Formulation and Evaluation of Topical Formulations of Bosweellic Acids Guggulosterones for the Treatment of Rheumatoid Arthritis

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Abstract

Rheumatoid Arthritis (RA) is a chronic immunological disorder with an unknown etiology that affects the general population and can cause disability due to joint destruction. Joint synovial inflammation, moderate ligament and bone destruction, and constant inactivity are the symptoms of RA. The most significant drawback of currently available powerfully developed medications is their danger and recurrence of side effects after discontinuation. Natural remedies are gaining popularity among RA sufferers due to the limitations of currently available pharmaceuticals. Plants that include inherent dynamic fixes that can be utilized to treat an infection or eliminate arthritis adverse effects are considered restorative plants. The main goal of the ongoing research was to enhance the natural gel of Boswellia serrata (Shallaki gum) for subterranean insect ligament action to achieve more notable therapeutic effects. An ongoing metabolic disorder that affects periarticular tissue and joints is rheumatoid arthritis. The most effective conventional treatment for rheumatoid arthritis is a plant called Shallaki. There is hence a need to employ Shallaki in home-made formulations because it is highly effective in treating osteoarthritis,

juvenile rheumatoid arthritis, delicate tissue fibrolite, and spondylitis without causing any side effects. One specific Ayurvedic remedy that has been used to remove the gum for the treatment of rheumatoid arthritis is boswellia serrata. For the most part, the benefits of boswellia are primarily intended to lessen the discomfort or irritability brought on by rheumatoid arthritis.

Keywords: Formulation, Evaluation, Topical Formulations, Bosweellic Acids, Guggulosterones, Treatment, Rheumatoid Arthritis

1. Introduction

Ailment affects the ligaments, tendons, and muscles that surround the joints. Depending on the area, side effects, seriousness, or age of the patient, it requires a different structure. Rheumatoid arthritis is a dangerous form of arthritis that can destroy the joint ligament, disfigure the affected area, and result in long-term, permanent disability. The shoulder and knees are usually affected by this illness. Rheumatoid arthritis is managed with the use of NSAIDs, fundamental and local corticotherapy, and/or physical therapy.

By releasing proinflammatory cytokines into the synovial depression, such as growth suppression factor (TNF-) and interleukin (IL-1), the flaming course is not completely predetermined. Expanding vascular cell penetration, hepatocyte production of protein C, and osteoclast activity with bone resorption are all effects of their distribution. These preventive reactions cause mild tissue damage, which results in joint injuries, functional incapacities, and agony that lowers one's level of enjoyment. Pharmacotherapy uses non-steroidal anti-inflammatory medicines as a means of regulating or reducing the provocation cycle by preventing the body's production of prostaglandins.

In general, arthritis causes joint discomfort and is one of the most well-known diseases, affecting people of all ages. More than 20% of the entire population of India suffers from arthritis. A chronic immunological disorder with an unknown cause, rheumatoid arthritis (RA) is characterized by joint synovial inflammation and mild ligament and bone obliteration that leads to increasing stability. Long ago, it was discovered among the early inhabitants of Local America; yet, it may have appeared in Europe after the seventeenth century. Favorable to incendiary cytokines including interleukin (IL)-1, IL-6, and cancer putrefaction factor (TNF-) are important disease-transmission intermediaries. Before spreading to the larger joints, arthritis often starts in the tiny joints of the hands and feet. The inflamed synovial, the joint covering, swells and then destroys the articular ligament and bone, resulting in joint deformity and mild physical impairment. Knobs, pericarditis, aspiratory fibrosis, fringe neuropathy, and Amy loidosis are among the extra-articular features.

The Boswellia serrata Family Burseraraceae tree, which is mostly found in India, produces oleo-gum tar that is used for its patent. Insect joint and mitigating action have been mentioned in ancient ayurvedic texts like as Sushruta Samhita and Charaksamhita. The gum's mitigating action is attributed to the presence of triterpenic corrosive, namely -boswellic corrosive.

Due to improved resistance and a decreased risk of adverse drug reactions, non-manufactured, typical medications obtained from plant-based sources are currently more popular on a global scale. There aren't any supporting analyses about the formulation and evaluation viewpoint,

nevertheless. The WHO's study on quality assurance for medicinal plants The current review was completed to identify the gel of Boswellia serrata separately involving various gelling specialists in fluctuating, to assess its actual boundaries, and to set up determinations for the finished therapeutic item. This was done in response to the board for restrictive therapeutic item's (CPMP) note for direction on details, which is positive estimated toward this path.

