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Study on Development, Valuation and Design of Herbal Gel

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Abstract: -Herbal medicines is still the mainstay of about 75-80% of the world's population, mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with human body and lesser side effects. Herbal medicines consist of plant or its part to treat injuries, disease or illnesses and are used to prevent and treat diseases and ailments or to promote health and healing. It is a drug or preparation made from a plant or plants and used for any to such purpose. Herbal medicines are the oldest form of health care known to mankind. Gel formulations prepared with Carbopol934, HPMC K 100 M and Xanthan gum showed good homogeneity, no skin irritation, good stability and anti-inflammatory activity. However, the Xanthan gum-based gel proved to the formula of choice, since it showed the highest percentage of extrudability, good spreadability and rheological properties. Formulation F5 with 1 % leaves extract and F11 with 1% root extract of Clerodendrum serratum showedthe best formulation with significant anti-inflammatory activity. Formulation 5 and F11 shows approximately equal anti-inflammatory activity. Hence, there is no need to used roots for the preparationof medicines for anti-inflammatory action.

Key Word: Formulation, Plant Extracts, Drug System

INTRODUCTION: -

Inflammation: Inflammation is a complex process, which is frequently associated with pain and involves occurrences such as: the increase of vascular permeability, increase of protein denaturation and membrane alteration. When cells in the body are damaged by microbes, physical agents or chemical agents, the injury is in the form of stress. Inflammation of tissue is due to response to stress. It is defensive response that is characterized by redness, pain, heat, and swelling and loss of function in the injured area. Inflammation is one of the body's nonspecific internal systems of defense, the response of a tissue to an accidental cut is similar to response that results from other type of tissue damage, caused by burns due to heat, radiation,

bacterial or viral invasion.[1] Inflammation dilutes, destroys, or walls off harmful agents that have entered the body. It activates a sequence of biological events to heal the damage. The most common causes of inflammation are infections, burns and trauma, and many types of immune reactions.

Classification of inflammation:

Inflammation may broadly classify into three categories;

Acute inflammation;

Chronic inflammation;

Miscellaneous;

Topical Drug Delivery System:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentrations. The route of administration has a significant impact on the therapeutic outcome of a drug. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g., acne) or the cutaneous manifestations of a general disease (e.g., psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominates the system for topical delivery, but foams, spray, medicated powders, solutions, as well as medicated adhesive systems are also in use. [3]

External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.

Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissuesfor local activity. Advantages of Topical Drug Delivery System: [5]

Avoidance of first pass metabolism.

Convenient and easy to apply.

Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes,

Achievement of efficacy with lower total daily dosage of drug by continuous drug input. Avoidsfluctuation in drug levels, inter- and interpatient variations.

Ability to easily terminate the medications, when needed.

A relatively large area of application in comparison with buccal or nasal cavity

Ability to deliver drug more selectively to a specific site.

Providing utilization of drugs with short biological half-life,

Improving physiological and pharmacological response.

Improve patient compliance.

Provide suitability for self-medication.

Disadvantages of Topical Drug Delivery System: [5]

Skin irritation of contact dermatitis may occur due to the drug and/or excipients.

Poor permeability of some drugs through the skin.

Possibility of allergenic reactions.

Can be used only for drugs which require very small plasma concentration for action

Enzyme in epidermis may denature the drugs

Drugs of larger particle size not easy to absorb through the skin

Classification of Topical Drug Delivery System:

Classification of Topical Drug Delivery System based on physical state-

Introduction to Herbal Medicines: [6-8]

Ever since the birth of mankind of there has been a relationship between life, disease and plants. There is no record that people in prehistoric times used synthetic medicines for their aliments but they tried to make use of the things they could easily procure. The most common thing they could find was there in environment i.e. the plants and animals. World Health Organization (WHO) has defined herbal medicinesare finished, labelled medicinal products that contain active ingredients, aerial or underground parts of the plants or other plant material or combination. Herbal formulations have reached widespread acceptability as therapeutic agents like anti-microbial, anti-diabetic, anti-ageing, anti- arthritic, anti- depressant, anti-anxiety, anti-inflammatory, anti-HIV, treatment of cirrhosis, asthma, migraine, Alzheimer's disease and memory enhancing activities.

