

Evaluation of Cubosomal Gel as a Topical Delivery System for Rheumatoid Arthritis

*Ramjivan Singh¹, Shailesh Sharma², Shrishti Singh³

¹Research Scholar, Shyam University, Dausa, Rajasthan

²Research Scholar, Shyam University, Dausa, Rajasthan

³Maharishi Arvind College of Pharmacy, Rajasthan

*Corresponding Author

Email ID rjsingh101094@gmail.com

ABSTRACT

A chronic inflammatory disease, rheumatoid arthritis (RA) significantly impacts synovial joints and is associated with high socioeconomic costs, increased mortality, and progressive disability. Advances in nanotechnology, particularly the use of cubosomes, enhance drug delivery and extend drug availability in polymeric gels, providing potential benefits over standard treatments. **Aim:** To develop and evaluate a drug-loaded cubosomal gel for topical delivery in the management of rheumatoid arthritis. **Materials and method:** A drug-loaded cubosomal gel was prepared using Carbopol 940 (1% w/v) as the gelling agent and incorporated with cubosome dispersion at a 2:1 dispersion-to-gel ratio (w/w). The formulation was evaluated for pH, viscosity, spreadability, *in vitro* drug diffusion, and release kinetics using zero-order, first-order, Hixson–Crowell, and Korsmeyer–Peppas models. *In vivo* skin-irritation study in Wistar rats according to the Draize method. Anti-arthritis activity was evaluated in a CFA-induced arthritis model using paw edema and arthritic scoring, with marketed diclofenac gel used as the standard treatment. **Results:** The cubosomal gel showed a pH of 7.29, viscosity of 5746.44 cP, and spreadability of 17.105 g•cm/sec, demonstrating favorable characteristics for topical application. *In vitro* drug-release analysis indicated strong alignment with the Hixson–Crowell model ($R^2 = 0.994$), suggesting that drug release is mainly related to changes in surface area and particle size. Tolerability was confirmed by a low Primary Irritation Index of 0.1667. In a CFA-induced arthritis model, the gel significantly reduced paw edema, with thickness decreasing to 4.873 ± 0.229 mm by day 28, compared to 8.086 ± 1.127 mm in the disease-control group and 4.72 ± 0.412 mm for the marketed diclofenac. The arthritic score improved from 3.083 ± 0.381 in controls to 1.166 ± 0.288 after treatment, contrasted with 0.750 ± 0.250 for marketed diclofenac gel. **Conclusion:** The developed cubosomal gel demonstrated satisfactory physicochemical properties, sustained drug-release behaviour, negligible dermal irritation, and substantial anti-arthritis activity in CFA-induced arthritis.

Keywords: Rheumatoid arthritis; Cubosomal gel; Anti-arthritis activity; Skin irritation; Diclofenac

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Introduction

A chronic, systemic inflammatory illness that mostly affects synovial joints, rheumatoid arthritis (RA) causes enormous socioeconomic burdens, increased death rates, and progressive disability (Negi et al., 2024). RA is caused by the rapid infiltration of macrophages, neutrophils, chondrocytes, and fibroblasts into the synovial space. These cells produce pro-inflammatory mediators such as TNF- α , ROS, prostaglandins, interleukins, proteases, and vasoactive amines (Derksen et al., 2017). Disease progression is further complicated by systemic symptoms, such as infection, glucocorticoid-induced osteoporosis (GIOP), and involvement of extra-articular organs such as the heart, lungs, neurological system, and musculoskeletal system (Wu et al., 2022). According to the 2019 Global Burden of Disease (GBD) study, an estimated 18 million people worldwide suffer from RA (Cai et al. 2023). Nanotechnology emerged as a promising solution to counteract the major setbacks of

traditional dosage forms. Cubosomes are nanoparticles, exhibiting characteristic cubic structures, and formed by the emulsification of amphiphilic lipids in water in the presence of a stabilizer, to impart colloidal stability (Eldeeb et al., 2019). Cubosomes' topical applicability can be further enhanced by including them into a polymeric gel, which increases their viscosity, lengthens their residence duration at the application site, and makes administration easier. (Praveen et al., 2021). Gels based on carbopol offer appropriate rheological properties and can be a useful medium for cubosomal dispersions (Kumari et al., 2025). In addition to offering continuous medication release and minimizing needless systemic exposure, such a combination approach may improve local drug availability (Almohari et al., 2022).

