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# Formulation And Evaluation OfPolyherbal Suspension Effective In RheumatoidArthritis

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## 1. INTRODUCTION:

A systemic autoimmune disease that causes progressive joint deterioration, rheumatoid arthritis (RA) is characterised by symmetric synovial joint inflammation. The etiology and pathophysiology of RA remain poorly understood despite the disease's significant research. However, it is evident that cytokines are a major factor in activating synovial cells, which causes inflammation and joint degeneration in arthritic joints.

Based on their various contributions to the development of the illness, it is commonly accepted that the cytokines TNF-a, IL-1, and IL-6 are the key actors in the pathogenesis of RA. In order to treat RA, anti-TNF-a and anti-IL-1 medicines are now available. TNF-a and IL-1 have thus been specifically targeted in the development of RA therapy. However, not all RA patients respond well to these medications.

Additionally, the use of presently available biologics, particularly anti-TNF-a medications, has drawn criticism due to the elevated risk of infection in patients on cytokine antagonist therapy. As a result, research into novel cytokines and other RA treatment options is ongoing.

Immunology research has made significant discoveries on a cytokine called IL-17, which is generated by TH17 cells.

Evidence suggests that the cytokine IL-17 has potent pro-inflammatory effects and can increase inflammation brought on by other cytokines, including TNF. Additionally, IL-17 may encourage bone and joint deterioration by activating osteoclasts and matrix metalloproteinases. A novel member of the type I cytokine superfamily, IL-21 binds to a composite receptor made up of the common cytokine receptor chain and the private IL-21R receptor.

T cells from a patient with RA's peripheral blood or synovial fluid released a lot of cytokines after being stimulated by IL-21, however blocking IL-21 greatly reduced the amount of inflammatory cytokine production in RA synovial cell cultures.

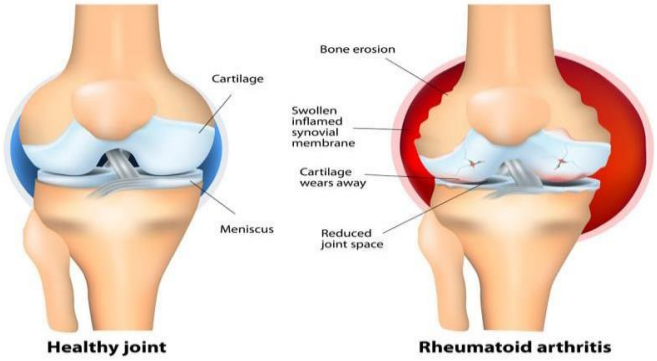



Fig.1: Rheumatoid arthritis joints

## Effect of Rheumatoid arthritis on Joints :

- A joint is where two or more bones meet They allow you to bend, twist turn freely.
- The joint is held together by a capsule which stops the bones from moving too far, and inside the capsule, there is an inner lining called the synovium. This makes a thick fluid, called synovial fluid, that protects the joint.
- The ends of the bores are covered with a thin layer of slippery tissue called cartilage.

