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Formulation and Evaluation of Polyherbal Gel for Anti-inflammatory Activity

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ABSTRACT
Inflammation is the tissue's immunologic response to injury, characterized by mobilization of white blood cells and antibodies, swelling, and fluid accumulation according to the International Association for the Study of Pain. Herbal medicines are natural remedies derived from plants. However, they elicit concerted pharmacological intervention of several compounds that interact with multiple targets instead of a single compound that interacts with a single target. 10 batches of polyherbal gel formulations were developed using extracts of Curcuma amada, Piper nigrum and Lodhra (Symplocos racemosa), menthol and Capsaicin. Formulation F1 to F5 were prepared using Carbopol 934 and F6 to F10 were prepared using HPMC K4M as gelling agent. Developed formulations were evaluated for various evaluation parameters for gel such as Physical Examination, Determination of pH. Viscosity Measurement, Spreadability, Extrudability, Washability and In-vitro diffusion study. Formulation F2 showed good spreadability of 32.48±0.65 g.cm/sec. It was found that as concentration of gelling agent (Carbopol 934 and HPMC K4M) increases spreadability decreases. Extrudability of all polyherbal gel formulation was found to be between 73.06 % to 95.37%. Results showed that, as concentration of gelling agent increases; % drug diffusion decreases. Release of components from polyherbal formulations prepared using Carbopol 934 was found to be better as compared with polyherbal formulations prepared using HPMC K4M. In vitro anti-inflammatory activity of gel formulation can be attributed to its polyphenol contents. F2 formulation was found to be stable. Developed formulation is needed to be scaled up on pilot scale; also clinical trials are necessary to carry out the successful launching of polyherbal topical gel formulation for management of pain.
Keywords: *Capsaicin, Curcuma amada,in-vitro anti-inflammatory activity, Menthol, Piper nigrum, Polyherbal formulation, Symplocos racemosa.*

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INTRODUCTION

Number of plants from Zingiberaceae family are used in traditional system of medicine. *Curcuma amada* (White turmeric) is one member of this family which is traditionally used as carminative and stomachic [1]. Literature survey indicates the presence of multiple chemical constituents in these rhizomes. However, very few references about the evaluation of pharmacological activity of the extract are available indicating its carminative, stomachic and CNS activity [2]. The extract exhibited hypercholesteremic effect in rabbits and showed presence of antibiotic principle with strong inhibitory activity on *Aspergillus niger* and *Trichophyta rubrum*. The rhizomes are used for the treatment of inflammatory conditions as a household remedy on empirical basis [3, 4]. *Piper nigrum* commonly known as black pepper, it belongs to the family piperaceae. The plants are indigenous and cultivated in hot and moist parts of India [5]. Black pepper is used as spice as well as medicine by itself or as a part of some herbal remedies in combination with other well-known herbs and spices [6]. Pungent alkaloid piperine is the main therapeutically active constituents of *pipper nigrum* [7]. *Symplocos racemosa* (Symplocaceae) commonly known as "Lodhra" in Sanskrit or "Rodhra, is a small, evergreen tree upto 6 m in height. It is found in the plains and lower hills throughout North and East India [8]. The bark is dark grey and rough; and is useful in diarrhea, dysentery, eye diseases, fever, ulcer, scorpion sting, diabetes, and liver disorders [9]. It has been scientifically reported as an antimicrobial, anticancer and has beneficial effects in gynaecological disorders [10]. Menthol (also "mint camphor"), is a volatile oil extract derived from the genus Mentha (mint), is widely available in natural and synthetic forms. Menthol has been used as a topical pain reliever since ancient times [11]. Capsaicin is a compound found in chili peppers and responsible for their burning and irritant effect. In addition to the sensation of heat, capsaicin produces pain and, for this reason, is an important

tool in the study of pain. Capsaicin, a major ingredient of hot pepper, was considered to exhibit an anti-inflammatory property [12].

