RESEARCH PAPER

Formulation and Evaluation of Transdermal Drug Delivery Systems Based on Niosomal Gel on Febuxostat

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ABSTRACT

Background:
Febuxostat, a non-purine xanthine oxidase inhibitor, is widely used for the management of hyperuricemia and gout. However, its oral administration is associated with limitations such as gastrointestinal adverse effects, hepatic toxicity, and variable bioavailability. Transdermal drug delivery systems, particularly niosomal gels, offer an attractive alternative by providing sustained release, improved stability, and enhanced skin permeation while reducing systemic side effects. Niosomes are non-ionic surfactant-based vesicles that can encapsulate both hydrophilic and lipophilic drugs and enhance their permeation through the skin.

Objective:
To formulate and evaluate transdermal drug delivery systems based on niosomal gel for febuxostat, aiming to improve drug permeation, sustain release, and reduce systemic adverse effects.

Methods:
Niosomes were prepared using the thin-film hydration technique with varying concentrations of non-ionic surfactants (Span 60, Tween 60) and cholesterol. The prepared niosomes were evaluated for vesicle size, zeta potential, polydispersity index, entrapment efficiency, and surface morphology. The optimized niosomal dispersion was incorporated into a Carbopol-based gel and evaluated for pH, viscosity, spreadability, drug content, in vitro drug release, and ex vivo skin permeation studies using Franz diffusion cells. Stability studies were conducted as per ICH guidelines.

Results:
The optimized niosomal formulation exhibited a mean vesicle size in the nanometric range, acceptable PDI, negative zeta potential, and high entrapment efficiency. The niosomal gel showed pH compatible with skin, good spreadability, and uniform drug content. In vitro drug release studies demonstrated sustained release of febuxostat from the niosomal gel over an extended period compared with conventional gel. Ex vivo skin permeation studies revealed significantly enhanced drug permeation across the skin from the niosomal gel formulation. Stability studies indicated that the formulation remained stable under accelerated storage conditions with minimal changes in physicochemical properties.

Conclusion:
The niosomal gel-based transdermal drug delivery system developed in this study represents a promising approach for the delivery of febuxostat. The formulation demonstrated sustained drug release, enhanced skin permeation, and good stability, suggesting its potential as an effective and patient-friendly alternative to oral therapy for hyperuricemia and gout. Further in vivo studies and clinical evaluations are warranted to confirm its therapeutic efficacy and safety.

Keywords: Febuxostat; Niosome; Transdermal drug delivery; Niosomal gel; Hyperuricemia; Gout; Skin permeation; Sustained release

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1. INTRODUCTION

Pharmaceutical research has been paying more attention to niosomal gel formulations because of their potential to improve therapeutic efficacy and drug delivery. Such sophisticated delivery systems can be advantageous for feuxostat, a xanthine oxidase inhibitor mainly necessity hyperuricemia and gout. An summary of niosomal gel formulations designed especially for Febuxostat is provided here. Drugs that HLB encapsulated in niosomes, which are non-ionic surfactant-based vesicles. They are made up of cholesterol and surfactants, which offer a flexible platform for medication delivery. The encapsulated drug's stability, bioavailability, and controlled release are all improved by niosomes. Niosomes are microscopic lamellae bilayered and range in 10 to 10,000 nm. In the aqueous phase, non-ionic surfactants self-associate to create them. They have a spherical form and are made up of lamellar structures, both unilamellar and multilamellar. Drug penetration is enhanced when the medications are enclosed in niosomes. Both hydrophilic and hydrophobic medications can be contained in them. medications that are hydrophilic can be administered by either entrapping the drug in particle or by adsorbing on the surface of the bilayer; hydrophobic medications are administered by encasing the drug in a bilayer of non-ionic surfactants. Non-ionic surfactants, lipids, and polymers make up niosomes; lipids give the niosomes their stiffness and correct structure, while surfactants improve penetration. [(1)]

Niosomes are gaining a lot of interest due to their benefits, which include consistency of content, low cost, easy storage, stability both chemically and physically, and the availability of different surfactants for niosomal formulations. A niosomal formulation reduces the amount of time that a medication degrades, inactivates it after delivery, and guards against adverse effects. Niosomal gel formulations are used to treat a number of illnesses, including psoriasis, gout, arthritis, and fungal infections. [(2)] Niosomes are multi lamellae vesicles that are produced by hydrating synthetic non-ionic surfactants, either with or without the addition of sterols. Niosomes are subject of much research lately due to their potential as a delivery system for medications, hormones, antigens, and other biologically active substances.

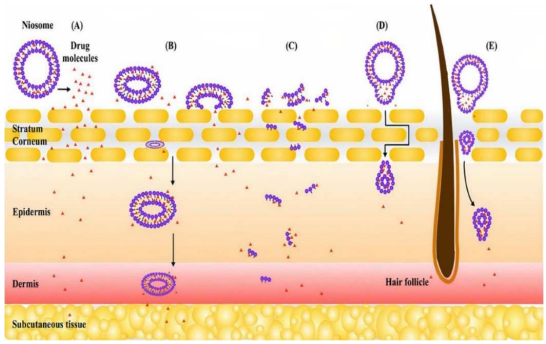


Fig 01- Non-ionic Surfactant-based Nano vesicle

Also to address issues with medication instability, insolubility, and fast degradation. The steroidal system in niosomes enhances the bilayer's stiffness, modifies its fluidity and permeability, and shields the molecules dreadful conditions brought on by undesirable biological effects. Niosomes are generally favored over liposomes because to their superior chemical stability and economy. Generally speaking, niosomal medication carriage to investigated via a number of delivery methods, such as transdermal, intramuscular, peroral, and intravenous.[(3)] Because of its bilayer, which allows for continuous release of the drug within, niosomes function as drug enter, releasing the drug in a regulated way. It also used for TDD. Medication is given to specific body area where the desired therapeutic effect is needed. Decreasing the amount that must be given in order to produce the intended result. [(4)]

