ETHOSOMAL GEL: A NEW STRATEGY FOR GOUTY ARTHRITIS

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ABSTRACT

Gouty arthritis is a sudden, painful attack of joint inflammation due to over production and deposition of uric acid crystals in the tissues and blood or more commonly. This acid can form needle-like crystals in a joint and cause of a sudden onset of a painful, hot, red, swollen joint particularly in the first metatarsophalangeal joint. The most common factors that increases the chance of gouty arthritis are excess consumption of purine rich foods, alcoholic drinks especially beer, beverages sweetened with high-fructose corn syrup, obesity. It can be diagnosed by detecting uric acid (monosodium urate) crystals in an aspirated sample of the affected joint fluid. New treatments choices available today are NSAIDs, corticosteroids, xanthine oxidase inhibitors. The basic idea behind incorporating NDDS in herbal medicine is that, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. Here we are incorporating the herbal extracts into ethosome which will target the desired site and potentiate the therapeutic action and the bioavailability of the formulation is also increased. Another advantage is that, the bioactive constituents in the herbal formulations show enhancement in stability, sustained release from formulation, protection from toxicity and improved therapeutic efficacy. The main purpose of developing alternative drug delivery technologies is to increase efficiency and safety in the process of drug delivery and to make it more patient compatible.

KEYWORDS: Gout, Ethosome, NSAIDs, herbal medicine, NDDS.

INTRODUCTION[1,2,3]

The first who identified Gouty arthritis was Egyptians and named it as podagra. The disease was called as 'the unwalkable disease' by Hippocrates. He also mentioned gouty arthritis as a lifestyle disease, called as 'arthritis of the rich' Tophi which is crystallized monosodium urate deposits that occur as as a result of chronic hyperuricemia was identified by Galen. The Latin word *gutta* (or 'drop'), is the root of origin for the word gout and referred to an excess of one of the four 'humors' – which in equilibrium maintains the state of wellbeing.

Gouty arthritis occurs as a result of excessive consumption of purine rich foods such as alcohol, meat, seafood etc. So it can be called as the 'disease of kings'. Elevation of serum uric acid (SUA) levels is the Essential prerequisite for the development of gouty arthritis. As a result of hyperuricemia monosodium urate crystals precipitates in the joints, connective tissue, and parenchymal organs including the kidneys.

Types[2,3]

According to the various stages through which gout progresses, they can be categorized as different types of gout.

Asymptomatic hyperuricemia

During this stage, a person has no symptoms of gout, but uric acid levels are above 6.0 mg/dL. At this stage, treatment is not required, though urate crystals are being deposited in tissue and causing slight damage. Regular monitoring of uric acid levels and making healthy diet and lifestyle adjustments can help to reduce future attacks in this stage.

Acute gout

This stage occurs when the urate crystals that have been deposited suddenly cause acute inflammation and intense pain. This sudden attack is referred to as a "flare" and will normally subside within 3 to 10 days. Flares can sometimes be triggered by stressful events, alcohol and drugs, as well as cold weather.

Interval or intercritical gout

This stage is the period in between attacks of acute gout. It is a symptom-free time, when their joints are functioning normally. Subsequent flares may not occur for months or years, though if not treated, over time, they can last longer and occur more frequently. However, even when symptoms are absent, ongoing deposits of uric acid crystals continue to accumulate, silently. Additional and more painful attacks of gout are likely to

continue unless the uric acid is lowered to below 6.0 mg/dL.

Chronic tophaceous gout
This is a late stage of gout. Permanent damage may have occurred in the joints and the kidneys. The patient can suffer from chronic arthritis and develop tophi, big lumps of urate crystals, in cooler areas of the body such as the joints of the fingers. It takes a long time without treatment to reach the stage of chronic tophaceous gout - around 10 years. It is very unlikely that a patient receiving proper treatment would progress to this stage.

Pseudogout
One condition that is easily confused with gout is pseudogout. The symptoms of pseudogout are very similar to those of gout.

