DESIGN, DEVELOPMENT & EVALUATION OF *Curcuma longa, Zingiber Officinale* AND *Alllium sativum*- A POLYHERBAL PHARMACEUTICAL GEL FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid Arthritis (RA) is an auto-immune disease which triggers degeneration of cartilage and is accompanied by pain, rigidity, and synovial inflammation. Many synthetic and semi synthetic drugs are regarded as a standard of care, considering there is no cure but due to their side effects patient restrict themselves from continue the drug therapy. According to currently available literature, certain herbs like *Curcuma longa*, *Zingiber officinale* and *Allium sativum* can aid in the treatment of such condition. Among other route of drug administration, because it avoids the gastrointestinal discomfort, first-pass effects, and metabolic breakdown linked to oral drug administration, the topical method of medicine delivery has gained popularity. Furthermore, they are less oily and may be readily removed from the skin's surface. The current study aimed to design a topical herbal gel incorporating herbs extract and to analyze its drug release potential. Three formulations were prepared via dispersion method and evaluated, each encompassing different proportion of herb extracts along with isopropyl alcohol, 1.5% Carbopol (940), tri-ethanol-amine, methyl paraben, propyl paraben, propylene glycol and sufficient amount of distill water. A number of characteristics were evaluated like colour, appearance, consistency, pH, Spreadability, Extrudability, and *in- vitro* drug release. The results obtained were encouraging and formulation containing *Curcuma longa*, *Allium sativum* and *Zingiber officinale* with 200mg of extract was found optimum for all parameters.

Keywords: RHEUMATOID ARTHRITTIS , AUTO-IMMUNE DISEASE, *Curcuma longa*, *Zingiber officinale*, *Allium sativum*, EXTRUDABILITY

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that mostly affects the joints and is a chronic disorder. Pain, inflammation, and heat are frequently the outcomes. Pain and stiffness generally grow worse after resting. The wrist and the metacarpophalangeal joint are the two

joints on either side of the body that are affected the most commonly. In addition to other body components, the illness can also impact the skin, eyes, lungs, heart, nerves, and blood. Low red blood cell counts, heart or lung inflammation, and other symptoms all indicate a problem. Fatigue and a fever are other potential symptoms. Typically, symptoms appear over the period of a few weeks or months. Although there is no known aetiology for rheumatoid arthritis, it is thought to be. [1]

Present therapy: The goal of drug therapy in RA are: Ameliorate pain, swelling and joint stiffness; prevent articular-cartilage damage and bony erosion and prevent deformity and preserve joint functioning. Although, ultimate objective of rheumatoid arthritis treatment is now to attain the lowest degree of arthritic disease activity and, if feasible, remission, while minimising joint damage and strengthening physical function and quality of life. The majority of these goals are accomplished through the combination of non-steroidal anti-inflammatory medications (NSAIDs), disease-modifying anti-rheumatic medicines, and physical therapy, corticosteroids, and biological agents, nevertheless a list of adverse impacts is also encompassed [2]

Proposed therapy: Herbal therapy offers another therapeutic option for RA, and a variety of medicinal plants are now being studied in order to generate a new medication. There is an urgent need to research the full therapeutic potential and any potential risks of these herbals with the objective to provide novel and safer therapy choices with fewer side effects. The recommended therapy is a gel formulation of the following three natural remedies for the treatment of rheumatoid arthritis:

- *Curcuma longa*
- *Allium sativum*
- *Zingiber officinale*

Curcumin, Demethoxy-curcumin, *and* Bisdemethoxy-curcumin are the major alkaloids found in *curcuma longa.* Reviews of the literature indicate that these alkaloids inhibit nuclear factor kappa-light-chain-enhancer of activated B cells, hence reducing the inflammatory response of tumour necrosis factor-alpha (TNF-alpha) stimulated human endothelial cells (NF-kB). [3]

Allium sativum contain Allicin, 1,2-vinyldithiin, allixin, S-allyl-cysteine, alliin, and other organo-sulfur components are phytoconstituents. Literature reviews demonstrate that these ingredients are beneficial because they reduce the expression of the HLA-B27 gene while reducing the synthesis of cytokines such interleukin-6, interleukin-8, and TNF-. .[4]

Zingiber officinale comprise the phytochemicals 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Reactive oxygen species (ROS) have a critical role in the pathophysiology of diseases like arthritis, according to several studies in the literature. .[5]

For local disorders, drug administration to the skin is an effective, focused therapy. The topical medicine distribution method has advantages over the oral administration method. This approach is becoming more popular since it eliminates first-pass effects, gastrointestinal discomfort, and metabolic deterioration. .[6] Topical formulations are preferred as a means of delivering medications despite the fact that they are less greasy and may be easily washed off the skin. Gels are three-dimensional matrices created by two interpenetrating systems where the colloidal gelator/gallant particles are evenly distributed throughout the dispersion medium

or solvent. Compared to other topical medicine administration methods, gels have a longer retention time at the target site.[7]

METHODS

- **Collection of plant powder:** The plant powder of *Curcuma longa, Zingiber officinale, Allium sativum* was procured and purchased from the Bhagvati Herbal and Healthcare, Vapi, Gujrat.