Thus, the goal of this study is to create and assess a drug-loaded cubosomal gel for topical rheumatoid arthritis treatment.

1. Materials and method

1.1 Materials and chemical used

Tofacitinib-loaded optimized cubosomal dispersion obtained from our previously communicated formulation study was used for gel preparation. Carbopol 940, propylene glycol, glycerine, methyl paraben, propyl paraben, and triethanolamine were used for preparation of the cubosomal gel, with distilled water as the aqueous vehicle. Complete Freund's adjuvant (CFA) was used for induction of experimental arthritis, and marketed 1% w/v diclofenac gel (FASTAC-DS) served as the standard treatment. All chemicals and reagents were of analytical grade.

1.2 Preparation of Gel formulation

The cubosomal gel was prepared by adding a weighed amount of Carbopol 940 (1% w/v), which was dispersed in distilled water containing methyl paraben, propyl paraben, and glycerine, and allowed to hydrate overnight. Propylene glycol was then incorporated to adjust the consistency of the gel. The prepared gel was further mixed with an appropriate amount of cubosomes dispersion in a ratio of 2:1 (dispersion: gel, w/w). The mixture was stirred for 5 minutes to obtain a uniform cubosomal gel (Barreiro-Iglesias et al., 2003).

Table 1: Composition of Gel

Ingredients	Quantity
Cubosome dispersion	20ml
Carbopol 940 (gm)	1gm
Propylene glycol	10 ml
Methyl paraben	0.2 ml
Propyl paraben	0.1 ml
Glycerine	1 ml
Triethanolamine	Qs
Water	100ml

2.3 Characterization of Gel Formulation

2.3.1 Physical Evaluation:

Physical parameters such as color and appearance were evaluated.

2.3.2 Spreadability:

Spreadability was determined by the apparatus which consists of a wooden block, which was provided by a pulley at one end (Pounikar et al., 2012).

2.3.3 Viscosity:

Viscosity of gel was determined by using Brookfield rotational viscometer at 50 rpm using spindle no.64. The viscosity determination of samples was repeated three times.

2.3.4 pH:

The pH of various gel formulations were determined by using digital pH meter. The measurement of pH of each formulation was carried out in triplicate and the average values are represented. The pH of dispersions was measured using pH meter (Majumdar and Dave, 2013).

2.3.5 In vitro drug diffusion study

The *in vitro* drug diffusion study was carried out using the diffusion cell method. The withdrawn samples were analyzed at 294 nm using a UV spectrophotometer (Sarika et al., 2021 & Praveen et al., 2024).

• In vitro drug release kinetics

The drug release kinetics of cubosomal gel were determined by plotting the following kinetic models, using the data collected from *in vitro* release studies (zero order, first order, and Hixson Crowell equations). The mechanism of drug release was determined by using the Korsmeyer-Peppas equation (Paarakh et al., 2018).

2.4 In-vivo Skin irritation study

2.4.1 Animals and treatment

Adult albino Wistar rats, weighing 150-180g, were obtained from the Pinnacle Biomedical Research Institute's in-house facility in Bhopal, India. They were acclimatized for 7 days, fed standard rat feed from Keval Sales Corporation, Vadodara, and provided with water ad libitum throughout the study.

2.4.2 Activity II: In-vivo skin irritation study (OECD 404)

The dorsal area of each rat was shaved carefully without damaging the skin 24 hours before application. For testing, TF Gel was applied separately to the intact skin of designated animals. Approximately 0.5 g of each formulation was uniformly applied to a 2 cm × 2 cm area and gently covered with a gauze patch to prevent removal. The patches were secured and left in place for 4 hours, after which the residual formulation was removed by gentle wiping with a saline-moistened cotton swab. Animals were observed at 1, 24, 48, and 72 hours post-application for any signs of erythema, edema, or other visible skin reactions. Skin reactions were scored according to the Draize scoring system, and the Primary irritation index (PII score) was calculated for each formulation. The study was conducted in accordance with ethical guidelines for the care and use of laboratory animals.

2.4.3 Activity: In-vivo Anti- arthritis Activity

After an acclimatization period of seven days, animals were randomly divided into four groups (n

= 6/group) as normal, induced, standard and Test treatment group.

