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Advances in Bioresearch

ORIGINAL ARTICLE

Development and Evaluation of Herbal Nanogel in the Pain Management of Rheumatoid Arthritis

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ABSTRACT
Joint pain and destruction are hallmarks of rheumatoid arthritis (RA), a chronic inflammatory disease. This study aims to develop and evaluate a herbal nanogel with curcumin and quercetin for RA pain management. Conventional treatments, such as NSAIDs and corticosteroids, often lead to adverse side effects, prompting the need for alternative therapies. This study explores. the creation and assessment of an innovative herbal nanogel for RA topical pain relief. The nanogel exhibited significant anti-inflammatory and antioxidant effects in vitro. The nanogel was prepared using the physical method with carbopol 934, propylene glycol, and methylparaben This herbal nanogel presents a promising alternative for RA pain management. The prepared nanogel was tested for various parameters such as Differential scanning colorimeter, pH, viscosity, Spredablity, drug content and in vitro drug release. The prepared Nanogel exhibit the good physical properties, where F5 formulation was found as an optimized batch. Further investigation is needed to examine the long-term effects of this herbal formulation and explore its potential for large-scale production
Keywords: Rheumatoid Arthritis (RA), Curcumin, Joint Pain , Nanogel Quercetin, Pain Management

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INTRODUCTION

One of the most prevalent illnesses and a major contributor to joint dysfunction and disability in adults is arthritis [1]. Rheumatoid arthritis, the most common type of arthritis, is an autoimmune disease that is characterized by swelling, stiffness, and pain in the peripheral joints. It is brought on by the release of pro-inflammatory mediators such as IL-1β and TNF-α. Rheumatoid arthritis is treated with a variety of drugs, including DMARDs (disease-modifying anti-rheumatic medications), analgesics, steroidal and non-steroidal anti-inflammatory medicines, and monoclonal antibodies (MAbs) that only reduce symptoms [2] But these medications have a host of severe side effects, including immunosuppressive effects, toxicity, protein loss, nephrotoxicity, and lack of target selectivity, which ultimately lead to poor patient compliance [3,4]. Since RA affects about 0.5% of people worldwide, it presents a significant healthcare cost to both individuals and society as a whole [5].

PAIN MECHANISM IN RHEUMATOID ARTHRITIS -

According to the International Association for the Study of Pain, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." In response to intense mechanical, chemical, or thermal stimuli, specialized sensory fibers known as nociceptors fire, potentially revealing tissue damage.[7] Nociceptor activation typically causes pain and serves as an alert system for changes in homeostasis, including inflammatory reactions from tissue damage. [8] The autoimmune condition rheumatoid arthritis (RA) has subgroups that are seropositive and seronegative, ACPAs, or anti-citrullinated peptide antibodies which cause severe joint injury and increased mortality, are present in seropositive patients.[9]In order to create immune

complexes that trigger the complement system and inflame synovium, ACPAs attach to autoantigens[10] Immune responses, both innate and adaptive, are involved in RA. Dendritic cells, macrophages, and mast cells are examples of innate immune cells. release agents of inflammation, such as chemokines and cytokines. This attracts neutrophils and activates adaptive immune cells including T, B, and plasma cells, which worsen inflammation. IL-6 and TNF-α are two important cytokines that are targeted by effective RA medicines since they are essential to this process. [11] The catabolic condition that inflammation induces in the joint is typified by the hypertrophied synovium, or synovial pannus, which eats away at tissue. Through the action of enzymes such as matrix metalloproteinases (MMPs) and interactions between RANK-L and RANK receptors, synovial fibroblasts become inflammatory, leading to the degradation of cartilage and erosion of bone.[12]

PAIN AND CYTOKINES

The activation of pain sensitization and stimulation of nociceptors are largely dependent on inflammatory cytokines. Specifically, nociceptors have been shown to be directly activated via TNF- α, lL-17A, lL-1β,lL-5, lL-6. The discovery in neuroimmunology that IL-1β was the cytokine that initially to be recognized as hyper-algesic was a significant one . It sensitizes nociceptors by: - Activating Nav1.8 sodium channels by phosphorylation mediated by p38 MAPK, which increases action potential production and causes mechanical and thermal hyperalgesia.

- Enhanced expression of TRPV1 on nociceptors by activation of IL-1R1, which contributes to sensitization to thermal pain. Indirectly and directly, IL-6 increases pain sensitivity:
- Increased expression of TRPV1 and TRPA1 due to direct nociceptors activated by gp130.
- Indirect stimulation by means of prostaglandin synthesis.[13]

TNF-α is prostaglandin-dependent and causes pain sensitivity through TRPA1 and TRPV1. Additionally, it modifies nociceptor sensitivity by phosphorylating the sodium channels Nav1.8 and Nav1.9 through p38 MAPK.

IL-17 plays a major function in the sensitization to pain, especially in inflammatory illnesses such as psoriasis and rheumatoid arthritis (RA). It produces hyperalgesia and increases neuronal excitability by raising Prostaglandins, TNF-α, IL-1β, CXCL-1, endothelin 1, and

In conclusion, two ways that IL-1β, IL-6, TNF-α, and IL-17 contribute to pain and its sensitization are via prostaglandin synthesis and the activation of sodium or TRP channels [14]

STRUCTURES OF SYNOVIAL JOINTS AND PAIN -

Nociceptor pain originates in the subchondral bone and synovium. Normally, cartilage is avascular and aneural. Chronic inflammation in rheumatoid arthritis (RA) enhances articular afferent activity and synovial innervation.

