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Preparation of Boswellia Capsules for Rheumatoid Arthritis

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ABSTRACT: Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body, including skin, eyes, lungs, heart, nerves and blood. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present. Often, symptoms come on gradually over weeks to months.Boswelliaserrataplant is obtained from dried stem bark of plant Boswelliaserrata and belongs of family Burseraceae. It includes anti-inflammatory, ant arthritic, and analgesic properties. It has been used for osteoarthritis, rheumatoid arthritis, bursitis, and tendonitis. Other uses include ulcerative colitis, painful menstruation, and abdominal pain.
KEYWORDS: Boswelliaserrata , Rheumatoid arthritis, osteoarthritis, Inflammatory, HPTLC, HPLC, Capsules.

I. INTRODUCTION:

Capsule is the most versatile of all dosageforms.Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin. There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two pieces” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatin capsule is also called as “one piece”. Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms.

Advantages of Capsules

• Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
• They are attractive in appearance
• They are slippery when moist and, hence, easy to swallow with a draught of water.
• As compared to tablets less adjuncts are required.
• The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
• They are economical
• They are easy to handle and carry.
• The shells can be opacified (with titanium dioxide) or colored, to give protection from light.

Rheumatoid arthritis (**RA**) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints.Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body.The disease may also affect other parts of the body, including skin, eyes, lungs, heart, nerves and blood.This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart.Fever and low energy may also be present. Often, symptoms come on gradually over weeks to months.

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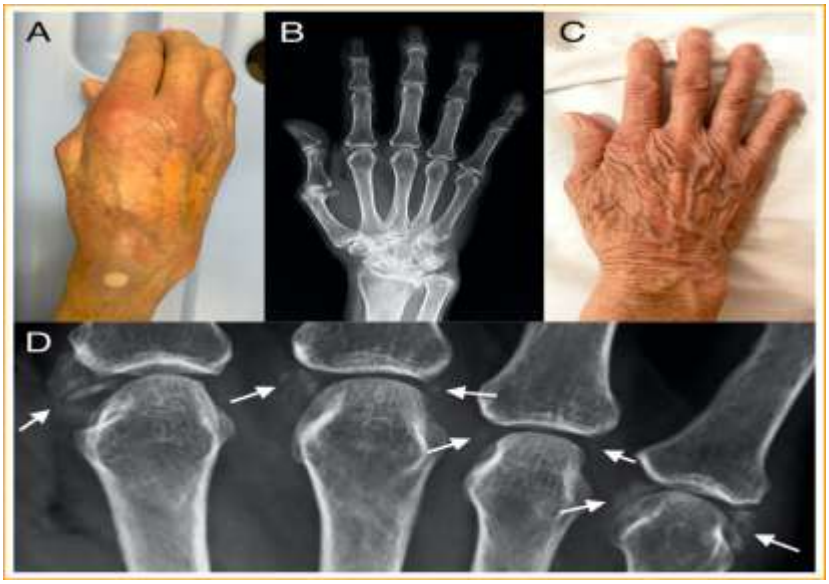

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The term rheumatoid arthritis is based on the Greek for watery and inflamed joints. The goals of treatment are to reduce pain, decrease inflammation, and improve a person's overall functioning.This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms.Disease-modifying anti- rheumatic drugs (DMARDs), such as hydroxychloroquine and methotrexate, may be used to try to slow the progression of disease.Biological DMARDs may be used when disease does not respond to other treatments.However, they may have a greater rate of adverse effects.Surgery to repair, replace, or fuse joints may help in certain situations Onset is most frequent during middle age and women are affected 2.5 times as frequently as men.

SIGNS AND SYMPTOMS:

RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, such as osteoarthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent. The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic. The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical.

PATHOPHYSIOLOGY:

RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in joints and other organs where it manifests.[citation needed]The clinical manifestations of disease are primarily inflammation of the synovial membrane and joint damage, and the fibroblast-like synoviocytes play a key role in these pathogenic processes.Three phases of progression of RA are an initiation phase (due to non-specific inflammation), an amplification phase (due to T cell activation), and chronic inflammatory phase, with tissue injury resulting from the cytokines, IL–1, TNF-alpha, and IL–6.