Group I was kept as normal untreated control (5ml/kg saline),

Group II: Disease control (0.2 mL CFA-induced arthritis, (CFA, Sigma Aldrich))

Group III: Standard treatment (Marketed 1%w/v Diclofenac gel, FASTAC-DS)

Group IV: Test treatment (TF Cubosomal Gel 1% w/v)

2.4.4 Paw edema

Paw diameter was taken on the 0, 1st, 3rd, 5th, 7th, 14th, 21st and 28th day by using electronic digital calipers.

2.4.5 Arthritic score

The morphological feature of the arthritis like redness, swelling and erythema was monitored by set visual criteria as follows: normal paw = 0, mild swelling and erythema of digits = 1, swelling and erythema of the digits = 2, severe swelling and erythema = 3, gross deformity and inability to use the limb = 4.

2.4.6 Histopathology

The Paw tissues were immersed in 10% formalin solution for histopathological examination. Stained slides were dehydrated in various ascending grades of alcohol, cleared in xylene, and mounted in Canada balsam. Sections were viewed microscopically.

2.4.7 Statistical Analysis

Results are provided as Mean±SD (n=6). Results were analyzed statistically using one-way analysis of variance (ANOVA) followed by Bonferroni t-test. P < 0.05 was considered as level of significance while comparison between groups.

3 Results

3.1 Evaluation of cubosomal gel for appearance, pH, viscosity and spreadability

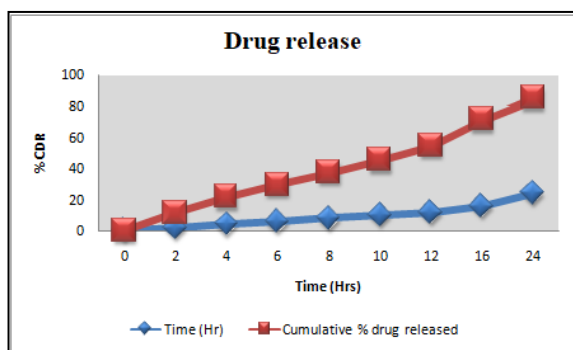
The pH of the gel was found to be 7.29, which is close to neutral. The viscosity of the cubosomal gel was measured as 5746.44 centipoises, indicating a moderately high consistency. The spreadability of the gel was found to be 17.105 g·cm/sec, with a spreading time of 19 seconds. This suggests that the gel possesses good spreading characteristics, allowing it to be easily applied over the skin with minimal effort.

3.1.1 *In-vitro* release study by drug diffusion method

Table 2: *In-vitro* release study

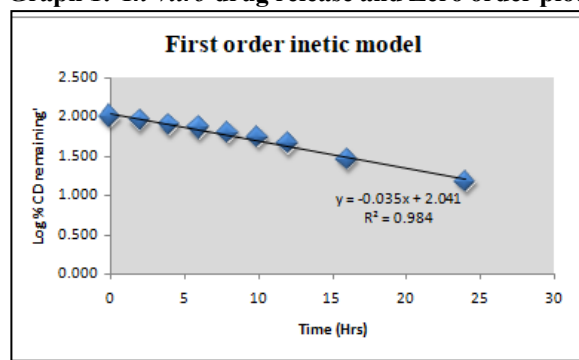
Time (hrs)	Cumulative release (%)	Standard deviation	Log concentration	Log time	Log cumulative release	Concentration	Weight
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	% drug released	initial drug present	error term	average % drug remaining	mean	average % drug released	release	of % drug remaining (wt)	
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	11.54	88.46	1.414	1.947	0.301	1.062	11.54	4.456	0.186
4	21.87	78.13	2.000	1.893	0.602	1.340	21.87	4.275	0.367
6	29.47	70.53	2.449	1.848	0.778	1.469	29.47	4.132	0.510
8	37.58	62.42	2.828	1.795	0.903	1.575	37.58	3.967	0.675
10	45.37	54.63	3.162	1.737	1.000	1.657	45.37	3.794	0.848
12	54.61	45.39	3.464	1.657	1.079	1.737	54.61	3.567	1.075
16	71.39	28.61	4.000	1.457	1.204	1.854	71.39	3.058	1.584
24	85.27	14.73	4.899	1.168	1.303	1.931	85.27	2.451	2.101