ROUTES OF NOCICEPTORS -

Local immune cells' inflammatory mediators trigger nociceptors, which then send pain signals to the brain via the spinothalamic tract and dorsal root ganglion (DRG). Allodynia, or Hyperalgesia and pain resulting from non-painful stimulants, or enhanced discomfort resulting from unpleasant stimuli, are brought on by inflammation because it decreases the threshold for nociceptor activation. Inflammatory mediators in RA nociceptor activation and sensitization are discussed in the following section.[15]

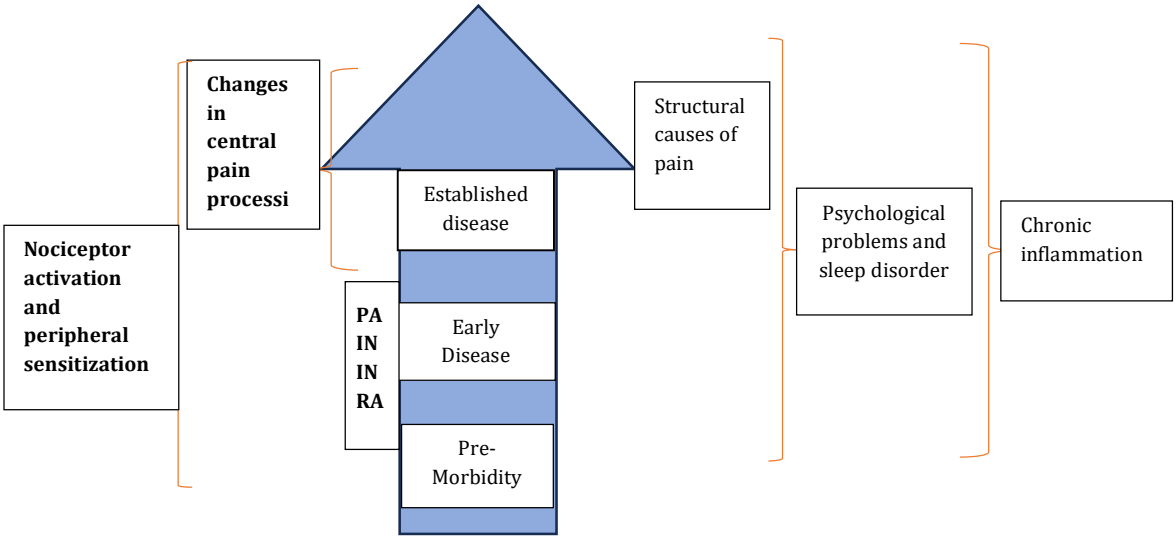

Figure 1- Summarizes the several processes that cause pain in rheumatoid arthritis

NATURAL SOLUTIONS FOR HANDLING PAIN IN RHEUMATOID ARTHRITIS:

Research has demonstrated that bioactive components derived from a variety of herbal plants have anti-inflammatory, analgesic, and immunomodulatory characteristics, rendering them very valuable in the management of rheumatoid arthritis pain. Although conventional treatments have severe side effects and limits, they can effectively manage symptoms. Herbal medicines, which provide a comprehensive and natural approach to pain management, have become more popular as a result of this. These medicines' biological effects on the human body are attributed to their bioactive components, which are naturally occurring substances found in plants.

CURCUMIN

Native to Southeast Asia, especially India, (*Curcuma longa*) turmeric is a curry spice having a vivid yellow hue. The active ingredient that is originating from the turmeric rhizomes called as diferuloylmethane or 1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione curcumin. Many curcuminoids are present in it, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin (77%, 17%, and 3%, respectively) Recent studies have demonstrated the diverse biological and pharmacological characteristics of curcumin, including its anti-inflammatory, hepatoprotective, andanticarcinogenic, thrombosuppressive, antiarthritic, and regulation of numerous signaling pathways. The function of curcumin in the state of inflammation: at various doses, curcumin markedly reduced the concentrations of C-reactive protein (CRP), TNF-α, IL-1β, and IL-6), cyclic citrullinated peptide antibodies, IFN, and MMP-1 and MMP-3 synthesis in the serum.[16]

QUERCETIN

Quercetin (Qu), also called 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy4H-chromen-4-one (Figure 1), is a chemical that belongs to the flavonol family. It is distinguished by having a 3-hydroxyflavone backbone. Research has demonstrated the efficacy of quercetin in the treatment of RA. In RA, quercetin controls inflammatory reactions. In a recent study, quercetin was demonstrated to prevent prostaglandin E2, cyclooxygenase (COX)-2, matrix metalloproteinases, and RA synovial fibroblasts from proliferating in response to IL-1b. Furthermore, the researchers discovered that quercetin causes RA synovial fibroblasts to undergo apoptosis. Quercetin suppresses the activation of MAPK and the level of COX-2 caused by lipopolysaccharides. In femoral organ cultures, quercetin inhibits the production of osteoclasts and inhibiting nuclear factor kappa (NF-jB) and AP-1 to reduce bone resorption.[17]

NANOGEL

Particles at the nanoscale are known as nanogels that are swelled in a suitable solvent and are created by chemically or physically crosslinked polymer networks. When bifunctional networks that are cross-linked and comprise both nonionic and polyionic polymers were firstly represent, the word "nanogel" (NanoGelTM) was employed to explain the movement of polynucleotides (PEI, or cross-linked polyethyleneimine) and poly (ethylene glycol), or PEG-cl-PEI (16–18). The unexpected boom of interest in nanotechnology has made it necessary to develop nanogel systems, which have proven to be effective for distributing drugs in a controlled, sustained, and targetable manner. As polymer sciences have grown, it

has become imperative to prepare intelligent nano-systems that can aid in both therapy and the advancement of clinical trials.[19]

Nanogels are better than conventional drug delivery technologies because:

1. Both passive and active drug targeting can be obtained by controlling the Surface characteristics and particle size to prevent Phagocytic cells from rapidly removing the drug.
2. Steady and regulated drug uncork at the intended location, enhancing treatment effectiveness and mitigating adverse effects. Drug loading can be accomplished without undergoing chemical reactions and is quite high, which is crucial for maintaining the drug's active ingredient.
3. The ability to penetrate tissues through either the transcellular or paracellular routes, which enables it to enter even the smallest capillary vessels due to their extremely small volume.
4. Very biodegradable and friendly with the body [20].