2. Literature Review

Singh et al. (1987) focused on the moderating effect of the fluid and ethanol concentrates of stems of Polygonum glabrum in four separate test models: the adjuvant-induced polyarthritis test, the severe carrageenan-induced paw edema test, and the granuloma pocket test. According to the review, parenteral administration of the fluid and ethanol separates was more effective than oral administration.

Muddtahiret al. (1987) tested the antimolluscidal improvement of the watery and brutal concentrate of P. glabrum leaves against Biomphalariaglabrata and Lymnaeatruncatula Reflect as well as the anthelmintic action of P. glabrum leaves against Hymenolepis nana var genial of the mouse at pieces of 200-600 mgkg1. Against B. glabrata and L. truncatula, unwanted concentrations have independently demonstrated 100% and 40% death.

Nizare et al. (2007) evaluated the energizing effects of an aqueous concentrate of Polygonum glabrum leaves using a variety of models, including the L-dopa-induced hyperactivity and forceful conduct test, the tail suspension test, and the conduct despair test. The monoamine systems of dopamine and norepinephrine were thought to mediate the plant's energizing movement.

Brewer's yeast-induced pyrexia in mice was used by Basha et al. (2011) to test the antipyretic effect of Polygonum glabrum whole plant methanol concentrate. In the assessment, a fundamental drop in yeast-brought temperature was detected, supporting the counter-pyretic effect.

According to Kironet al. (2012), the methanol concentrate of Polygonum glabra leaves has antibacterial and parasite-hostile effects against pathogenic strains of Candida albicans and Candida tropicalis as well as microorganisms including Staphylococcus aureus, Micrococcus luteus, and Pseudomonas aeruginosa. The most challenging organisms were P. aeruginosa, S. aureus, and M. luteus. Because the concentrate demonstrated 11mm of resistance against both Candida albicans and Candida tropicalis, it was also noted that the concentrate's antifungal potential was essential.

Faheemuddin et al. (2016) evaluated the insect diabetic action of P. glabrum leaf methanol concentrate in alloxan-impelled diabetic animals. However, histopathological examinations of the rat pancreas revealed that the insulin-radiating beta pancreatic cells had recovered from the damage caused by alloxan. A 400 mg/kg portion of P. glabrum methanol leaf concentrates showed a reduction in fasting blood glucose levels. In the oral glucose obstruction test, the P. glabrum methanol concentrate enhanced the glucose flexibility.

Hanumanthachaet al. (2007) reported that the watery concentrate of Argyreiaspeciosa roots at dosages of 100 and 200 mg/kg fundamentally improved memory and successfully reversed

amnesia caused by diazepam, scopolamine, and normal maturing. Additionally, the watery concentrate decreased acetyl cholinesterase level in mind homogenate, showing its true capacity in limiting learning and memory deficits, particularly in mature mice.

Karimulla and Pavan Kumar (2012) assessed the counter ulcer profile of the ethanol concentrate of Ochna obtusatausing Ethanol, indomethacin, pyloric ligation (PL), and cold limitation stress actuated gastric ulcer models in Pale skinned person rodents and detailed that the ethanol concentrate of the entire plant of Ochna obtusata have against ulcer properties that might be because of cytoprotective system.

In vitro cell reinforcing capabilities of methanol, ethanol, petrol ether, chloroform, and watery concentrate of Ochna obtusata were evaluated by Kumar et al. (2014). Ochna obtusata has been discovered to have the cell reinforcement movement in a somewhat secondary manner in each of the tested techniques.

Dasari Rajesh et al., (2019) reported that the ethanol concentrate of the complete Ochna plant was an enemy of atherosclerotic action when the high-fat diet was activated. The analysis of the creature model demonstrated that the plant's ethanol extract had a significant hypolipidemic capacity.

3. Boswellia serrta

(Family - Burseraceae) is used in the insect gout formulation due to its soothing, anti-ligamentary movement brought on by dynamic compound contained non-cyclic triterpenic acids, particularly Boswellic acids (figure 1). Additionally, it has both hepatoprotective and immunomodulatory actions. Boswellic acids are a brand-new, explicit, non-red sox inhibitor of 5-lipoxygenase, a substance linked to the corrosive breakdown of arachidonic acid. Boswellia serrata's phytochemical composition includes natural balm, gum, and tar.It contains monoterpene, diterpenes, and sesquiterpenes in its rejuvenating ointment. Pentose and hexose sugars, together with various oxidizing and stomach-related catalysts, make up the medication's gum component. Boswellic corrosive, the active moiety of a restricted non-cyclic triterpene corrosive, makes up the majority of the sap segment.

