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"Formulation and Evaluation of Topical Herbal Gel For the Treatment of Arthritis''

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ABSTRACT:
The present work deals with the Development and Evaluation of Poly-Herbal Anti-inflammatory Formulation containing alcoholic extract of xanthium strumarium ,Vitexnegundo leaves, , lantana camara& linseed oil for treatment of arthritis. The gel was prepared using polymer carbopol 940 (1% w/v), propylene glycol 400, triethanolamine, propylparaben, methyl paraben and required amount of distilled water. Various conc. of extract were taken for formulations (F1 to F3). Prepared formulations (F1 to F3) were evaluated for various parameters like colour, appearance, consistency, viscocity, pH, spreadability, stability along with anti-inflammatory activity by using model carageenan induce paw edema in rats. F3 formulation was found optimum for all the parameter.

KEYWORDS: VitexNegundo, xanthium strumarium , lantana camara, xanthium strumarium, pH, Carbopol.

I. INTRODUCTION:

Arthritis is an auto immune disorder that affects about 0.5-1 % of the population worldwide. The drugs commonly prescribed for Rheumatoid Arthritis are steroidal, non-steroidal anti-inflammatory, disease modifying antirheumatic and immunosuppressant drugs that are known to produce various side effects including gastrointestinal disorders, immunodeficiency and humoral disturbances. NSAIDS Couses severe liver damage on prolonged used,Manypetients becomes resistant to the pain killer drugs because the prolonged use of these drugs Couses drug Tolerance in petients. So the petients are widely promoted towards Herbal ancient Ayurvedic treatment. Those petients use veriousveriousleaf,Bark, roots and different parts of medicinal plants in a nonsuitabble dosage form. For the satisfactory treatment of arthritis there is a need to develop a suitable gel of such medically important plant which are not available in market.

Xanthium strumarium (rough cocklebur, clotbur, common cocklebur, large cocklebur, woolgariebur)is a species of annual plants of the family Asteraceae. It probably originates in North America and has been extensively naturalized elsewhere.Whole plant of Xanthium strumanrium as well as all parts separately is used in medicine have shown dose dependant analgesic and antiinflammatory actions of petroleum ether extracts. demonstrated notable diuretic effect of the herb. Phenolic compounds are known to have wide range of biological activites. Catechol detected here might be responsible for antiinflammoatory activity. Flavonoids also are anti-inflammatory. Alkaloids are well known for their extraordinary spectrum of pharmacological activities especially as central nervous system depressant.

Vitexnigundolinn: Vitexnegundo L. commonly known as Nirgundi belongs to family Verbenaceae. Vitexnegundo Linn.use for cure various types diseases. Traditionally the leaves of are documented to possess antibacterial, antitumor, astringent, febrifuge, sedative, tonic and vermifuge. This species is globally distributed in Indo-Malesia, cultivated in America, Europe, Asia and West Indies. Within India, it is found throughout the Maharashtra. Vitex contains the flavonoids, casticin, chryso-splenol and vitexin. Vitex contains Chrysophenol D. which is a substance with anti-histamine properties and muscle relaxant. Leaves contains two alkaloids nishindine and hydrocotylene. The main compounds are viridiflorol (19.55%), beta-caryophyllene (16.59%), sabinene (12.07%].aordinary spectrum of pharmacological activities especially as central nervous system depressant.

Lantana camara L., commonly known as red sage from Verbenaceae family, is a noxious weed

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Lantana camara L. has been well studied chemically. Two active toxic principles lantadene α and β are considered the most important. In addition, two new pentacyclictriterpenoidslancamarinic acid and lancamarinin have been obtained from the aerial parts of Lantana camara L. Different parts of this plant are used in traditional medicine for the treatment of febrile illness, skin infections, and diarrhea. However, Only a small proportion of the Lantana camara L have been tested to confirm their anti-inflammatory activity. To date, no comprehensive literature is available concerning their usage as an anti-inflammatory. It is thus important to preserve valuable herbal knowledge which could be useful for future drug discovery efforts. The aim of the present review was to compile extensive literature evidence of both in vitro and in vivo studies that reported the anti-inflammatory activity of Lantana camara L.

The aim of current research trend is to discover newer drugs from plant kingdom which may provide therapeutic cure and which also should be cost effective, thus would be widely accepted developing nation like India.

II. MATERIAL AND METHODS

Carbopol 940, Propylene glycol 400 (LOBA CHEMIE PVT.LTD, Mumbai); Propylparaben, Methyl Paraben, EDTA (ResearchLab Fine Chem Industries, Mumbai); Triethanolamine (SAMAR CHEMICALS, Nagpur) All other chemicals used were of analytical grade.