MATERIAL AND METHODS

MATERIALS

Materials	Role	Suppliers
Curcumin	Anti-Arthritic activity	New Neeta Chemicals
Quercetin	Anti-inflammatory activity	New Neeta Chemicals
Carbopol 940	Gelling agent, polymer	Research Lab fine chemicals, Mumbai.
Methylparaben	Preservative	Research Lab fine chemicals, Mumbai.
Propylene glycol	Humectant, plasticizer, Penetration enhancer	Research lab fine, Mumbai

FORMULATION OF NANOGEL

The use of carbapol 934, propylene glycol, triethanolamine, methyl paraben, and distilled water in an amount that allowed for the manufacture of 10 grams of herbal gel in accordance with table number.

Steps to Take:

A magnetic stirrer was used to continuously swirl distilled water while dispersing the necessary amount of carbapol 934.[First Phase]

Water is used to dissolve the calculated amounts of methyl paraben and propylene glycol. [The second phase]

Phase 1 has been continuously stirred while phase 2 and drug extract are introduced.

Next, homogenize the nanogel to create nanoparticles by reducing the size of the particles. that are contained inside it.

In order to modify the pH, add triethanolamine to the above formulation.

Fig. 2 Formulation Of Batches

Table 1 - Composition of different Formulation Batches

Ingredients (%w/w)	B1	B2	B3	B4	B5	B6	B7	B8	B9
Curcumin(gm)	0.1	0.1	0.1	0.1	**0.1**	0.1	0.1	0.1	0.1
Quercetin(gm)	0.1	0.1	0.1	0.1	**0.1**	0.1	0.1	0.1	0.1
Carbopol 934(gm)	0.2	0.05	0.018	0.231	**0.125**	0.2	0.05	0.125	0.12
Propylene Glycol(gm)	1.2	1	1.3	1.4	**1.1**	0.1	1.2	1.1	1
Methyl Paraben	0.1	0.1	0.1	0.1	**0.1**	0.1	0.1	0.1	0.1
Triethanolamine	Add few drops to adjust pH to 6-6.5								
Distilled Water	Quantity Sufficient								

EVALUATION OF NANOGEL

Organoleptic qualities:

Analyzing the gel's organic qualities involves looking at things like color, texture, appearance, homogeneity, and uniformity. Visual observation and recording of the color were done. By rubbing it between fingertips, the homogeneity of the gel was verified. Skin was treated with gel to evaluate its consistency and texture.

Ph: The pH of the produced gel batches measured using a digital pH meter. The pH measured by dipping an electrode into 0.5 grams of dissolved material in 10 milliliters of distilled water.[21]

Viscosity:

Using a brook field viscometer with spindle number L4, the viscosity of the prepared preparations was ascertained. In a beaker with a thermostatic jacket on, the formulation whose viscosity was to be measured was added. The spindle was permitted to enter the gel, and while the equipment was kept at 25 °C, a reading of 60 rpm was recorded.[22]

Spreadability:

One prerequisite for a gel to satisfy optimal criteria is its capacity to spread evenly. The term refers to the region where a gel easily disperses when applied topically or another place that is impacted. The spreadability value of a formulation has an impact on its medicinal efficacy as well. The gel's spreading diameter (1 g) between two horizontal plates was measured to see how far it could spread after a minute. To test spreadability, a standard 50 g load was added to the upper plate. The diameter of the spread circle was measured in centimeters, and the average of three computations is what was obtained. [23]

$S = M*L/T$,

where L is the glass slide's length

M = weight fastened to the upper slide.

T = time it takes to move the slides

Drug content:

1g of nanogel dissolved in ethanol and filtered to produce a clear solution. Using a UV spectrophotometer, the absorbance of the gel was determined at 372 nm and 425 nm, respectively. to detect the presence of the drugs curcumin and quercetin. A standard plot of the relevant medication was made using a comparable solvent. The conc. and drug content were ascertained by using the absorbance data and the same standard plot [13]

In vitro drug release study:

Using a Franz diffusion cell, the in vitro drug release from gel was performed at 370C ± 0.50C and 100 RPM.

The dissolution media, phosphate buffer (pH 6.8), was utilized. At prearranged intervals, one milliliter of the dissolution liquid was removed and replaced with fresh. The sample was taken out at regular intervals and examined using a UV spectrophotometer to determine whether the drugs quercetin and curcumin were present at 372 nm and 425 nm, respectively.

Device: Franz diffusion cell

pH 6.8 Phosphate Buffer as the media

Time span: 0, 15, 30,..., 90 minutes.

It is 37°C (0.5°C) outside.

Centrifuged test:

In this test, two phases of the gel formulation were observed to separate after each of the nine batches was placed in the centrifuged testing apparatus.

PRE – FORMULATION STUDIES:

1] Ultraviolet Spectroscopy:

UV spectroscopic technique for Curcumin Estimation:

The stock solution made by diluting 10 mg of curcumin, which had been carefully weighed, in 70 ml of ethanol in a second volumetric flask measuring 100 ml. After 15 minutes of sonication, the flask produced a clear solution, and the volume was changed to get a solution with 100 ug/ml.