Risk Factors[4]
1. **Age and gender:** Men produce more uric acid than women, though women's levels of uric acid approach those of men after the menopause.
2. **Genetics:** A family history of gout increases the likelihood of the condition developing.
3. **Lifestyle choices:** Alcohol consumption interferes with the removal of uric acid from the body. Eating a high-purine diet also increases the amount of uric acid in the body.
4. **Lead exposure:** Chronic lead exposure has been linked to some cases of gout.
5. **Medications:** Certain medications can increase the levels of uric acid in the body; these include some diuretics and drugs containing salicylate.
6. **Weight:** Being overweight increases the risk of gout as there is more turnover of body tissue, which means more production of uric acid as a metabolic waste product. Higher levels of body fat also increase levels of systemic inflammation as fat cells produce pro-inflammatory cytokines.
7. **Recent trauma or surgery:** Increases risk.
8. **Other health problems:** Renal insufficiency and other kidney problems can reduce the body's ability to efficiently remove waste products, leading to elevated uric acid levels. Other conditions associated with gout include high blood pressure, diabetes and an underactive thyroid gland.

Tests and Diagnosis[3,4,7]
Gouty arthritis is difficult to diagnose as its symptoms are similar to those of other health conditions. Before going for gout diagnosis the patient history and physical condition shpuld be closely monitored. Following are the latest diagnostic techniques available for gouty arthritis.

Synovial Fluid (SF) Examination[8,9]
Aspiration of gout nodules (arthocentesis) and visualization of monosodium urate crystal is the considered the gold standard for gouty arthritis. The joint fluid is undergone physical, visual, microscopic and chemical examination. In physical and visual inspection, volume, viscosity, colour and clarity of the fluid is checked. Too much fluid volume and less viscous joint fluid indicates inflammation. Healthy joint fluid is colourless or straw coloured. Abnormal fluid may appear cloudy and even appears coloured due to the presence of blood cells.In microscopic analysis the presence of uric acid crystal, white blood cell count, red blood cell count and presence of microorganism is analysed. A large deviation from normal white blood cell count especially neutrophils indicate infectious gout. Presence of microorganism can be detected by microscope or confirmed by culture study. The synovial fluid is chemically analysed for the presence of uric acid, glucose, lactate dehydrogenase and protein levels to confirm gouty arthritis. The elevated levels of uric acid content, LDH and protein indicate infectious gouty arthritis. In gouty arthritis the glucose level will be less than that of normal.

Ultrasonography (US)[10,11]
Synovial inflammation can be monitored by power Doppler ultra sonography. Musculoskeletal ultrasound can detect early deposition of monosodium urate crystal in the joint or in tophus. From the ultrasonography results we can evaluate synovial thickness, synovial effusion and bone erosion. Double contour (DC) sign on US is very specific for non-tophaceous urate crystal deposition on articular cartilage. Erosions are most commonly found in the first MTP joint (medial surface). Other synovial signs on US specific for gout are erosions, intrasynovial hyperechogenicity, hyperechoic areas and brightly stippled foci.

Dual-Energy Computerized Tomography (DECT)[12,13]
This type of imaging can detect the presence of monosodium urate crystals in the joint even though it is not accurately inflamed. This enables visualisation of urate deposits by analysis of the chemical composition of the scanned materials. It can be used for visualisation, charecterisation and quantification of monosodium urate crystal deposits. The basic principle behind DECT is to differentiate materials based on their relative absorption of X-rays at different photon energy levels.

Treatment[4,5,6,13,14,15,16]
Diet and Lifestyle Changes
1. Achieve ideal body weight.
2. Cessation of smoking.
3. Healthy diet and optimal exercise.
4. Good hydration.

Weight gain is a significant risk factor for gout in men, whereas weight loss reduces the risk. Intake of high fructose corn syrup should be restricted because the fructose contributes to increased uric acid production as a by-product of adenosine triphosphate catabolism. Patients with gout should limit their intake of purine rich animal protein (e.g., organ meats, beef, lamb, pork, shellfish) and avoid alcohol (especially beer). Purine rich

vegetables do not increase the risk of gout. Consumption of vegetables and low-fat or non-fat dairy products should be encouraged.