- **Extraction process**

    - ***Curcuma longa***: [10]
      A thimble containing 50 g of powdered turmeric powder had been employed to make the Soxhlet system for the extraction of Curcuma longa, and 250 ml of acetone was poured gradually. The extraction experiment was setup at 60 °C and was completed in 8 hours. Acetone was removed. Extract of a dark brown colour was collected and dried.

    - ***Allium sativum***: [11]
      250ml of hexane was used as the solvent while the powder was processed utilising a Soxhlet apparatus. The operating temperature was in the 50 to 60^{o}C range. Six hours were spent on the extraction procedure. The surplus solvent is eliminated by refluxing the oil at 70 ^{o}C.

    - ***Zingiber officinale***: [12]

      Using a maceration technique, 95% ethanol was utilised to extract the powder. Distillation was implemented to evaporate the solvent in order to create the thick, pasty substance. There was water permeating the dense, pasty bulk. In water that has been dried and pressed to remove any imbedded particles, the *Zingiber officinale* resin crystallises.

- **Evaluation of plant powder:** The evaluation was carried out by various parameters:-

    - **Determination of Quantitative data:** [8]

    - **Moisture content:** A suitable moisture level must be maintained since too much moisture might encourage the growth of microbes and hydrolytic processes. A 2-gram sample was transferred in a Petri dish following two hours at 130 °C of heating, weighing, and drying. Weight was once more recorded on the petri plate.

    - **Total Ash value:** Weigh the silica crucible when it's empty. Approximately to roughly 1 gm, the air-dried plant powder was placed in to the form-weighed condition. In muffle furnace, the sample was heated to a temperature for about 4500^{o}C for four hours, it slowly started to burn until it became white, signifying the lack of carbon. It was dried, then weighed one again.

- **Acid insoluble ash value:** The ash was treated with twenty-five parts of two M HCl for 5 minutes. Filtering the mixture, collecting the insoluble residue on ashless filter paper, washing it with hot water, and then lighting it on fire for four hours in a tared crucible at a temperature no greater than 4500 °C were the next steps. Weigh after being desiccated to chill it. Calculations were made to determine the amount of acid-insoluble ash in relation to the crude herb powder.

- **Water soluble ash value:** The ash was used to heat 25ml of water. Insoluble material from the filtering process was gathered on ashless filter paper, washed with hot water, and burnt for four hours at a maximum temperature of 500°C. After being desiccated to chill it, it was weighed. The weight of the insoluble remaining components was calculated after subtracting the whole weight of ash. The ash that dissolves in water makes up the weight difference. The amount of water-soluble ash in the air-dried coarse herb powder was calculated.

❖ **Phytochemical Evaluation:** [9]

Test for Carbohydrate

1. **Molish test**- Prepare a methanolic extract of the medicine, add some drops of α-naphthol solution to it, and then add concentrated sulfuric acid through the test tube's wall. The presence of carbohydrates is indicated by a ferocious ring at the intersections where they cross.
2. **Benedicts test**- Benedict's reagent should be added to the alcoholic before boiling it in a water bath, extract. The test solution will show one of three colours depending on how much reducing sugar is present: green, yellow, or red.

Test for Proteins

1. **Biuret test**- Add a few drops of 1% copper sulphate solution and 4% sodium hydroxide to 3ml of the test solution (Biuret reagent). A pink or violet hue indicates that there is protein in the sample.

Test for Alkaloids

1. **Dragendroff's test**: Dissolve the herbal crude drug extract in chloroform. Drops of Dragendroff's reagent should be added (potassium bismuth iodide) to the residue after evaporating the chloroform to acidify it. Precipitate that is orange or red in colour suggests the presence of alkaloid.
2. **Mayer's test**- when a few drops of Mayer's reagent are added to 2 to 3 ml of filtrate. There develops a creamy precipitate.
3. **Wagner's test**- A reddish brown colour is produced Wagner's reagent and 2-3 ml of filtrate are combined.

Test for Tannins

1. **Bromine water test**: Water containing bromine has plant extract added. Tanning in the sample is indicated by a deep blue or deep green colour.