These traditional medicines take part in a significant position in health services around the world. The opioids or non-steroidal anti-inflammatory drugs, widely used to reduce the inflammation of various types, possess severe side effects like redness, itching etc. As a result, a search for other alternatives seems to be necessary which would be more beneficial. Gel formulations are used to deliver the drug topically because of easy application, increase contact time and minimum side effects as compare to other topical preparation and oral administration [13]. Hence present study was aimed to prepare polyherbal gel for in-vitro anti-inflammatory activity.

MATERIAL AND METHODS

Materials

Dried rhizomes of *Curcuma amada*, dried fruits of *Piper nigrum* and Lodhra (*Symplocos racemosa*) bark were purchased from local market of Nashik. The plant materials were authenticated by Prof. Manohar Gulab Gavit, Department of Botany, MVPS KAANMS Arts, commerce and Science College, Dist. Nashik (Maharashtra). (Authentication No. KAANMS/2020-21/56/Herbarium 3). Capsaicin was provided as a gift sample by Naturite Agro Products Limited Hyderabad, India. Menthol was purchased from S. D. Fine Chemicals, Mumbai. Carbopol 934 and HPMC K4M were obtained from N R Chem, Bombay. All other chemicals used were of analytical grade.

Methods:

Preparation of Plant Extract:

Ethanolic extract of White turmeric (*Curcuma amada*) Rhizome (EECA), Methanolic extract of Black pepper(*Piper nigrum*) fruits (MEPN) and Methanolic extract Lodhra (*Symplocos racemosa*) Bark (MESR) was carried out and evaluated for various phytochemical screening in previous study by authors. These extracts were used for preparation of polyherbal gel using Carbopol 934 and HPMC K4M as gelling agent.

Formulation of Polyherbal Gel:

Preparation of gel base

Gelbase were prepared by cold mechanical method described by Schmolka *et al.* Carbopol 934/HPMC K4M was dissolved slowly with stirring in 60 mL of demineralized water for 1 h to avoid agglomeration Then disodium edetate and triethanolamine were dissolved in 10 mL of demineralized water separately and stirred for 10 min. Propylene glycol (4.83ml) was mixed in 12 mL of demineralized water with stirring for 10 min. Disodium edetate and triethanolamine solution were added to Carbopol 934/HPMC K4M solution and the pH was then adjusted to 7.4 by stirring the solution for 10 min. Then propylene glycol solution was added with stirring for 10 min until a clear consistent gel base was obtained [14].

Preparation of gel formulation

10 formulations were prepared using different concentrations of extracts EECA, MEPN, MESR. Formulation F1 to F5 were prepared using Carbopol 934 and F6 to F10 were prepared using HPMC K4M as gelling agent. (Table 1)

EECA, MEPN, MESR, Menthol and Capsaicin were added as a drug to gel base with continuous stirring till drug got dispersed completely. The prepared gel was filled and sealed in the aluminum collapsible tube. A similar procedure was followed for base control gel without the extract and other active ingredient [14, 15, 16].

Evaluation of Polyherbal Topical Gel

Physical Examination

All formulated gels were packed in containers and then tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates [17].

Determination of pH

The pH of each gel formulation was measured using pH meter. The pH meter was calibrated with standard buffer solution at pH 4, 7 and 9 before it's use. Before taking the reading, for 10 min the electrode was inserted in the sample at room temperature and then reading of pH were noted [18, 19, 20].

Viscosity Measurement

The viscosity of gel formulation (0.5g each) were assessed for viscosity using Brookfield's Rheometer (R/S-CPS+ Rheometer with C75-2 measuring system) at 30 rpm and room temperature (25±2°C) [21].

Spreadability

The apparatus was modified and it consists of a wooden block with pulley at one end. A rectangular ground glass plate was fixed on the block. Gel (about 2 gm) was placed on the lower plate and was sandwiched between lower and upper glass plate having the same dimension, provided with the hook. The 500mg weight was placed on the top of the two plates for 5 minutes to expel air and to get uniform

film of gel. Excess of gel was scraped off. Upper plate was subjected to a pull of 50gm. Time (Sec) required by the upper plate to cover a distance of 10cm was noted. This spreadability was calculated from following equation. Shorter the time interval better the spreadability [22].