Curcumin calibration curve in ethanol:

The highest wavelength was found by scanning the 200–800 nm range in the working standard solution of extract at 100 ug/ml. It was found that the maximum wavelength of curcumin was 425 nm. Standard extract solutions ranging in ug/ml from 2 to 10 were obtained by transferring 0.2-1 ml into five distinct 10 ml volumetric flasks containing stock solution. The volume of the volumetric flask was filled with distilled water. To measure the absorbance of different solutions and determine absorptivity, Beer's Lambert law was applied.

Quantification of Quercetin via UV Spectroscopy:

Setting up the stock solution:

A precisely weighed 10 milligram quantity of quercetin was moved to a second 100 milliliter volumetric flask and diluted with 70 milliliters of ethanol. After 15 minutes of sonication, the flask produced a clear solution, and the volume was changed to get a solution with 100 ug/ml.

Quercetin calibration curve in ethanol:

The wavelength at which the maximum was obtained was ascertained by scanning the 200–600 nm range in the working standard solution of extract at 100 ug/ml. 372 nm was found to be the maximum wavelength of quercetin. A range of 2 to 10 ug/ml of standard extract solutions were obtained by transferring 0.2-1 ml of the stock solution into five different volumetric flasks (10 ml). In order to fill the volumetric flask, distilled water was deployed. Absorbtivity was calculated and different solutions' absorbance was tested using Beer's Lambert law**.**

STUDIES ON DRUG EXCIPIENT COMPATIBILITY:

Test for physical compatibility:

To investigate the compatibility and interactions of drug excipients, a physical compatibility test was conducted. The correct ratio of 1:1 was used to combine the medication and excipient. The mixtures were put into separate glass vials and kept in room temperature storage. Samples were inspected for color and appearance after 15 days in order to prepare them for testing for drug-excipient compatibility.

DSC:

Figure displays the thermograms of the drug sample and the Nanogel loaded with quercetin and curcumin. Peak shifting was seen in the loaded gel, where the peak at the end was measured at 123.40 and the peak for quercetin was measured at 168.08 and the peak for curcumin at 185.21. The peak was then found close to the difference between 62 and 70, according to the above observation

RESULT AND DISCUSSION

Evaluation of Organoleptic Properties

Table 2 – Evaluation of organoleptic Properties

Formulations	Physical appearance		
	Colour	Consistency	Homogeneity
F1	Turmeric Yellow	Very Good	Yes
F2	Pale yellow	Good	Yes
F3	Turmeric yellow	Excellent	Yes
F4	Light yellow	Very Good	Yes
F5	**Turmeric yellow**	**Excellent**	**Yes**
F6	Yellowish orange	Good	Yes
F7	Dark orange	Fair	NO
F8	Turmeric yellow	Good	Yes
F9	Turmeric yellow	Excellent	Yes

All formulations (F1–F9) were assessed for colour, consistency, and homogeneity. Most exhibited a characteristic turmeric yellow appearance, with minor variations ranging from pale yellow to dark orange. Consistency was rated as excellent for F3, F5, and F9; very good for F1 and F4; good for F2, F6, and F8; and fair for F7. Homogeneity was satisfactory in all formulations except F7, which showed phase inconsistency. Overall, F3, F5, and F9 demonstrated superior physical properties and were identified as optimal formulations for further investigation.

pH, spreadability, and viscosity of GEL :

Batches	pH	Viscosity(cps)	Spreadability (gm*Cm/sec)
F1	7.55	3988	7.2
F2	7.42	1852	5.2
F3	6.83	2778	6.4
F4	6.72	4112	5.3
F5	**6.68**	**1986**	**7.4**
F6	6.44	3900	5.5
F7	6.91	1823	6.8
F8	7.11	2341	4.4
F9	6.74	2665	7.3

Table 3 - pH , Viscosity and Spreadability of gel

The physicochemical characteristics of the prepared formulations (F1–F9) are summarized in Table X. The pH of all batches ranged from 6.44 to 7.55, indicating that the formulations are within an acceptable range for topical application and are unlikely to cause skin irritation. Among the batches, F1 exhibited the highest pH, while F6 showed the lowest value.

Viscosity measurements revealed considerable variation among formulations, with values ranging from 1823 cps (F7) to 4112 cps (F4). Higher viscosity observed in F4, F1, and F6 suggests better retention at the application site, whereas lower viscosity in F7 and F2 may contribute to improved ease of application.

Spreadability values ranged between 4.4 and 7.4 gm·cm/sec. Formulations F5 and F9 demonstrated superior spreadability, indicating better applicability and uniform distribution on the skin surface, while F8 exhibited the lowest spreadability.

Overall, the results suggest an inverse relationship between viscosity and spreadability. Based on the combined evaluation of all parameters, formulations F5 and F9 showed a more desirable balance of physicochemical properties, making them suitable candidates for further development.