Test for Saponin

1. **Foam test**: A tiny amount of extract is added to a test tube along with some water, and the test tube is vigorously agitated. Saponin is present if foam appears and lasts for 10 minutes.

Test for Flavonoids

1. **Lead actetate solution**: Yellow precipitate from an herb extract in a 10% lead acetate solution confirms the presence of flavonoids.
2. **Shinoda test**: The dried extract is mixed with 5ml of 95 percent ethanol before being given a few drops of hydrochloric acid and a few pieces of magnesium shavings. A pink colour develops.

Test for Glycoside

1. **Legal's test**: Dry extract is pyridine-treated to make it alkaline, and then sodium nitro-prusside solution is added. The test solution results in a pink to red colour.
2. **Keller-Killiani test**: Involves adding a few drops of glacial acetic acid to 2 ml of ferric chloride solution, resulting in a distinctive two-layer pattern with the top-most layer turning blue-green and the lower layer exhibiting reddish brown.

Test for steroids

1. **Salkowski test**: Add chloroform and concentrated sulfuric acid to the extract and well mix. Organic layer glows red, whereas the mineral acid layer fluoresces greenish yellow.

- **Identification process**

  - **Thin layer chromatography**: It is a technique that is widely employed in the study of chemistry to separate and pinpoint the individual components of a mixture. It is highly useful for figuring out the concentration and purity of various chemicals in a sample. In the examination, an adsorbent material is lightly deposited on a flat surface, such as a glass plate or plastic sheet (usually silica gel G or alumina). The sample mixture is applied in a spot or line at the plate's base. The plate is then put in a developing chamber with a solvent or mobile phase, which advances the plate by capillary action. While moving, the mobile phase carries the various elements in the sample mixture. The separation of components is based on the affinity of component towards the stationary phase.
    After development is complete, the TLC plate is removed from the chamber, dried, and visualised in various ways. UV light exposure is a common method

that can help with the visibility of fluorescent compounds on the plate. Another visualisation technique involves using chemical reagents to enhance the visibility of the separated spots or bands, such as iodine vapours or specific staining chemicals. [13]

- **Gas chromatography**: It is a technique for locating and identifying a volatile oil mixture. Gas acts as the mobile phase and liquid coated on a solid support serves as the stationary phase in gas liquid chromatography, where partition is the separation concept applied. Vaporized and combined with gaseous mobile phase is the to-be-separated mixture. A material's solubility in two immiscible liquids at a constant temperature, or its partition coefficient, is used to separate the components. [14]

- **Formulation of Pharmaceutical gel:** The dispersion process was used for production of the anti-rheumatoid arthritis gel. In a beaker, the appropriate quantity of Carbopol was sprinkled over water. To give the carbopol time to grow, the beaker was left unattended for 15 minutes. A weighted amount of propylene glycol was then added. and the extracts of *Curcuma longa* and *Zingiber officinale* were added to the beaker, while the extract of *Allium sativum* was added to isopropyl alcohol and the above-mentioned extract solution was blended with continuous stirring. The extract slurry was likewise rendered and poured into the beaker holding the carbopol mixture. After the slurry was properly dispersed, the required amount of MP and PP were added as preservatives, while tri-ethanol-amine was added while stirring continuously to neutralise the gel and keep its pH.

Table 1: Composition of topical gel formulation containing herbal extracts

S no.	Ingredients	F_1	F_2	F_3
1	**Extract of *Curcuma longa***	100 mg	150 mg	200 mg
2	**Extract of *Zingiber officinale***	10 mg	150 mg	200 mg
3	**Extract of *Allium sativum***	1.0 ml	1.0 ml	1.0 ml
4	**Carbopol 940**	1.4 g	1.4 g	1.4 g
5	**Isopropyl Alcohol**	2.4 ml	2.4 ml	2.4 ml
6	**Propylene Glycol**	12.0 ml	12.0 ml	12.0 ml
7	**Tri-ethanol-amine**	q.s	q.s	q.s
8	**Methyl - paraben (B.P.)**	0.2 gm	0.2 gm	0.2 gm
9	**Propyl -paraben (B.P.)**	0.02 gm	0.02 gm	0.02 gm
10	**Distill- water**	q.s (100ml)	q.s (100ml)	q.s (100ml)

- **Evaluation of pharmaceutical gel** [15-17]**:** as per standard guideline, following parameters are calculated.

  - **Physicochemical properties**

All of the designed herbal Rheumatoid Arthritic gel were visually investigated for physiochemical properties, and the findings were computed and reported.

- **Measurement of pH**

  To gauge the pH of the gel compositions, a digital pH metre was employed. 1 g of gel was combined with 100 ml of distilled water, and the combination was let to stand for two hours. The pH of each gel was assessed.