The medications' ability to target a particular region, decrease clearance rates, and protect encapsulated pharmaceuticals all contribute to their greater therapeutic efficacy. Medication targeting lowers the dosage, which consequently lowers the adverse effects. The niosomes' vesicular architecture allows them to encapsulate both lipophilic and hydrophilic molecules. Lipophilic compounds are captured by partitioning into the lipophilic domain of bilayers, whereas hydrophilic medicines are often adsorbed on the surfaces of the bilayers or contained in the inner watery core. [(5)] Vesicular assemblies require energy input to form, and all methods which entail hydrating a combination with the option to reduce the size of the resulting colloidal dispersion. Due to their capacity to transport a wide range of therapies, so used as DD vehicles to enable medication targeting, controlled release, and permeability increase. Actually, niosomes can be modified to function as therapeutic reservoirs for the regulated release of a medication to improve bioavailability and get a therapeutic impact over a longer length of time. This is achieved by varying

the surface charge, composition, and concentration of various additives. [8, 9]

Furthermore, it has been discovered that drug ionization alters the vesicles' physicochemical characteristics and percutaneous permeation profiles. Since niosomes can be readily derivatized to increase vesicles' versatility and affinity for the target site, also thoroughly possible carters for sustained and TDD in recent decades. Niosomes that generate surfactants are biodegradable, immunogenicity-free, and biocompatible. Some drugs, like nimesulide, flurbiprofen, piroxicam, ketoconazole, and bleomycin, have higher bioavailability when incorporated into niosomes as opposed to being taken alone. [6,7]

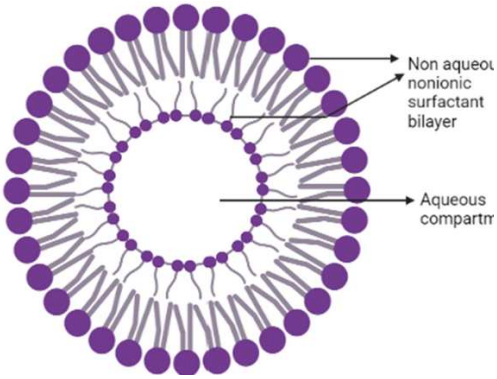


Fig 02- Structure of Niosome

Advantages of Niosomes:

1. The main benefits of these vesicular drug carriers are as follows: NDD is a promising drug delivery technique for regulated and TDD. [8]
2. To switch DD rate and supply normal vesicle in external nonaqueous phase
3. Boost the stability of the medication that is entrapped.
4. Increase the epidermal penetration of medicines and increase the oral bioavailability of poorly absorbed medications.
5. The surfactants are recyclable, biocompatible and non-immunogenic.
6. By delaying the medication's clearance from the bloodstream, shielding it from the biological environment, and limiting its effects to the targeted cells, they enhance the therapeutic efficacy of the drug molecules.
7. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to adjust the delivery rate of medicine and administer normal vesicle in external nonaqueous phase.
8. By delaying the medication's clearance from the bloodstream, and limiting its effects to the targeted cells, they enhance the therapeutic efficacy of the drug molecules.
9. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to adjust the delivery rate of medicine and administer normal vesicle in external nonaqueous phase.
10. They recover the salutary enactment of the drug molecules

Advantages of Niosomal Gel

1. Enhanced Drug Stability: Niosomes protect the encapsulated drug from degradation.
2. Controlled Release: They provide sustained release, improving therapeutic efficacy and reducing dosing frequency.
3. Increased Bioavailability: Niosomes can improve the bioavailability of drugs by enhancing their absorption through the skin or other membranes.
4. Reduced Side Effects: Targeted delivery can reduce systemic side effects.

1.2 Formulation of Niosomal Gel

The formulation of a niosomal gel involves several steps:

Preparation of Niosomes:

1. Sonication: The formed niosomes are sonicated to reduce their size and achieve uniformity.
2. Incorporation into Gel
3. The prepared niosomes are then incorporated into a suitable gel base. Commonly used gelling agents include Carbopol, HPMC (Hydroxypropyl Methylcellulose), or other polymers.
4. The gel base is typically prepared by dispersing the gelling agent in water, adjusting the pH, and adding the niosomal suspension.

1.3 Characterization of Niosomal Gel

1. Particle Size and Distribution: Ensuring the niosomes are within the optimal size range for stability and penetration.
2. Encapsulation Adeptness: The percentage of Febuxostat encapsulated within the niosomes.
3. In Vitro Release Studies: To evaluate the proclamation profile of Febuxostat gel.
4. Stability Studies: Assessing the stability.
5. Permeation Studies: Evaluating ability of niosomal gel to deliver Febuxostat or other biological membranes.

1.4 Therapeutic Benefits for Febuxostat

1. Improved Patient Compliance: The gel form is more user-friendly and may enhance patient adherence to the treatment regimen.
2. Localized Delivery: Can provide localized drug delivery, reducing systemic exposure and potential side effects.
3. Effective Management of Gout: Enhanced delivery of Febuxostat can lead to better management of uricemia and more effective control of gout.

1.5 Conclusion

The development of a niosomal gel formulation for Febuxostat presents a promising approach to improve the drug's therapeutic profile. By leveraging the benefits of niosomes, such a formulation can potentially offer enhanced drug stability, controlled release, increased bioavailability, and reduced side effects, ultimately improving patient outcomes in the treatment of gout and hyperuricemia.

For a detailed formulation and specific studies, consulting recent pharmaceutical research papers and reviews on niosomal drug delivery systems would provide comprehensive insights.

TDDS give different ROA to oral and injectable way, providing controlled release, improved bioavailability, and reduced systemic side effects. Febuxostat, a non-purine selective inhibitor of xanthine oxidase, is commonly used to manage hyperuricemia . Despite its effectiveness, oral administration is associated with gastrointestinal disturbances and variable pharmacokinetics. Niosomes, non-ionic surfactant-based vesicles, have gained attention for their ability to enhance drug stability, permeation, and bioavailability, making them suitable for transdermal applications.

1.6 Introduction to the Ether Injection Method

The ether injection method is a preparation of nanoparticles, liposomes, and other colloidal carriers. This method leverages the principles of solvent evaporation and phase separation to encapsulate hydrophobic drugs or other active ingredients within lipid or polymer matrices. Due to its simplicity, versatility, and scalability, the ether injection method has become a popular choice for producing nanocarriers designed to mend the solubility, stability, and bioavailability of low perspiration.