S= M x L/T

Where, S= Spreadability, M=Weight tied to upper slide, L=Length of the glass slide, T=Time taken for plates to slide the entire length (sec).

Extrudability

The gel formulations were filled in standard capped collapsible aluminum tubes and sealed by crimping to the end. The weights of the tubes were recorded. The tubes were placed between two glass slides and were clamped. 0.5 g was placed over the slides, and then, the cap was removed. The amount of the extruded gel was collected and weighed. The percent of the extruded gel was calculated [23, 24].

Grittiness

All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence, obviously the gel preparation fulfills the requirement of freedom from particular matter and form grittiness as desired for any topical preparation [20, 24, 25, 26].

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually [27].

***In-vitro* diffusion study**

The *in-vitro* diffusion of all polyherbal formulation and marketed Diclofenac sodium Gel 0.5% was studied using the classical standard cylindrical tube fabricated in the laboratory a simple modification of glass tube of 15 mm internal diameter and 100 mm height. The commercial semi-permeable membrane cellophane, presoaked overnight in the freshly prepared dissolution medium (phosphate buffer pH 6.8), was tied to one end of open cylinder (open at both the sides), which acted as a donor compartment. 1 g of polyherbal formulation was placed inside this compartment. The diffusion cell membrane acted as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment comprising of 25 ml of phosphate buffer (pH 6.8) in a 100 ml beaker. The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 37° ± 0.5°C. At specific time intervals, 1 ml aliquot of sample was withdrawn from the receptor compartment and replaced with fresh buffer solution. The aliquot was analyzed for the drug content using UV-VIS spectrophotometer at determined wavelength after appropriate dilutions against reference using phosphate buffer pH 6.8 as blank [14, 28].

Selection of Satisfactory Formulation of Polyherbal Gel

Among 10 polyherbal gel formulation satisfactory formulations were selected on the basis of pH, viscosity, spreadability, homogeneity, extrudability and washability.

Evaluation of Satisfactory formulation

Thixotropy Analysis

The rheological study of Lisinopril ion-Pair Gel of F2 formulation and plain Lisinopril gel (0.5g each) were assessed for viscosity using Brookfield's Rheometer (R/S-CPS+ Rheometer with C75-2 measuring system) at 30rpm and room temperature (25±2°C) [29].

TABLE 1: COMPOSITION OF POLYHERBAL TOPICAL GEL

Code	EECA(g)	MEPN(g)	MESR(g)	Menthol(g)	Capsaicin (g)	Carbopol 934 (g)	HPMC K4M (g)	TEA (g)	Disodium EDTA (g)	Propylene Glycol (g)	Methyl paraben (g)	Propyl paraben (g)	Water (100 g)
F1	1	1	1	1	1	0.5	-	1.5	0.005	5	0.1	0.05	q.s.
F2	2.67	2.67	2.67	1	1	1.0	-	1.5	0.005	5	0.1	0.05	q.s.
F3	4.33	4.33	4.33	1	1	1.5	-	1.5	0.005	5	0.1	0.05	q.s.
F4	6	6	6	1	1	2.0	-	1.5	0.005	5	0.1	0.05	q.s.
F5	7.67	7.67	7.67	1	1	2.5	-	1.5	0.005	5	0.1	0.05	q.s.
F6	1	1	1	1	1	-	0.5	1.5	0.005	5	0.1	0.05	q.s.
F7	2.67	2.67	2.67	1	1	-	1.0	1.5	0.005	5	0.1	0.05	q.s.
F8	4.33	4.33	4.33	1	1	-	1.5	1.5	0.005	5	0.1	0.05	q.s.
F9	6	6	6	1	1	-	2.0	1.5	0.005	5	0.1	0.05	q.s.
F10	7.67	7.67	7.67	1	1	-	2.5	1.5	0.005	5	0.1	0.05	q.s.