- **Determination of viscosity**

  The gel's viscosity has been assessed using a Brookfield viscometer. 10g of gel was accurately weighed and placed to a 10ml glass beaker. Spindle no. S64 was chosen and submerged in the gel. The reading was recorded in centipoises after the viscometer was rotated for 20 rpm (revolutions per minute) until the reading stabilised.

- **Spreadability**

  It is put together using a wooden block that the pulley provides at one end. This stone was mounted with a square ground glass plate. Around 1 g of extra gel was placed on this ground plate as part of the investigation. Next, a glass plate with the same measurements as the fixed ground plate and the hook was placed on top of the gel sandwiched between this plate and the other one. To create a homogenous layer of gel between the plates and eliminate air, a 1 kg weight was put on top of the plates for 5 minutes. Marginally, extra gel was scraped off.

  $$\text{Spreadability} = M \times L/t$$

  Where, L= length of glass slide, M= weight tied to upper slide and T=time

- **Extrudability**

  Using the Pfizer hardness tester, the extrudability test was conducted. An aluminium tube contained 10g of gel. The plunger was altered to successfully grip the tube. 30 seconds were spent with a pressure of 1 kg/cm2. The amount of extruded gel was measured. Down the tube, this procedure was repeated three times at equally spaced intervals. The exam was administered three times.

- **Drug content**

  The gel was dissolved in a volume of 50cc of phosphate buffer 7.4. The volumetric flask containing the gel solution underwent two hours of manual agitation to ensure the loaded drug's solubility. This solution underwent spectrophotometric analysis and filtration.

- ***In-vitro* diffusion study**

  In a Franz diffusion cell designed to assess gel release following disintegration across a cellophane membrane, herbal gel compositions have been the focus of diffusion experiments. Using a gel sample (1 gm) in a cellophane membrane

and phosphate buffer as the dissolving solution, the diffusion experiments were conducted at 37°C. At intervals of thirty, sixty, ninety, one quarter, and two tenths of an hour, five millilitres of each sample were taken out and replaced with an equivalent amount of dissolution. The samples were analysed for drug concentration using distilled water as a reference.

RESULTS AND DISCUSSION

- **Evaluation of Plant powder**

  - **Determination of Quantitative data**

Table 2: Quantitative data of Herbs

Parameter (%)	*Curcuma longa* (NMT %w/w)	*Zingiber officinale* (NMT % w/w)	*Allium sativum* (NMT %w/w)
Total ash value	7	5	4
Acid insolube	1.2	0.3	0.45
Water soluble	6.3	0.83	0.5
Moisture content	5.29	4.56	5.12

The three metrics, total ash, acid insoluble ash, and moisture content of *Curcuma longa* should not exceed 10%, 2%, and 7%, respectively, according to **Indian pharmacopoeia**. Similarly, **Ayurvedic pharmacopoeia** established *Zingiber officinale* requirements of not more than 8% ash value, 1% acid insoluble ash, and 7% moisture content. Furthermore, the **Indian pharmacopoeia** specifies ash vale, acid insoluble ash, and moisture content for *Allium sativum* as not exceeding 5%, 1%, and 7%, respectively. All of these values are restricted in or studied.

  - **Phytochemical evaluation**

Table 3: Phytochemical Evaluations of Herb extracts

Test	*Curcuma longa* powder	*Zingiber officinale* powder	*Allium sativum* powder
Carbohydrates			
• Molish's test	+	+	+
• Benedict's Reagent	-	+	-
Proteins			
• Biuret's Reagent	+	+	+
Saponins			
• Foam test	-	+	+

Tannins			
• Bromine water	-	-	+
Alkaloids			
• Mayer's	+	+	+
• Dragendroff's	+	+	+
• Wagner's	+	+	+
Flavonoids			
• Shinoda	+	+	+
• Lead acetate	+	+	+
Steroids			
• Salkowski	-	-	+
Glycosides			
• Legal's	+	-	+
• Keller- killiani	-	-	+

Alkaloids, flavonoids, and a number of other phyto-constituents have all been shown to be useful in the treatment of RA in the past. The alkaloid added to herbal components has anti-inflammatory properties by inhibiting the nuclear factor kappa light chain activator of activated B cells (NF-kB) signalling pathway and functioning as an immune-modulator by reducing cytokine activity. By lowering the synthesis of TNF-alpha, interlukin-1, and interlukin-6 in macrophage cell lines, some terpenes or phenolic compounds present in plants or medications inhibit the action of pro-inflammatory cytokines. [18]

❖ Identification

o TLC of Curcuma longa

Table 4: TLC of *Curcuma longa* Extract

S.no	Distance-travelled by solute (cm)	Distance travelled by Solvent (cm)	Retardation - factor (Rf)
1	5.6	12	0.46
2	6.8	12	0.56
3	9.4	12	0.77

According to Literature Review, the separation, purification and identification of curcumanoids from *Curcuma longa* with the solvent system Chloroform: ethanol: glacial acetic acid in the ratio 94:5:1 (vol/vol) and as a result identified the Rf 0.75, 0.55 and 0.37.[10] Here, the Rf is calculated to be 0.46, 0.56 and 0.77.