Skin The skin is a most extensive and readily accessible organ of the human body. The skin of the average human being covers an area of about 2 square meter and weighs 4.5-5 kg, about 16 % of body weight. It also receives 1/3 rd of the total blood supply. Most topical preparation are meant to be applied to the skin and hence basic knowledge of skin and its physiological function and biochemistry is very important for designing topical formulations. The pH of the skin varies from 4 to 5.6. Sweat and fatty acids secreted from sebum influence the pH of the skin surface. It is suggested that acidity of the skin helps in limitingor preventing the growth of pathogens and other organisms [9-10].

Anatomy-Physiology of skin: - The skin is multi-layered organ and anatomically has many histological layers. Skin is an anatomic barrier between the body and its environment and contributes to about 16- 18% of normal body weight. The overlaying outer layer is called epidermis; the layer below epidermis iscalled dermis. Beneath the dermis are subcutaneous fatty tissues [9-11].

Gel: A gel is a solid or semisolid system of at least two constituents, consisting of condensed mass enclosing and interpenetrated by a liquid. Gels and jellies are composed of small number of solids dispersed in relatively large amount of liquid, yet they possess more solid-like than liquid-like character. The characteristic of gel and jelly is the presence of some form of cutaneous structure, which provides solid-like properties.

DRUG AND POLYMER PROFILE

Plant Profile:

Clerodendrum serratum:

Bharangi is botanically termed as Clerodendrum serratum. Clerodendrum serratum Linn. Is a genus of flowering plants in the **Verbenaceae. family. Bharangi** grows throughout India.

Ayurvedic Properties and Actions:

Fig. 1 Clerodendrum serratum

Rasa: Katu, Tikta, Kasaya**Guna:** Laghu, Ruksa **Virya:** Usna V

Ipaka: Katu

Karma: Dipana, Kaphahara, Pacana, Vatahara, Swasahara

Habit:

Clerodendrum serratum is a perennial shrub 0.9-2.5 m high.

Stem- Scarcely woody not much branched, bluntly quadrangular and young parts are usually glabrous.

Leaves- are sessile or nearly so and opposite or sometimes ternate, passing upwards into bracts. 12.52- 15 by 5.7-6.3 cm, sometimes reaching up to 28 cm long, narrowly obovate- oblong or sub-elliptic, acutebase, acuminate tip, coarsely and sharply serrate margins and glabrous. Petioles are very stout and 6 cmlong.

Flowers: - Numerous, in lax pubescent dichotomous cymes with a pair of acute bracts at each branching and a flower in the fork, each in the axial of a large leafing bract and collectively forming a long lax terminal usually pyramidal erect penicle 15-25 cm long; pedicels often twisted so as to make the large lower corolla.

Bracts: -1.3-3.8 cm long, from obovate to lanceolate, pubescent, and often coloured.

Fruit- Fruit is drupe 6 cm long, somewhat succulent, broadly obovoid, dark purple When ripened.

EXPERIMENTAL:

Methods:

Preformulation study:

Preformulation studies are needed to ensure the development of a stable as well as effective and safe dosage form. It is a stage of development during which the pharmacist characterizes the physic-chemicalproperties of the drug substances and its interaction with various formulation components. Goals of **Preformulation study**:

To determine the necessary physicochemical parameter of a new drug substance.

To establish its incompatibility with excipients of formulation.

PHARMACOGNOSTIC INVESTIGATION:

Collection and Authentication:

Collection of Clerodendrum serratum (Linn) moon.

The fresh leaves and roots of Clerodendrum serratum (Linn) moon (Verbenaceae) Were collectedat the flowering stage in August.

B. Organoleptic Characterization:

Colour, odour, shape, test and size of the rhizomes and bark were observed

C. Physicochemical Characters:

After botanical evaluation, the shade-dried plant material was subjected to size reduction to get coarse powder and then passed through sieve no. 43 to get uniform powder. Then, the uniform powder was subjected to standardization with different parameters as per literature.