II. MATERIAL AND METHOD:

PLANT INRODUCTION

METHODOLOGY :

Preparation of dried powder extract: The Dry bark of B. serrata was cleaned, dried and grinded as a powder and stored for experimentation.2 Cold extraction process was used for the preparation of drug. About 20 g powdered material was mixed in 100 ml distilled water and ethanol in conical flasks

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separately; both flask were kept for 24 hours for maximum drug extraction from bark. After 24 hours both extracts were filtered through muslin cloth and centrifuged at 4000 rpm for 10 minutes at 4°C. The supernatant was allowed to evaporate under the vacuum conditions at 50 ± 2oC.

Organoleptic Characters:
The color, odor, taste, texture of the dried powder extract were observed.

Determination of Ph:
Take 1g of sample and add 100 ml of Milli-Q-water and shake well. Now note the PH in PH meter.

Physical properties:

1.Bulk density and Tapped density: It was determined by taking 10g of choornam in a graduated measuring cylinder and tapped on a wooden surface. The initial volume and the tapped volume will be noted. From the initial volume bulk density will be calculated and from the tapped volume tapped density will be calculated using the formula.

Bulk density = weight taken/bulk volume

Tapped density = weight taken/tapped volume

2.Angle of Repose: It was determined by using funnel method. The powder will be allowed to flow through a funnel fixed on a stand to form a heap and the angle of repose will be calculated using the formula.

Angle of repose, $\theta = \tan^{-1} h/r$

Where,

h = Height of heap

r =Radius of heap

3.Hausner Ratio (HR): Hausner's ratio is related to inter particle friction and as such can be used to predict the powder flow properties. It can be calculated using formula

Hausner's Ratio =Tapped density/Bulk volume

4.Compressibility/Carr's Index (CI):Carr's index is an indirect method of measuring the powder flow from bulk density. It will be calculated using the formula

Carr's Index =Tapped density – bulk volume X 100
Tapped density

Phytochemical screening of herbal drug

Qualitative phytochemical evaluation

Name of the Phyto-chemicals	Procedure
Steroids	1 ml of extract + 10 ml of chloroform + equal volume of concentrated sulphuric acid
Terpenoids	2 ml of extract + 2 ml of acetic anhydride and concentrated sulphuric acid
Fatty acids	0.5 ml of extract + 5 ml of ether + allowed to evaporate on filter paper and dried
Tannins	2 ml of extract + few drops of 1 % lead acetate
Saponins	5 ml of extract + 20 ml distilled water + agitated in graduation cylinder for 15 minutes
Anthocyanins	2 ml of extract + 2 ml of 2N hydrochloric acid and ammonia
Leucoanthcyanins	5 ml of extract + 5 ml of isoamyl alcohol
Coumarins	3 ml of 10 % sodium hydroxide + 2 ml of extract
Emodins	2 ml of ammonium hydroxide + 3 ml of benzene added to the extract
Alkaloids	2 ml of extract + 2 ml 1 % hydrochloric acid + heated gently. Few drops of Mayer's and Wagner's reagent were added to the mixture.
Phenols	2 ml of extract + 2 ml of 2 % Ferric chloride
Flavonoids	3 ml of extract + few fragments of magnesium ribbon + 2 – 3 drops pf concentrated hydrochloric acid

Determination of Total Boswellic acid by Acid-Base Titration:

Standardization of 0.01N Sodium Hydroxide

Preparation of 0.01N Sodium Hydroxide Solution:

Weigh 5g of Sodium Hydroxide pellets, add 600 ml of Milli-Q-Water and Sonicate for 10 minutes.

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Standardization of 0.01N Sodium Hydroxide

Weigh 40 mg of Benzoic acid, add 30 ml of Milli-Q-Water and then add 2 drops of Phenolphthalein indicator. Titrate against 0.01N Sodium Hydroxide until Permanent pink color is obtained.

$$\frac{\text{Weight of Benzoic acid in mg}}{122.12 \quad X \quad \text{ml of 0.01N NaoH}}$$

$$= \frac{(\text{Titre value-Blank value}) \times 0.00456 \times \text{N of NaoH}}{\text{Weight of Sample in g} \times 0.01} \times 100$$

Mineral Acid:

Weigh accurately 200 mg of Boswelliaserrata dry extract, add 30 ml of Milli-Q-Water and Sonicate for 10 minutes. Then add 2 drops of Phenolphthalein and titrate against 0.01N Sodium Hydroxide until Permanent pink color is obtained. Perform Blank Titration.

$$= \frac{(\text{Titre value-Blank value}) \times 0.00365 \times \text{N of NaoH}}{\text{Weight of Sample in g} \times 0.01} \times 100$$

Total Boswellic acid = Total Acid – Mineral Acid.