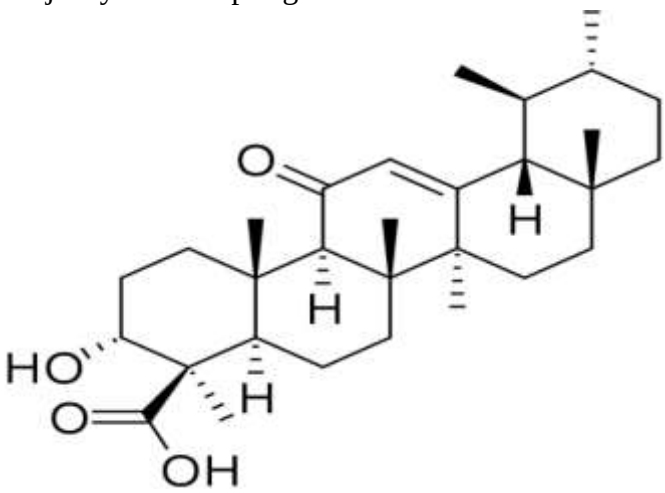

Figure 1: The Boswellic Acid Structure

4. Materials and Methods

We bought Boswellia serrata powder from Sun Pure Engineers Pvt. Ltd. in Mumbai along with Carbopol940, Pluronic F127, HPMC K4M, Triethanolamine, Ethanol, Propyl Paraben, Methyl Paraben, and Rose Joyful Oil, among other ingredients.

4.1. Preparation of gel:

- **Preparation of gel with Carbopol 940:**

1. Set up a gel comprising Shallaki separate and let Carbopol 940 gelling agents absorb water for two hours.
2. Triethanolamine and mixes were used to kill.
3. Loads of medication dissolves in propylene glycol and ethanol that have been preweighed.
4. Combine 3 into 1 and shake for 20 minutes.
5. This scattering allows pH to vary and hydrate for 60 minutes; the appropriate pH range is 6.8 to 7.0.
6. The mixture was delicately stirred with a spatula during the ph change to create a uniform gel.

- **Preparation of gel with HPMC K4M:**

1. In 1ml of propylene glycol, which also contained an addition, 1gm of precisely measured medication was added to a container.
2. Purified water was first used to disperse HPMC K4 M, and then it was heated to between 70 and 900 degrees Celsius while being constantly mixed, and then it was allowed to cool.
3. The HPMC K4 M preparation was then given 1% w/v medication overlaid to a propylene glycol solution.
4. The mixture was vigorously blended in a cold environment, and water was added to get the volume up to 20 ml. It was then thoroughly mechanically combined to produce gels that were properly attired.

- **Preparation of gel with Pluronic F127:**

1. To prepare Pluronic F127solution, the measured amount of Pluronic F127 was dissolved in water and stored for a brief period of time in a cooler.
2. Methyl and propyl paraben are dissolved in scalding hot water to prepare the gel formulation.
3. Triethanolamine and mixtures were used to kill.
4. Large amounts of medication degrade in propylene glycol and ethanol that have been preweighed.
5. Remove all of the fixing ingredients, including ethanol, rose-scented oil, propylene glycol, and methyl and propyl paraben.
6. Blend was meticulously stirred with a spatula throughout the pH change to create a uniform gel.

Table 1: Different Boswellia serrata Resin Gel formulations' ingredients

S. N0.	Ingredients (gm)	F1	F2	F3	F4	F5	F7	F8	F6
1.	Shallaki	2	2	2	2	2	2	2	2
2.	Carbopol	0.2	0.3	0.4	-	0.3	0.4	0.6	0.6
3.	HPMC K4M	-	-	-	0.4	-	-	0.4	0.4

4.	Pluronic F127	-	-	-	-	3	3	3	3
5.	Methyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
6.	Propyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
7.	Glycerin	2	2	2	2	2	2	2	2
8.	Ethanol	4	4	4	4	4	4	4	4
9.	Rose mmery oil	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
10.	Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
11.	Propylene glycol	2	2	2	2	2	2	2	2
12.	Dist. Water (upto)	30	30	30	30	30	30	30	30

4.2. Evaluation of topical Gel formulation

- **Physical Assessment:**

Actual limits, including those related to variety and appearance, were assessed and are displayed in table number 3.