DRUG CONTENT

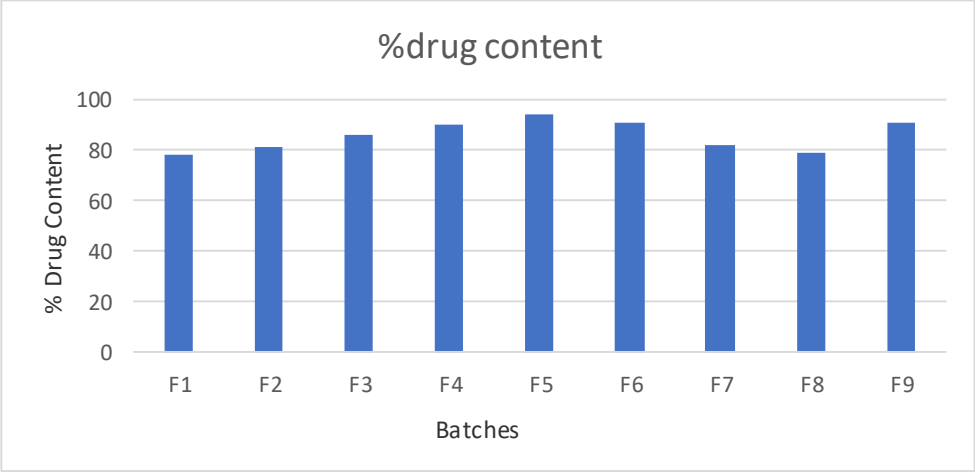

Figure 1: % Drug Content Curcumin

The Curcumin drug content ranged from ~78% to 95%, indicating satisfactory incorporation across all batches. F5 showed the highest content, followed by F4, F6, and F9, while F1 and F8 exhibited comparatively lower values. Overall, F5 and F9 demonstrated better drug loading and uniformity, making them suitable for further development.

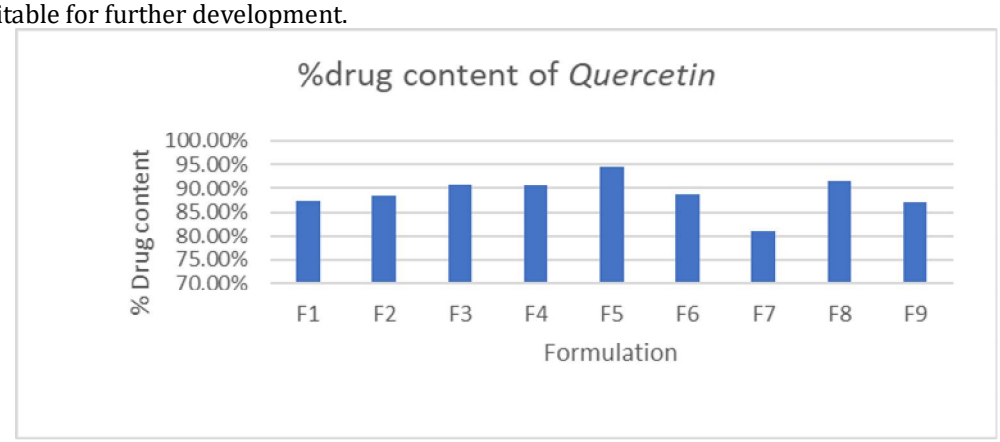

Figure 2: % Drug Content Quercetin

The Quercetin drug content ranged from ~81% to 95%, indicating good incorporation across all formulations. F5 showed the highest drug content, followed by F3, F4, and F8, while F7 exhibited the lowest value. Overall, F5 and F8 demonstrated better drug loading and uniformity, making them suitable for further optimization.

UV analysis of *Curcumin :*

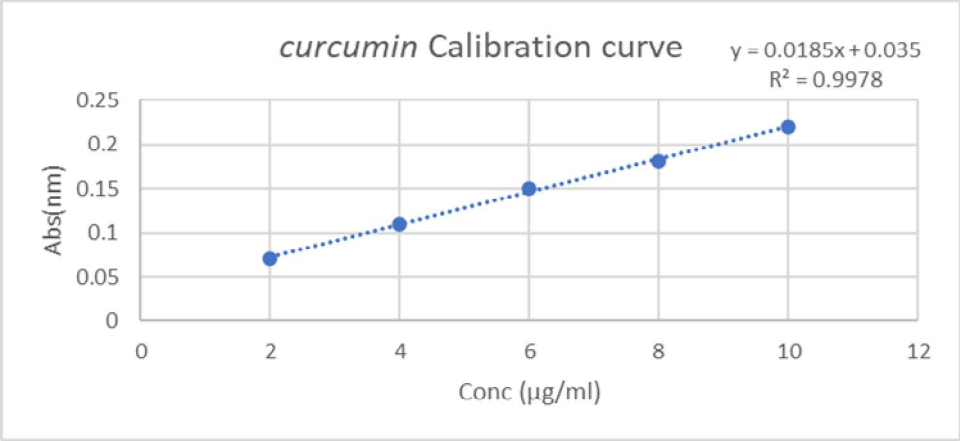

Fig 3 : Calibration Curve Of Curcumin At 425nm

The calibration curve of Curcumin exhibited good linearity over the concentration range of 2–10 µg/mL, with a regression equation of $y = 0.0185x + 0.035$ and a correlation coefficient ($R^2 = 0.9978$). The high R^2 value indicates excellent linear relationship between concentration and absorbance, confirming the reliability and accuracy of the analytical method for quantitative estimation of Curcumin.

