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Research

Formulation and Evaluation of Curcuminoids and Flurbiprofen Granules Loaded Capsule and Its *In-Vitro* Anti-Rheumatic Activity

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by joint pain, stiffness, and progressive cartilage destruction. The present study aims to formulate and evaluate curcuminoids and flurbiprofen granules loaded capsules for their potential anti-rheumatic activity. Curcuminoids, derived from Curcuma longa, exhibit potent anti-inflammatory and antioxidant properties but suffer from poor bioavailability. Flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID), effectively alleviates RA symptoms but is associated with gastrointestinal side effects. To overcome these limitations, this study explores the development of a combination formulation to improve therapeutic efficacy. The granules were prepared using the wet granulation method and encapsulated in hard gelatin capsules. The physicochemical properties of the formulations were assessed, including Fourier Transform Infrared Spectroscopy (FTIR) for compatibility studies, solubility analysis, and in-vitro dissolution studies to determine the drug release profile. The anti-rheumatic potential of the formulation was evaluated using *in-vitro* models, including free radical scavenging (DPPH assay) and albumin denaturation inhibition assays to assess anti-inflammatory properties. The optimized formulation F4 exhibited significant drug release and anti-rheumatic activity, suggesting its potential as a novel therapeutic approach for RA management.

Keywords: Curcuminoids, Flurbiprofen, Granules, Capsules, Anti-rheumatic Activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects synovial joints, leading to chronic inflammation, pain, and progressive cartilage destruction. It is characterized by immune-mediated damage to synovial tissues, ultimately resulting in joint deformities and disability.[1,2] Current treatment strategies include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-

rheumatic drugs (DMARDs). However, long-term use of these treatments is associated with significant side effects, including gastrointestinal complications, hepatotoxicity, and cardiovascular risks. [1,3,4]

Curcuminoids, derived from turmeric (Curcuma longa), have been extensively studied for their potent anti-inflammatory, antioxidant, and immunomodulatory properties. Despite their promising therapeutic potential, curcuminoids exhibit poor bioavailability due to rapid metabolism, low water solubility, and limited absorption.[5] Flurbiprofen, a commonly used NSAID, provides effective pain relief in RA but is associated with gastrointestinal irritation.[6] Combining curcuminoids with flurbiprofen may enhance anti-rheumatic efficacy while reducing adverse effects.

This study aims to formulate and evaluate granules loaded with curcuminoids and flurbiprofen, encapsulated in hard gelatin capsules, to improve drug solubility, release profile, and therapeutic effectiveness.

MATERIALS AND METHODS

The active pharmaceutical ingredients Curcumin and Piperine were procured from Yucca Enterprises, Mumbai, India, Flurbiprofen was procured from Ulfcar Chemicals Pvt. Ltd. Faridabad, India. To enhance solubility and stability, Beta-cyclodextrin was procured from A B Enterprises, Mumbai and Eudragit L100 from Brisben Chemicals, Mumbai. Additional excipients such as Croscarmellose sodium and Starch were procured from Nice Chemical Pvt. Ltd.Kerela, India along with Lactose from Thermo Fisher Scientific Pvt. Ltd. Bengaluru, India. The analytical and formulation processes utilized high-precision equipment, including a Shimadzu AX200 electronic balance for accurate weighing, a Shimadzu IR Spirit spectrometer for infrared analysis, and a Shimadzu 1800 UV-visible spectrophotometer for spectroscopic evaluation.

Methods

Pre-Formulation Studies

Organoleptic Properties

The physical characteristics such as state, colour, odour, and taste of the raw materials were observed.[7]

Melting Point Determination

The melting point of Curcumin, Piperine, and Flurbiprofen was determined by the capillary tube method using a Thiele tube.[7]

Solubility Studies

The solubility of Curcumin, Piperine, and Flurbiprofen was determined in methanol, distilled water, 0.1N HCl, and PBS 7.4 buffer. Excess drug was added to 10 ml of the solvent, shaken for 15 min, filtered, and analysed spectrophotometrically.[7, 8]

Development of Calibration Curve[7, 8, 9, 10, 11]

The standard calibration curve was constructed using 0.1N HCl and PBS 7.4 buffer. Stock solutions were prepared, and serial dilutions (5-30 µg/mL) were made. Absorbance was recorded at 423.5 nm (Curcuminoids), 342.5 nm (Piperine), and 246 nm (Flurbiprofen).