EECA: Ethanolic extract of White turmeric (Curcuma amada) Rhizome, **MEPN**: Methanolic extract of Black pepper (Piper nigrum) fruits, **MESR:** Methanolic extract Lodhra (Symplocos racemosa) Bark, **TEA**: Triethanolamine, q.s.: Quantity sufficient

Skin irritation study

Three Wistar rats were housed in cages fitted with perforated floors. Water and standard rat feed were given ad libitum. The room temperature was maintained at 22 ± 3°C with 30-70 % relative humidity. The light conditions were controlled to give12 h artificial light (8 am to 8 pm) each day. Twenty four hours before the test (dose application), hair on the back and flanks of each rat were shaved cleanly, exposing approximately 4 cm^2 area of skin. The F2 polyherbal gel formulation was evenly applied to 3 cm^2 area of the closely clipped skin of each rat. Skin reaction at the site of application was subjectively assessed and scored once daily at 1, 24, 48, 72 h, 7 and 10 days (post-test observation period) accordingly. [14, 30].

Stability Studies

The main objective of the stability testing is to provide evidence on how the quality of the drug product varies with time under the influence of temperature and humidity. The stability study for the topical herbal gel formulation was done as per ICH guidelines in a stability chamber for a period of 6 months. The selected topical polyherbal gel formulation F2 was placed in a humidity chamber at 25°C ± 2°C/60% RH ± 5% RH, 32°C ± 2°C/60% RH ± 5% RH and 40°C ± 2°C/75% RH ± 5% RH. Samples were withdrawn at an initial, first, second, third and sixth months and evaluated for change in homogeneity, pH and viscosity [14].

In-vitro Anti-Inflammatory

Inhibition of albumin denaturation

In vitro anti-inflammatory activity was determined by inhibition of protein (egg albumin) denaturation method.

Control Solution (50 ml): Phosphate buffer saline (28ml) of pH 6.4 was transferred to freshly prepared egg albumin (2ml) and distilled water (20ml) was added to this, to prepared control solution.

Standard Solution (50 ml): Phosphate buffer saline (28ml) of pH 6.4 was transferred to freshly prepared egg albumin (2ml) and (20ml) solution of diclofenac sodium of different concentration ranges from 10 - 2000 µg/ml was added to this, to prepared standard solution.

Test Solution (50 ml): Phosphate buffer saline (28 ml) of pH 6.4 was transferred to freshly prepared egg albumin (2 ml) and (20ml) solution of F2 formulation of different concentration ranges from 10 - 2000 µg/ml was added to this, to prepared test solution.

All the solutions were incubated at 37 ± 2 °C for 15 minutes and it was then heated at 70 °C on a water bath for 5 minutes. The solutions were allowed to cool at room temperature. The absorbance was then measured using UV-Visible spectrophotometer at 660 nm using vehicle as blank [31, 32].

The percentage inhibition of protein denaturation was calculated from the control using below under formula:

Percentage inhibition = (Abs Control –Abs Sample) X 100/ Abs control

RESULTS AND DISCUSSION

Formulation of Polyherbal Topical Gel

Formulation F1 to F5 were prepared using Carbopol 934 and F6 to F10 were prepared using HPMC K4M as gelling agent successfully.

Evaluation of Polyherbal Topical Gel

Physical Examination

All 12 formulations of polyherbal gel were found to be homogeneous and in good appearance and consistency with no any agglomerates and gritty particles.

Determination of pH

The pH values of all the formulations were in the close range of neutral pH (6.22-6.86) and hence it caused no skin irritation.

Viscosity Measurement

Viscosity of all formulations was found to be between 3.96±0.26 Pa.S to 12.63±1.06 Pa.S. It was found that concentration of gelling agent (Carbopol 934 and HPMC K4M) increases viscosity increases. Among all formulation; F2 containing 1 % of Carbopol 934 showing excellent viscosity of 7.61±0.34 Pa.S.