Total Acid:

Weigh accurately 200 mg of Boswelliaserrata dry extract, add 30 ml Methanol and Sonicate for 10 minutes. Then add 2 drops of Phenolphthalein and titrate against 0.01N Sodium Hydroxide Solution until Permanent pink color is obtained. Perform Blank Titration excluding the sample.

Preparation and standardization of herbal capsule :

Preparation of herbal capsule:

1.Granulaton

Precautions: Ensure personal protection including caps, gloves, masks and safety goggles during batch processing. Check the weight of all ingredients before addition. Ensure that the integrity of the sieve before and after sifting.

I. Transfer 30.00 Kg Boswelliaserrataoleo resin extract and 0.500 Kg Curcuma longa extract then pass through S.S Sieve 20# using mechanical sifter and transfer to double cone blender.
II. Transfer 0.004 Kg Silicon dioxide S.S Sieve 30# using mechanical sifter and transfer to the same double cone blender for 10 minutes.
III. Transfer 6.200 Kg Microcrystralline Cellulose 102 (E460(i), 2.00 Kg Cross linked carboxy methyl cellulose sodium (E468) and pass through S.S Sieve 20 # using mechanical sifter and transfer to a double cone blender with granules and operate the blender for 10 minutes.
IV. Transfer 0.400 Kg of Talc (E553b), 0.500 Kg Magnesium stearate(E470b) extract and pass through S.S Sieve 40 # using mechanical sifter and transfer sifted powder to double cone blender with granules and operate the blender for 5 minutes.

In process check:

S.NO.	Parameters	Limits
1.	Moisture content	NLT 2.0% - NMT 5.0%
2.	Bulk density	0.420-0.520 gm/ml

Collect the lubricated granules into PVC containers lined with double poly bags.

3.Manufacturing of capsule filling:

Note: check the area is clear of previous product, materials and documents, Capsules should be stored in Plastic Containers lined with Poly bags.

I. Set the Automatic Capsule filling machine for "0" Size Capsule with desired Dosing Disc.
II. Fill the final granules obtained from Stage I using Transparent "0" Size Transparent HPMC Plain Capsule Shells.
III. Transfer the approved blend of Stage II to capsule filling area. Load the granules and initiate filling. Collect the filled Capsules and verify for the parameters mentioned in the below table.

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Parameters	Limits	No. of Capsules
Description	"0" Size Transparent HPMC Capsules shells containing cream color granular powder	10
Target filled capsule weight	400.00 mg + weight of a "0" Size HPMC empty Capsule shell	20
Gross weight of 20 Capsules	±2.5 %*	20
Net Content of filled Capsules	400.00 mg ± 5 %	10
Joint Length of filled Capsules	NLT 20.80 mm & NMT 21.30 mm	10
Disintegration Time	NMT 15 minutes	6

De-dust manually and collect the filled capsules in suitable plastic containers lined with Poly bag.
Check and record the weight of the filled capsules.

Storage conditions of finished product:

Storage Conditions of Filled Capsules:

The Filled Capsules are to be stored below 25 C at cool dry place free from moisture in a double lined poly bag in HDPE Containers **(50 g Silica gel bag placed in between two poly bags)**. The Filled Capsules are to be packed within 5 days from the date of Filled Capsules.

COMPOSITION:

Each capsule contains extracts of Medicinal plants:

Name of the Ingredient	Common Name	Parts used	Label claim
Boswellia (Boswelliaserrata)	Sallaki	Oleo resin	300.00 mg
Haridra (Curcuma longa)	Turmeric	Rhizome	5.00

Dosage Form : ORAL SOLID CAPSULES
Product Description: "0" Size Transparent HPMC capsules shells containing cream color granular powder
Generic Name : BOSWELLIA **CAPSULES**
Product Shelf life: 24 months from the date of manufacturing
Storage Condition : Store below 25 C in a dry place, protect from light and moisture
Therapeutic Category : Anti-Rheumatic

1. Physical appearance:

The capsules will be evaluated for their physical appearance like colour, appearance,tasteetc.