Drug-excipient compatibility study

FTIR can be used to investigate and predict any physiochemical interaction between different excipient. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and excipient. A physical mixture of drug and excipient were prepared. It was scanned from 4000 to 400 cm^{-1} in a FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and physical mixture and peak matching was done to detect any appearance or disappearance of peaks.[12]

Formulation of Granules

Granules containing Curcuminoids, Piperine, and Flurbiprofen were prepared using the wet granulation technique with Beta-cyclodextrin as a complexing agent, Eudragit L100 as a polymer, and Croscarmellose sodium as a super disintegrant.[13, 14] (Table 1)

Table 1: Composition of granules

Ingredients	Curcuminoid granules			
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Curcuminoids	200	200	200	200
β- cyclodextrin	200 (1:1)	200 (1:1)	400 (1:2)	400 (1:2)

Piperine	5	5	5	5
Croscarmellose	35 (5%)	70 (10%)	35 (5%)	70 (10%)
Lactose	246	211	46	11
Magnesium stearate	7	7	7	7
Talc	7	7	7	7
		Flurbiprofen granules		
Flurbiprofen	100	100	100	100
Eudragit L100	10 (4%)	15 (6%)	20 (8%)	25 (10%)
Lactose	135	130	125	120
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5
Total	**950mg**	**950mg**	**950mg**	**950mg**

Post-Formulation Studies

Weight Variation Test

Twenty capsules were randomly selected, and individual weights were compared with the average weight. Capsules were considered acceptable if they contained not less than 95% and not more than 110% of the stated amount of active ingredient.[8,15]

Drug Content Estimation

Ten capsules were randomly selected. The granules were removed, dissolved in methanol, and diluted to a suitable concentration. The absorbance was measured at respective wavelengths using a UV-visible spectrophotometer.[8,15]

***In-Vitro* Dissolution Studies**

Dissolution studies were conducted using a USP Type I (Basket type) dissolution apparatus. Capsules were placed in 900 ml of 0.1N HCl (2 hrs) followed by PBS 7.4 pH (10 hrs) at 37 ± 0.5°C and 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed at respective wavelengths.[15] (Table 2)

Table 2: Dissolution Parameters

Parameter	Condition
Apparatus	USP Type I (Basket)
Dissolution Medium	0.1N HCl (2 hrs), PBS 7.4 pH (10 hrs)
Temperature	37 ± 0.5°C
Rotation Speed	50 rpm
Sample Volume	5 mL

***In-Vitro* Anti-Rheumatic Activity Studies**

DPPH Free Radical Scavenging Assay

The antioxidant activity was determined using the DPPH assay. Different concentrations (50-250 µg/ml) of the formulation were incubated with 2.4 ml of DPPH solution and 1.6 ml of ethanol. Absorbance was measured at 517 nm, and percentage scavenging was calculated.[16, 17]

Equation: DPPH Scavenged (%) = [(A0 - A1)/A0] × 100

Where A0 = absorbance of control and A1 = absorbance of test solution.

Albumin Denaturation Method

The anti-inflammatory activity was evaluated by incubating Bovine Serum Albumin (BSA) with the formulation at different concentrations (50-250 µg/ml). The solution was heated at 37°C for 15 min, cooled, and absorbance was measured at 660 nm.[18, 19, 20]

Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean ± SD. Statistical significance was determined using one-way ANOVA, with $p < 0.05$ considered significant.

RESULTS AND DISCUSSION

Pre-Formulation Studies

Organoleptic Properties

The organoleptic properties of Curcuminoids, Piperine, and Flurbiprofen were assessed and compared with standard reference values. Curcuminoids appeared as an orange-yellow crystalline powder with an aromatic odour and a bitter taste, whereas Piperine was light green with a pungent odour. Flurbiprofen was a white amorphous powder with a pungent odour. These findings were in agreement with reported literature, confirming the purity and identity of the drugs. (Table 3)

Table 3: Organoleptic Properties of Selected Drugs

Drug	Appearance	Odour	Taste
Curcuminoids	Orange-yellow crystalline powder	Aromatic	Bitter
Piperine	Light green crystalline powder	Pungent	Spicy
Flurbiprofen	White amorphous powder	Pungent	Slightly bitter