- **Homogeneity:**

After being placed in the compartment, all generated gels were examined visually for homogeneity to determine their appearance and the presence of any totals as shown in table no 3.

- **pH:**

By using a sophisticated pH meter, the pH of various gels is not completely fixed. A exact 2.5gm of gel was measured out, dispensed into 25ml of purified water, and then stored for two hours. Every Formulation's pH was calculated three times, and the typical attributes are included. Using a pH meter, the pH of the scatterings was calculated as shown in table no 3.

- **Spread ability:**

The mechanism, which is made up of a wooden block that was supplied by a pulley toward one side, spread not completely developed. Using this method, the spread capacity was calculated based on the gels' characteristics of slip and drag. On this ground slide, a large amount of the gel under investigation (about 2 g) was placed. The gel was then placed in a sandwich between this glass slide and another glass slide with a fixed ground slide element, creating the snare. To remove air and provide a consistent gel coating between the slides, a weight of 1 kg was placed there for 5 minutes. The edges rejected extra gel that was present. The top plate was then pulled 50 g after that. Watch the amount of time (in a flash) needed for the top slide to move 6.5 cm with the help of a string fastened to the snare. Better Spread capacity is demonstrated by a smaller span, as seen in table no. 3. The preceding recipe was used to determine the spread capacity:

$$\boldsymbol{S = M \times L / T} \qquad (\mathbf{1})$$

Where S is the spread capacity, M is the dish's weight (attached to the higher slide), L is the glass slide's travel distance, and T is the time (in seconds) required to totally isolate one slide from the others.

- **Viscosity:**

Using a Brookfield rotational viscometer at 6 rpm, the thickness of homegrown produce is not completely settled. At the end of the two minutes, each reading was done in sync with the example. As shown in table no. 3, the consistency assurance of tests was repeated numerous times.

- **Stability Study:**

The steady focus is on behaviors that follow ICH guideline. The enhanced formulation's characteristics and the way the drug was released showed no significant change. Studies on the prospective Boswellia serrata gel's transient soundness were conducted over a period of many months in a reliable chamber. To determine the dependability profile shown in table no. 3, tests for PH and consistency were run.

5. Results and Discussion

50 mg of Boswellia serrata sap were precisely measured and dispersed in 50 ml of pH 5.5 phosphate support to make a stock arrangement. From this arrangement, 10 ml was taken and added to 100 ml of refined water in a volumetric jar to make the desired volume. The composition was then sonicated for 10 minutes after that. This contract is referred to as a stock agreement.

- Using distilled water, 2, weakening was produced from stock at concentrations of 2, 4, 6, 8, and 10 g/ml.
- To measure the absorbance in expanding requests for fixation, the twofold bar UV spectrophotometer observed the pre-arranged arrangement mentioned above.

Table 2: phosphate buffer calibration curve for boswellia serrata resin

Sr. no.	Concentration (ug/mg)	Absorbance (λmax observed at 254nm)
1	2	0.2300
2	4	0.3200
3	6	0.4300
4	8	0.5400
5	10	0.6300