Plant material collection and authentification:

The leaves of Vitexnegundo collected from local area of Amravati and the leaves of xanthium strumariumcollected from local area of dongarpipla (Maharashtra) in January 2021. Thelantana camara from BarsaiyaAyurvedic Shop, Amrawati. The above herbs were authentified by K. Zambre principal and head of department of medicinal chemistry BSPM's college of pharmacy Ambajogai.

Extract preparation:

The collected materials were washed thoroughly in water, chopped, air dried for a week at 35-40°C and pulverized in electric grinder and exhaustively extracted successively in soxhlet apparatus, using petroleum ether, ethanol respectively. The extracts were concentrated under reduced pressure.**Formulation of Gel:**

Carbopol 940 (1 % w/w) and purified water were taken in a beaker and allowed to soak for 24 hr. Stirred by mechanical stirrer at 400 to 650 rpm. Add ethanolic extract Vitexnegun, xanthium strumarium , lantana camara of were dispersed in alcohol in separate container then add this in carbopol 940. Then neutralized with sufficient quantity of Triethanolamine. Propylene glycols 400 as penetration enhancer, methyl paraben and Propylparaben as preservatives were added slowly with continuous gently stirring until the homogenous gel was formed. The formulation of developed gel formula given in table no. 1.

Table No. 1: Formulation table showing composition of F1, F2 and F3 gel formulation

Intgredient	F 1	F 2	F 3
Ethanolic extract of Vitexnegundo	100 mg	150 mg	200 mg
Ethanolic extract of xanthium strumarium ,	100 mg	150 mg	200 mg
Ethanolic extract of lantana camara	50 mg	50 mg	50 mg
Carbopol 940	1 gm	1 gm	1 gm
Alcohol	2 ml	2 ml	2 ml
Methyl paraben	0.2 gm	0.2 gm	0.2 gm
Propylparaben	0.02 gm	0.02 gm	0.02 gm
EDTA	0.01 gm	0.01 gm	0.01 gm
Propylene glycol 400	4 ml	4 ml	4 ml
Wintergreen oil	2 ml	2 ml	2 ml
Triethanolamine (To maintain pH7)	Q. S.	Q. S.	Q. S.
Water	100 ml	100 ml	100 ml

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Evaluation of Developed Gel Formulation:

Following are the parameters for the evaluation of gel as per standard guidelines.

1. Physicochemical parameters:

All the formulated herbal gels for inflammation were tested for the physiochemical parameters like appearance, colour, odour, homogenicity by visual inspection and the result are shown in Table no. 2.

2. pH:

Weighed 20gm of each gel formulation were transferred in 10ml of beaker and measured it by using digital pH meter i.e. EquipTronics. Formulation was carried out in triplicate and the average values are represented [10] .pH of the topical gel formulation should be between 3-9 to treat the skin infection. The results are shown in Table no. 3.

3. Spreadability:

Spreadability was determined by the apparatus which consists of a wooden block, which was provided by a pulley at one end. By this method spreadability was measured on the basis of slip and drag characteristics of gels. An excess of gel (about 2.5 g) under study was placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with a hook. A 1 kg weight was placed at the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 50 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 5 cm was noted . A shorter interval indicated better spreadability. Spreadability was calculated using the following formula.

$$S = \frac{M * L}{T}$$

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

4. Viscosity:

Viscosity of herbal gel was determined by using Brookfield rotational viscometer. The correct spindle was selected (spindle No. 4) for the given product then the operating condition was setup. Then the viscosity was measured directly at 6-rpm speed by keeping the torque constant. The mean was obtained. The viscosities of all formulations have been found to be in the centipoises at room temperature, and the results are shown in Table no. 3. The viscosity of gelling agents in the gelling layer be within range of about 1000 cps to about 100,000cps. The viscosity is determined by following formula:

Viscosity (centipoises) = Dial Reading × Factor

Factor: For model LV- 4(spindle) at 6 RPM is 1M (M=1000)

5. 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. 500 gm 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 (>90% extrudability: excellent, >80% extrudability: good, >70% extrudability: fair).