Extractive values: [1,2]

Alcohol soluble extractive value:

Macerated 5 gm of the air-dried drug coarsely powdered drug (leaves and roots), with 100 ml ofalcohol the specified strength in a closed flask for twenty-four hours shaking frequently during six hours and followed to stand for eighteen hours. Filtered rapidly, taking precautions against loss of solvents, evaporate 25 ml of the filtrate to dryness in a tared flat bottomed shallow dish, and dried at 1050c to constant weight and weighed. b) Water Soluble extractive value: Macerated5 gm of the air-dried drug, coarsely powdered (leaves and roots), with 100 ml of Chloroform- water the specified strength in a closed flask for twenty-four hours, shaking frequently during sixhours and followed to stand for eighteen hours. Filtered rapidly, taking precautions against loss of solvents, evaporate 25 ml of the filtrate to dryness in a tared flat bottomed shallow dish, and dried at 1050C, to constant weight and weighed. Calculated the % of water-soluble extractive with reference to the air-dried drug.

Determination of Ash value:

Determination of total ash:

Incinerated about 2-3 gm accurately weighed, of the ground drug in a tared silica dish at a temperature not exceeding 4500C until free from carbon, cool and weight. If a carbon free ash cannot be obtained in this way, exhaust the charved mass with hot water, collected the residue onan ashless filter paper, incinerated the residue and filter paper, added ignited at a temperature notexceeding 4500C. Calculated the % of ash

with reference to the air-dried drug.

Determination of Acid-Insoluble ash:

To the crucible containing total ash, add 25 ml of dilute hydrochloric acid. Collected the insolublematter on an ashless filter paper (Whatman 41) and washed with hot water until the filtrate is neutral. Transferred the filter paper containing the insoluble matter to the original crucible, dry on a hot-plate and ignite to constant weight. Allowed the residue to cool in a suitable desiccator for 30 minutes and weighed without delay. Calculated the content of acidinsoluble ash with reference to the air-dried drug.

Determination of Foreign Matter:

The sample shall be free from visible signs of mold growth, sliminess, stones, rodent excreta, insects or any other noxious foreign matter when examined as given below. Take a representativeportion from a large container, or removed the entire contents of the packing if 100 g or less, andspread in a thin layer in a suitable dish or tray. Examined in daylight with unaided eye. Transfer suspected particles, if any, to a petri dish, and examined with 10x lens in daylight.

In-vitro anti-inflammatory study of extract

Inhibition of albumin denaturation the anti-inflammatory activity of Clerodendrum Serratum was studiedby using inhibition of albumin denaturation technique which was studied according to Mizushima et al and Saket et al followed with minor modifications. The reaction mixture was consisting of test extract and 1% aqueous solution of albumin fraction, pH of the reaction mixture was adjusted using small amountof 1 N HCL. The sample extract was incubated at 370C for 20 min and then heated to 510C for 20 min,after cooling the samples the turbidity was measured at 660 nm. The experiment was performed in triplicate. The Percentage inhibition of protein denaturation was calculated as follows:

Percentage inhibition= (abs Control-Abs Sample) × 100/ Abs control

Drug-Excipients compatibility study: -

Study of interaction of the drug with excipients by physical compatibility study: -

Each excipient used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each excipient was thoroughly blended with drug extract to increase drug- excipients molecular contacts and also to accelerate the reaction if possible.

Each drug extract excipientsblend was taken separately into vials and kept for one month study at 400c and at 75% RH for 2 weeks and observe the changes. After 30 days storage of drug extract with excipients in various ratio at room temperature, samples were observed for physical changes but there were no physical changes observed in the mixture of Clerodendrum Serratum extract and polymer combination.