Melting Point Determination

The melting points of the pure drugs were evaluated to confirm their stability and purity. Curcuminoids, Piperine, and Flurbiprofen exhibited melting points of 183°C, 130°C, and 110°C, respectively, which aligned with standard literature values.(Table 4)

Table 4: Melting Points of Selected Drugs

Drug	Observed Melting Point (°C)	Standard Melting Point (°C)
Curcuminoids	183	183
Piperine	130	130
Flurbiprofen	110	110

Solubility Studies

The solubility profiles of the three compounds were assessed in different solvents. All three drugs were freely soluble in methanol, sparingly soluble in pH 7.4 PBS, and insoluble in distilled water. This indicates the need for formulation strategies to enhance bioavailability.

Standard calibration curve

The R^2 value of Curcuminoids, piperine and flurbiprofen in 0.1N HCL and PBS 7.4 pH was found to be 0.9984 and 0.9991, 0.9995 and 0.9973, 0.998 and 0.9983 respectively.

FTIR Analysis

In F4 formulation the structural functional groups in the FTIR showed prominent peaks associated with ketone, hydroxy, methoxy, amine and fluorine groups are with the reference IR data. From that results we confirmed that Curcuminoids granules and Flurbiprofen granules are within the IR references data.

***In-Vitro* Drug Release Studies**

The dissolution profiles of Curcuminoids, Piperine, and Flurbiprofen formulations (F1-F4) were assessed using the USP Type I Basket method. (Table 5, Fig 1)

Table 5: Drug Release Profile of Formulations (F1-F4)

	% Cumulative drug release of Flurbiprofen			
Time (hrs.)	F1	F2	F3	F4
0	0	0	0	0
3hr	35.77	21.16	17.53	11.063
4hr	47.54	30.45	25.02	18.35
6hr	58.81	48.68	43.61	37.27
8hr	98.92	72.56	60.48	56.08
10hr	-	98.04	98.89	78.3
12hr	-	-	-	99.12

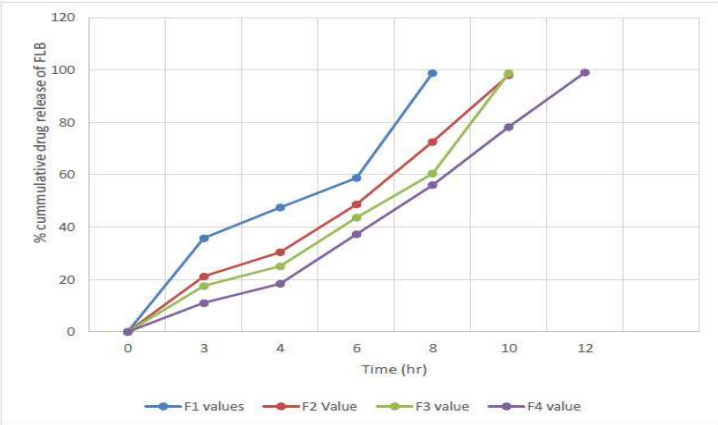

Fig 1: *In-Vitro* Drug Release Profile of (F1-F4)

The cumulative drug release of Flurbiprofen varied across formulations: F1 achieved 98.92% release at 8 hours, F2 and F3 reached 98.89% at 10 hours, and F4 exhibited 98.04% release at 12 hour.

***In-Vitro* Antioxidant Activity**

The antioxidant activity of the formulations was evaluated using the DPPH free radical scavenging assay. (Table 6, 7) (Figure 2).

Table 6: Percentage free radical scavenging activity of DPPH

	Percentage radical scavenge activity (% RSA)	
Concentration	**Standard**	**F4**
50µg/ml	14.51	4.10
100µg/ml	31.23	26.18
150µg/ml	57.09	44.47
200µg/ml	76.34	60.88
250µg/ml	95.26	76.02