6. Drug Content (Content of Uniformity):

The drug content was determined by taking 1ml of the formulation and diluting it to 100 ml with distilled water. Aliquot of different concentration was prepared Vikram CH, et al. J Sci Res Pharm, 2018;7(2):13-17 © 2012, JSRP. All Rights Reserved http://www.worldinventiapublishers.com/ by withdrawing 1ml from above solution and further diluted to 10 ml with phosphate buffer 7.4, Vitexnegundo, Boswelliaserrata and Berberisaristata was determined at 250 nm, 260 nm and 348nm respectively by using UV-Vis spectrophotometer. The absorbance of other solutions also taken against blank solution by using respective λmax (Shimadzu UV/VIS spectrophotometer-1700). The % Drug content in all formulations was in the range of 40-85% indicating uniform distribution of drug. It was calculated by using the equation, which was obtained by linear regression analysis of calibration curve [13] . Drug content of three gel formulation given in table no. 3

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formulations	Appearance	colour	Odour	Homogenetly
1	Smooth	Pale yellow	Characteristics	Homogenous
2	Smooth	Dull Green	Characteristics	Homogenous
3	Smooth	Yellowish green	Characteristics	Homogenous

Table No. 2: Physicochemical Parameters

formulation	pH	Spredability g.cm/sec	Viscosity at 6rpm(centipois)	% Extrudation	%Drug content
1	5.75	27.77	58666.6	70.04	82.6 %
2	5.75	21.13	33000	71.81	92.1 %
3	6.05	22.06	32666.6	76.89	92.8 %

Table No. 3: Results of evaluation parameters of various gel formulations

7. In-vitro drug release study:

The in-vitro diffusion studies were carried out using Franz diffusion cell apparatus and semi-permeable cellophane membrane. Cellophane membrane (egg membrane & rat skin), previously soaked overnight in phosphate buffer 7.4 was mounted by tied and sandwiching between the donor and receiver compartment. Franz diffusion cell with a diameter 3.7 cm was used in in-vitro release studies. A glass tube with both end open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. A one gram sample was accurately weighed and placed on a semipermeable cellophane membrane to occupy a circle of 3.7 cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7 cm diameter and made water tight by rubber band. The tube (donor compartment) was immersed in a beaker containing 100 ml of phosphate buffer pH 7.4 (receptor compartment). The cell was immersed to a depth of 1 cm below the surface of buffer. The system temperature was maintained at 37°±1° and speed was maintained at 30 rpm throughout the experiment by magnetic stirrer (Fig.2.2). Samples 5 ml were withdrawn at intervals of 0, 1, 2, 3, 4, 5 and 6 hour, the volume of each sample was replaced by the same volume of fresh buffer to maintain constant volume. The samples were filtered through Whatman filter paper, diluted up to 10 ml and absorbance was taken by UV spectrophotometer at respective ʎmax. The experiment was carried out triplicate and average value is reported [13] .

8. Stability studies:

The stability study was performed as per ICH guidelines.The formulated gel was filled in collapsible tubes and stored at different temperatures and humidity viz [14] ,

1) 25°C±2°C/60%RH±5%RH
2) 30°C±2°C/65%RH±5%RH
3) 40°C±2°C/75%RH±5%RH

Samples were evaluated for various criteria after 3 months. The tests carried out for the stability samples were appearance, pH, drug content uniformity, spreadability, and extrudability. The methodology adopted for all the above mentioned studies was similar to procedure discussed previously.

Table No. 4: Diffussion study

In vitro drug diffusion study time (hr)	F1	F2	F3
0	0	0	0
1	10.8	13.7	14.04
2	13.7	25.5	27.85
3	23.5	34.4	36.57
4	31.9	46.9	48.71
5	43	56.2	57.2

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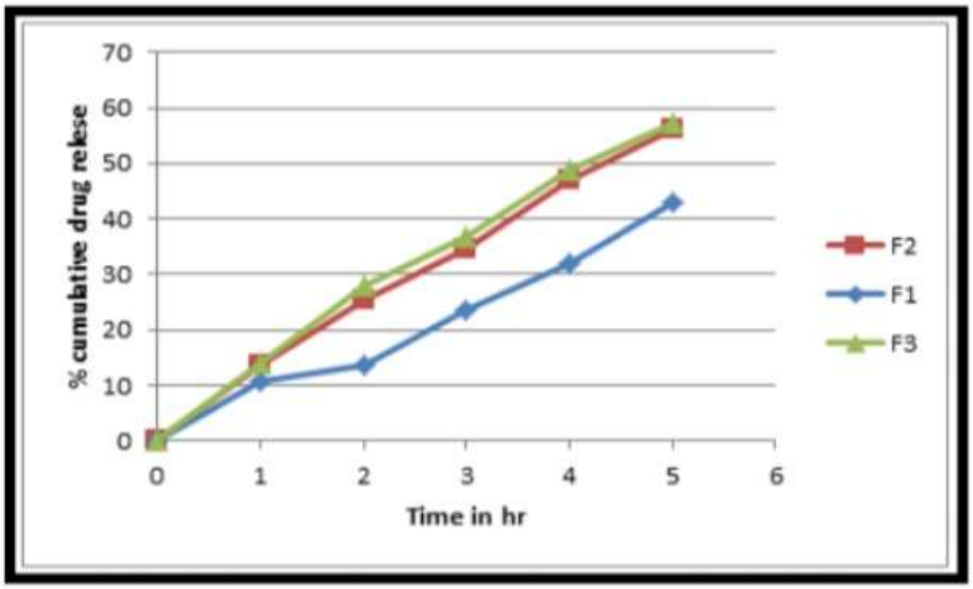