Pharmacological options[17]
The majority of gout cases are treated with medication. Medication can be used to treat the symptoms of gout attacks, prevent future flares, and reduce the risk of gout complications such as kidney stones and the development of tophi. Commonly used medications include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids. These reduce inflammation and pain in the areas affected by gout and are usually taken orally.

NSAIDs: The choice amongst NSAID depends on the patients response and tolerability. In patients with gastrointestinal intolerance to NSAIDs, cyclooxygenase-2 (COX-2) inhibitors e.g. etoricoxib may be used.

Colchicine: Oral colchicine is first-line treatment for acute gout attacks along with oral NSAIDs. It works best when commenced within 36 hours of first symptoms of an acute attack. A loading dose of 1 mg followed one hour later by 0.5 mg and then continued (up to 0.5 mg 3 times daily) until the acute attack resolves or the patient develops vomiting. A reduced dose of 0.5 mg daily or on alternate days is used in elderly or those with hepatic or renal dysfunction. The long-term adverse effects of colchicine include reversible axonal neuromyopathy (less than 1%). Patients should be advised to stop taking colchicine and tell their physician if they experience leg weakness or pain. Treatment should be discontinued if any signs or symptoms of nerve or muscle damage are present. The rare risk of rhabdomyolysis is increased when colchicine is used concomitantly with statins or clarithromycin (Biaxin), especially in older adults or those with chronic kidney disease; therefore, close monitoring is recommended

Corticosteroids (CS)
Aspiration of an affected joint followed by injection of corticosteroids is ideal treatment of acute mono articular gout. when colchicine, NSAIDs or oral corticosteroids are contraindicated. Where NSAIDs or colchicine cannot be used or are ineffective, oral prednisolone (0.5 mg /kg/day for five days) is preferred. A single dose of depot methyl prednisolone acetate 80 mg or triamcinolone 40-80 mg intramuscularly or methylprednisolone succinate (0.5-2.0 mg/ kg) intravenously may also be given. ACTH 25-40 IU subcutaneously/ intramuscularly every 8 hours for 1-14 days, is another option. ACTH may inhibit gouty inflammation by activating melanocortin type 3 receptor peripherally.

Probenecid: Probenecid increases urinary excretion of uric acid and is typically used as a second-line treatment because of numerous drug interactions. Of particular concern, probenecid increases blood levels of methotrexate and ketorolac, which may result in severe toxicity. Probenecid may be used in combination with allopurinol or febuxostat when one drug does not independently lower serum uric acid to target levels. Nephrolithiasis is a common adverse effect that may be avoided by high fluid intake and urine alkalization with potassium citrate.

Long-Term Management of Gou is accomplished by the use of urate lowering therapy with; xanthine oxidase inhibitors, uricosuric drug and pegloticase.

Serum urate lowering therapy should be initiated to prevent recurrences in persons with a history of gout and any one of the following: at least two flares per year (one per year in persons with chronic kidney disease stage 2 or greater), tophi, or a history of nephrolithiasis. Serum urate should be lowered to a target of less than 5 to 6 mg per dL (297 to 357 μmol per L), depending on the crystal and tophaceous burden. Normal serum urate levels do not exclude the diagnosis of gout. They should be monitored periodically to assess preventive therapy in patients with recurrent gout and a history of elevated urate levels. Urate-lowering therapy should be continued for three to six months after a flare if there are no ongoing symptoms. Therapy should continue indefinitely if there are ongoing signs or symptoms (e.g., one or more tophi on examination).

Pegloticase: Pegloticase (Krystexxa) is an intravenous uricase approved by the FDA in 2010. The mechanism of action involves metabolism of uric acid to allantoin. It is a third-line agent and is indicated for treatment of refractory gout. It is usually administered by a rheumatologist and is given every two weeks at a cost of more than $5,000 per dose.