UV Analysis Of *Quercetin :*

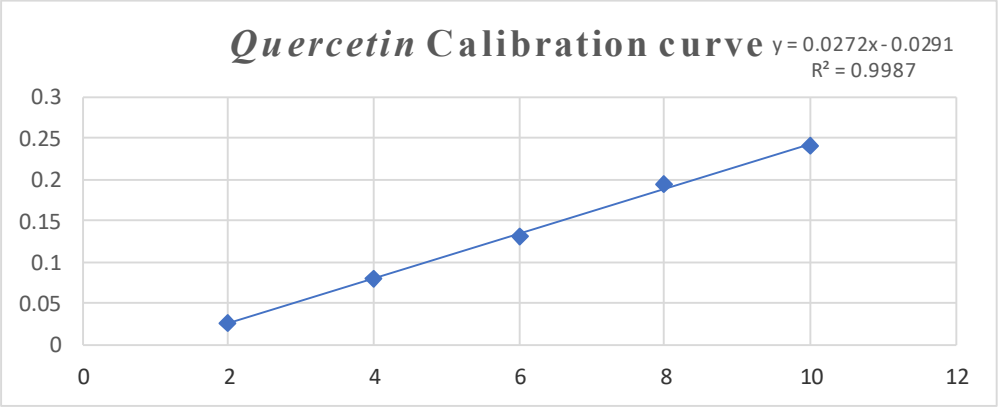

Fig 4: Calibration Curve of Quercetin at 372

The calibration curve of Quercetin showed good linearity over the concentration range of 2–10 µg/mL, with a regression equation of $y = 0.0272x - 0.0291$ and a correlation coefficient ($R^2 = 0.9987$). The high R^2 value indicates a strong linear relationship between concentration and absorbance, confirming the accuracy and reliability of the method for quantitative estimation of Quercetin.

Viscosity:

The discrepancy between the Expected R2 of 0.8670 and the Adjusted R2 of 0.9274 is less than 0.2, indicating a reasonable agreement

Model terms are considered significant when P-values are less than 0.0500. Here, A is an important model term.

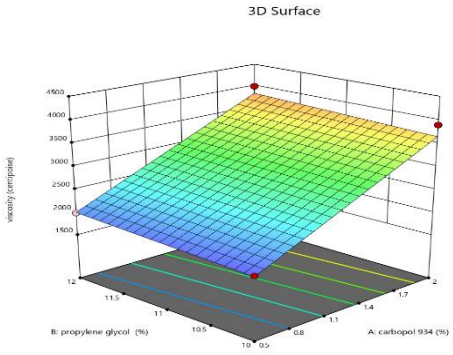

Fig 5: Responses surface curve representing a 3D effect of carbopol 934 and propylene glycol on viscosity.

Spreadability :

When P-values are less than 0.0500, model terms are deemed significant. B is a crucial model term in this instance. The Adjusted R2 differences are smaller than 0.2 of 0.8515 and the expected R2 of 0.7339, showing a satisfactory concur.

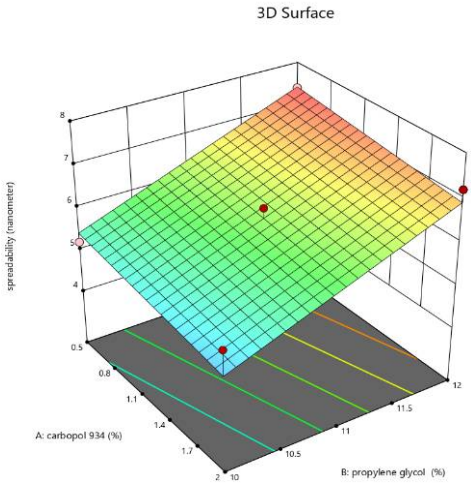

Fig 6: Responses surface curve representing a 3D effect of carbopol 934 and propylene glycol on spreadability.

In Vitro Drug Release :

The drug release study of all 9 batches was carried out by using a Franz diffusion cell with phosphate buffer (pH 6.8) solution and the F4 batch shows maximum drug release in a particular time interval.