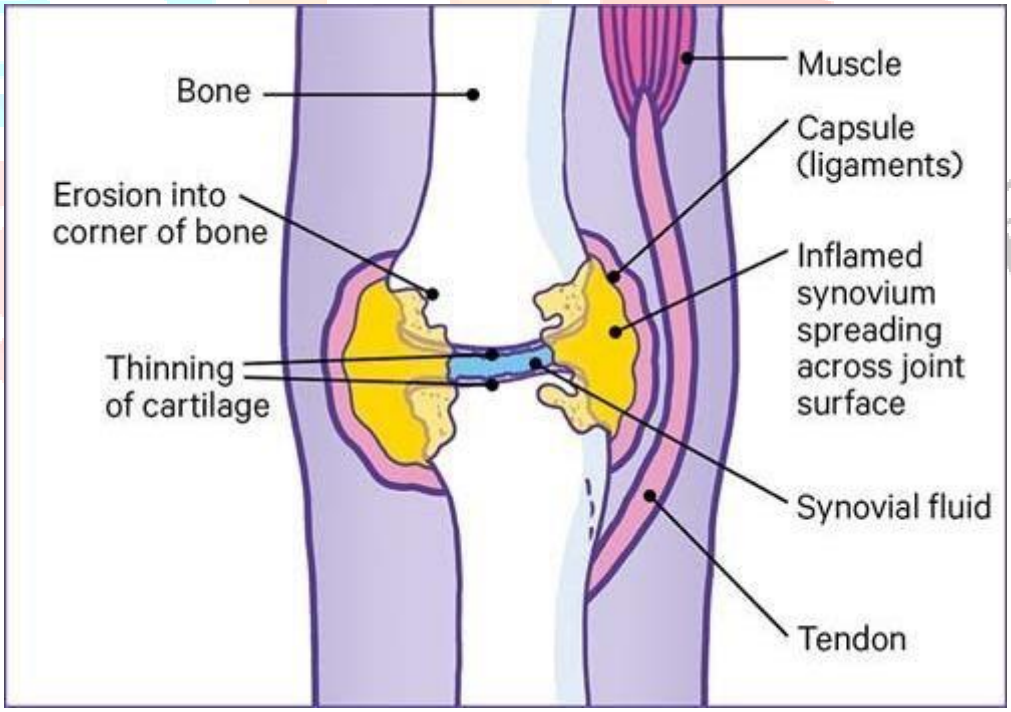



Fig 2: Joint Affected By RA

This acts as a protective cushion, stopping the bones from rubbing against each other. Strong cords called tendons anchor the muscles to the bones. When we move, our muscles pull the tendons, which then Pulicur bones in certain directions

- Inflammation is the body's way to heal itself after an infection or injury. It increases the flow of blood and fluid to the affected area making It swollen, red, painful and hot.
- However, if you have rheumatoid arthritis. the body mistakenly sends inflammation to joints, even though there's no infection to fight This inflammation isn't needed and can cause problems.
- When the inflammation goes down, the joint capsule can remain stretched. This means it can't hold the joint in its proper position, which causes the joint to become unstable.

## a) Symptoms

**The main symptoms of rheumatoid arthritis are:**

- Joint pain
- Joint swelling, warmth and redness
- Stiffness, especially first thing in the morning or after sitting still for a long time.
- Tiredness and lack of energy – this can be known as fatigue
- A poor appetite (not feeling hungry)
- Weight loss
- A high temperature, or a fever
- Sweating
- Dry eyes – as a result of inflammation
- Chest pain – as a result of inflammation.
- A few people develop fleshy lumps called rheumatoid nodules, which form under the skin around affected joints. They can sometimes be painful, but usually are not.

Fig no 3 : Joint Swelling

Fig no 4: Rhuematic Nodules

**Factors Affecting RA**

- **Age**

Rheumatoid arthritis affects adults of any age, although most people are diagnosed between the ages of 40 and 60.

- **Sex**

Rheumatoid arthritis (RA) is two to three-fold more frequent in women than in men and a strong association with sex hormones has been demonstrated.

There is strong evidence that autoimmunity is under genetic control, and genes in sexual chromosomes can play a role in supporting the female prevalence.

On the other hand, it is widely accepted that sex hormones--estrogens in particular-- may regulate the immune response by favoring the survival of forbidden autoreactive clones and ultimately the prevalence of autoimmunity in women.

- **Genetics**

The "Bermuda triangle" of genetic, environmental factors and autoimmunity triggers the onset and prolongation of synovitis underlying Rheumatoid Arthritis.

The heritability of RA has been estimated to be about 60%. Genetic factors including class II major histo-compatibility antigens/human leukocyte antigens (HLA), as well as non-HLA genes have been implicated in the pathogenesis of Rheumatoid arthritis.

- **Weight**

If you are overweight, you have a significantly greater chance of developing rheumatoid arthritis than if you are a healthy weight.