1.7 Historical Background

Ether injection method was developed as an alternative to more complex and labor-intensive nanoparticle preparation techniques. It emerged from the need for efficient and reproducible methods to create uniform nanocarriers suitable for drug delivery applications. Over the years, it has been refined and optimized, becoming a standard procedure in many laboratories.

1.7.1 Basic Principle

The core principle of the ether injection method involves dissolving the drug and/or lipid, diethyl ether, which is then inoculated in aq. phase under continuous stirring. Organic solvent evaporates upon injection, leading to the precipitation of the drug or lipid, forming nanoparticles suspended in aq. phase. This process fallouts encapsulation active ingredient within the nanoparticles.

1.7.2 Advantages of the Ether Injection Method

1. Simplicity:The ether injection method is straightforward and does not require specialized or expensive equipment, making it accessible to most laboratories.
2. Versatility:This method can be used to encapsulate of hydrophobic drugs and API, making it highly versatile for various applications.
3. Scalability:The procedure can be easily scaled up from laboratory to industrial production levels, facilitating the development of commercial pharmaceutical products.
4. Control Over Particle Size:By adjusting parameters such as injection rate, stirring speed, and solvent concentration, researchers can control the size and uniformity of the nanoparticles.

1.7.3 Applications

Drug Delivery: Creation of liposomes and polymeric nanoparticles for the targeted delivery of hydrophobic drugs, enhancing their solubility and bioavailability.

Gene Therapy: Preparation of lipid-based vectors for the delivery of genetic material.

Diagnostic Imaging: Production of nanoparticles for use as disparity proxies in imaging techniques such as MRI and CT scans.

Vaccines: Formulation of nanoparticle-based vaccine conveyance immune response.

1.7.4 Challenges & Considerations

While ether injection method offers several advantages, it also presents challenges that must be addressed:

- Residual Solvent:
  - Ensuring complete removal of the organic solvent is crucial to avoid potential toxicity issues.
- Reproducibility:
  - Achieving consistent particle size and encapsulation efficiency requires careful optimization and control of the process parameters.
- Compatibility:
  - The choice of solvent and its compatibility with the active ingredient and lipid or polymer matrix must be carefully considered.

The ether injection method remains a valuable technique of nanotechnology and DD due to its simplicity, versatility, and effectiveness. By understanding and optimizing the various parameters involved, researchers can utilize this method to develop innovative and effective nanocarrier-based therapeutics.

1.8 Introduction to Drug Delivery Systems

DDS acts a crucial role in modern medicine by improving the efficacy, safety, and convenience of therapeutic agents. These systems encompass a broad range of technologies designed to conveyance drugs to out of harm's way accomplish their preferred upshot.

1.8.1 Importance of DDS

1. Enhanced Efficacy and Safety:
   - Traditional drug administration methods often suffer from poor bioavailability, rapid degradation, and nonspecific distribution & suboptimal therapeutic effects. DDS improve the bioavailability and therapeutic efficacy while reducing side effects.
2. Controlled Release:
   - DDS proclamation drugs at a precise frequency, prolonging their therapeutic action and reducing the frequency of administration.
3. Targeted Delivery:
   - Advanced DDS can target specific tissues or cells, enhancing the drug's therapeutic effects on the intended site while minimizing systemic exposure and associated side effects.
4. Protection of Drugs:
   - Many drugs are sensitive to degradation by the body's enzymes or by environmental factors. DDS can protect these drugs until they reach their target site.

1.9 Types of Drug Delivery Systems

1. Conventional Systems:
   - Tablets and Capsules: Oral dosage forms are the most common and convenient, but they often face challenges with bioavailability and first-pass metabolism.
   - Injectables: Provide direct delivery into the bloodstream or tissues, ensuring higher bioavailability but may require medical assistance for administration.
2. Advanced Delivery Systems:
   - Nanoparticles: Nanocarriers such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles can encapsulate drugs, enhancing their solubility, stability, and targeting capability.
   - Microparticles: Used for the controlled release of drugs over extended periods.
   - Hydrogels: Hydrophilic polymer networks that can swell and release drugs in response to specific stimuli.
   - Transdermal Patches: Deliver drugs through the skin, providing controlled release and improving patient compliance.
   - Implants: Biodegradable or non-biodegradable devices implanted in the body to provide long-term drug release.
3. Targeted Delivery Systems:
   - Ligand-Conjugated Systems: Use ligands such as to mark specific cell receptors.
   - Stimuli-Responsive Systems: Proclamation drugs in rejoinder to explicit spurs such as pH, temperature, or enzymatic activity.
   - Gene Delivery Systems: Exploit viral or non-viral vectors to deliver genetic material for therapeutic purposes.

1.9.1 Challenges and Future Directions

1. Biocompatibility and Toxicity:
   - Ensuring that drug carriers are biocompatible and do not induce adverse immune responses or toxicity.
2. Scalability and Manufacturing:
   - Developing scalable and reproducible manufacturing processes for complex DDS is critical for their commercial success.
3. Regulatory and Ethical Considerations:
   - Navigating the regulatory landscape and addressing ethical concerns, particularly with advanced and targeted delivery systems such as gene therapies.
4. Patient Compliance and Acceptance:
   - Designing DDS that are user-friendly and improve patient compliance is crucial for the success of therapeutic regimens.
5. Personalized Medicine:
   - Future DDS will likely focus on personalized medicine, where drug delivery is tailored to the individual's genetic makeup, disease state, and response to therapy.

Drug delivery systems represent a crucial intersection of pharmacology, materials science, and engineering, aimed at optimizing therapeutic outcomes. DDS offer the potential for more effective, safer, and patient-friendly treatments. The continuous advancements in DDS technology hold promise for revolutionizing the way diseases are treated, making therapies more precise, efficient, and accessible.

1.10 Niosomes in Drug Delivery

1.10.1 Composition and Structure

1. Niosomes stay vesicles formed by readymade of non-ionic surfactants in an aq. phase, often stabilized by cholesterol.
2. It encapsulate in HLB.

Advantages

- Biocompatibility and Biodegradability: HLB niosomes are generally less noxious and irritant compared to ionic surfactants.
- Enhanced Drug Stability: Encapsulation in niosomes protects filth.
- Controlled Release: Niosomes can provide a unremitting pass of the encapsulated drug, reducing the frequency of administration.
- Improved Skin Permeation: The vesicular structure can interact with the stratum cornea, enhancing invasion through crust.