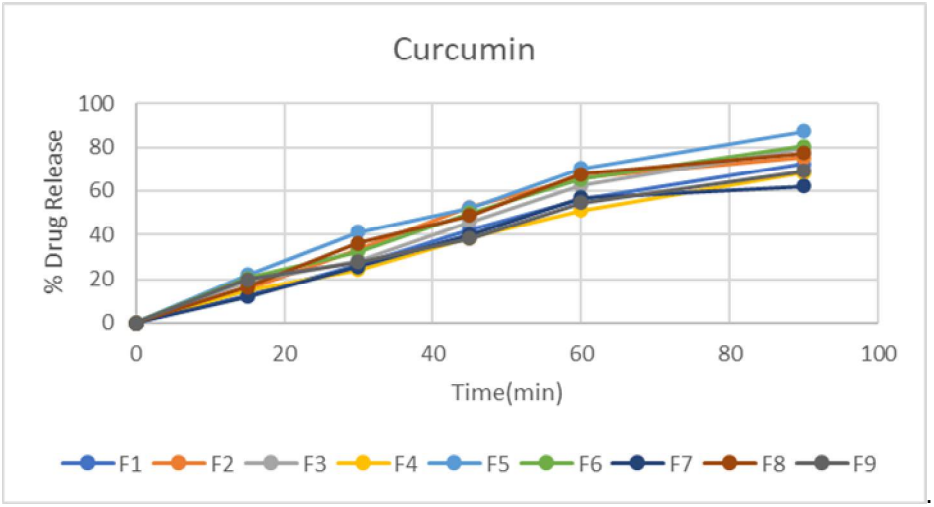

Fig 7 : Curcumin Drug release

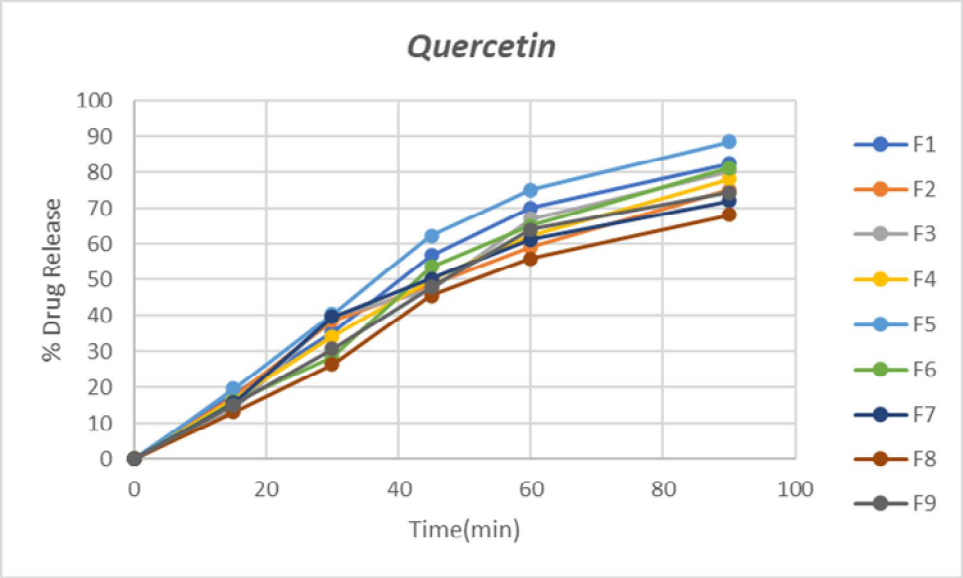

Fig 8 : Quercetin drug release

Centrifugation Test :

Table Preliminary screening results of formulated batches (B1–B9)

Batch	Result
B1	No
B2	No
B3	No
B4	No
B5	No
B6	No
B7	Yes
B8	No
B9	No

The centrifugation test was conducted to assess the physical stability of the formulations under accelerated conditions. The results revealed that batches B1–B6, B8, and B9 showed no phase separation, indicating good stability and uniform dispersion of components. In contrast, batch B7 exhibited phase separation, suggesting instability under stress conditions.

The absence of phase separation in most formulations confirms the effectiveness of the formulation strategy, indicating proper emulsification and compatibility among ingredients. The stability observed in these batches reflects their ability to withstand mechanical stress, which is essential for ensuring product shelf life and performance.

However, the instability observed in B7 may be attributed to inadequate mixing, improper ratio of excipients, or incompatibility between formulation components. This suggests the need for further optimization of this batch, particularly in terms of emulsifier concentration or processing conditions.

Overall, the findings demonstrate that the majority of formulations possess satisfactory physicochemical stability, with B1–B6, B8, and B9 identified as stable candidates for further evaluation, while B7 requires reformulation to enhance its stability profile.

DSC :

The thermograms of drug sample and nanogel are shown in fig where,

S1- Curcumin

S2- quercetin

S3 - Gel

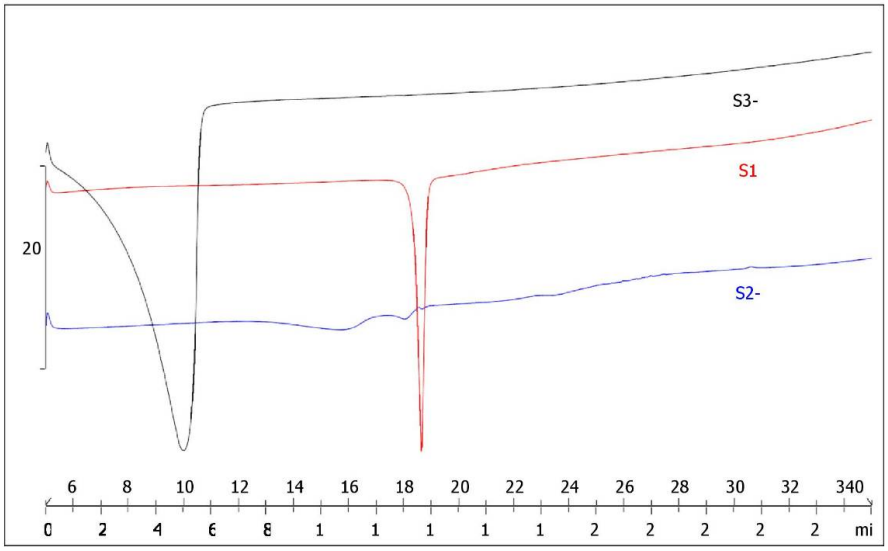

Fig : DSC of drug sample (curcumin and quercetin) and Nanogel formulation

The Differential Scanning Calorimetry (DSC) thermograms of curcumin, quercetin, and the developed nanogel formulation are presented in Figure X. The pure drug sample (Curcumin-S1) displayed a distinct sharp endothermic peak around 180°C, corresponding to its melting point and confirming its crystalline nature.

In contrast, the nanogel formulation (quercetin -S2) exhibited a broadened and less intense peak with slight thermal shift, indicating reduced crystallinity and partial conversion of the drug into an amorphous or molecularly dispersed state within the polymeric matrix. This transformation suggests efficient drug encapsulation and uniform distribution.

The Nanogel (S3) showed no characteristic melting peak, reflecting its amorphous structure. Notably, the absence of additional peaks or significant shifts confirms physicochemical compatibility between the drug and excipients.

Overall, the DSC findings demonstrate successful nanogel formulation with decreased crystallinity and enhanced drug dispersion, which may improve solubility and bioavailability.