Fig. 2: Graphical representation of drug diffusion studies of gel formulations

Table No. 5: Stability study of herbal gel formulation

Colour			
Formulation	**At Room Temperature**	**At 40± 2°C/75±5% RH**	**Stored in freeze**
I	No change in Colour	Slight Change in colour	No change in Colour
II	No change in Colour	Slight Change in colour	No change in Colour
III	No change in Colour	Slight Change in colour	No change in Colour
Phase Separation			
Formulation	**At Room Temperature**	**At 40± 2°C/75±5% RH**	**Stored in freeze**
I	No Phase Separation	No Phase Separation	No Phase Separation
II	No Phase Separation	Slight Phase Separation	No Phase Separation
III	No Phase Separation	No Phase Separation	No Phase Separation
pH			
Formulation	**At Room Temperature**	**At 40± 2°C/75±5% RH**	**Stored in freeze**
I	5.75	5.63	5.78
II	5.75	5.24	5.09
III	6.03	6.37	5.09
Viscosity at 6 rpm (centipoises)			
Formulation	**At Room Temperature**	**At 40± 2°C/75±5% RH**	**Stored in freeze**
I	58666.6	66160	41660
II	33000	57166	54160
III	32666.6	33000	32000
Spreadability (g. cm/sec)			
Formulation	**At Room Temperature**	**At 40± 2°C/75±5% RH**	**Stored in freeze**
I	27.77	31.77	29.05
II	21.13	33.59	33.5
III	22.06	27.77	27.06

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III. RESULT AND DISCUSSION :

All physiochemical evaluation parameter of gel formulation are given in Table no. 2 from the result evident that all three gel formulation having good gelling property and homogenicity. The pH of all three formulations ranged between 5.75 to 6.05 which is acceptable for topical formulation. The extrudability of gel formulation from the collapsible tube varied from 70-76 g/cm2 whereas the results of spreadability varies from 22 to 27 g.cm/sec. A comparative study of viscosity and spreadability showed that the viscosity of the formulations increases, spreadability decreases and vice versa. From the results, it is clearly evident that all three optimized formulation showed good extrudability, homogenecity, viscocity and spreadability. The developed gel formulations were subjected to stability study as per ICH guidelines for the period of three months. By observing that effect of aging, viscosity, pH, spreadability, extrudability, it was confirmed that the developed gel posses good stability. It was observed that slight phase separation of F2 occurring at 40°C temperature. Other formulations showed good stability. The pH was constant throughout the study to about 6.5 and the gel did not produce any irritation upon application to the skin. The drug content uniformity of the gels were found in the range of 82-92%, F3 formulation contain more drug content as compared to other two gel formulations. F3 shows greater drug release 57.2% as compared with F2 drug release which is 56.2% in 5hrs.

IV. CONCLUSION

The present study demonstrated that Vitexnegundo has rich source of secondary metabolites. These findings suggested that Vitexnegundo could be a potential source of natural antioxidant having great importance as a therapeutic agent and preventing oxidative stress related degenerative diseases. Further purification, identification and characterization of the active compounds would be our priority in future studies. Vitexnegundo have been meticulously studied for its chemical constituents and pharmacological studies. Taking into account its anti-inflammatory and anti-tumor and anti-arthritic and anti-ulcer activity plant is of great importance. However, lot of investigation could be made in the field of tissue culture and biotechnology o improve the yield of require chemical constituents within the plant. Few toxicological and analytical studies have been reported. The work could also be done in this direction to ensure free utility of this plant. This research work is carried out to develop a new topical herbal gel formulation for topical application. The prepared herbal gel was further evaluated for pH, Viscosity and extrudability, Spreadability, Drug content uniformity, In-vitro diffusion study, and stability Studies. The pH of all the formulations was in the range compatible with normal pH range of the skin. The drug content released was also above average. The rheological behaviors of the gel formulations were studied with Brookfield viscometer. The results indicated the viscosity of gel formulations was consistent neither too thick nor too thin. A comparative study of viscosity and Spreadability showed that with increase in viscosity of the formulation, the Spreadability decreased and vice versa. The gel formulation F3 was found to have all the desirable properties. Based on the above parameters, the formulation F3 is concluded as most promising formulation and in vitro model can be use for evaluation of its biological potency and it will useful for further clinical application.

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