A REVIEW ON: HYDROGEL FORMULATION IN AN EFFECTIVE TARGETED DRUG DELIVERY OF ANTI-GOUT DRUG.

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ABSTRACT:

Gout is a metabolic condition that results in joint inflammation. Taking painkillers or anti-inflammatory drugs can help reduce the pain. It is the kind of arthritis that is most understood and explained. The epidemiology of it is examined. A deeper comprehension of the condition is made possible by new discoveries into the pathophysiology of both acute and chronic gouty arthritis and hyperuricemia. Because of their hydrophilic structure, hydrogel products are a class of polymeric materials that can hold a lot of water in their three-dimensional networks. The creation of hydrogel for the treatment of gout is the foundation of this review. Topical gel formulations are designed to be applied to the skin or specific mucosal surfaces for transdermal penetration or local action of medication.

KEYWORDS: Gout, Topical Hydrogel, classification, applications.

INTRODUCTION:

Hydrogels consist of polymer network that absorbs and retain vast quantities of water| Hydrophilic groups in the polymeric network hydrate in aqueous environments to form a hydrogel structure(Ahmed 2015a). Another description is that it is a polymeric material that will no dissolve in water but shows the ability to expand and keep a large amount of water inside its structure. Because of their high-water content, they are quite flexible, much like genuine tissue. The hydrophilic functional group affixed to the polymeric backbone gives its ability to absorb water, whilst the crosslinks interconnected network chains provide it its opposition to dissolution(Terkeltaub 2009a). A type of arthritis called gout is caused by the formation of monosodium urate (MSU) crystals in the joints|(Ragab, Elshahaly, and Bardin 2017a). When the concentration of uric acid at physiological pH exceeds its solubility limit, which is 6.7-7 mg/dl, it may nucleate and form crystals in tissues|and joints(Malpure et al. 2018).

The human purine metabolism culminates in uric acid, which is produced by the hypoxanthine-xanthine-uric acid cascade. Xanthine oxidase (XO) catalyzes both of the aforementioned reactions. The two pharmacological approaches now used to decrease urate in gout include increasing urine uric acid excretion with a uricosuric drug and decreasing urate synthesis with allopurinol, a xanthine oxidase (XO) inhibitor(Arshad et al. 2018). Gout treatment usually

includes NSAIDS steroids or colchicine, probenecid, allopurinol, and febuxostatl etc(Abdullah et al. 2023). The present review is based on the preparation of hydrogel for treatment of gout.

Advantages:

- Hydrogel has more strength and elasticity.
- Hydrogel has excellent transparency and is simple to work with.
- Their elevated water content gives them A certain amount of adaptability that is strikingly akin compared to natural tissue.
- In addition to being injectable, they are biocompatible and biodegradable.
- A change in temperature, pH, or metabolite concentration can be sensed by hydrogel, which can then release its load.
- Timely release of medications or nutrients(Anon n.d.).

Disadvantages:

- Expensive.
- The maggot may need to be fastened with a secondary dressing because it is non-adherent and can cause discomfort.
- Sterilization is challenging.
- Red eyes, dehydration, and hypoxia due to contact lens deposition reactions(Anon n.d.).

Gout:

An instance of arthritis is gout. It happens when blood levels of uric acid rise and lead to joint inflammation. One joint is frequently affected by the excruciating ailment known as acute gout. Chronic gout is characterized by recurrent flare-ups of inflammation and discomfort. There could be more than one damaged joint. (Fig. 1).