Spreadability

Spreadability of all formulations of polyherbal gel was found to be in between 12.38±1.93 g.cm/sec to 45.58±1.56 g.cm/sec. Formulation F2 showed good spreadibility of 32.48±0.65 g.cm/sec. It was found that concentration of gelling agent (Carbopol 934 and HPMC K4M) increases spreadability decreases.

Extrudability

Extrudability of all polyherbal gel formulation was found to be between 73.06 % to 95.37%. Formulation F2 showed % extrudability 94.54 hence considered as excellent extrudability.

Washability

Among all 10 formulations of polyherbal gel formulation F1, F2, F6 and F7 was found to be having excellent washability.

In-vitro diffusion study

The in-vitro diffusion of all polyherbal formulation and marketed Diclofenac sodium Gel 0.5% was studied. Results showed that, as concentration of gelling agent increases; % drug diffusion decreases. Release of components from polyherbal formulations prepared using Carbopol 934 was found to be better as compared with polyherbal formulations prepared using HPMC K4M. Polyherbal formulation F2 containing 1 gm of Carbopol 934 showed better drug release as compared to all other polyherbal formulations and marketed Diclofenac sodium Gel 0.5%. Results are shown in Figure 1.

TABLE 2. EVALUATION OF POLYHERBAL GEL

Formulation	Consistency	Ph	Viscosity (Pa.S)	Spreadibility (g.cm/sec)	Homogeneity	Washability
F1	Fluid	6.22±0.13	4.86±0.89	45.58±1.56	Homogeneous	Excellent
F2	Semisolid	6.84±0.38	7.61±0.34	32.48±0.65	Homogeneous	Excellent
F3	Semisolid	6.35±0.43	8.97±0.66	24.73±1.08	Homogeneous	Good
F4	Semisolid	6.43±0.19	10.42±0.91	18.94±1.44	Homogeneous	Good
F5	Stiff	6.73±0.44	12.63±1.06	12.38±1.93	Homogeneous	Good
F6	Fluid	6.38±0.15	3.96±0.26	46.31±1.42	Homogeneous	Excellent
F7	Fluid	6.86±0.42	4.53±0.43	38.49±1.81	Homogeneous	Excellent
F8	Semisolid	6.72±0.39	6.73±1.28	31.92±1.33	Homogeneous	Good
F9	Semisolid	6.64±0.23	9.68±1.08	25.66±1.27	Homogeneous	Good
F10	Stiff	6.82±0.67	11.39±1.44	21.34±1.08	Homogeneous	Good