- **TLC of *Zingiber officinale***

According to **Ayurvedic Pharmacopoeia**, the TLC of alcoholic extract of *Zingiber officinale* on silica gel G plate using solvent system when seen under UV seemed to be at Rf. 0.16, 0.35 and 0.69. Here, our Rf appears to be at 0.19 and 0.63.

Table 5: TLC of *Zingiber officinale* Extract

S. no	**Distance travelled by solute (cm)**	**Distance travelled by solvent (cm)**	**Retardation - factor (Rf)**
1	2.3	12	0.19
2	7.5	12	0.63

- **Gas chromatography of *Allium Sativum***

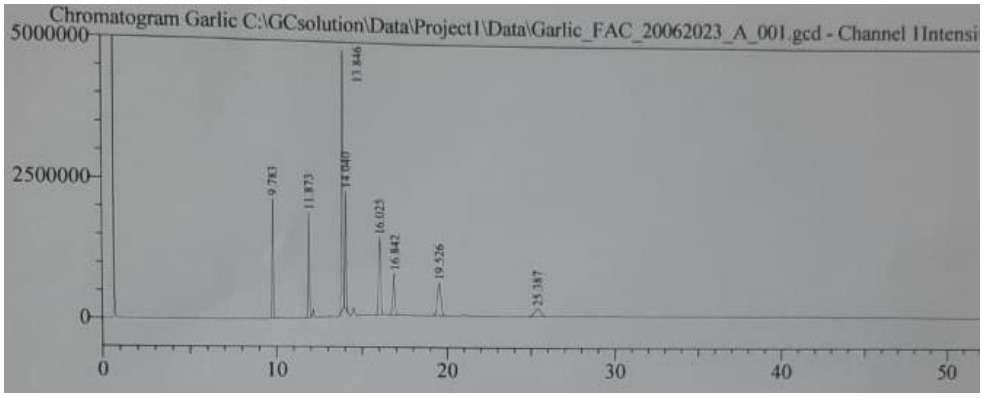


Table 6: Chemical compound derived from *Allium sativum* by gas chromatography

Retention time (min)	**Compound**
9.763	3-vinyl-1,2-dithiocyclohex-5-ene
11.373	Dimethyl tetrasulphide
13.846	Diallyl tetrasulfide
14.040	3H-1,2,4-Triazole-3-thione
16.542	Tri-sulphide
19.526	p- cymene

- **Evaluation Parameter of gel**

  - **Physicochemical parameters**

Table 7: Physical parameters of gel

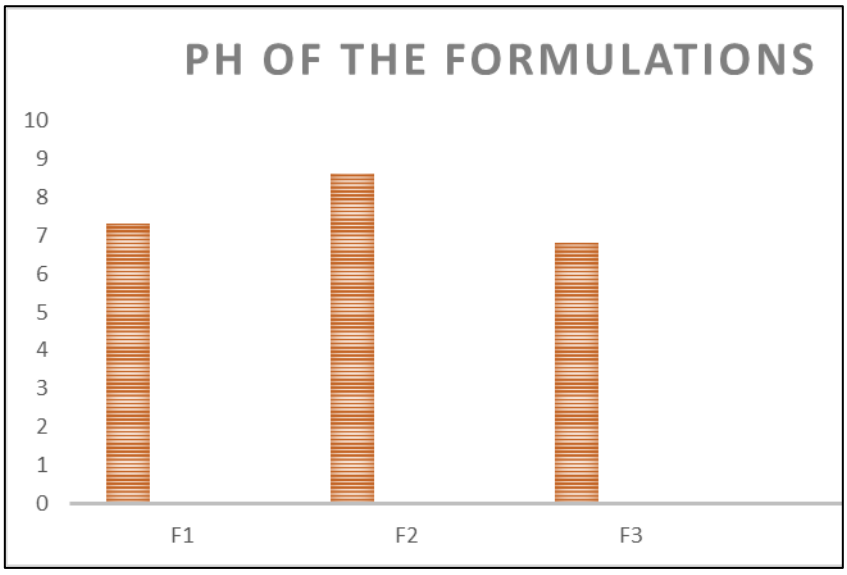
Formulation	Appearance	Colour	Odour	Homogenesity
F_1	Smooth	Dark- brown	Characteristic	Homogenous
F_2	Smooth	Brownish orange	Characteristic	Homogenous
F_3	Smooth	Light brown	Characteristic	Homogenous

❖ **Measurement of pH**

The pH range of the topical preparation utilized in earlier studies was between 4.0 and 6.0. Skin's typical pH range is between 4.0 and 7.0. If needed, neutralize the pH using tri-ethanol-amine.