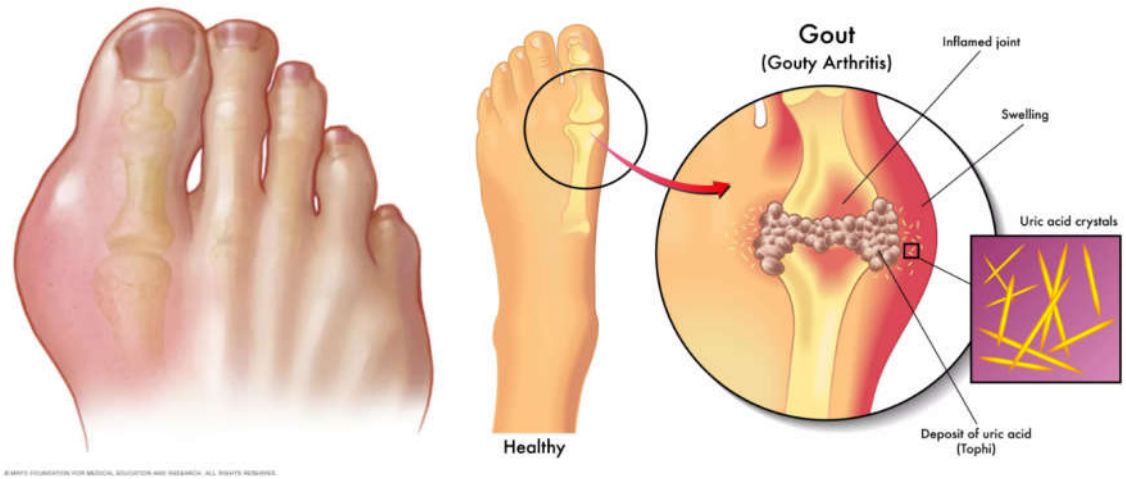

Fig. 1: Gout Disease

Epidemiology:

One to four percent of the general population suffers with gout. It affects 3– 6% of males and 1% –2% of women in Western countries. Prevalence may rise by as much as 10% in some nations. For men and women over 80, the prevalence increases to 10% and 6%, respectively. Gout affects 2.68 out of every 1000 people annually. Men are 2-6 times more likely than females, experience it. The prevalence of gout is steadily rising globally as a result of unhealthy eating patterns like fast food, inactivity, and rising rates of obesity and metabolic syndrome(Terkeltaub 2009b).

Pathophysiology:

1. Urate crystal production:

A metabolic condition called gout is brought on by an increase in uric acid production. acid^0. One byproduct Because purine metabolism is uric acid. Hypoxanthine oxidase transforms purines into hypoxanthine, which is then transformed into uric acid in the body. An enzyme called uricase, which is easily eliminated by the kidneys, transforms uric acid into allantoin in mammals^0. The primary cause of gout is an elevated serum uric acid level brought on by a decline in renal excretion^0. Renal reabsorption and secretion have a major role in uric acid excretion. The process of uric acid reabsorption involves the urate transporter 1. Increased uric acid production and reduced excretion raise serum uric acid concentrations, which are then transformed into monosodium urate crystals(Terkeltaub 2009b).

Four pathophysiological stages can be thought of as the progression of hyperuricemia and gout: the development of hyperuricemia, crystallization of monosodium urate, the clinical manifestation of flare-ups of gout brought on by a severe inflammation reaction to the crystals, and the clinical manifestation of advanced illness marked through tophi(Ashiq et al. 2018). Some patients present with advanced disease without previous gout flares.

Hyperuricemia:

One crucial stage in the progression of gout is hyperuricemia (figure 1). The last byproduct of purine nucleotide breakdown is urea Serum urate and the chance of developing gout are raised by diets rich in purines or other dietary variables (such as use of alcohol and sugar) that cause purine nucleotides to degrade(Ashiq et al. 2018). Because of excessive urate production, medical diseases such as myeloproliferative diseases and psoriasis that cause fast cell turnover also raise serum urate concentrations. The kidney and gut control urate excretion, and low urate excretion raises serum urate levels. The straight proportionality between serum creatinine and urate concentrations highlights the significant function of renal excretion. The renal excretion of urate is also decreased by diuretics like furosemide and elevated circulating insulin concentrations (in the context of high body mass index as well as metabolic syndrome)(Ragab, Elshahaly, and Bardin 2017b).

Hyperuricemia, which is caused by either excessive or insufficient excretion of urea, promotes the creation of Crystals of monosodium urate. Monocytes possess the capacity for phagocytosis these crystals; however, a further signal via TLR2 and TLR4 is necessary to fully activate the NLRP3 inflammasome and produce proinflammatory IL-1β, which causes acute flare-ups of gouty arthritis. Monosodium urate crystals are bound by neutrophil extracellular traps

during flare resolution. The development of tophi may potentially be facilitated by aggregated neutrophil extracellular traps (fig. 2).