** All values represent mean ± standard deviation (n=3)*

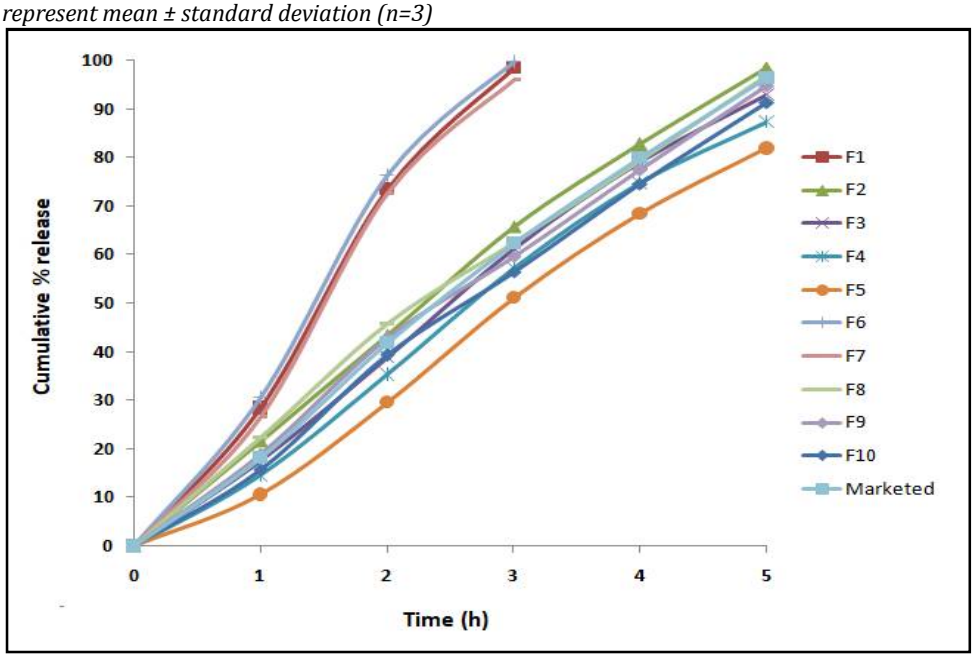

Fig. 1: In-vitro diffusion study of polyherbal gel (F1 to F10) compared with marketed formulation

Selection of Satisfactory Formulation of Polyherbal Gel

On the basis of pH, viscosity, spreadability, homogeneity, extrudability, washability and in-vitro drug diffusion study; formulation F2 containing 1 % of Carbopol 934 showing homogenous formulation with pH 6.84±0.38, viscosity 7.61±0.34 Pa.S, excellent spreadability of 32.48±0.65 g.cm/sec and excellent washability, extrudability and in-vitro diffusion. Hence formulation F2 was considered as optimized formulation and was used for further evaluation.

Evaluation of Satisfactory Formulation

Thixotropy Analysis

Rheological study of 0.5 g of F2 formulation was carried out. Results are summarized in Table 3. Viscosity diagram and thixotropy analysis of are shown in Figure 2 and 3.

Skin irritation study/ acute dermal toxicity

The prepared polyherbal gel (F2 formulation) was evaluated for its skin irritant effect. Results of skin irritation test indicate that prepared polyherbal gel did not produce irritation, redness, or edema on application it was free from dermatological reaction. As no erythema or edema was observed for F2 formulations, even after 10 days of study, indicating that the prepared polyherbal gel formulation was found to be safe.