Anti – Oxidant Activity (DPPH) method :

Radical scavenging capability was computed using the following equation and reported as a percentage effect (E%): $(Abs_{Control} - Abs_{sample}) / Abs_{Control} * 100$

To create antiradical curves that could be utilized to determine the EC50 values, various sample concentrations were used. Plotting of antiradical curves showed their comparative ability to scavenge on the y axis and their concentration on the x axis.[24]

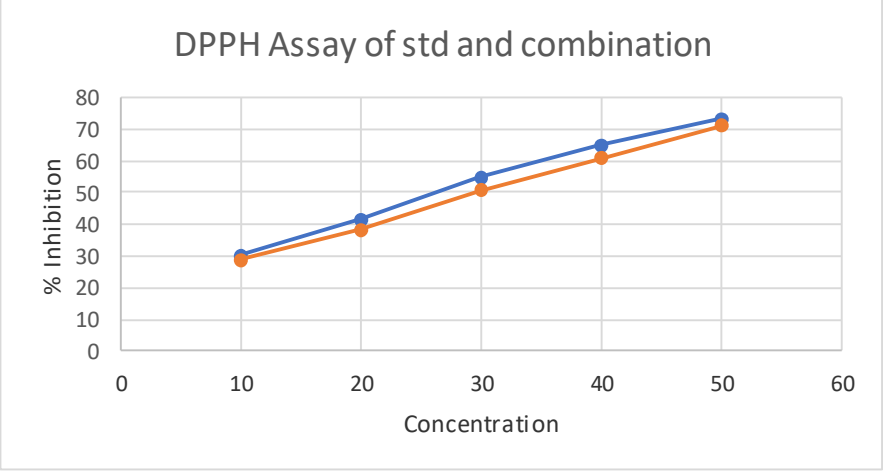

Fig: DPPH Assay of (Formulation and Std)

The DPPH radical scavenging assay of the curcumin–quercetin loaded nanogel revealed a clear concentration-dependent increase in % inhibition. The formulation exhibited slightly lower antioxidant activity than the standard across all tested concentrations, while maintaining a comparable trend. At 50 µg/mL, the standard showed maximum inhibition (~73%), whereas the nanogel formulation achieved ~70% inhibition, indicating substantial free radical scavenging capacity.

The antioxidant effect is primarily attributed to the synergistic action of curcumin and quercetin, both rich in phenolic and flavonoid structures capable of donating electrons or hydrogen atoms to neutralize DPPH radicals. The marginal reduction in activity compared to the standard may result from intermolecular interactions within the nanogel matrix or partial entrapment affecting immediate availability of active compounds.

Anti – Inflammatory Activity

To evaluate the in vitro anti-inflammatory potential of EBl, the previously reported technique was slightly modified and the inhibition in albumin denaturation approach was employed. Measurements of absorbance were made using a UV spectrophotometer at 660 nanometer after letting it come to room temperature Using the following formula, the % inhibition of protein denaturation was calculated. In the IC50 data, aspirin was identified as the positive control and DMSO as the negative control. These findings were presented.[25]

Percentage Inhibition(%) = $\frac{\text{A Control} - \text{A sample}}{\text{A Control}}$

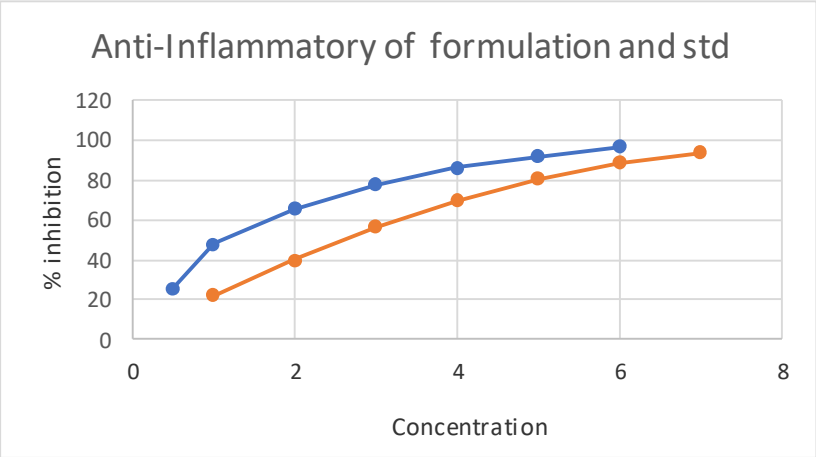

Fig : Anti- inflammatory of formulation and Standard

The anti-inflammatory activity increased in a concentration-dependent manner for both the standard and the formulation. The standard exhibited higher % inhibition at all concentrations, reaching a maximum of ~96%, while the formulation showed slightly lower activity (~93%) at the highest concentration.

The curcumin–quercetin loaded nanogel exhibited a significant, concentration-dependent increase in anti-inflammatory activity. The optimized formulation showed inhibition values comparable to the standard at higher concentrations, indicating effective drug release and synergistic action. The enhanced activity can be attributed to improved solubility, stability, and bioavailability of curcumin and quercetin within the nanoscale delivery system, facilitating better penetration at the inflammatory site [23, 24]. Although slightly less potent than the standard, the formulation demonstrates promising therapeutic potential as an alternative anti-inflammatory system.

CONCLUSION

Curcumin and quercetin were used in the current study's successful creation and assessment of a herbal nanogel formulation for the management of rheumatoid arthritis pain. A straightforward and economical procedure was used to Formulate the nanogel formulation, and each batch's physicochemical characteristics—such as pH, viscosity, spreadability, and drug content—were assessed. Optimized match showed the most promising qualities among the batches, suggesting that it could be a stable and successful topical formulation. With its appropriate pH, viscosity, and spreadability, the optimized match ensured patient compliance and simplicity of application. The medication content study also showed that

the active components were distributed uniformly, guaranteeing constant therapeutic efficacy. Additionally, the formulation's herbal bioactive ingredients, quercetin and curcumin, are well-known for their analgesic, anti-inflammatory, and antioxidant qualities. Making possibilities for rheumatoid arthritis pain management. Overall, the herbal nanogel that was formulated, and the optimized batch, shows practical, safe, and effective topical formulation for the treatment of rheumatoid arthritis discomfort.

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