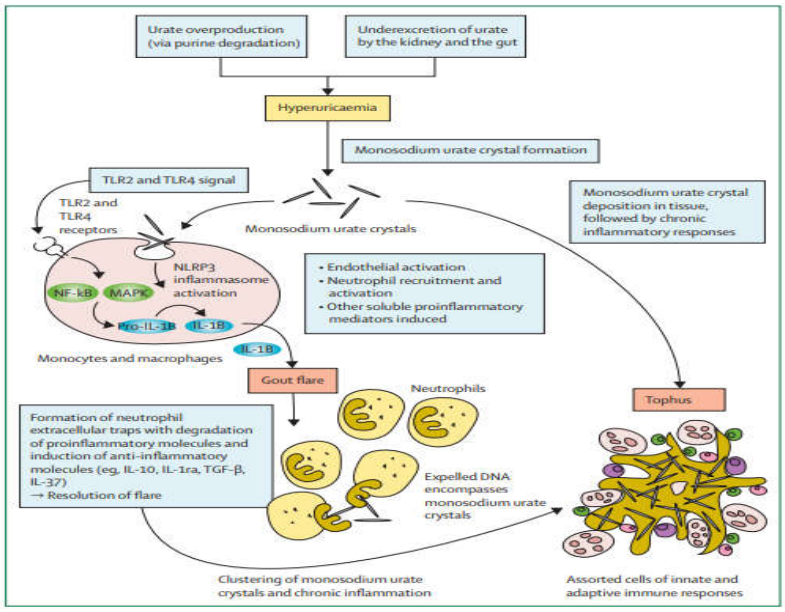

Fig 2: Progression of hyperuricemia to gout

Causes of Gout:

- **High Uric Acid**: Overproduction or poor elimination of uric acid.
- **Diet**: Purine-rich foods (like red meat, shellfish), alcohol, sugary drinks, and foods high in fructose can raise uric acid levels.
- **Obesity**: Increases uric acid production and reduces its elimination.
- **Dehydration**: Impairs the kidney's ability to eliminate uric acid.
- **Genetics**: Family history can increase risk.
- **Medical Conditions**: Gout risk factors include metabolic syndrome, high blood pressure, and kidney disease.
- **Medications:** Some medications, such as aspirin and diuretics, might cause an increase in uric acid levels.
- **Age and Gender**: More common in men over 40, and in women after menopause.
- **Other Triggers**: Stress, injury, fasting, and surgery can also trigger attacks.

Effect of gout on joints:

- **Acute Pain and Inflammation**: Gout often starts with sudden, severe pain in a joint, typically on the big toe (called podagra). The affected joint becomes red, swollen, and warm to the touch, making movement difficult.
- **Joint Damage:** Recurrent bouts of gout can cause persistent joint damage if ignored. inflammation, which may cause long-term damage to the affected joints.

- **Joint deformities**: Chronic attacks can lead to joint deformities, where the structure of the joint is altered.
- **Reduced mobility**: Ongoing joint damage can result in stiffness and difficulty moving the affected joint.
- **Tophi Formation**: Over time, uric acid crystals can Crystals of uric acid can form lumps known as Under the skin, tophi around the joints. These are often visible around joints like the fingers, elbows, and ears, and can cause further joint damage if not treated.
- **Chronic Gout**: With repeated flare-ups, gout can become chronic, affecting multiple joints and leading to persistent pain, inflammation, and potential long-term joint damage.

Hydrogels:

Hydrogels are polymer networks that have the ability to absorb and retain vast quantities of water. The polymeric network contains hydrophilic groups that get hydrated. in watery the media thereby creating hydrogel structure(Ahmad et al. 2018).

Classification of hydrogel products:

I. Categorization Based on source(Ullah et al. 2015)

1. Hydrogels made naturally:

Natural hydrogels possess strong characteristics of cell attachment and are both biocompatible and biodegradable. There are two basic types of natural polymers used to make natural hydrogels: polymers such as hyaluronic acid proteins like collagen, gelatin, and lysozyme, as well as alginate and chitosan.

2. Artificial hydrogels:

In contrast to their natural counterparts, they are more practical because they are capable of intended to have a far wider range of chemical along with mechanical Qualities. One type of materials that is frequently employed in biomedical applications is hydrogels based on polyethylene glycol due to their non-toxicity, compatibility, and low immunogenicity.

3. Hybrid hydrogels:

They are a blend of hydrogels made of natural and artificial polymers. A variety of Biopolymers that exist naturally, including collagen and dextran, and Chitosan has been mixed using artificial polymers, including Polyvinyl alcohol with poly (N-isopropylacrylamide).

Classification based on Polymeric composition(Zaman et al. 2015)

1. Homo-Polymeric Hydrogels: A polymer network made out of one species of a monomer, a basic structural element of every A homo-polymeric hydrogel is a network of polymers. The kind of monomer and the method of polymerization can determine whether a homopolymer has a cross-linked skeleton.

2. Co-polymeric hydrogels: Two or more different species of monomers having a minimum of one hydrophilic element, organized randomly, in blocks, or alternately throughout the polymer network's chain, make up co-polymeric hydrogels.