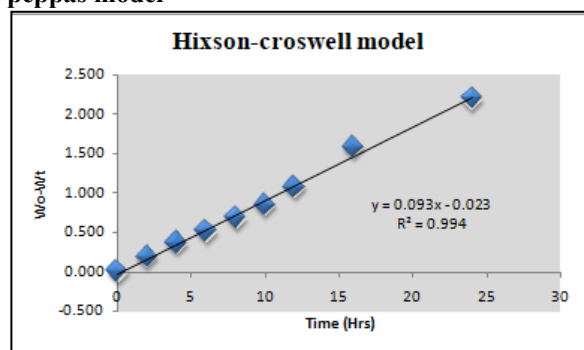
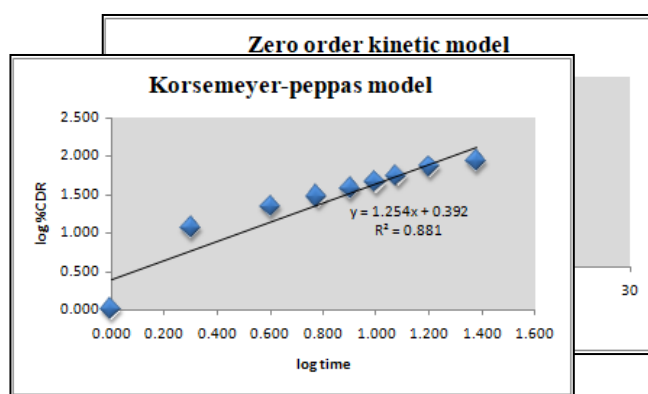


					8				9
					0				1

Graph 1: In-vitro drug release and Zero order plot



Graph 2: In-vitro Zero order plot and Korsmeyer-peppas model



Graph 3: Hixson-Crowell plot

The drug release kinetics of the TF gel formulation were assessed using various mathematical models: zero-order, first-order, Korsmeyer–Peppas, and Hixson–Crowell. The Hixson–Crowell model demonstrated the highest regression coefficient ($R^2 = 0.994$), indicating it best describes the drug release mechanism, which is influenced by changes in surface area and particle size during dissolution. The first-order model also showed a significant regression value ($R^2 = 0.984$), suggesting the release rate is concentration-dependent, decreasing over time as the drug concentration diminishes.

3.2 In-vivo Skin Irritation Study of Test Sample TF Gel

The skin irritations study of TF Gel a Primary Irritation Index (PII) of 0.1667, indicating very negligible irritation as per Draize classification.

Table 3: Skin irritation studies of TG Gel using Draize scoring

Rat No.	Erythema score				Edema score				PI Score	PII Index
	1	2	4	7	1	2	4	7		
	h	h	h	h	h	h	h	h		
A1	0	0	0	0	0	0	0	0	0.0	0.16
A2	0	0	0	1	0	0	0	0	0.125	
A3	0	0	1	2	0	0	0	0	0.375	

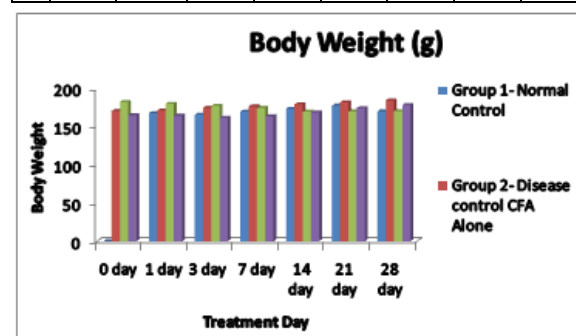
3.3 In-vivo Anti-arthritis study**3.3.1 Body Weight Assessment**

Animals treated with TF Cubosomal Gel showed an improvement in body weight indicating good tolerability of the formulation. The standard diclofenac-treated group maintained a comparatively stable body weight profile during the treatment period.

Table 4: Body Weight (g) of rats at 0, 1,3,7,14,21 and 28 day.