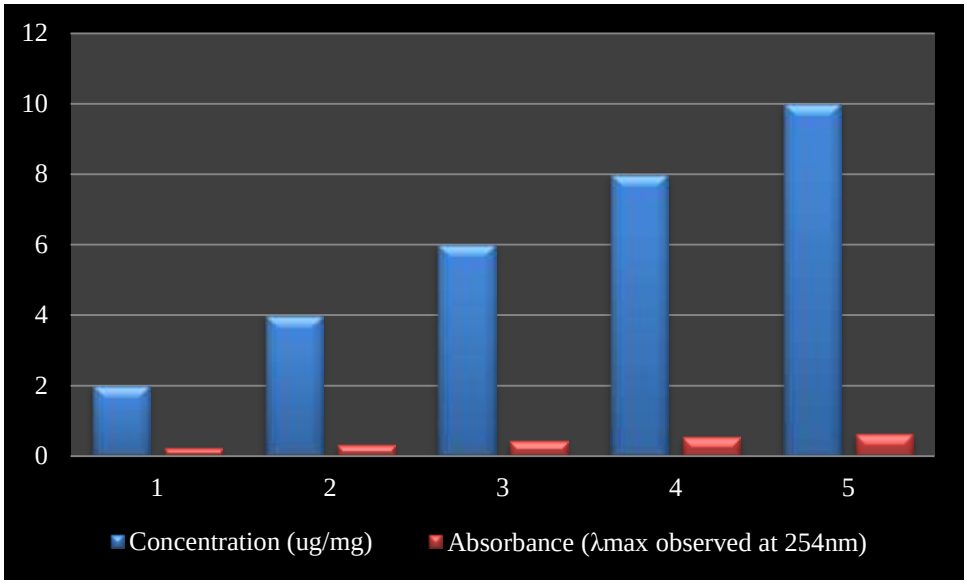

Figure 2: phosphate buffer calibration curve for boswellia serrata resin

5.1. Study on the compatibility of drug excipients

Using a poly pack, the medication and excipients were combined properly in a 1:1 ratio. Presently, the mixtures were placed in glass vials, and tests were run for 21 days in a solidness chamber at 400C. Glass vials containing polymers and airplane medicine were also arranged identically.

5.2. Infrared Fourier Transform Spectroscopy:

The similarity analysis of medication excipients was supported by FTIR analysis.

5.3. Evaluation Studies

Real-world appearances, PH, thickness, spread capacity, and homogeneity of various formulations

Table 3: Physical Characteristics, PH, Viscosity, Spreading Capability, and Homogeneity of Different Formulations

Sr. no.	Batch	Appearance	Homogeneity	PH	Spread ability (gm/sec)	Viscosity
1	F1	Yellow	Homogeneous	5.07	22.38	53400
2	F2	Yellow	Homogeneous	5.07	24.32	52000
3	F3	Yellow	Homogeneous	5.07	27.30	64220
4	F4	Yellow	Homogeneous	5.07	24.07	47000
5	F5	Yellow	Homogeneous	5.07	30.23	55700
6	F6	Yellow	Homogeneous	5.07	32.24	22000
7	F7	Yellow	Homogeneous	5.07	33.05	23555.5
8	F8	Yellow	Homogeneous	5.07	23.05	60400

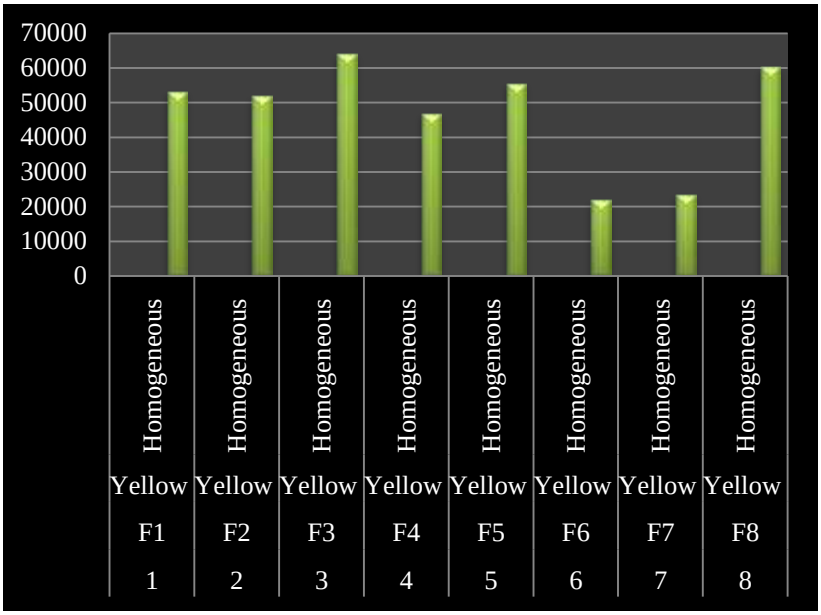

Figure 3: Physical Characteristics, PH, Viscosity, Spreading Capability, and Homogeneity of Different Formulations

5.4. In-vitro drug release study:

Utilizing a Franz dissemination cell device and semi-porous cellophane film, in-vitro dispersion studies were conducted. In order to mount the cellophane film, it was sandwiched between the contributor and collector compartments after being freshly saturated for the time being in phosphate cushion 5.5. For in-vitro discharge studies, a Franz dissemination cell with a width of 3.7 cm was used. As a penetration cell, a glass tube with both ends open, a 10 cm level, and an exterior measurement of 3.7 cm was used. A one-gram test with a 3.7 cm diameter circle was carefully measured and applied to a semi-permeable cellophane layer. The stacked layer was placed over the lower open end of a 3.7 cm wide glass container and secured with an elastic band to make it watertight. The cylinder (contributor compartment) was submerged in 100 ml of phosphate support pH 5.5 in a separate container (receptor compartment). The outer layer of support was 1 cm deep, and the cell was buried there. A charming stirrer maintained the framework's temperature at 37°1° and its speed at 30 rpm throughout the analysis. Tests 5 ml were taken out at intervals of 1, 2, 3, 4, and 5 hours. To maintain a constant volume, a comparable amount of fresh cushion was added to replace each example's volume. Using a UV spectrophotometer, the samples were split by man channel paper, diluted to 10 ml, and the absorbance was determined at a particular maximum of 254. Three times as much of the investigation was done, and typical value is accounted for.