1.10.2 Febuxostat and Its Limitations

- Pharmacokinetics: Febuxostat is well absorbed orally but has variable bioavailability due to far-reaching FPM. Oral direction associated with adverse gastrointestinal effects.
- Need for Alternative Delivery Systems: To mitigate the side effects and enhance therapeutic outcomes, alternative delivery systems like TDDS are being explored.

1.10.3 Niosomal Gels for Transdermal Delivery

Formulation of Niosomal Gels:

- Niosomal gels combine the benefits of niosomes and hydrogels, providing a convenient and effective means of drug delivery.
- The gel matrix, often composed of polymers like Carbopol, provides a suitable medium for niosome dispersion and facilitates skin application.

Advantages:

1. Enhanced Drug Permeation: Niosomes enhance drug permeation.
2. Controlled Release: The gel matrix can sustain

Studies on Niosomal Gels:

Various studies have demonstrated niosomal gels improving TDS of drugs like ketorolac, diclofenac, and others, showing enhanced permeation, stability, and patient compliance.

Application of Niosomal Gels for Transdermal Delivery of Febuxostat

Febuxostat is a xanthine oxidase inhibitor used to manage hyperuricemia in patients with gout. Despite its effectiveness, OA of febuxostat with GI adverse effect & variable bioavailability due to first-pass metabolism. To address these limitations, the transdermal delivery of febuxostat using niosomal gels offers a promising alternative.

Niosomal Gels in Transdermal Delivery

Niosomes:

1. Niosomes are vesicles formed by non-ionic surfactants and cholesterol, which encapsulate drugs, enhancing their stability and permeation.
2. They offer biocompatibility, controlled release, and enhanced drug permeation through the skin.

Gel Formulation:

1. Composition: Gels are formulated using polymers such as Carbopol, which provide a semi-solid medium that is easy to apply and controls drug release.
2. Benefits: Gels are non-greasy, provide cooling effects, and can be designed for sustained drug release.

Formulating and evaluating Febuxostat

A medication used primarily to treat chronic gout and hyperuricemia, involves several steps and considerations to ensure its efficacy, safety, and quality. Below is an overview of the process, encompassing the drug's formulation, methods of evaluation, and key factors involved in its development.

Formulation of Febuxostat

Active Pharmaceutical Ingredient (API) Selection

Febuxostat is the API, chosen for its potent xanthine oxidase inhibition, reducing uric acid levels in the body.

1. Excipients Selection
    1. Binders: For example, microcrystalline cellulose to help the tablet hold together.
    2. Disintegrants: Such as sodium starch glycolate to facilitate tablet disintegration.
    3. Fillers: Like lactose monohydrate to add bulk to the formulation.
    4. Lubricants: Magnesium stearate to prevent ingredients from sticking to manufacturing equipment.
    5. Coating Agents: Hypromellose for film-coating to mask the taste and improve stability.
2. Formulation Process:
    1. Wet Granulation: Mixing the API with excipients and using a granulating fluid to form granules.
    2. Drying: Removing the granulating fluid through drying.
    3. Milling: Achieving uniform granule size.
    4. Compression: Compressing the granules into tablets.
    5. Coating: Applying a film coating for taste masking and protection.

1.10.4 Key information about Febuxostat

Febuxostat is a medication primarily used to treat chronic gout and hyperuricemia in patients who are unable to tolerate or are not responsive to allopurinol, the more commonly used treatment for these conditions. It is a xanthine oxidase inhibitor, which means it obstruct the enzyme xanthine oxidase that helps produce uric acid in the body.

1. Brand Name: Uloric is the most well-known brand name for febuxostat.
2. Mechanism of Action: Febuxostat inhibits xanthine oxidase, an enzyme involved preventation of painful gout attacks.
3. Dosage: The typical starting dose for febuxostat is 40 mg OD, which may be augmented to 80 mg OD if serum uric acid echelons are not adequately controlled.
4. Side Effects: Common side effects include liver aberrations, queasiness, joint pain, and rashes. Serious side effects can include cardiovascular events like heart attacks and strokes, which has led to some concerns and warnings about its use.
5. Precautions: Febuxostat on azathioprine or mercaptopurine.
6. Monitoring: Steady observing of liver utility tests is indorsed due to the potential for liver enzyme abnormalities. Uric acid levels should also be monitored to ensure the medication is effectively controlling hyperuricemia.
7. Comparisons with Allopurinol: Febuxostat is often reserved for patients who cannot tolerate allopurinol due to hypersensitivity or side effects. It is generally considered more expensive than allopurinol.
8. FDA Warning: Heart failure or heart-related problems when compared to allopurinol.

Structure of Febuxostat [15,16, 17]

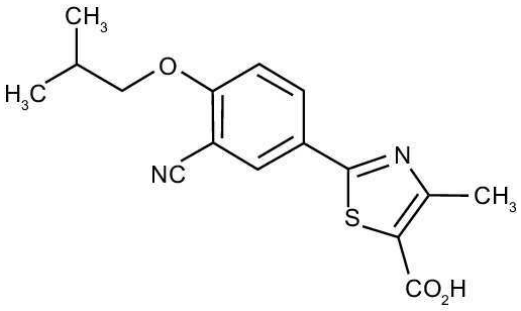


Fig 03- Structure of Febuxostat

Use of Febuxostat

Febuxostat treat gout and hyperuricemia in patients who cannot tolerate or have not responded adequately to allopurinol, another commonly used medication for these conditions. Here's a detailed overview of its use:

Indications

- Chronic Gout: Febuxostat helps reduce uric acid levels, which can prevent gout attacks.
- Hyperuricemia: It is used in conditions associated with excessive uric acid production or impaired excretion.

Mechanism of Action [20]

An inhibitor of xanthine oxidase is called fruxostat. It functions by preventing the conversion of hypoxanthine to xanthine and xanthine to uric acid by the enzyme xanthine oxidase. Febuxostat lowers the body's uric acid synthesis by blocking this enzyme.

Dosage and Administration [21]

- Febuxostat is usually taken orally OD.
- Typical 40 mg/d, which may be increased to 80 mg/d.
- Dosage adjustments may be necessary based on kidney function and individual patient response.