- below 18.5-you're in the underweight range
- between 18.5 and 24.9 you're in the healthy weight range
- between 25 and 29.9 you're in the overweight range
- between 30 and 39.9 you're in the obese range

- **Stages of rheumatoid arthritis**

- Stage 1: In early stage rheumatoid arthritis, the tissue around your joint(s) is inflamed. You may have some pain and stiffness. If your provider ordered X-rays, they wouldn't see destructive changes in your bones.
- Stage 2: The inflammation has begun to damage the cartilage in your joints. You might notice stiffness and a decreased range of motion.
- Stage 3: The inflammation is so severe that it damages your bones. You'll have more pain, stiffness and even less range of motion than in stage 2, and you may start to see physical changes.
- Stage 4: In this stage, the inflammation stops but your joints keep getting worse. You'll have severepain, and loss of welling stiffness mobility

- **POLYHERBAL FORMULATION**
- **Herbal Medicines**

Herbal medicines are plant based medicines made from differing combinations of plantparts.

E.g. leaves, flowers and roots. Each part can have different medicinal uses and the many types of chemical constituents require different extraction methods. Both fresh and dried plant matter are used depending upon the herb. Herbal medicines which formed the basis of health care throughout the world since the earliest days of mankind are still widely used, and have considerable importance in international trade. Recognition of their clinical, pharmaceutical and economic value is still growing, although this varies broadly between countries.

Plant is an important source of medicine and plays a key role in world health. Medicinal herbs or plants have been known to be an important potential source of therapeutics orcurative aids.

The use of medicinal plants has attained a commanding role in health system all over the world. Many countries in the world, that is, two-third of the world's population depends on herbal medicine for primary health care. The reasons for this is because of their better cultural acceptability, better compatibility and adaptability with the humanbody and pose lesser side effects.

Medicinal plants may be defined as those plants that are commonly used in treating and preventing specific ailments and discases and that are generally considered to be harmful to humans. Medicinal plants have provided mankind a large variety of potent drugs to alleviate or eradicate infections and suffering from diseases in spite of advancement in synthetic drugs, some of the plant-derived drugs still retained their importance and relevance.

- **Advantages of Herbal Drugs**

1. High low/minimum cost
2. Complete accessibilities
3. Enhanced tolerance
4. More protection
5. Fewer side effects
6. Potency and efficacy is very high

- **Disadvantages of Herbal Drugs**

1. Not able to cure rapid sickness and accidents

2. Risk with self-dosing

3. Complexity in standardizations.

- **Polyherbal formulation:**

Polyherbal formulation (PHF) is the use of more than one herb in a medicinal preparation. The concept is found in Ayurvedic and other traditional medicinal systems where multiple herbs in a particular ratio may be used in the treatment of illness. It is used in these systems for the treatment of many diseases, including diabetes. Historically, the Ayurvedic literature "Sarangdhar Samhita" dated centuries ago in 1300 A. D. has highlighted the concept of polyherbalism in this ancient medicinal system. In the traditional system of Indian medicine, plant formulations and combined extracts of plants are chosen rather than individual ones. It is known that Ayurvedic herbals are prepared in a number of dosage forms, in which mostly all of them are PHF. Due to synergism, polyherbalism confers some benefits which is not available in single herbal formulation.. Drug formulation in Ayurveda is based on 2 principles: Use as a single drug and use of more than one drug. The last is known as polyherbal formulation. The idea of polyherbalism is peculiar to Ayurveda even though it is tricky to explain in term of modern parameters. The Ayurvedic literature Sarangdhar Samhita tinted the idea of polyherbalism to attain greater therapeutic efficacy. Polyherbal formulation has been used all around the earth due to its medicinal and therapeutic application. It has also recognized as polyherbal therapy or herb- herb combination.

- **Advantages of polyherbal formulation**

1. Presence of multiple active compounds
2. Exert synergistic, potentiative, agonistic and antagonistic actions
3. Maximum therapeutic efficacy with minimum side effects
4. Act on multiple targets at the same time to provide a through relief.
5. Due to synergism, polyherbalism offers some great benefits which lacks in single herbal formulation.
6. Better therapeutic effects can be reached with a single multi-constituent formulation
7. Reduce risk of deleterious side effect

## 2. Drug Profile

### Plant Profile

**a) NEEM**

Fig 5: NEEM

*Azadirachta Indica*

Family: *MELIACEAE*

Neem is a tall evergreen tree having small brightgreen leaves. It is u
feet tall.

the steam of a neem tree can grow up to a diameterof 2.5-3 m.

