration were spherical and confined to a narrow size range of 200-550 nm.

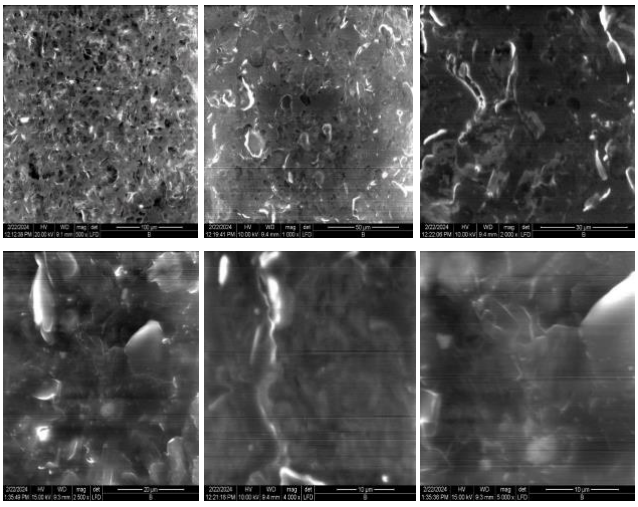

Fig. 4: SEM image of ketoprofen loaded guggulosomes formulation FF2

Transmission Electron Microscopy (TEM)

TEM images of loaded and unloaded guggulosomes captured at 18,500x magnification (below) showed spherical nanosized particles ranging from 100 to 500 nm in diameter, consistent with the DLS size readings. A dark ring surrounding each vesicle in the micrographs corresponds to the lipid bilayer of the guggulosome. In Fig. 5, the drug-loaded vesicles contain rounded internal particles, providing evidence that ketoprofen was successfully encapsulated within the guggulosome core.

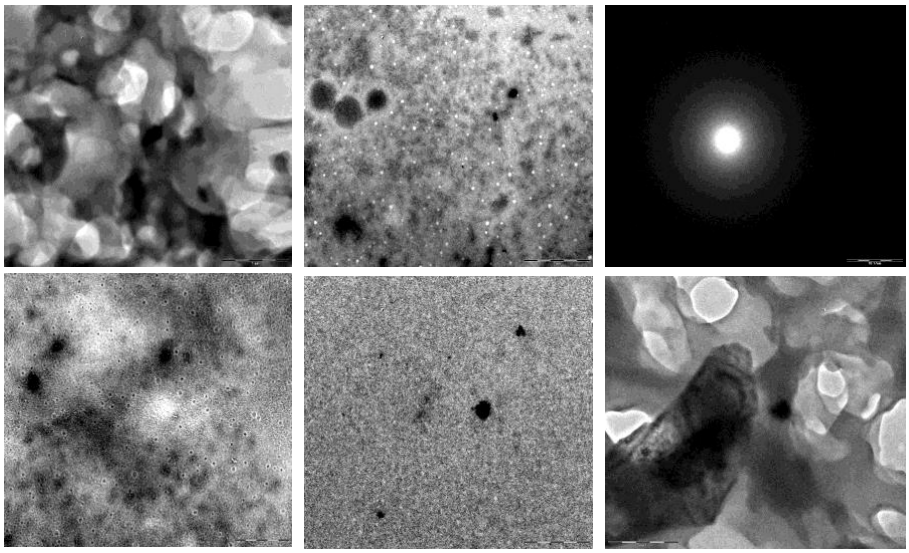

Fig. 5: TEM image of ketoprofen loaded guggulosomes formulation FF2

In-vitro drug release:

At the 24-hour endpoint, the lipid film hydration guggulosomes achieved 60.24 ± 3.012% cumulative drug release. Varying the guggul lipid and cholesterol levels at a fixed ketoprofen load tuned the release profile across batches. The release curves for FF1 to FF6 are plotted in the figure below; at 24 h the pure drug and the formulations gave the following cumulative release values: pure drug 58.45 ± 2.922, FF1 41.26 ± 2.063, FF2 60.24 ± 3.012, FF3 49.56 ± 2.478, FF4 32.14 ± 1.607, FF5 42.19 ± 2.109, and FF6 34.12 ± 1.706. FF2 produced the highest cumulative release, attributable to its greater drug loading within the vesicles. The 60.24 ± 3.012% release from FF2 extended over 24 h, exhibiting a burst phase during the initial 8 h followed by a gradual taper that plateaued by 18 h. Cholesterol stiffened the lipid bilayer, which together with guggul lipid acted as a rate-limiting barrier governing ketoprofen efflux from the vesicles. FF4

returned the lowest release, in line with its higher cholesterol content and consequently more rigid vesicles.

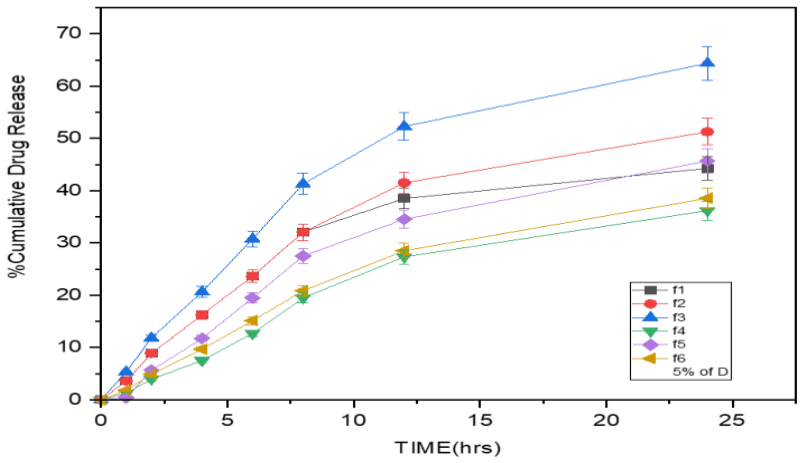

Fig. 6: % Cumulative Drug Release Graph of Optimize Formulation

Viscosity:

The viscosities of gel batches FF1 to FF6 were measured at 32 ± 1 °C; values for the optimised gel spanned 11175 ± 58.75 to 6392 ± 319.6

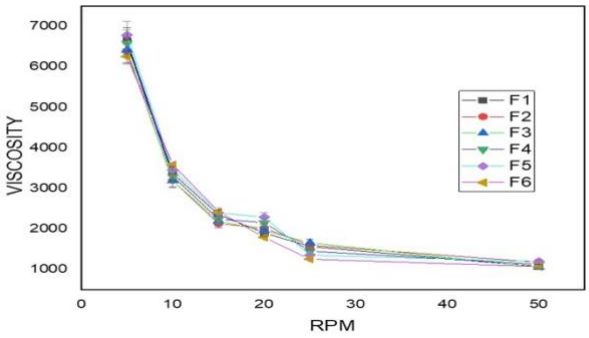

Fig. 7: Viscosity Graph of Optimize Formulation

Determination of pH:

For each gel, 2.5 g was dispersed in 25 ml of purified water and the pH was logged on a digital pH meter. The values across batches FF1-FF6 occupied the 5.9 to 6.8 range, the optimised gel

returning a pH of 6.5, which sits comfortably within the range deemed acceptable for cutaneous use.

Determination of Homogeneity:

Visual examination confirmed that all gel batches exhibited acceptable appearance and elegance, and each was scored with a (+) sign reflecting satisfactory homogeneity.

Table 3: Homogeneity of all final formulation

Formulation	Homogeneity
FF1	++
FF2	++
FF3	++
FF4	++
FF5	++
FF6	++

Determination of Spreadability:

Spreadability, defined as the time in seconds taken for two slides framing a gel sample under a defined load to separate, is inversely related to spread quality; shorter separation times signify better spreadability. The tabulated values for ketoprofen guggulosomal batches FF1-FF6 fell within 13.65 ± 0.445 to 20.84 ± 0.239, confirming that the optimised guggulosomal preparation displays acceptable spreadability

Table 4: Spreadability of all final formulation

Formulation	Spreadability
FF1	13.65± 0.445
FF2	15.89 ±0.67
FF3	16.56± 0.61
FF4	18.03± 0.548
FF5	15.82 ±0.410
FF6	20.84 ±0.239

Entrapment Efficiency(EE%):

FF2 returned the strongest entrapment efficiency (93.26%) among the batches and FF5 the weakest (79.15%). Entrapment progressively climbed with rising guggul lipid content, but no further meaningful gain was seen once the level surpassed 3%, suggesting that guggul lipid governs entrapment up to this threshold.

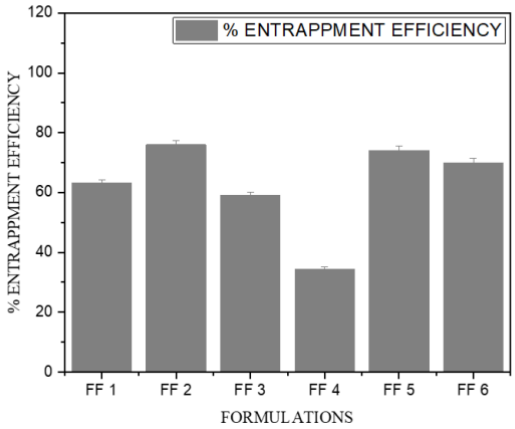

Fig. 8: Entrapment Efficiency Graph of All Formulation

Determination of % drug content:

Table 5: % drug content of all formulation

Formulation	% drug content
FF1	91.71± 0.917
FF2	96.27± 0.962
FF3	94.06± 0.940
FF4	95.68± 0.956
FF5	92.1± 0.921
FF6	94.15± 0.941

Extrudability:

The ease with which a gel is expelled from its tube directly affects both clinical use and patient acceptance; a stiff gel will not flow readily, whereas a gel of very low viscosity flows uncontrollably, so a balanced consistency is required. All the gel batches examined here delivered acceptable extrudability.

Table 6: Extrudability study of various gel formulations

Formulation	Weight of Formulation	Weight of gel extruded	Extrudability amount(%)	Grade
FF1	20.1	14.1	70.14	Good
FF2	20.64	16.56	80.23	Good
FF3	20.95	15.21	72.60	Good
FF4	20.26	15.58	76.90	Good
FF5	20.23	16.87	83.39	Good
FF6	20.87	13.48	64.59	Fair

Conclusion

A 0.0020% w/v solution of ketoprofen in chloroform exhibited its UV absorption maximum at 254 nm.

This work confirmed that ketoprofen can be successfully entrapped within guggulosomal vesicles produced by lipid film hydration. Centrifugal ultrafiltration across all batches established FF2 as the formulation with the strongest entrapment; its vesicles measured 462.6 nm with a PDI of 0.256 and carried a surface charge of -6.01 mV. Comparing the infrared spectrum of pure ketoprofen with that of the loaded vesicles revealed no notable peak displacement, indicating that the drug and the lipid excipients had not chemically interacted. Across the physicochemical attributes assessed, namely pH, viscosity, spreadability, homogeneity and drug content, FF2 again returned the most favourable values, and its in vitro release profile demonstrated a clearly more sustained delivery than both the pure drug and the other batches. Release was progressively extended as the guggul content in the formulation was raised, consistent with its barrier role within the vesicular bilayer. These outcomes reaffirm the long-standing Ayurvedic standing of the oleo-gum resin derived from Commiphora mukul (also known as Commiphora wightii) as a valuable medicinal and pharmaceutical material.

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