Contraindications and Precautions

- Hypersensitivity: Patients with a notorious antipathy to febuxostat
- Cardiovascular Disease: Febuxostat increased risk of CVS events.
- Liver Disease: Liver function should be monitored during treatment, as febuxostat can cause liver enzyme elevations.

Adverse Effects [22]

Common side effects of febuxostat include:

- Queasiness
- Joint pain
- Rash
- Liver function abnormalities

Less common but serious side effects may include:

- Cardiovascular events (e.g., myocardial infarction, stroke)
- S-J Syndrome
- Liver toxicity

Drug Interactions [23]

- Febuxostat interrelate by means of azathioprine, mercaptopurine, and theophylline.

Monitoring [24]

- Regular observing of serum uric acid levels is commended to ensure the effectiveness of the treatment.
- Liver panel performed periodically to detect any potential liver damage.
- Patients should be scrutinized for CVD.

Patient Counseling [25]

- Patients should be advised to take febuxostat as prescribed and not to discontinue use without consulting their healthcare provider.
- Lifestyle modifications, such as dietary changes and increased fluid intake, may also be recommended to help manage gout and reduce uric acid levels.

2.LITRATURE REVIEW

1. Becker MA et ai. (2005): This extensive, randomized, controlled clinical trial examined the effects of febuxostat and allopurinol on urate-lowering efficacy, incidence of gout flare-ups, and alterations in tophus area in patients with gout and hyperuricemia. A substantial proportion of subjects receiving daily febuxostat (80 or 120 mg) compared to subjects receiving allopurinol (300 mg) were able to reach all urate-lowering end points, which required serum urate concentrations of less than 6.0 mg per deciliter. Both febuxostat and allopurinol administrations caused a rapid (within two weeks) and long-lasting decrease in the concentration of serum urate. The clinical outcomes of the febuxostat and allopurinol groups were identical in terms of the decrease in tophus area and gout flare-ups.

2. Takano Y et al. (2005): For almost three decades, allopurinol, a purine analogue, has been utilized in therapeutic settings to inhibit xanthine oxidase (XO) to treat hyperuricemia and gout. However, due to structural similarities with purine molecules, various enzymes involved in the metabolism of pyrimidines and purines are inhibited by allopurinol, its main active product, oxypurinol, and their respective metabolites. A strong non-purine XO inhibitor, fruxostat (TEI-6720, TMX-67) is presently being tested in clinical settings to treat hyperuricemia and gout. In this work, we defined the mechanism of

febuxostat reduction of XO activity and examined the effects of febuxostat on a number of enzymes involved in purine and pyrimidine metabolism. With Ki and Ki' values of 0.6 and 3.1 nM, respectively, Febuxostat showed strong mixed-type inhibition of the activity of pure bovine milk XO, suggesting inhibition of both the reduced and oxidized forms of XO. On the other hand, the following purine and pyrimidine metabolism-related enzymes were not significantly affected by febuxostat at concentrations up to 100 muM: the enzymes guanine deaminase, purine nucleoside phosphorylase, orotate phosphoribosyltransferase, hypoxanthine-guanine phosphoribosyltransferase, and orotidine-5'-monophosphate decarboxylase. These results demonstrate that febuxostat is a potent, purine-free, selective XO inhibitor that may be useful in the treatment of hyperuricemia and gout.

3. Pacher P et al. (2006): Over the course of several decades, the cornerstone of the clinical care of gout and diseases linked with hyperuricemia has been the archetypal xanthine oxidase (XO) inhibitor allopurinol. According to more recent research, XO is also implicated in inflammatory illnesses, chronic heart failure, and a number of ischemic and other tissue and vascular damage. Both in small-scale human clinical trials and on experimental animals, allopurinol and its active metabolite oxypurinol demonstrated great promise in the treatment of these disorders. The promising results revived strong interest in the creation of further, unique series of XO inhibitors for a range of therapeutic applications, even though some of the favorable effects of these drugs might not be attributable to the inhibition of the XO.

4. Schumacher HR Jr et al (2008): to assess the efficacy and safety of placebo, allopurinol, and febuxostat in lowering urates in a substantial group of patients with hyperuricemia and gout, including those with impaired renal function. Compared to allopurinol (300 or 100 mg) or placebo at all examined dosages, febuxostat more effectively lowered and maintained serum urate levels <6.0 mg/dl in individuals with gout and hyperuricemia, including those with mild to moderately impaired renal function. For a period of 28 weeks, a group of subjects (n = 1,072) with gout and hyperuricemia (serum urate level > or = 8.0 mg/dl) and normal or impaired renal function (serum creatinine level >1.5 to < or = 2.0 mg/dl) were randomly assigned to receive either a placebo, 300 or 100 mg of allopurinol, or 80 mg, 120 mg, or 240 mg of febuxostat once daily.

5. Pranshu Tangri et al. (2011): Niosomes have been shown to be non-ionic surfactant vesicles that can be produced by hydrating synthetic nonionic surfactants, either with or without the addition of lipids such as cholesterol. These are vesicular structures that resemble liposomes and can be employed to transport both lipophilic and amphiphilic medications. Because they are non-ionic and less toxic, niosomes hold great promise as a medication delivery vehicle. They also enhance the therapeutic index of the medicine by limiting its activity to the targeted cells. The preparation techniques, characterizations, release kinetics-influencing parameters, benefits, and uses of niosomes are the main topics of this review study.

6. Pranshu Tangri et al. (2011): The purpose of the study is to create and examine a drug gel composed of both real and fake polymers. Gel measurement structures are excellent drug delivery methods because they provide for precise medication discharge control and natural drug security. The gel's various physicochemical components that affect its properties are also investigated. We have gathered references from recently published analysis and survey papers. Data from 20–25 publications were gathered. The qualities of drug gel that are evaluated include gelling power, solidity, bioadhesion, spreading ability, microbiological research, and in vitro discharge. Our investigation has led us to the conclusion that the delivery of skin medications is a fascinating process for both local and basic medications and is frequently employed in the treatment of provocative conditions like skin diseases and external muscle injuries.