Table 8: pH of formulation

Formulations	pH
F_1	7.3 ± 0.38
F_2	8.6 ± 0.21
F_3	6.8 ± 0.08

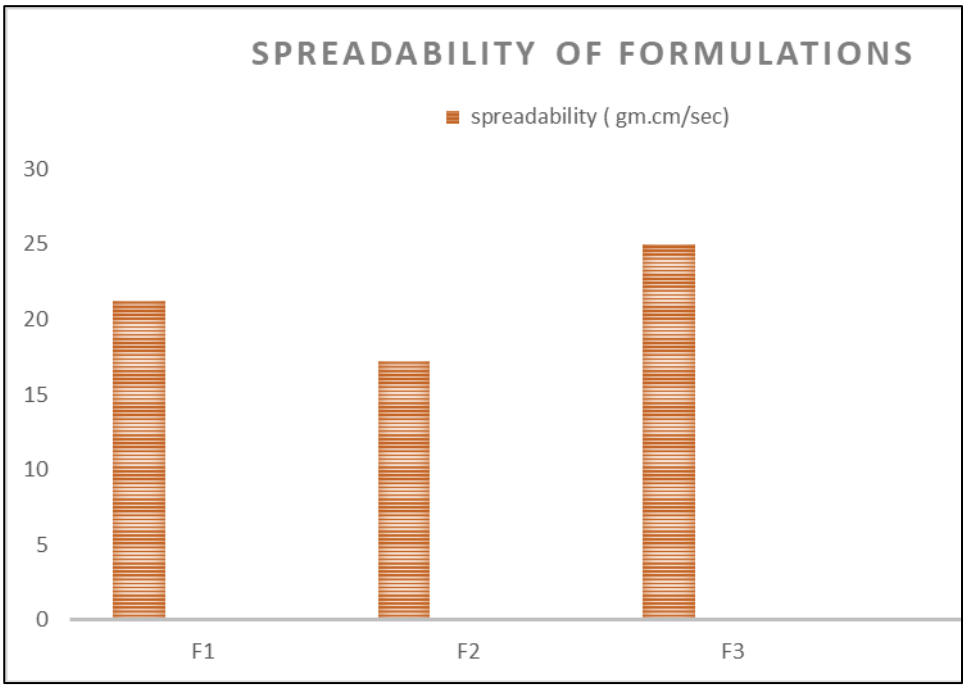


❖ Spreadability , Viscosity and Extrudability

The three formulations with gel in the layer undergoing gelling possess viscosities between 1000 to 100,000 centipoise [20]. The percentage for Extrudability of gel is (Extrudability > 90% excellent, > 80% decent, > 70% fair) [19]. In our study the values are under limits.

Table 9: Spreadability, Viscosity and Extrudability of gel

Formulations	Spreadability (gm.cm/sec)	Viscosity (cps)	Extrudability (%)
F_1	21.25 ± 0.87	23980 ± 1.57	86.87 ± 3.5
F_2	17.23 ± 1.12	23590 ± 0.94	89.25 ± 4.3
F_3	24.97 ± 0.57	22460 ± 0.23	92.63 ± 3.2



❖ Drug content

All three formulation, medication content the value of gel was found to be 85-90 %. Among the three formulations F_2 is considered to have better drug content than other formulated formulations