S. No.	Group	Body Weight (g)						
		0 day	1 day	3 day	7 day	14 day	21 day	28 day
I	Group 1- Normal Control	170	16	16	17	17	17	17
		.6±	8.3	6.3	0.3	4.0	8.3	0.6
		3.0	±2.	±4.	±1.	±1.	±3.	±3.
		55	08	04	52	00	05	05
I	Group 2- Disease control CFA Alone	171	17	17	17	18	18	18
		.3±	2.0	5.3	7.3	0.0	2.6	5.0
		2.5	±3.	±4.	±3.	±6.	±8.	±4.
		16	46	93	05	55	14	00
			4	2	5	7	4	0

I	I	e						
I	I	Group 3- Standard group Diclofenac gel (Marketed)	183	18	17	17	17	17
			.0±	0.6	8.0	5.3	0.3	0.6
			19.	±1	±1	±2	±2	±2
			92 ^{ns}	9.6	9.9	4.6	2.8	1.9
				5	7	6	5	3
I	V	Group 4- Treated with Cubosomal Gel	165	16	16	16	16	17
			.6±	5.0	2.3	4.3	9.3	5.0
			1.5	±1.	±1.	±2.	±2.	±2.
			27 ^{ns}	73	52	51	08	00
				2	7	6	1	0

**Graph 4: Body Weight Assessment****3.3.2 Paw Edema Analysis**

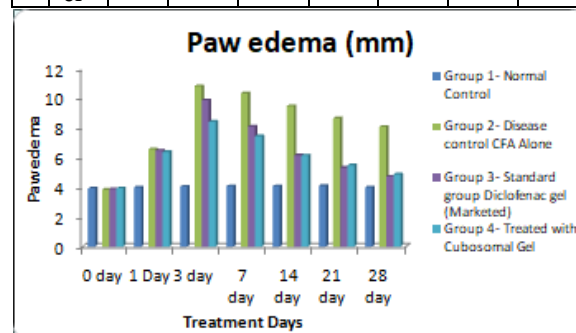
Sub plantar injection of CFA produced a marked increase in paw thickness in the disease control group, treatment with TF Cubosomal Gel significantly

reduced paw edema and the reduction was comparable to the marketed diclofenac gel, which decreased paw thickness to 4.72 ± 0.41 mm by the end of the study, demonstrating potent anti-inflammatory activity.

Table 5: Paw edema (mm) of rats at 0, 1, 3, 7, 11, 14, 21 and 28 day

S. No	Group	Paw edema (mm)						
		0 day	1 Day	3 da	7 da	14 da	21 da	28 da
I	Group 1- Normal Control	3.92 ± 0.040	3.99 ± 0.066	4.05 ± 0.094	4.07 ± 0.082	4.08 ± 0.089	4.09 ± 0.092	3.96 ± 0.066
II	Group 2- Disease control CFA Alone	3.84 ± 0.095	6.57 ± 0.190**	10.83 ± 0.715***	10.33 ± 0.236***	9.48 ± 0.108***	8.65 ± 0.203***	8.06 ± 0.127***
III	Group 3- Standard diclofenac	3.87 ± 0.070	6.48 ± 0.357**	9.87 ± 0.291***	8.09 ± 0.206**	6.15 ± 0.625***	5.32 ± 0.451*	4.72 ± 0.12 ^{ns}

gel (Marketed)							
I V	Group 4- Treated with Cubosomal Gel	3.92 ± 0.032	6.38 ± 0.257***	8.43 ± 0.300***	7.45 ± 0.147***	6.15 ± 0.317***	5.49 ± 0.280**



Graph 5: Paw edema

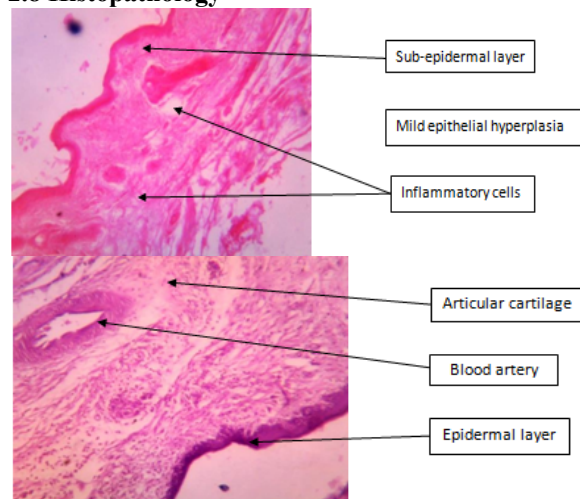
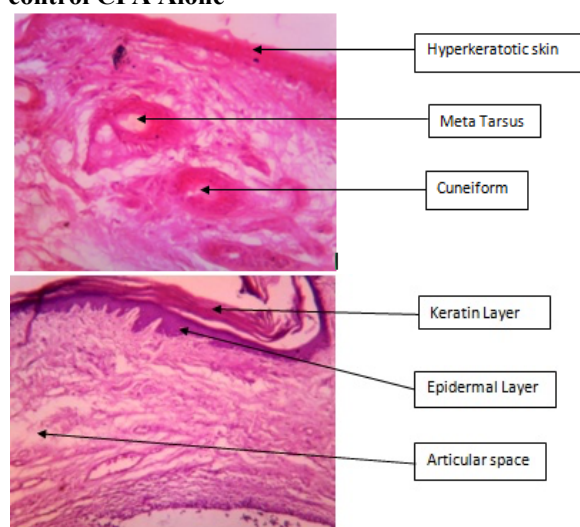
3.3.3 Arthritic score