7. kore, et al. (2011): It was discovered that the Newcastle disease vaccine was placed into a span 20-based niosome by the use of a lipid film hydration technique. Three batches comprising Span 20, cholesterol, and diacetyl phosphate at micro molar ratios of 10:10:1, 15:15:1, and 20:20:1 were produced using the haemagglutination test. The encapsulation efficiency of the batches was then evaluated. Utilizing transmission electron microscopy, the vesicles' morphology was investigated.

8. Saag KG et al. (2011): Febuxostat was well tolerated by gout patients with moderate-to-severe renal impairment and demonstrated efficacy in reducing serum UA levels. There was no discernible decline in renal function and considerably lower serum UA levels in patients who were randomly assigned to take febuxostat. By month 12, neither the estimated GFR nor the serum Cr level changed significantly from baseline in either of the febuxostat groups as compared to the placebo group. When comparing the two febuxostat groups to the placebo group at month 12, the percentage of patients with a serum UA level of less than 6.0 mg/dl was considerably higher (both P < 0.001). In 78.1% of patients getting 30 mg of febuxostat twice daily, 87.5% of patients receiving 40/80 mg of febuxostat once day, and 78.1% of patients receiving a placebo, there was at least one treatment-emergent adverse event (TEAE). Renal function analyses and renal failure and impairment were the categories in which TEAEs were most commonly implicated.

9. Khanna D et al. (2012): Gout is a disease that causes the body to accumulate too much uric acid. It manifests as a variety of clinical and pathologic symptoms and is partially caused by hyperuricemia, which is defined as a serum urate level more than 6.8 or 7.0 mg/dL. Monosodium

urate monohydrate crystals that are deposited in supersaturated extracellular fluids of the joint and at certain other locations cause most of the pathologic and clinical features of gout.Most patients experience recurrent episodes of acute, episodic arthritis at initially, although the condition can also become recurrent in most cases. Gout can also appear as persistent arthritis in one or more joints. As a pathognomonic sign of gout, tophi are primarily found in articular, periarticular, bursal, bone, auricular, and cutaneous tissues. They can be identified by physical examination, imaging techniques, and pathological examination. Urolithiasis is one of the renal symptoms of gout, usually accompanied by an acidic urine pH. Although it is thought to be an unusual clinical symptom of gout, chronic interstitial nephropathy, which is driven by monosodium urate monohydrate crystal formation in the renal medulla, can occur in severe illness.

10. SB Shirsand et al. (2012): Research has shown that because niosomes can alter pharmacokinetics, bioavailability, and lower toxicity, they are becoming more and more significant in drug delivery. Niosomes used topically have the ability to prolong a drug's residence duration in the stratum corneum and epidermis while decreasing the drug's systemic absorption. It can function as drug-containing reservoirs, and the drug release rate and affinity for the target site can be changed by modifying the vesicular composition or surface characteristics. Ketoconazole, a broad range imidazole derivative, works well to treat systemic as well as superficial fungal infections. Using different ratios of non-ionic surfactants (Span 40, 60, and Tween 60) and cholesterol (CHO), ketoconazole niosomes were created by a thin film hydration method with the goal of minimizing the side effects associated with topical conventional drug administration and improving the low skin penetration. The size, shape, entrapment efficiency, and in vitro drug release of the formulations were evaluated.

11. Rita Muzzalupo et al. (2015 Studies show that niosomes, which are vesicular nanocarriers, are attracting a lot of attention as potential transdermal drug delivery systems due to their capacity to modify the way that drugs are absorbed systemically through the skin, improve drug penetration, and function as a local depot for long-term drug release. Numerous hypotheses have been proposed to explain why niosomes enhance the transdermal delivery of medications. Niosomal carriers can be used to transdermally transport a variety of pharmacological compounds, including substances with antioxidant, anticancer, anti-inflammatory, antimicrobial, and antibacterial properties. The objective of this review is to gather an extensive range of current research in this intriguing field, with an emphasis on techniques for enhancing niosome functionality.

12. White WB, Saag KG et al. (2018): Regarding rates of adverse cardiovascular events, febuxostat was found to be non-inferior to allopurinol in individuals with gout and significant concomitant cardiovascular problems. Febuxostat was associated with greater all-cause and cardiovascular death rates than allopurinol. Hyperuricemia, arthropathy, tophus formation, and urolithiasis are the hallmarks of gout, a chronic illness that is linked to a higher risk of cardiovascular and chronic renal disease. Those with gout have a significantly higher risk of cardiovascular events, including death, than those without gout. When the Food and Drug Administration (FDA) released a guidance document outlining specific requirements for the cardiovascular safety assessment of antidiabetic therapies, researchers in other therapeutic areas, including those studying gout therapies, began to investigate cardiovascular safety with similarly designed trials.

13. Ahmed A. El-Shenawy et al. (2020): Research revealed that the medication febuxostat (FXT) inhibits xanthine oxidase (XO) and is prescribed to treat gout. Using a cold technique, FXT loaded nanosized ethosomes were produced with different amounts of soy lecithin (SL) and ethyl alcohol. The generated ethosomes were characterized by size, FT-IR, entrapment efficiency (DEE), in vitro release, kinetic analyses of the in vitro release profile, in vitro skin penetration and deposition, and stability analysis. The selected ethosomal formulation was mixed into HPMC gel after its drug content was assessed by ex vivo diffusion tests on rat skin.

14. Navni Sharma et al. (2022): The purpose of this work was to create and describe the Febuxostat (FB) Nano-Structured Lipid Carriers (NLCs) that were included into the gel to treat gout. FB is a Xanthine Oxidase (XO) inhibitor medication used to treat hyperuricemia and chronic gout. Since FB is a BCS class II medication, its water solubility is extremely low, which contributes to its poor wettability and poor solubility, which results in poor dissolving. This work employed the hot high-pressure homogenization approach to enhance the physicochemical properties of FB.

15. Alaa D. Noor, Nawal A. Rajab et al. (2022): The major goal of the current study, according to the study, is to create tolmetin niosomes as vesicular carriers, where the tolmetin is prorated inside the vesicle for an extended period of action, and then choose the best formula following characterisation. Niosomes are created via the thin film hydration process, which involves hydrating a mixture of various cholesterol levels and non-ionic surfactants like span20,40,80, and tween 20, 40, 80. Tolmetin is a nonsteroidal anti-inflammatory medication that is frequently used to treat rheumatoid arthritis. Studies were conducted on the impact of cholesterol level, ultrasonication period, and non-ionic surfactant type and amount.