The bark is rough and can be pale or greyish- blackin colour.

Neem tree bears small white coloured flowers and star shaped with
pleasant smell.

The tree generally hears fruits between the age of 3and 5 and the fr
edible.

Antifungal. Boosts immunityPurified blood.

Common Names : 1) Sanskrit: Nimba , Arishta , Ravipriya

2) English : Neem , Margosa Margosa

3) Telgu : VepaKingdom: plantae

Order: Sapindales

## A) There are numerous benefits and uses of neem leaves as follows:

**1. Treats Acne:**

Neem has an anti-inflammatory property which helps reduces acne. *Azadirachta Indica* also helps reduce skin blemishes.

**2. Nourishes Skin:**

Neem is a rich source of Vitamin E which help repair damaged skin cells.

**3. Treats Fungal Infections:**

Neem has scientifically proven antifungal property which helps treat fungal infections.

**4. Useful in Detoxification:**

Neem can prove useful in detoxification both internally and externally. Consumption of neem leaves or powder stimulates kidneys and liver increasing the metabolism and eliminating the toxins out of the body. Externally, neem scrubs or paste can be used to remove germs, bacteria, dirt, etc from your skin preventing rashes and skin diseases.

**5. Increases Immunity:**

Neem is known for its antimicrobial and antibacterial effects. These properties play a huge role in boosting immunity.

**6. Insect & Mosquito Repellent:**

You can burn a few neem leaves to ward off the insects. This is also effective against different types of mosquitoes. From all the home remedies for malaria, neem is the best for treating the early symptoms of malaria.

**7. Prevents Gastrointestinal Diseases:**

Neem's anti-inflammatory properties help reduce inflammation of the gastrointestinal tract which helps reduce a series of diseases like constipation, stomach ulcer, flatulence,etc.

**8. Treats Wounds:**

Neem leaves have an antiseptic property which is why it is used to heal wounds.

**9. Reduces Dandruff:**

Neem is extensively used in shampoos and conditioners. *Azadirachta Indica* has antifungal and antibacterial properties which help eliminate dandruff and strengths yourhair.

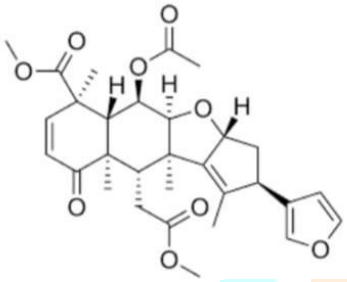
**10. Reduces Joint Pain:**

Application of neem oil or extract on the affected area can help reduce pain and discomfort. Hence it is widely used for treating arthritis.

- **Active profile** **Nimbidin**

Nimbidin is a mixture of tetranortriterpenes and is the major active principle of the seed oil of *Azadirachta indica* A. Juss (Meliaceae) possessing potent antiinflammatory and antiarthritic activities.

**Structure:**



- **General profile of Nimbidin**

| | |
|---|---|
| Molecular Formula | (1R.2R,5R,6S,10R, 115, 12R. 15R, 16R,188,19R)-6-(furan-3-yl)-11.16.18 trihydroxy-1,5,10,15-tetramethyl-13-oxapentacyclo [10.6.1.02,10.05,9.015,19]nonadec-8-en-4-one |
| Molecular Formula | C30H3609 |
| Molecular Weight | 442.24 |
| Molecular Formula | it is soluble in polar organic solvents (methanol, ethanol, acetone, chloroform, ethyl acetate) and slightly soluble in water (1.29 g $1^{1}$) |
| Melting point | 202.0-205.50 °C |

## b) *Boswellia Serrata* Plant

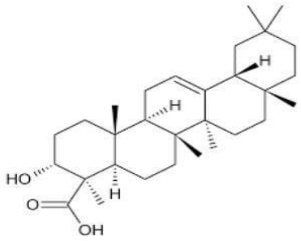
**Family**: *Buraseraceae*

Some studies suggest that boswellia may haveanti-inflammatory and antioxidant effect. But large-scale, independent clinical trials are needed.Boswellia serreta used for arthritis & also used formany other purposes, including asthma, diabetes & stroke. Boswellia serreta are avoding during pregnant or breastfeeding.