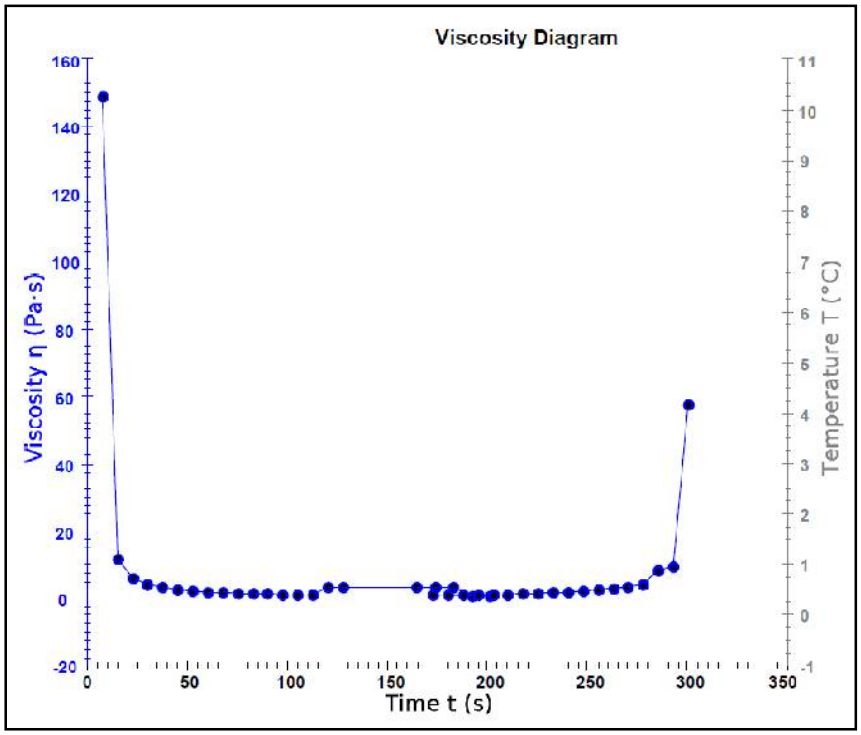

Fig. 2. Viscosity diagram

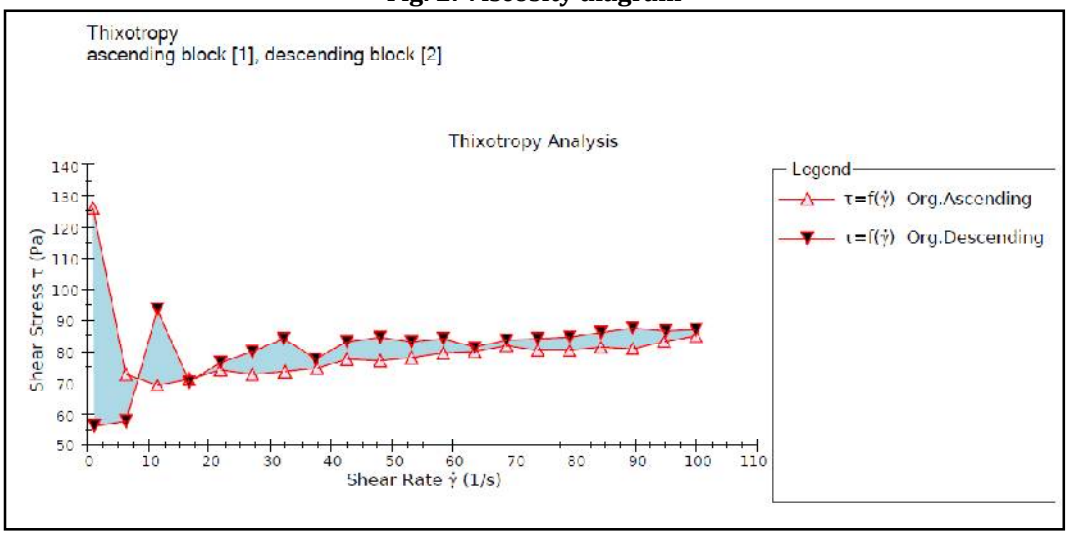

Fig. 3. Thixotropy analysis

Stability Studies

In order to ensure the quality of polyherbal gel formulation throughout the shelf life, stability study was performed as per ICH guidelines on F2 formulation as it exhibited better quality characteristics. Negligible change in homogeneity, pH and viscosity was observed after 0,1,2,3 and 6 months of stability testing. Results of the study clearly revealed that the formulated topical polyherbal gel F2 is found to be stable.

In-vitro Anti-Inflammatory

Inhibition of albumin denaturation

In order to investigate the mechanism of the anti-inflammation activity, the ability of extract to inhibit protein denaturation was evaluated. It is simple and convenient method to evaluate the anti-inflammatory activity. Present findings revealed that polyherbal gel formulation F2 and Diclofenac

sodium (reference) exhibited a concentration-dependent inhibition of protein denaturation ranges from 10-50 µg/ml. Maximum inhibition of 82.40% was observed at the concentration of 50 µg/ml of F2 formulation. Diclofenac sodium showed the maximum inhibition, 85.47% at the concentration of 50 µg/ml.