3. NEED AND OBJECTIVES

3.1 NEED OF WORK:

The examination of the creation and assessment of a TDDS based on a niosomal gel of Febuxostat addresses significant limitations of current oral therapies. By enhancing bioavailability, lowering adverse effects and increasing patient adherence, and offering a non-invasive and controlled release mechanism, this study aims to provide a superior therapeutic choice for patients with hyperuricemia and gout. The potential benefits justify the need for thorough research and development in this area. [1]

1. Enhanced Bioavailability

- Problem: Oral administration of Febuxostat has variable and sometimes poor ioavailability due to first-pass metabolism and gastrointestinal degradation.
- Need: A transdermal delivery system bypasses the first-pass effect, potentially enhancing bioavailability and ensuring a more consistent therapeutic effect.

2. Reduced Side Effects [2]

- Problem: Oral Febuxostat can cause gastrointestinal side effects and systemic adverse reactions.
- Need: Transdermal delivery can localize the drug's action, reducing systemic exposure and minimizing side effects.

3. Sustained Drug Release [3]

- Problem: Oral formulations require frequent dosing to maintain therapeutic levels, leading to patient non-compliance.
- Need: A transdermal system can provide sustained drug release, improving patient compliance by reducing the dosing frequency.

4. Improved Patient Compliance [4]

- Problem: The need for daily oral medication can lead to non-adherence in chronic conditions like gout.
- Need: A transdermal gel, applied less frequently, is more convenient and can improve patient adherence to the treatment regimen.

1. Targeted Drug Delivery [7]

Problem: Reduced medication attentiveness at the intended site and off-target effects are possible consequences of systemic drug dispersion.
Need: Drug delivery that is targeted, attentiveness the medication at the target, and may enhance therapeutic results is possible with transdermal niosomal gel.

2. Control over Drug Release [8]

- Problem: Oral formulations may lead to peaks and troughs in drug plasma levels.
- Need: Transdermal delivery allows for a controlled release profile, maintaining steady drug levels and enhancing therapeutic efficacy.

3. Minimizing Drug Degradation [9]

- Problem: Degradation of fabuoxostat might occur in the GIT system.

- Need: Transdermal delivery can protect the drug from degradation, preserving its efficacy.

3.2 OBJECTIVES OF WORK:

The goal of developing and accessing a TDDS based on a niosomal gel of Febuxostat can be outlined as follows:

1. Formulation of Niosomal Gel: [1]
   - Develop a niosomal gel containing Febuxostat to enhance its bioavailability and therapeutic efficacy.
   - Optimize the preparation process of niosomes, including the selection of surfactants, cholesterol, and other excipients to achieve desired characteristics such as particle size, entrapment efficiency, and stability.
   - Incorporate the prepared niosomes into a gel base to facilitate transdermal application.
2. Characterization of Niosomes: [2]
   - Characterize the prepared niosomes for morphology, entrapment efficiency, zeta potential, and particle size utilizing methods including TEM, DLS, & others.
   - Analyze the niosomes' stability over time and in various storage scenarios.
3. Formulation of Transdermal Gel: [3]
   - Develop a suitable gel formulation incorporating the niosomes, ensuring appropriate consistency, spreadability, and drug release profile.
   - Optimize the gel formulation by varying the concentration of gelling agents and other excipients to achieve desired rheological properties and stability.
4. In Vitro Evaluation: [4]
   - Perform in vitro drug release tests to assess Febuxostat's niosomal gel release characteristics.
   - Conduct in vitro skin penetration tests on removed animal or hominid skin in order to

evaluate the niosomal gel's potential for transdermal delivery.
- Compare the permeation profile of the niosomal gel with conventional formulations to demonstrate the advantage of the niosomal system.

4 PLANS OF WORK

5 MATERIALS AND METHODS [3, 4]

1. Materials

Table no. 01-List of Excipients

Sr. no	Material	Agent
1	Febuxostat	API
2	Surfactants	Span 60, Tween 60
3	Cholesterol	160 to 200 mg
4	Solvents	Chloroform, Methanol
5	Gelling Agents	Carbopol 940, HPMC
6	Buffers	Phosphate buffer salin (PBS) pH 7.4
7	Other Chemicals	Triethanolamine, Distille Water

6. DRUG AND EXCIPIENT PROFILE

6.1 DRUG PROFILE:

Febuxostat is a medication primarily utilized as a gout remedy. Here is a detailed drug profile for Febuxostat.

Chemical Name [1]

The chemical name of Febuxostat is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

Chemical Structure

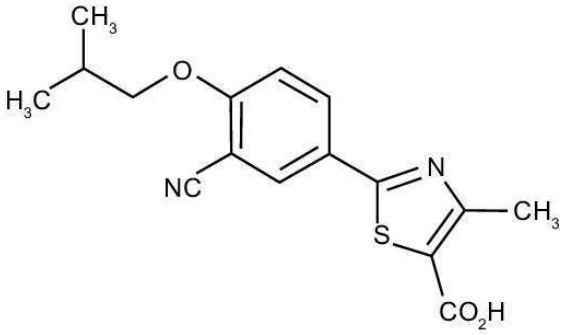


Fig 04- Structure of Febuxostat

Molecular formula: $C_{16}H_{16}N_2O_3S$

Molecular weight: 316.374 g/mol

Physical state: Crystalline powder that is white and hygroscopic

Color: White

Bioavailability: 85%

Solubility: Aq. Buffer, DMF

Dose strength: 40 mg, 80 mg

Half life: 4 to 12 hrs.

Melting point: 207 to 211 ^{0}C, logP: 3.8

6.2 MECHANISM OF ACTION: [2]

1 Xanthine Oxidase Inhibition:

The purine degradation pathway involves two steps that xanthine oxidase catalyzes: the conversion of hypoxanthine to xanthine and xanthine to uric acid.

Febuxostat lowers the synthesis of uric acid by blocking xanthine oxidase activity. Febuxostat helps preclude the fabrication of uric acid crystals in joints and tissues, which cause excruciating gout symptoms, by reducing blood levels of uric acid.