KINGDOM: - *Plantea*

ORDER: - Sapindales

- **Boswellic acids**
- **Structure**




- **General profile of Boswellic acids**

Fig 6: BOSWELLIA SERRETA

| | |
|---|---|
| Chemical Name | 3R,4R.4aR,6aR, 6bS,8aR,11R,128, 12aR, 14aR, 14bR)-3-hydroxy-4,6a,6b,8a,11,12,14b-heptamethyl-2,3,4,5,6,7,8,9,10,11,12,122, 14,14a- tetradecahydro-1H-picene-4-carboxylic acid |
| Melting Point | 238.0-240.00 °C |
| Molecular Weight | 456.7 |
| Molecular Formula | C30H4803 |
| Solubility | Boswellic acids are sparingly soluble in water only to the extent of 17 mmol/dm3, but their solubility in typical hydrotrope solutions can be increased severalfold |

- **SUSPENSION:**

A heterogenous mixture in which the solid particles are spread throughout theliquid without dissolving in it. Absorption rate of suspension is higher than tablet.

Fig 7: SUSPENSION

- **FORMULATION OF SUSPENSION**

A suspension is a specific category or kind of dispersion system in which the internal, or suspended phase. is uniformly dispersed throughout the exterior, or suspending medium or vehicle, by mechanical agitation. With the help of one or a specific combination of suspending agent(s), the interna phasewhich is made up of a homogeneous or heterogeneous distribution of solid particles with a range of sizesis kept consistently in time throughout the suspending vehicle. The suspended particles also show a minimal degree of solubility in the external phase, unlike a solution. The system is referred to as a colloidal suspension when the suspended solidshave a size of less than one micrometer.

- **Oral Suspensions**

An oral suspension's solids composition can differ significantly, mere instance, antibiotic preparations may contain 125 to 500 mg of active solid material per 5 ml (teaspoonful) dose, whereas drop concentrates may deliver the same amount of insoluble medication in a mere 2 ml dose. For oral administration, antacids and radiopaque suspensions frequently have quite substantial levels of suspended material as well. The vehicle could be a syrup, sorbitol solution, or gum-thickened water with artificial sweeteners added because, in addition to the safety of the components, flavor and mouth feel are crucial formulation considerations.

## 4. Material And Method

- **Materials**

| Sr No | Particulars | Manufactuers/ Suppliers |
|---|---|---|
| 1 | *Azadirachta indica (Nimbidin)* | Priya Vital Herbs Z-26/27 Commercial Enclave Mohan Garden Uttam Nagar New Delhi-110059 |
| 2 | *Boswellia serrata* (Boswellic acid) | Priya Vital Herbs Z-26/27 Commercial Enclave Mohan Garden Uttam Nagar New Delhi-110059 |

- **Chemicals and Reagents**

1. Tragacanth gum
2. Polyvinyl alcohol
3. Methyl paraben
4. Methyl orange

- **Apparatus and Instruments**

1. Beaker
2. Funnel
3. Mortar pestle
4. Stirrer
5. Measuring cylinder
6. Analytical weighing balance

## 5. Phytochemical Test

- **Phytochemical investigation of Nimbidin:-**
- **Test for terpenoids:-**

To the 2ml of chloroform add 5ml of plant extract (evaporated on water bath). Add 3ml conc. H2SO4 (boiled on water bath). Appearance of a grey coloration indicates presence of terpenoids.