Experimental design:

During formulation three gelling agents used at two different concentrations, resulting in six different batches of gels for leaves extract and six batches for root extract, total twelve batches prepared. In this case Carbopol 934, HPMC K 100 M and Xanthan gum, these three types of gelling agents were taken. Three

gelling agents were used as follows:

Carbopol 934 (at concentration 1% and 1.5%)

HPMC K 100 M (at concentration 1% and 1.5%)

Xanthan gum (at concentration 1% and 1.5%)

Gel composition was finalized after doing many trial and errors. And the composition finalized is described here. Same experimental design was applied for both types of extract which was results in totaltwelve batches of gel formulations. All the batches were prepared according to the experimental design.

Preparation of Gel: [9]

Preparation of gel with Carbopol 934:

Accurately weighed Carbopol 934 was taken in a beaker and dispersed in 50 ml of distilled water.Kept the beaker aside to swell the Carbopol for half an hour and then stirring should be done using mechanical/lab stirrer at 1200 rpm for 30 min. Take 5 ml of propylene glycol and requiredquantity of Extract. Take 5 ml propylene glycol in another beaker and add weighed quantity of propyl paraben and methyl paraben to it and stirred properly. After all, Carbopol dispersed, 1 gmextract and preservatives solutions were added with constant stirring. Finally, volume made upto 100 ml by adding remaining distilled water and Triethanolamine was added drop wise to the formulations for adjustment of required skin pH (6.8-7) and to obtain the gel at requiredconsistency.

Preparation of gel with HPMC K 100 M:

Accurately weighed 1 gm of extract was transferred to a beaker and dissolved in 10 ml of propylene glycol into which preservatives were added. HPMC K 100 M was made to disperse indistilled water then heated up to 80-900C with continuous stirring and it was allowed to cool. he1 %w/v extract loaded propylene glycol solution were added to HPMC K 100 M preparation andstirred vigorously to mix in cold condition and water was added to make up the volume up to 100ml and stirred in mechanical stirred well to get a uniform gel.

Preparation of gel with Xanthan gum:

Accurately weighed Xanthan gum was taken in a beaker and dispersed in 50 ml of distilled water.Kept the beaker aside to swell the Xanthan gum for half an hour and then stirring should be done using mechanical/lab stirrer at 1200 rpm for 30 min. Take 5 ml of propylene glycol and requiredquantity of Extract. Take 5 ml propylene glycol in another beaker and add weighed quantity of propyl paraben and methyl paraben to it and stirred properly. After all Xanthan gum dispersed, Extract and preservatives solutions were added with constant stirring.

Physicochemical evaluations: [10-13]Physical appearance:

The prepared gel formulations containing Clerodendrum Serratum were inspected visually for their color, homogeneity, consistency and phase separation.

Measurement of pH:

The pH of developed gel formulations was determined using digital pH meter. 1 gm of gel was dissolvedin

100 ml distilled water and kept aside for two hours. The measurement of pH of each formulation wasdone in triplicate and average values are calculated.

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 on slip and drag characteristics of gels. An excess of gel (about 2 gm) under study was placed on this ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed groundslide and provided with the hook. A one kg weighted was placed on the top of the two slides for 5 min. 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 80 gm. With the help of string attached tothe hook and the time (in sec.) required by the top slide to cover a distance of 7.5 cm be noted. A shorterinterval indicates better spreadability. Spreadability was calculated using the following formula:

$S = M \times L / T$

Where, S= Spreadability,

M= weight in the pan (tied to upper slide),L= Length moved by the slide,

T= Time (in sec.)

In-vitro anti-inflammatory activity of prepared herbal gel: [15]

The reaction mixture (5 ml) consisted of 0.2 ml of egg albumin (from fresh hen's egg), 2.8 ml of phosphate-buffered saline (PBS, pH 6.4) and 2 ml of gel solution so that final concentrations become 31.25, 62.5, 125, 250, 500, 1000µg/mL. A similar volume of double distilled water served as the control.Next, the mixture was incubated at 37±20C in a BOD incubator for 15 minutes and then heated at 700Cfor five minutes. After cooling, their absorbance was measured at 660nm by using the vehicle as a blank.Diclofenac sodium in the final concentration of (78.125, 156.25, 312.5, 625, 1250, 2500µg/mL) was usedas the reference drug and treated similarly for the determination of absorbance. The percentage inhibitionof protein denaturation was calculated by using the following formula:

$\%\ \text{inhibition} = 100 \times [Vt/Vc - 1]$

Where, Vt = absorbance of the test sampleVc = absorbance of control

Stability study: [16]

The optimized gel formulations were prepared; packed in aluminum collapsible tubes and subjected to stability studies at 40º C/75 % RH for a period of 3 month as per ICH Guidelines. Samples were withdrawn at 1 month time intervals and evaluated for physical appearance, pH, rheological properties, spreadability and extrudability.

RESULT AND DISCUTION

The present work aimed to increase stability of gel and to increase anti-inflammatory activity of gel formulation with Carbopol 934, HPMC K 100 M and Xanthan gum as well as to compare natural gelling

agent to synthetic gelling agent. The prepared formulations were characterized for physical appearance, pH, spreadability, viscosity, in-vitro anti-inflammatory study and in-vitro skin irritation study.

Preformulation study:

Organoleptic Characterization for Leaves and Root powder:

Table No.5: Organoleptic characteristics of extract

Leaves powder	Characteristics	Roof powder	Characteristic
Colour	Light reen	**Colour**	External surface light brown
Odour	odourless	**Odour**	Characteristic
Taste	pungent	**Teste**	Bitter, pungent and astringent

Physico-chemical Characters of Root Extract

Test	Observed value in %	Standard value
Total ASH	8.5	Not more than 11 %
Acid insoluable ash	0.7	Not more than 1 %
Alcohol soluable extraction value	5.4	Not more than 5 %
Water soluable extract	13.5	Not more than 11 %
Foreign matter	1.9	Not more than 2 %

SUMMARY: Utility of gel-based drug delivery systems are being employed in recent past for therapeutic effectiveness of topical applied drugs. Clerodendrum serratum is tradition anti-inflammatoryagent. It has analgesic, anti-oxidative properties. Topical route for Clerodendrum serratum was selectedup to avoid GIT irritation and to maximize the drug concentration at the site of action. The transdermal delivery of the drug is limited by the barrier properties of the skin that needs inclusion of penetration enhancers in the formulation. In the present study attempts were made to formulate and evaluate topical gels of Clerodendrum serratum. In our preliminary study the standardization of Clerodendrum serratumwas carried out for purity and identity. The Preformulation studies include identification, phytochemical evaluation, physicochemical evaluation, extraction, solubility was carried out. Drug extract-excipient study was done by physical method and theresult showed that the drug extract is compatible with all three polymers,

Carbopol 934, HPMC K 100 M and Xanthan gum. All the developed gels were evaluated for their physicochemical properties like appearance, pH values, rheological properties, spreadability, extrudability properties, skin irritation test,stability studies and anti-inflammatory activity studies. The pH range of Carbopol 934 gels, HPMC K 100 M gels and Xanthan gum gels were found to be suitable for topical application. The viscosity measurement was done for selected gels using Brookfield Viscometer at room temperature.

CONCLUSION: It can be concluded from the present investigation that proper selection of polymers and drug is a prerequisite for designing and developing a transdermal drug delivery. The physical compatibility studies suggest that polymers selected i.e. Carbopol 934, HPMC K 100 M and Xanthan gum were found to be compatible with drug Clerodendrum serratum. The varying concentration of the three polymers was found to affect the gel parameters like viscosity and spreadability. Gel formulationsprepared with Carbopol 934, HPMC K 100 M and Xanthan gum showed good homogeneity, no skin irritation, good stability and anti-inflammatory activity. However, the Xanthan gum-based gel proved tothe formula of choice, since it showed the highest percentage of extrudability, good spreadability and rheological properties. Formulation F5 with 1 % leaves extract and F11 with 1% root extract of Clerodendrum serratum showed the best formulation with significant anti-inflammatory activity. Formulation F5 and F11 shows approximately equal anti-inflammatory activity. Hence, there is no needto used roots for the preparation of medicines for anti-inflammatory action.

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