Table 10: drug content of the formulations

Formulations	Drug content (mean ± SD)
F_1	88.82 ± 1.03

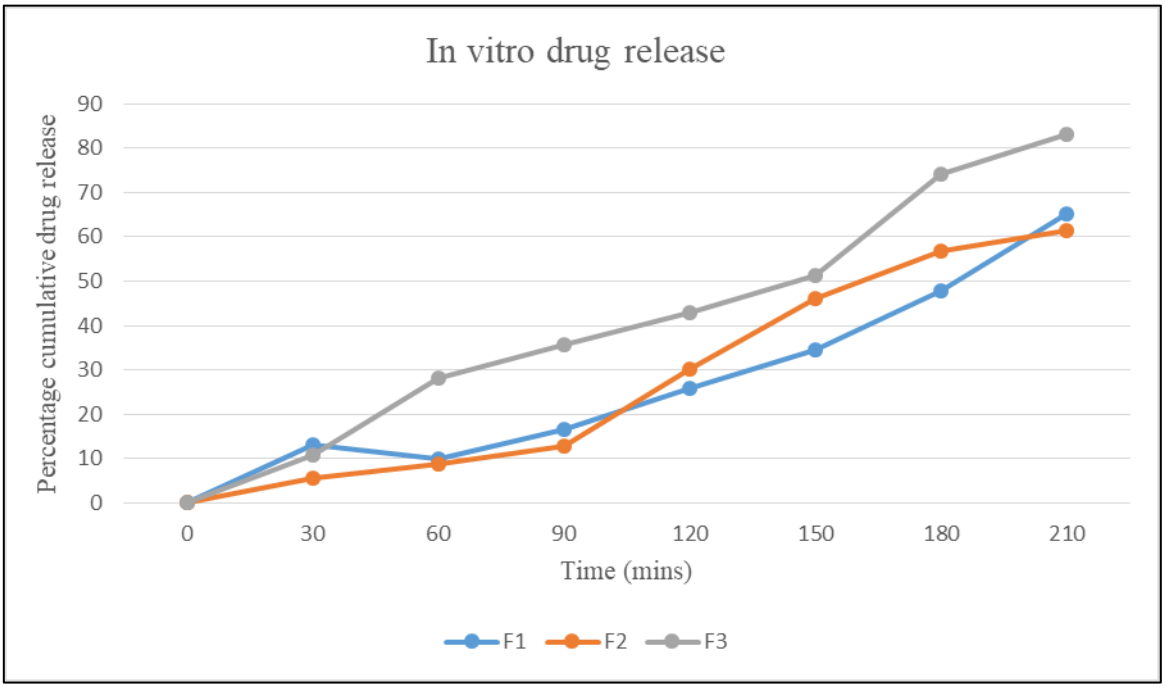
F_2	86.47 ± 1.11
F_3	89.36 ± 0.85

❖ ***In-vitro* Diffusion study**

According to our study, it is observed that all the three formulation are effective but among all three, F_3 formulation was considered to shows better disintegration or diffusion of gel in Franz diffusion cell.

Table 11: *In-vitro* diffusion release of the formulations

Time (mins)	F_1	F_2	F_3
0	0	0	0
30	13.12	5.65	10.81
60	09.82	8.83	28.10
90	16.64	12.92	35.61
120	25.86	30.32	42.80
150	34.45	46.23	51.42
180	47.82	56.82	74.10
210	65.30	61.36	83.23



CONCLUSION

Anti-rheumatoid arthritis drugs such as *Curcuma longa, Allium sativum, and Zingiber officinale* are employed to treat arthritis, inflammation, and pain . The primary goal of topical and dermatological dosage forms is to distribute medicine molecules across a localised region of skin in a convenient manner. Slow release is required to administer a medicine to the skin over an extended period of time, hence a dermatological delivery mechanism, such as gel, was examined. Aside from that, this gel form may decrease the frequency of dose intervals and enhance patient compliance. To identify the many types of chemical components, such as secondary metabolites, the extract was first submitted to phytochemical screening. The fractional product of *Curcuma longa*, *Allium sativum*, and *Zingiber officinale* included flavonoids and alkaloids, according to the findings of the phytochemical screening of the extracts. The gel was created using carbapol 940 and was examined for a smooth and homogenous look. It was easily spreadable and had a good mechanical property. The pH measurements indicated that all of the formulations were extremely comparable to skin pH, making them acceptable for application on skin. The current study's findings suggested that the complete medication was consistently distributed and that there was no precipitation in the formulation. Three gel formulas were tested for medication incorporation. When these formulae were compared, it was discovered that formula 3 had a smooth texture, a desirable pH, and high spreadability. To investigate the drug release behaviour from formulation, in vitro diffusion release of herbs from gel was done. According to the observed data, there is an increase in drug release with regard to time. Spreadability is critical for topical medication delivery systems in terms of patient compliance. The gel proved to have a fair percentage spread by weight, which would ensure skin application.

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REFERENCES

1. Snehal A.K, Parhad SV, Bairagi RS. A detailed review on Rheumatoid Arthritis. International Journal of Research Publication and Reviews: IJRPR. **2022** July: 3(7). 486-494
2. Ahmed S, Anuntiyo J, Malemud CJ, Haqqi TM. Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis: a review. Evidence-Based Complementary and Alternative Medicine. **2005** Sep 1;2:301-8.