3. Multi-polymer Interpenetrating hydrogel made of polymers (IPN): Two distinct components of a cross-linked natural or synthetic polymer make up this significant type of hydrogels' network system. In semi-IPN hydrogel, one element is a polymer that is cross-linked, while the other polymer is not cross-linked.

III. According to the biodegradability

1. Biodegradable Hydrogels: Hydrogels decompose naturally. Bio-degradable polymers found in nature include agar, fibrin, and chitosan. The synthetic biodegradable polymers include poly (N-isopropyl acrylamide), poly (aldehyde guluronate), and polyanhydrides.

2. Non-biodegradable hydrogels: The production of non-biodegradable hydrogels frequently uses a variety of macromers or vinylated monomers, including 2-hydroxyl ethyl methacrylate, ethylene glycol (methoxyl poly), 2-hydroxyl propyl methacrylate, and acrylamide.

IV. Classification based on configuration (Madduma-Bandarage and Madihally 2021)

Based on their physical characteristics and chemical composition, hydrogels can be divided into the following categories:

1.Non-crystalline and amorphous.
2.Semi-crystalline: An intricate combination of amorphous and crystalline phases.
3.Crystalline.

V. Classification Based on Type of Cross-linking(Ullah et al. 2015)

Depending on the physical or chemical characteristics of the cross-link junctions, hydrogels can be categorized into two groups.

1. Permanent junctions are found in networks that are chemically cross-linked.

2. Transient junctions are seen in physical networks and can result from physical interactions like hydrophobic or hydrogen bonding or from entanglements in polymer chains.

VI. Physical appearance-based classification

The preparation process's polymerization strategy determines whether hydrogels form as a matrix, film, or microsphere.

VII. Grouping based on network electrical charge(Ullah et al. 2015)

Four kinds of hydrogels can be distinguished based on whether or not they have an electrical charge on the cross-linked chains:

1. Nonionic or neutral.
2. Ionic, including cationic and anionic.
3. An amphoteric (ampholytic) electrolyte that contains both basic and acidic groups.
4. Zwitter ionic (polybetaines), which has both cationic and anionic groups.

DRUG RELEASE MECHANISM0

Diffusion controlled:

Diffusion-controlled drug release is most frequently utilized method for hydrogel. Diffusion controlled release is frequently modeled using Diffusion coefficients for Fick's law of diffusion can be either constant or variable. Drug diffusivities are typically estimated beforehand using hydrodynamic, free volume, or obstruction-based theories, or they are determined empirically.

Chemically controlled:

Molecule release that is governed by reactions taking place within a delivery matrix is known as chemically-controlled release. The most frequent processes that take place in Systems for delivering hydrogel are reversible or irreversible interactions between the network of polymers and the releaseable medication, or polymer chain cleavage by enzymatic or hydrolytic breakdown. Under some circumstances, the medication release rate will be regulated by the majority or surface erosion of hydrogels. However, the binding equilibrium might dictate the release of drugs rate If the molecules that bind drugs are added to the hydrogels.

Swelling controlled:

Diffusion of the medication is quicker than the swelling of hydrogel, resulting in swelling-controlled release. Moving boundary conditions are typically used to represent this phenomenon, in which molecules are released at the interface between the rubbery and glassy phases of swelling Diffusion-controlled release of drugs is the most often used hydrogel method.

Applications

1. Wound healing: Hydrogels' cross-linked nature allows them to retain both medications and water. Their ability to hold water allows them to hold and maintain wound exudates. A gel of polyvinyl pyrrolidine or polyacrylamide that contains 70–95% water(Brumberg et al. 2021).

2. Colon Specific Hydrogels: The colon's elevated levels of polysaccharide enzymes area of GI have resulted in the creation of colon-specific polysaccharide hydrogels. Drug delivery to the colon is the special function of dextran hydrogel.

3. Drug delivery in GI tract: Drugs are delivered to particular GIT sites via hydrogels. Drugs that contain hydrogels unique to the colon exhibit tissue-specificity inside the presence of microflora, and enzymatic activity or pH changes lead to drug breakdown(Su et al. 2021).

4. Rectal Delivery: Rectal medication distribution uses hydrogels with bioadhesive qualities(Madduma-Bandarage and Madihally 2021).

5. Transdermal Delivery: To administer medication via the transdermal route, several hydrogel-based drug delivery devices have been developed. Hydrogel-based formulations are being researched for transdermal iontophoresis to increase product penetration., specifically for nicotine and hormones.