Absorbance of control: 0.317

Table 7: IC_{50} of standard and F4

Types	IC_{50}
Standard	128.2µg/ml
F4	153.8µg/ml

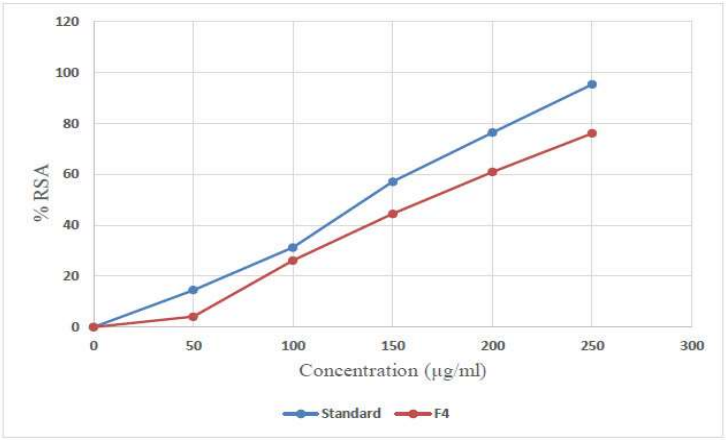

Fig 2: Percentage (%) DPPH scavenging of standard and F4

The *in-vitro* Antioxidant activity along with IC_{50} is summarized in table No. 6, 7. The percentage inhibition and antioxidant concentration were supported by straight line equation and R^2 value of F4 and standard. F4 showed percentage inhibition from 4.10 to 76.02 and standard drug presented percentage inhibition from 14.51 to 95.26 at different concentration 50, 100, 150, 200 and 250µg/ml. The IC_{50} of F4 and standard was found to be 153.8µg/ml and 128.2µg/ml respectively. Lower IC_{50} value indicates higher antioxidant value. F4 showed moderate antioxidant activity with percentage inhibition of 76.02 at 250µg/ml when compared to standard with percentage inhibition of 95.26 at 250µg/ml.

***In-Vitro* Anti-Inflammatory Activity**

The anti-inflammatory potential of the formulations was evaluated using the albumin denaturation method. (Table 8,9) (Figure 3)

Table 8: Percentage inhibition of Albumin denaturation

	Percentage inhibition	
Concentration	Standard	Formulation
50µg/ml	12.5	21.45
100µg/ml	27.05	36.5
150µg/ml	42.35	56.25
200µg/ml	59.64	77.12
250µg/ml	75.52	93.74
R^2	0.9974	0.998

Table 9: IC_{50} of standard and F4

Type	IC_{50}
Standard	131.66µg/ml
F4	170.28µg/ml
Absorbance of control: 0.08	

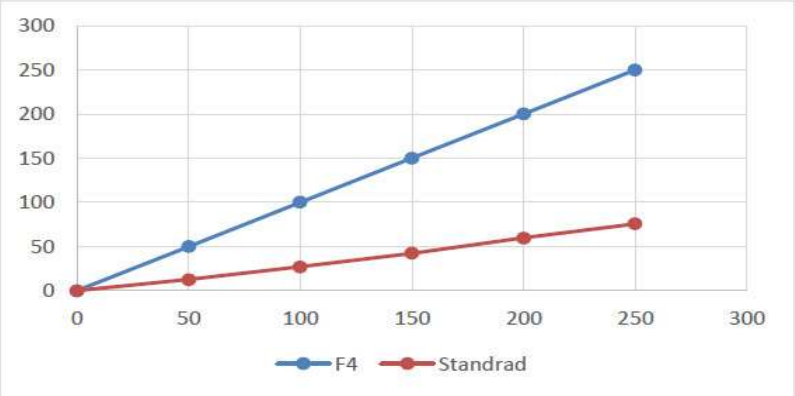

Fig 3: Percentage inhibition of albumin denaturation of standard and F4

The results indicated that formulation F4 exhibited significant inhibition of protein denaturation (93.74% at 250 µg/ml), compared to the standard (Aspirin) with 75.52% inhibition at the same concentration. The IC50 values for F4 and the standard were found to be 170.28 µg/ml and 131.66 µg/ml, respectively, confirming the potent anti-inflammatory activity of the optimized formulation.

CONCLUSION

The formulated curcuminoids and flurbiprofen granules loaded capsules exhibited promising physicochemical properties, sustained drug release, and potent *in-vitro* anti-rheumatic activity. The combination of curcuminoids with flurbiprofen offers a novel approach to RA management, potentially improving therapeutic outcomes while minimizing adverse effects. Further *in-vivo* studies and clinical trials are warranted to validate these findings and explore their clinical applications.

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