2 Description:

Weigh accurately 20 Filled capsules and note down the weight individually in milligrams up to one decimals. Remove the filled powder from capsules, weigh accurately 20 empty capsules and note down the weight orderly in milligrams upto one decimals. Determine the average mass of the filled weight and report in terms of milligrams.

Evalauation of herbal capsule:

Calculation:

$$\text{Average weight} = \frac{\text{20 Filled Capsule Weight} - \text{20 Empty Capsule Weight}}{20}$$

Average weight = _____ mg of Capsules

3. Weight variation of net content:

Weigh accurately 20 Filled capsules and note down the weight of each Capsules individually in milligrams up to one decimals. Remove the filled powder from capsules, weigh accurately 20 empty capsules and note down the weight of each Capsules individually in milligrams upto one decimals. Calculate the percentage variation of highest and lowest weight of the Capsules with maximum and minimum weight and report in terms of milligrams using the following formula.

Calculation:

Maximum weight of filled capsule in mg x 100

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$$\% \text{ Highest weight} = \frac{\text{Highest weight of filled capsule in mg}}{\text{Average weight of filled capsule in mg}} - (100)$$

$$\% \text{ Lowest weight} = \left(\frac{\text{Minimum weight of filled capsule in mg} \times 100}{\text{Average weight of filled capsule in mg}} - (100) \right)$$

4. Disintegration test:

Place one Capsule in each of the six tubes of the Disintegration test apparatus and add a disc to each tube. Suspend the basket rack assembly in water maintained at 37 ± 1 C. Operate the apparatus till the Capsules disintegrate and its residue passes through the mesh. Note down the time. If the Capsules adhere to the disc then repeat the test without the discs added to the tube.

5. Dissolution test:

Dissolution testing of capsule is carried out using USP dissolution apparatus type I (basket type). The capsule will be placed in the small wire mesh basket attached to the bottom of the shaft connected to a various speed motor. The basket is immersed in a dissolution medium in a 1000ml flask contains 900ml of 7.4ph phosphate buffer. The flask is maintained at 37 ± 2 °Celsius by a constant temperature bath. The shaft is rotated at 50 rpm. The timed is set for 1 hr. At every 15min interval the 10ml of sample will be pipette out and volume is maintained by replacing the 10ml of the buffer solution. The pipette sample will be taken in 100ml std flask and the volume will made up to 100m with buffer solution From the above sample solution, 1ml of solution will be filtered and taken in 10ml standard flask the volume will be made to 10ml with the buffer solution and the absorbance will be measured at 419nm. Repeat the procedure for various sample collected at different time interval and absorbance will be measured by UV-spectrometer.

6. Loss on drying:

Take a clean petridish and dry under 105 C for 10 minutes , to be employed in the test. Take out and keep in desiccator for cooling to room temperature. Weight and note down the empty weight accurately in gram up to four decimal places as (W1). Take 10 filled powder of capsules, triturate and take 1 gm of powder in weighing bottle (W2) and dry at 105 C for 3 hrs, to get constant weight. After drying is completed, cool in desiccators to room temperature. Weight, note down the weight accurately in gram up to four decimal places as (W3). Calculate the loss on drying by using the formula

Calculation:

$$\text{LOD} = \frac{W2 - W3}{W2 - W1} \times 100$$

Where,

W1 = Weight of Empty Petridish;

W2 = Weight of Sample + Weight of Empty Petridish

W3 = Weight of Sample after drying

7. Determination of pH:

Transfer 1 g of Capsule powder in a container and macerate with 100 ml of water in a closed container. Shake frequently about 15 minutes once and allow it to stand for one hour. Filter rapidly; collect the filtrate to measure pH.

8. Identification by HPTLC finger print profile:

Standard preparation:

Weigh and transfer 300 mg of Boswelliaserrata dry extract working standard into dry 100 ml volumetric flask. Add 60 ml Methanol and sonicate for 15 minutes and make up the volume with Methanol. Shake and filter.

Sample preparation:

Take 10 capsule filled powder, weigh and transfer 1 Capsule filled powder into dry 100 ml volumetric flask. Add 60 ml Methanol and sonicate for 15 minutes and make up the volume with Methanol. Shake and filter.