6. Delivery of drugs in the oral cavity: oral cavity: To provide localized care for oral illnesses such stomatitis, viral infections, fungal infections, periodontal disease, and malignancies of the oral cavity, the drug is incorporated into hydrogels and administered orally cavity(Ahmed 2015b).

7. Gene delivery: Through modifying the hydrogels' Nowadays, it is possible to effectively target and distribute nucleic acids to specific cells for gene therapy. Numerous hereditary and acquired disorders may benefit from the use of hydrogels(Madduma-Bandarage and Madihally 2021).

8. Tissue engineering: To introduce macromolecules into the cytoplasm of antigen-presenting cells, micronized hydrogels are utilized. Agarose, methylcellulose, and other naturally derived compounds are examples of natural hydrogel materials utilized in tissue engineering(Zaman et al. 2015).

9. Drug delivery through the eyes: The most common application for hydrogels is in ocular medication delivery systems. By localizing at the medication's site of action, hydrogel exhibits controlled or sustained release, which lowers the dosage needed or provides consistent drug administration, hence reducing the frequency of dosing or increasing the drug's effectiveness(Zaman et al. 2015).

MATERIALS AND METHOD:

Methods of Hydrogel Preparation:

Networks of hydrogels of hydrophilic polymer molecules. Although hydrogels are usually prepared using Sometimes, Monomers that are hydrophilic and hydrophobic are infrequently used.

In general, one can create hydrogels from synthetic or natural polymers. Because they are hydrophobic, synthetic polymers have a more powerful chemical structure than Organic polymers. Although durability also depends on mechanical strength, their mechanical strength causes them to deteriorate more slowly. These two conflicting qualities should be balanced in optimal design. Additionally, if natural polymers have the right functional groups or have been functionalized with radically polymerizable groups, hydrogels based on them can be produced. The polymerization techniques are described as follows:

Physical cross-linking:

It is the most popular and simple route for the creation of hydrogel through the physical cross-linking of polymers. Included in this physical cross-linking are the way ions interact, such as hydrophobic association, polyelectrolyte complexation, and hydrogen bonding.

Solution polymerization:

In these, the multifunctional crosslinking agent is used with either neutral or ionic monomers. UV radiation or an initiator of redox device can be accustomed to initiate the polymerization process thermally. The solvent acting being a heat sink, the main benefit of solution polymerization versus bulk polymerization. The hydrogels produced are cleaned with purified water to get rid of the extractable polymer, cross-linking agent, soluble monomers, oligomers, initiator, and other contaminants. As solvents, ethanol, water, benzyl alcohol, and Ethanol and water blends were used.

Polymerization by irradiation:

Initiators such ionizing radiation with high energy, like electron beams and gamma rays, have been employed to create hydrogels of unsaturated molecules. Radicals are created when an aqueous polymer solution is applied to the polymer chains exposed to radiation. Ultimately, a

cross-linked framework is created when macro-radicals on different chains recombine to create covalent connections.

Bulk polymerization: propagation, chain transfer,

One or more monomers can be used to make hydrogels in large quantities; the most popular type of hydrogel is made from vinyl monomers. A little quantity of cross-linking agent is present in the majority of hydrogel formulations. Chemical catalysts, UV light, or radiation can initiate the polymerization reaction. The initiator's selection is dependent about the type of solvents and monomers being used. The polymerized hydrogel can be made in many different ways, such as emulsions, rods, particles, membranes, and films.

Suspension polymerization:

This method creates spherical hydrogel microparticles that range in size from 1 μm to 1mm. This technique disperses in a non-solvent, the monomer solution to create a tiny droplet that is stabilized by a stabilizer. the polymerization that was initiated by the thermal breakdown of the free radical. In order to eliminate the initiator, cross-linking agent, and unreacted monomers, the produced Microparticle rinsed.

Free radical polymerization:

Key monomers utilized in this technique to produce hydrogels include amides, vinyl lactams, and acrylates. These polymers are functionalized with radically polymerizable groups or have appropriate functional groups. This approach makes advantage of the normal free-radical polymerizations' chemistry, including the propagation, chain transfer, initiation, and termination processes. During the initiation stage, radicals can be produced using a range of thermal, UV, visible, and redox initiators. The monomers respond to the radicals to transform turning them into active forms(Abdullah et al. 2023).