3. AloK A, Singh ID, Singh S, Kishore M, Jha PC. Curcumin–pharmacological actions and its role in oral submucous fibrosis: a review. Journal of clinical and diagnostic research: JCDR. **2015** Oct;9(10):ZE01.
4. Pareek S, Dixit M, Govil S, Jadhav I, Shrivastava D, Vahedi M, Bisen PS. Garlic and its role in arthritis management. InBioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases **2019** Jan 1 (pp. 245-252). Academic Press.
5. Tawde S, Gawde K, Mahind D, Mhaprolkar C, Sawant K, Surve C. GINGEL: Development and Evaluation of Anti-Arthritic Gel Containing Ginger (*Zingiber officinale*). Optimization. **2020**;11:12.
6. Nabi SA, Sheraz MA, Ahmed S, Mustaan N, Ahmad I. Pharmaceutical gels: a review. RADS Journal of Pharmacy and Pharmaceutical Sciences. **2016** Jun 19;4(1):40-8.
7. Tanwar YS, Jain AK. Formulation and evaluation of topical diclofenac sodium gel using different gelling agent. Asian J Pharm Res Health Care**. 2012**;4(1):1-6.
8. Agrawal PO, Baajpayee ME, Singh SP. Formulation and evaluation of herbal gel containing *Boswellia serrata*, *Curcuma longa* extract and oil of wintergreen for rheumatoid arthritis. International Bulletin of Drug Research. IBDR. **2013**;2(3):31-40.
9. Jamadar MJ, Shaikh RH. Preparation and evaluation of herbal gel formulation. Journal of Pharmaceutical Research and Education**. 2017**;1(2):201-4.
10. Revathy S, Elumalai S, Antony MB. Isolation, purification and identification of curcuminoids from turmeric (*Curcuma longa* L.) by column chromatography. Journal of Experimental sciences. **2011** Jun 27;2(7).
11. Dehariya N, Guha P, Gupta RK. Extraction and characterization of essential oil of garlic (*Allium sativa* L.). Int. J. Chem. Stud. **2021**;9:1455-9.
12. Gaikwad DD, Shinde SK, Kawade AV, Jadhav SJ, Gadhave MV. Isolation and standardization of gingerol from ginger rhizome by using TLC, HPLC, and identification tests. The Pharma Innovation. **2017** Feb 1;6(2, Part C):179.
13. Vanhaelen M, Vanhaelen-Fastre R. Quantitative determination of biologically active constituents in medicinal plant crude extracts by thin-layer chromatography—densitometry: I. *Aesculus hippocastaneum* L., Arctostaphyllos uva-ursi Spreng, Fraxinus excelsior L., *Gentiana lutea* L., *Glycyrrhiza glabra* L., *Hamamelis virginiana* L., *Hypericum perforatum* L., *Olea europea* L., *Salix alba* L. and *Silybum marianum* Gaertn. Journal of Chromatography A. **1983** Jan 1;281:263-71.
14. Al-Bukhaiti WQ, Noman A, Qasim AS, Al-Farga A. Gas chromatography: Principles, advantages and applications in food analysis. International Journal of Agriculture Innovations and Research. **2017** Jul;6(1):2319-1473.
15. Khan MR, Raza SM, Hussain M. Formulation and in-vitro evaluation of cream containing diclofenac sodium and *Curcuma longa* for the management of rheumatoid arthritis. Int J Pharma Sci. **2014**;4(4):654-0.
16. Choudhary V, lal Seervi K, Kamalja MD. Journal of Scientific Research in Pharmacy. Alcohol. **2012**;2(2ml):2ml.
17. Rampal S, Divya J, Singh Vikram RG. Formulation, optimization and evaluation of aceclofenac transdermal gel: A novel approach for penetration enhancement by herbal extract. J Pharm Sci Innov. **2015** Sep 2;4:262-9.
18. Santiago LÂ, Neto RN, Santos Ataíde AC, Fonseca DC, Soares EF, de Sá Sousa JC, Mondego-Oliveira R, Ribeiro RM, de Sousa Cartágenes MD, Lima-Neto LG, Carvalho RC. Flavonoids, alkaloids and saponins: Are these plant-derived compounds an

alternative to the treatment of rheumatoid arthritis? A literature review. Clinical Phytoscience. **2021** Dec;7(1):1-0.

19. Giri MA, Bhalke RD. Formulation and evaluation of topical anti-inflammatory herbal gel. Asian J Pharm Clin Res. **2019**;12(7):252-5.
20. Kashyap A, Das A, Ahmed AB. Formulation and evaluation of transdermal topical gel of ibuprofen. Journal of Drug Delivery and Therapeutics. **2020** Mar 15;10(2):20-5.