Xanthine oxidase inhibitor: Eg Allopurinol a xanthine oxidase inhibitor, is a first-line agent to prevent recurrent gout. In patients with gout and chronic kidney disease or congestive heart failure, allopurinol has the added benefit of preventing chronic disease progression. The starting dosage is 100 mg per day, and 300 mg per day is a common maintenance dosage. Dosing is guided by the target serum uric acid level. In patients with chronic kidney disease, low initial doses are recommended with slow titration to achieve target uric acid levels. Dosages higher than 300 mg may be used even in those with renal impairment as long as patients are closely monitored for adverse effects. Certain ethnic groups have a higher risk of a severe hypersensitivity skin reaction when starting allopurinol therapy. Screening for human leukocyte antigen-B*5801 genotype is recommended before initiating treatment in patients of Han Chinese or Thai descent, regardless of kidney function, or in Koreans with chronic kidney disease stage 3 or greater.

What is ethosome?[18,19,20]
They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in ethosomes which have various physicochemical characteristics i.e.

hydrophilic, lipophilic, or amphiphilic. Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of ethosomes may vary from tens of nano meters to microns (μ). Ethosomes are the modified forms of liposomes that are high in ethanol content.

The main difference between ethosomes and liposomes is in their composition. Ethosome comprises various types of phospholipid structures, water, and low molecular weight alcohol (ethanol or isopropyl alcohol) in high concentration that provide malleability to the vesicle membrane. The ethosomal lipids are in a more-fluid state than liposomes containing the same ingredients without ethanol. Thus the ethanol can act as a "mixing" agent for lipid vesicles and provide vesicles with softness characteristics, which allow them to increase their distribution in different skin layers. However, because of their high ethanol concentration, the lipid membrane is packed less firmly than conventional vesicles but has equivalent solidity, allowing a more malleable structure and enhance drug distribution ability in stratum corneum lipids. In the cases of drugs with high solubility, the presence of ethanol in ethosomes can exhibit high encapsulation efficiency and improved drug loading.

It has been reported that the decrease of ethanol concentration in the range of 20% to 45% can result in the increase in the size of ethosomes and makes the ethosomes unique. The non-aqueous phase (alcohol and glycol combination) may range between 22to 70%. And polyglycols like propylene glycol, transcutol RTM are used as skin penetration enhancer. Various phospholipids which are used as vesicle forming component are phosphatidylcholine (for instance: soya phosphatidylcholine, egg phosphatidyl-choline, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine) phosphatidic acid, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and phosphatidylinositol (PI). In addition, non-ionic surfactants (PEG-alkyl ethers) can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide etc can be added too. Cholesterol used at a range of 0.1% - 1% provide stability to the vesicle membrane. Such a composition enables delivery of high concentration of active ingredients through skin. Drug delivery can be modulated by altering alcohol: water or alcohol-polyol: water ratio.

In addition, soybean phosphatidylcholine (Phospholipon 90), ethanol, drug and distilled water can be served for production of Ethosomes.

Mechanism of drug penetration
The main advantage of ethosomes over the liposomes is the increased permeation of the drug into the stratum corneum. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases - ethanol effect and ethosomes effect.

Ethanol effect Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.

Ethosome effect Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So, the ethosomes permeates very easily inside the deep skin layers, where it gets fused with skin lipids and releases the drugs into deep layer of skin.

Ethosome for gouty arthritis
Ethosome carriers, developed by Touitou et al., are a modified form of liposomes that include a relatively high concentration of ethanol. They are very efficient at enhancing the skin permeation of a number of drugs to reach the deeper layer of skin or the systemic circulation. It has been shown that the physicochemical characteristics of ethosomes permit this vesicular carrier to transport active substances more effectively through the stratum corneum (SC) into the deeper layers of the skin than conventional liposomes.

Hence using ethosome as novel carrier for transdermal drug delivery we are expected to have better therapeutic results.

The anti-gouty arthritic activity is evaluated using.

MSU induced gout air pouch model[21,22]

And measurement of exudate volume and leukocyte count.

CONCLUSION

Management of gout has undergone major change in the last couple of years. Proper control of SUA to less than 6.0 mg% (or lower in presence of tophi) is the main aim with optimum management of comorbidities and patient education are of paramount importance. From this paper it can be concluded that Ethosomes provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Various hydrophilic drugs, cationic drugs, proteins and peptides can be easily administered through transdermal route by ethosomal encapsulation. So the main advantage is improved therapies. The ethosomal technology is safety and convenience of use. Important factors that need to be considered when developing alternate drug delivery systems.

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