- **Phytochemical investigation of Boswellic acid :-**
- **Test for triterpenoids:-**
- **Salkowski's test:-**

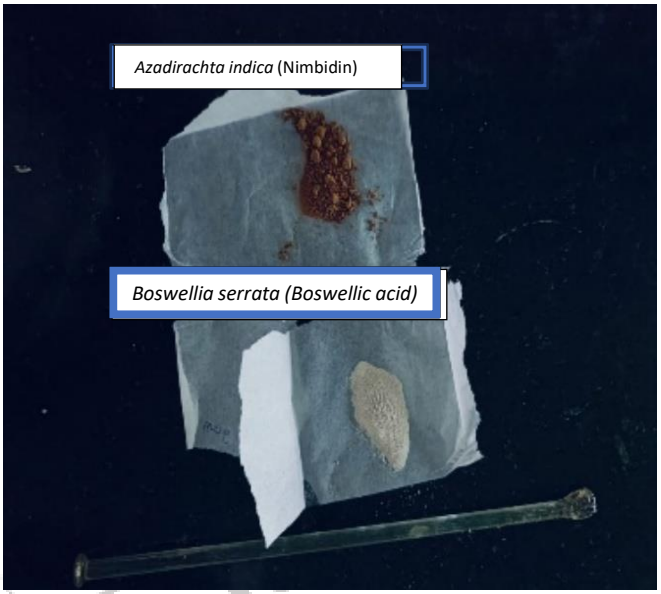
To the filtrate of plant extract add few drops of conc. $H_2SO_4$, shake well and allow to stand.Appearance of golden layer at the bottom indicates presence of triterpenoids.

- **Identification by IR spectroscopy:**

**1) Azadirachta indica**

*Azadirachta indica* 15 mg of Power was mixed properly then carefully triturated in a mortar pestle. At last this mixture was kept in on a plate and IR spectrum was taken using the Diffused Attachment reflectance mode.

*Boswellia serrata* 15 mg of Power was mixed properly then carefully triturated in a mortar pestle. At last this mixture was kept in on a plate and IR spectrum was taken using the Diffused Attachment reflectance mode.




## 6. Formulation

- **Polyherbal formulation 1: (100mg/kg)**

50mg/kg extract of *Azadirachta indica* and 50mg/kg *Boswellia serrata* was triturated with 0.02g methyl paraben, 0.02g Tragacanth gum, 3.5g Poyvinyl alcohol and 10ml distilled water and triturate well until suspension is formed.

- **Formulation Table**

| Batch Code | Nimbidin (mg) | Boswellic acid (mg) | Methyl paraben | Tragacanth Gum | Polyvinyl alcohol | Distilled water |
|---|---|---|---|---|---|---|
| F1 | 50 | 50 | 0.02 | 0.01 | 3.5 | Qt.Sufficient |
| F2 | 50 | 50 | 0.02 | 0.03 | 3.5 | Qt.Sufficient |
| F3 | 50 | 50 | 0.02 | 0.02 | 3.5 | Qt.Sufficient |

- **Design and evaluation of Polyherbal formulation:-**



- **CHECKLIST FOR SUSPENSION PERFORMANCE AND STABILITY TESTING:**

**a)** **Appearance** (macro) as viewed through a graduated glass cylinder or transparent container: Are the sediment's colour and look uniform at equilibrium? Exist any fractures or air pockets in the sediment at equilibrium? If there is leftover drainage above the sediment, is it uniform and modest, or is coagulated material stuck to the container's interior walls?

**b)** **Sedimentation Rate:-** Is the initial settling rate of the suspension (the falling height of the interface vs. time) equivalent when the sedimentation rate test is performed during shelf- life storage using an appropriate graduated cylinder?

**c)** **Sedimentation Volume and Redispersibility:** If gentle agitation is used, is the amount of sediment at equilibrium large enough to support uniform resuspension? Is the sediment volume consistent and comparable from batch to batch?

**d)** **Viscosity:-** Is the apparent viscosity of the suspension at equilibrium, as determined by an appropriate calibrated viscometer or rheologic equipment at a specific temperature, repeatable over time? Like pH, apparent viscosity is an exponential term, hence it makes sense to express data as log apparent viscosity.