Grafting to a support:

Grafting is the process of polymerizing a monomer ona preexisting polymers backbone. Chemical reagents or high-energy radiation therapy are used to activate the polymer chains. Branching and ultimately crosslinking is caused by the development on activated macroradicals of functional monomers.

Coacervation of complexity:

Coacervate gels that are complex are created by combining polyanions and polycations. This method's fundamental idea is that, Polymers having opposite charges will stick to each other and, based on the concentration and pH of the corresponding solutions, create soluble and insoluble complexes. One example is the coacervation of polycationic chitosan combined with polyanionic xanthan. Proteins that are less than their isoelectric point are probably combine to create a polyion complex hydrogel using anionic hydrocolloids because they are positively charged.

Characterization Of Hydrogels:

Physical attributes

Visual inspection was performed on the manufactured hydrogel formulations to assess their pH, color, homogeneity, consistency, grittiness, texture, and phase separation.

Determination of pH

A digital pH meter was used to measure the pH of the hydrogel compositions. The electrode was submerged in the gel formulation for 30 minutes until a steady reading was obtained after one gram of gel had been dissolved in 25 milliliters of distilled water. Additionally, continuous reading was observed. The measurement of pH of each formulation was done in triplicate and average values were calculated(Ahmed 2015b; Ullah et al. 2015).

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability study

Aluminum or metal collapsible tubes were used to hold the hydrogel compositions. The material was extruded by pressing the tubes, and the formulation's extrudability was checked(Ostróżka-Cieślik, Wilczyński, and Dolińska 2023).

Spreadability

Two standard-sized (6x2) glass slides were used. Over one of the slides was the hydrogel formulation whose spreadability was to be ascertained. The second slide was positioned atop the first so that the formulation was positioned between them along the slide at a speed of 6 cm/s. To ensure that the hydrogel formulation between the two slides was traced uniformly to produce a thin layer, 100 grams of weight was placed on the upper slide. The excess hydrogel formulation that was sticking to the slides was scraped off once the weight was taken off. One end of the upper slide was fastened to a string that weighed 20 grams, while the bottom slide was secured to the apparatus' board.hydrogel formulation(Jain et al. 2016; Srivastava et al. 2021).

$$\textbf{Spreadability} = (m.l / t)$$

Where,

S= Spreadability (gcm/sec),

m = weight (20 grams) attached to the top slide,

l = glass slide length (6 cm),

t is the amount of time in seconds.

Viscosity

Using a Brookfield digital viscometer, the prepared hydrogel's viscosity was measured. Using spindle number six, the viscosity was tested at 25^0C and 10 rpm. An adequate amount of gel was put into the proper wide-mouth container. The wide mouth container was filled with hydrogel in a way that would allow the viscometer's spindle to dip in it. At a steady temperature of 25 ±/1^0C, hydrogel samples were let to settle for 30 minutes prior to the measurements(Jain et al. 2016; Shah et al. 2024).

Drug Content

Weighed precisely to be equal to 100 mg of topical hydrogel was placed in a beaker, and 20 milliliters of phosphate buffer pH 7.4. This solution was mixed thoroughly and filtered using Whatman filter paper no.1z Then 1.0 ml of filtered solution was taken in 10 ml capacity of volumetric flask and volume was made upto 10 ml with a pH 7.4 phosphate buffer. This solution was analyzed using UV spectrophotometer at λmax 275 nm.

Drug release investigations conducted in vitro utilizing the pre-hydrated cellophane membrane

The hydrogel's ability to release drugs in vitro was assessed. Using a cellophane membrane, an in vitro diffusion investigation was conducted in a diffusion cell by Franz. The Franz diffusion cell was covered with a cellophane membrane. The dialysis membrane's donor compartment was used to apply the formulation. Twenty-five milliliters of pH 7.4 phosphate buffer were added to the reservoir compartment. For eight hours, the trial was conducted at 37 ± 1°C and 100 rpm. Samples were taken out of the reservoir compartment once every hour, and the absorbance at 275.0 nm was determined using spectrophotometry. The same amount of 7.4 pH phosphate buffer was added to the reservoir compartment each time(Biswal et al. 2014; Sabale and Vora 2012).

CONCLUSION:

Although topical hydrogels offer a promising method of treating gout, further research is required to completely comprehend their effectiveness and mechanisms of action, according to the review on the topic. The new method for delivering the medicine through the system by applying it topically to the skin is provided in this review. Thus, the objective of these reviews is to reduce gout by avoiding the systemic circulation of medications and instead providing a local effect to enhance drug efficacy and bioavailability, which in turn reduces gouty inflammation.

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