The disease control group had an arthritic score of 3.08 ± 0.38 , while the normal control group showed no arthritis. Treatment with diclofenac gel significantly reduced the score to 0.75 ± 0.25 , and TF Cubosomal Gel also reduced the score to 1.17 ± 0.29 , demonstrating effective suppression of arthritis progression.

Table 6: Effect of Cubosomal Gel sample on arthritis index score in CFA induced arthritis rats

S. No	Group	Arthritic Score
I	Group 1- Normal Control	0.00±0.00
II	Group 2- Disease control CFA Alone	3.083±0.381***
III	Group 3- Standard	0.750±0.250***

	group Diclofenac gel (Marketed)	
IV	Group 4- Treated with Cubosomal Gel	1.166±0.288***

Graph 6: Arthritic score**2.8 Histopathology****Group I Normal control and Group II Disease control CFA Alone****Group III: Standard group Diclofenac gel (Marketed) and Treated with Cubosomal Gel****4. Discussion**

The present study demonstrated the successful development of a drug-loaded cubosomal gel with suitable characteristics for topical application. The formulation exhibited a pH of 7.29, indicating acceptable compatibility for dermal administration. The viscosity (5746.44 cP) and spreadability (17.105 g·cm/sec) with a spreading time of 19 s indicated an appropriate balance between formulation consistency and ease of application. These characteristics are important for maintaining the formulation at the application site while allowing uniform distribution

over the skin. The *in vitro* release study demonstrated sustained drug release from the cubosomal gel. The release profile showed the best fit with the Hixson–Crowell model ($R^2 = 0.994$), followed by the first-order model ($R^2 = 0.984$), suggesting that changes in the surface characteristics of the drug-containing system contributed to the release process. The cubosomal structure, together with the Carbopol gel matrix, may have contributed to controlled drug liberation by regulating drug diffusion from the formulation. The formulation also demonstrated good dermal tolerability, with a Primary Irritation Index of 0.1667, indicating negligible irritation. This finding supports the suitability of the developed formulation for topical administration. In the CFA-induced arthritis model, the cubosomal gel produced a marked reduction in inflammatory paw edema. On day 28, paw thickness decreased to 4.873 ± 0.229 mm compared with 8.086 ± 1.127 mm in the disease-control group and 4.72 ± 0.412 mm in the marketed diclofenac group. Similarly, the arthritic score decreased from 3.083 ± 0.381 in the disease-control group to 1.166 ± 0.288 following treatment with the cubosomal gel, compared with 0.750 ± 0.250 for marketed diclofenac gel. These findings indicate substantial attenuation of CFA-induced inflammatory manifestations and demonstrate an anti-arthritic effect comparable to the marketed formulation.

Overall, the developed cubosomal gel exhibited satisfactory physicochemical properties, sustained drug release, good skin tolerability, and significant anti-arthritic activity, indicating its potential as a topical delivery system for the management of rheumatoid arthritis.

4. Conclusion

The present study concludes that the developed cubosomal gel provides a suitable approach for topical delivery in rheumatoid arthritis. The formulation demonstrated acceptable topical characteristics, controlled drug-release behaviour, good dermal tolerability, and effective attenuation of CFA-induced arthritic manifestations. The findings support the potential of cubosomal technology as an effective platform for improving localized anti-arthritic therapy and provide a basis for further investigation of cubosomal systems in the topical management of rheumatoid arthritis.

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