Mobile Phase Preparation:

n-Hexane : Ethyl acetate (6:4)

Chromatographic Conditions:

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Application volume : 4 - 8 µl
Migration distance : 70 mm
Adsorbent : HPTLC Silica gel Plate G254F (Aluminium)
Temperature : NMT 30 °C

Procedure: Pour 10 ml of the mobile phase solvent over the paper and tilt the chamber to equilibrate solvent level in both troughs, close the lid. Allow the chamber to saturate for 20 minutes. Apply the application volume of saturated and sample solution each as 8 mm band atleast 2 mm apart, 8 mm from the lower edge and at least 15 mm from left and right edges of the plate.

Dry the plate for 2 minutes with cold air. Measure and mark the developing distance of 70 mm from lower edge of plate (62 mm from application position). Pen the saturated chamber and introduce the plate with the layer facing the inside, close the chamber and wait for the solvent to reach the mark. Remove the plate from the chamber.

Dry the plate for 5 minutes with cold air (hair dryer). Examine the plate under Ultraviolet light at 254 nm. Derivatize with 10 % **Methanolicsulphuric acid** and dried at 105°C for 5 minutes. Examine the plate under Ultraviolet light at 366 nm and white light.

Acceptance criteria:

The chromatographic profile of sample solution is similar to that of the chromatographic profile of Boswelliaserrata dry extract standard.

9. Assay of keto derivative of - boswellic acid by HPLC:

Chromatographic condition:

HPLC System : HPLC System with UV-Visible/PDA Detector
Column : Water Reliant C18, 250mm × 4.6 mm; 5 m
Injection volume : 30 µL
Column Temperature : 27°C
Wavelength : 254nm (Keto Derivatives of Boswellic acid)
205nm (β-Boswellic acid)
Run time : 45 minutes
Diluent : Methanol

FlowGradient:

Time (min)	Flow Rate (ml/min)	A%
0	1.0	100
5	1.5	100
10	2.0	100
30	2.0	100
32	1.0	100
45	1.0	100

Mobile Phase Preparation:

Mix 900ml of Acetonitrile, 100ml of Milli-Q-water and 0.1mg of Glacial acetic acid (900 : 100 : 0.1). Sonicate for 15 minutes and degas it.

Preparation of Blank Solution:

Diluent as a Blank

Preparation of Standard Solution:

Weigh about 300.0mg of Boswelliaserrata dry extract and transfer into a 100ml volumetric flask. Add 60ml of diluents. Sonicate and heat gently to 10 minutes. Make up the volume with diluent and shake it well. Filter through 0.45 µm PVDF syringe filter.

Sample Preparation:

Weigh about 300.00 mg of sample into a 100 ml volumetric flask. Add 60 ml of diluent and sonicate for 10 minutes. Make up the volume with diluent and shake it well. Filter through 0.45 µm PVDF syringe filter.

Procedure:

Inject the following sequence into the chromatograph and record the chromatogram. Find out system suitability and measure the response of major peak.

Injection sequence table:

S.No.	Sample Name	No. of Injection

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1.	Blank	1
2.	Standard solution	6
3.	Sample solution-1	2
4.	Sample solution-2	2
5.	Bracketing Standard	1

Relative Retention Time (RRT):

Name of content	Analyte	RRT
Keto derivatives of β - Boswellic acid	11 – Keto - β - Boswellic acid	1.0
	3 – Acetyl – 11 - Keto - β - Boswellic acid	1.4

Calculation:

For Keto Derivative of Beta Boswellic acid

$$= \frac{AT}{AS} \times \frac{WS}{100} \times \frac{100}{WT} \times \frac{P}{100} \times \text{Average weight of capsule}$$

= _____ mg of Keto Derivative of β- Boswellic acid/ Capsule

Where,

AT = Mean area of Keto Derivative of β - Boswellic acid peak present in test solution

AS = Mean area of Keto Derivative of β - Boswellic acid peak present in Standard solution

WS = Weight of Boswelliaserrata working standard taken, in mg

WT = Weight of test sample taken, in g

P = Potency of Keto Derivative of β - Boswellic acid working standard, in % (as is basis)

For % Label Claim (LC):

$$= \frac{\text{mg of Keto Derivative of } \beta \text{ - Boswellic acid, found in sample}}{\text{Label Claim of Keto Derivative of } \beta \text{ - Boswellic acid}} \times 100$$

Conclusion and Result:

The polyherbal capsule will lead to the treatment of diabetic from the natural source with lesser side effect. This may be useful for the development of new antidiabetic agent from plant resources.

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