**e)** **pH Value:-** In order to reduce "pH drift" and electrode surface coating with suspended particles, the pH value of aqueous suspensions should be measured at a certain temperature and only when equilibrium settling has been accomplished. To stabilize the pH for reading, electrolytes shouldn't be supplied to the suspension's external phase because doing so will compromise the suspension's physical stability.

**f)** **Miscellaneous Testing:-** With the proviso that the container is thoroughly mixed before testing, assays for potency, preservative effectiveness, compatibility with container/closure systems, off-torque, and simulated-use testing can be handled similarly to those used for conventional liquid solutions.

Testing for suspension product dissolution is still developing. Using a secure Durapore (polyvinylidene fluoride) membrane pouch (Millipe Products Div., Bedford, MA) of a suitable porosity and suspending it "tea bag" style in a suitable dissolution medium using the USP Method I paddle apparatus appears to be the best approach at the moment. To obtain repeatablefindings, experimental conditions must be optimized.

## 7. Results:

➢ **Physico-chemical parameters of drugs**

**A)** ***Azadirachta indica* (*Nimbidin* 90%)**

- Physico-chemical parameters of Nimbidin

| **Sr. No** | **TEST** | **Results** |
|---|---|---|
| 1 | Apperance | Brown fine powder |
| 2 | Odour | Characteristic |
| 3 | Taste | Characteristic |
| 4 | Loss on drying | 4.52% |
| 5 | Bulk density | 49.2g/100ml |

***B)*** ***Boswellia serrata (Boswellic acid 90%)***

- Physico-chemical parameters of *Boswellic acid*

| **Sr. No** | **TEST** | **Results** |
|---|---|---|
| 1 | Apperance | White fine powder |
| 2 | Odour | Characteristic |
| 3 | Taste | Characteristic |
| 4 | Loss on drying | 4.58% |
| 5 | Bulk density | 46.2g/100ml |

## 8. Evaluation Table - 100 mg/kg Concentration:

| Parameter | F1 | F2 | F3 (Optimized) |
|---|---|---|---|
| Appearance | Cloudy | Cloudy | Cloudy |
| pH | 6.8 | 6.9 | 7.2 |
| Viscosity | 45 cp | 50 cp | 55 cp |
| Sedimentation Volume | 2.3 ml | 2.1 ml | 1.8 ml |
| Redispersibility | Moderata | Easy | Easy |

## 9. DISCUSSION:

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disorder affecting the synovial joints and typically producing symmetrical arthritis that leads to joint destruction, which is responsible for the deformity and disability. The consequent morbidity and mortality has a substantial socioeconomic impact. The prevalence of Rheumatoid arthritis is consistent worldwide affecting, about 0.5-1% of the population. It usually occurs in the people hetween 25 and 55 year of age. Women are affected more often than men at ratio of 3 to 1 2. Adjuvant induced arthritis (AIA) in rats is a chronic inflammatory disease characterized by infiltration of synovial membrane in association with destruction of joints resembles Rheumatoid arthritis in humans. Rheumatoid arthritis progress in three stages. The first stage is the swelling of the synovial lining, causing pain, warmth, stiffness, redness and swelling around the joints. Second is the rapid division and growth of cell, or pannus, which causes the synovium to thicken. In the third stage, the inflamed cell releases enzyme that may digest the bone and cartilage, often causing the joints to loses its shape and alignments, more pain and loss of movements.

In the present study, rats were selected to induce arthritis because rats develop a chronic swelling in multiple joints with influence of inflammatory cells, erosion of joint cartilage and bone destruction. It has close similarities to human rheumatoid disease. The determination of paw swelling is apparently simple, sensitive and quick procedure for evaluating the degree of inflammation and the therapeutic effects of drugs. Chronic inflammation involves the release of number of mediators like cytokines (IL-IB and TNF-a). These mediators are responsible for the pain, destruction of bone and cartilage that can lead to severe disability. However, standard drug and poly-herbal formulations extract significantly suppressed the swelling of the paws. In the present investigation, the migration of leucocytes into the inflamed area is significantly suppressed by the standard drug and poly-herbal formulations.

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