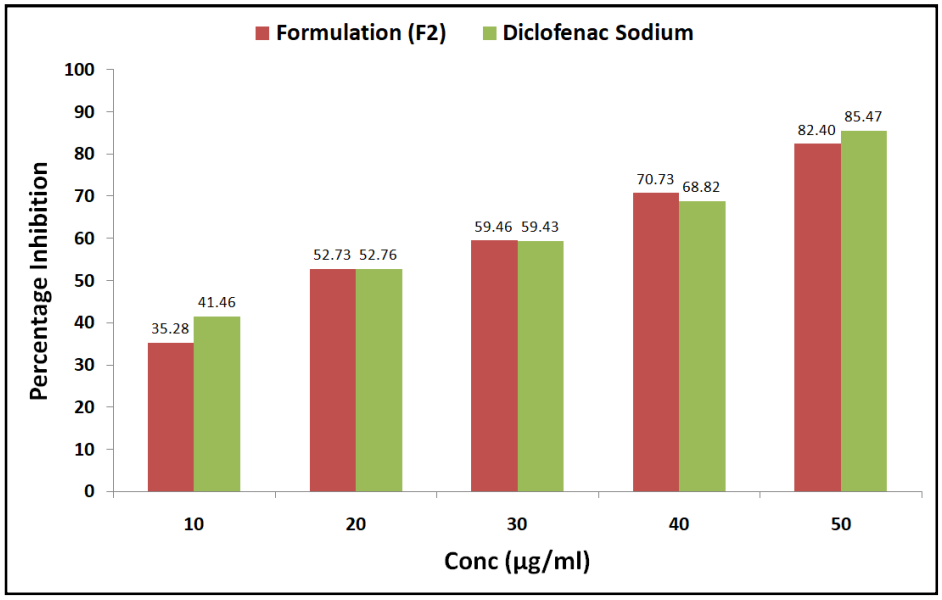

Fig. 4. Effect of polyherbal formulation (F2) on heat induced protein denaturation

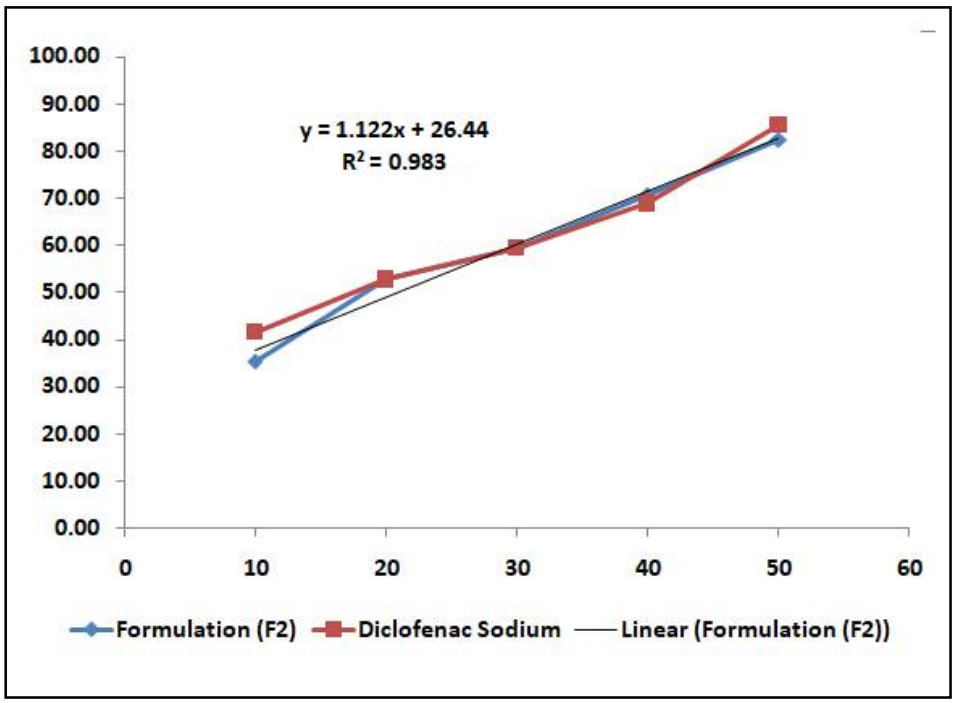

Fig. 5. Correlation between % inhibition of formulation (F2) and Diclofenac sodium

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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