Table 4: Study of Boswellia serrata [F1-F8] in vitro diffusion

Time (min/hr)	**% Drug release**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	31.5	34.03	31.3	33.4	37.4	30.1	28.3	20.0

2	40.2	40.3	42.5	42.5	43.2	40.4	42.5	43.2
3	60.2	60.7	63.4	63.4	66.2	62.3	63.4	67.4
4	72.3	73.4	73.32	73.32	78.3	70.7	72.8	73.5
5	72.2	72.32	75.2	75.2	80.55	78.2	77.5	98.4

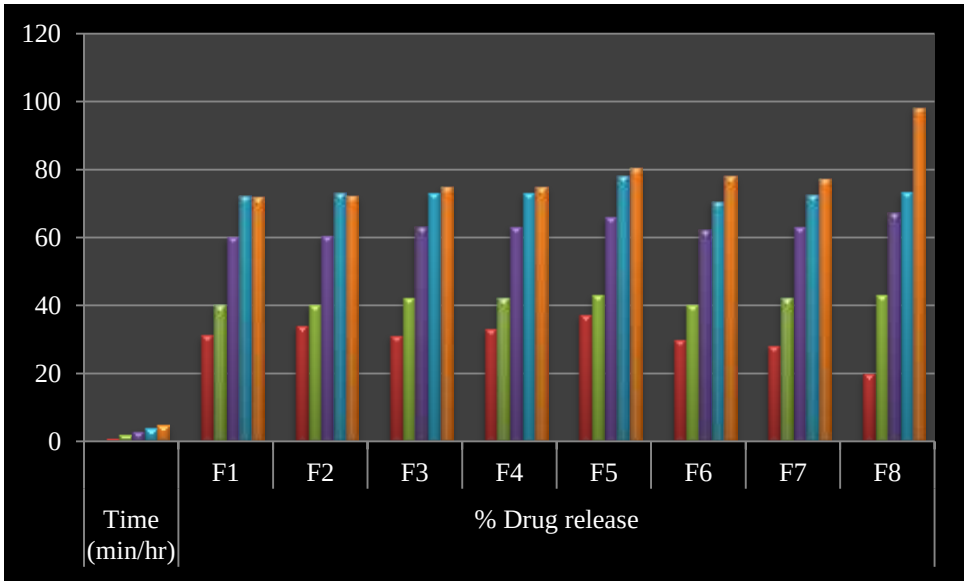

Figure 4: Study of Boswellia serrata [F1-F8] in vitro diffusion

5.5. Stability Study:

A sufficient amount of the gel formulation was squeezed into a strength holder and maintained in a soundness chamber at 450 c and 75 % RH.

Table 5: analysis of the stability of the formulation

Sr. no.	Parameter	Stability after 1 month of a optimized batch F5	Stability after 2 month of a optimized batch F5	Stability after 3 month of a optimized batch F5
1	Colour	Yellow	Yellow	Yellow
2	Physical Apprearance	No change	No change	No change
3	Drug Content (%)	89.45%	89.40%	89%
4	PH	5.08%	5.08%	5.08%
5	consistency	Smooth	Smooth	Smooth

6. Conclusion

The vast majority of plants depicted in this study clearly demonstrated the value of using natural plants to treat rheumatoid arthritis, as well as their potential as a source for new drugs or as a starting point for new drug development. According to our analysis, the development of Boswellia serrata (Shallaki) gel is an ideal topical pharmaceutical delivery method to facilitate drug administration, minimize broad phase 1 digestion, aid in increasing bioavailability, and

furthermore reduce side effects. Different Boswellia serrata (Shallaki) formulations were evaluated, and the F5 formulation was deemed to be the best formulation.

Shallaki removed the FTIR formulation since he believed that the excipients and the medication did not work together. While HPMC fails to create the desired gel consistency The FTIR analysis revealed that the generated item is a mixture of the drug and the polymers used, but not the response item containing the excipients used. For formulation F5, a good in vitro drug discharge was observed. As a result, the boswellic acid-based enemy of gout gel has incredible promise for the treatment of gout.

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