2 Selectivity:

Febuxostat is a non-purine selective inhibitor of xanthine oxidase. This means it specifically targets xanthine oxidase without significantly affecting other enzymes in the purine and pyrimidine metabolic pathways.

3 Uric Acid Reduction:

By tumbling the production of uric acid, Febuxostat helps to decline the whole uric acid concentration in the blood (serum urate levels). This can lead to a reduction in gout flares over time and can help dissolve tophi (deposits of uric acid crystals in tissues).

6.3 PHARMACOKINETICS: [3]

Febuxostat's pharmacokinetic properties include its absorption, distribution, metabolism, and elimination. Here is a detailed overview:

1. Absorption

Bioavailability: Febuxostat is readily absorbed when used orally.

Peak Plasma Concentration (Cmax): Reached within 1-1.5 hours after dosing.

Effect of Food: Taking Febuxostat with food does not significantly affect its overall absorption.

2. Distribution
Volume of Distribution (Vd): Approximately 50 L.

Protein Binding: A high percentage of plasma proteins, mainly albumin (99.2%), are linked.

3. Metabolism

The liver undergoes substantial metabolism of floxostat.
Primary Metabolic Pathways:

Use of uridine diphosphate for fusion glucuronosyl transferase (UGT) enzymes: UGT1A1,3,9,7

Oxidation by cytochrome P450 (CYP) enzymes: CYP1A2, CYP2C8, and CYP2C9.

Metabolites: The primary metabolites are inactive.

4. Elimination
Half-life (T1/2): Around 5-8 hours.

Excretion:

1. Approximately 49%.

2. Approximately 45% is excreted in the feces.

Renal Excretion: Less than 10%

6.4 Summary of Key Pharmacokinetic Parameters
Excretion: 49% urine (less than 10% unchanged), 45% feces

Understanding these pharmacokinetic properties helps in optimizing dosing regimens and managing potential drug interactions and side effects.

Adverse Effects of Febuxostat [5]

Febuxostat can cause a range of adverse effects, varying from common and mild to rare and severe. Here's a detailed list:

Common Adverse Effects
1. Liver Function Abnormalities:

   Elevated liver enzymes (e.g., ALT, AST)

   Hepatic dysfunction

2. Gastrointestinal:

   Nausea

   Diarrhea

3. Musculoskeletal:

   Arthralgia (joint pain)

4. Dermatologic:

   Rash

6.5 EXCIPIENTS PROFILE:
1. Materials: Obtain Febuxostat, surfactants (e.g., Span 60, Tween 60), cholesterol, and other required chemicals. Select appropriate gelling agents (e.g., Carbopol 934, HPMC).

6.5.1 Drug Interactions of Febuxostat [6]
A. Major Drug Interactions

1. Azathioprine and Mercaptopurine:

Interaction: Febuxostat can significantly increase the plasma concentrations of azathioprine and mercaptopurine.

Effect: This can lead to severe toxicity, including bone marrow suppression.

Recommendation: Concomitant use is contraindicated.

2. Theophylline:

Interaction: Febuxostat may rise the plasma concentrations of theophylline when using.

Effect: Increased risk of theophylline toxicity.

Recommendation: Monitor theophylline levels closely; dosage adjustment may be necessary.

3. Didanosine:

Interaction: Febuxostat may increase didanosine exposure.

Effect: Enhanced risk of didanosine-associated toxicities.

Recommendation: Caution is advised if these drugs are co-administered.

B. Moderate Drug Interactions

1. Warfarin:

Interaction: Febuxostat may alter the metabolism of warfarin.

Effect: Potential changes in INR levels, leading to increased bleeding risk or lessen the anticoagulant's effects

Recommendation: Keep a close eye on your INR and modify your warfarin dosage as needed.

2. Cyclophosphamide:

Interaction: Potential for increased toxicity when used together.

Effect: Enhanced risk of adverse effects related to cyclophosphamide.

Recommendation: Use with caution and monitor for toxicity.

3. Antacids:

Interaction: Antacids containing aluminum hydroxide and magnesium hydroxide may decrease the absorption of Febuxostat.

Effect: Reduced efficacy of Febuxostat.

Recommendation: Take Febuxostat at least 1 hour before or at least 2 hours after antacids.

4. Other Considerations

1. CYP450 Enzyme Interactions:

a. CYP1A2, CYP2C8, and CYP2C9: Febuxostat is metabolized by these enzymes. Concomitant use of strong inhibitors or inducers of these enzymes could alter Febuxostat levels.

b. Recommendation: Monitor for altered efficacy or toxicity and adjust dose as necessary.

2. UGT Enzyme Interactions:

a. UGT1A1, UGT1A3, UGT1A9, and UGT2B7: Febuxostat undergoes metabolism via these pathways. Drugs that inhibit or induce UGT enzymes could impact Febuxostat levels.

b. Recommendation: Adjust dose based on clinical response and drug interaction potential.

C. Summary of Drug Interactions

- Contraindicated: Azathioprine, Mercaptopurine
- Significant Interactions: Theophylline, Didanosine
- Moderate Interactions: Warfarin, Cyclophosphamide, Antacids
- Enzyme Interactions: CYP450 (CYP1A2, CYP2C8, CYP2C9), UGT (UGT1A1, UGT1A3, UGT1A9, UGT2B7)

D. Clinical Considerations

1. Monitor Therapy: Regular monitoring and dose adjustments may be necessary when Febuxostat is used with interacting drugs.

2. Patient Counseling: Inform patients about potential interactions and advise them should disclose to medical professionals all of their medications, including over-the-counter medications and vitamins.

By being aware of these potential drug interactions, healthcare providers can better manage patients on Febuxostat and minimize the risk of adverse effects.

Stability and Storage Conditions of Febuxostat [7]

Proper storage and handling of Febuxostat are essential to maintain its stability and efficacy. Here are the recommended conditions:

Stability

- Shelf Life: The shelf life of Febuxostat tablets typically ranges from 24 to 36 months, depending on the manufacturer. Always refer to the specific product labeling for accurate information.
- Formulation: Febuxostat is typically formulated as film-coated tablets, which helps protect the active ingredient from environmental factors that could degrade its stability.

Storage Conditions

- Temperature: Store Febuxostat at room temperature, ideally between 20°C to 25°C .
- Humidity: Protect from moisture.
- Light: Store Febuxostat in its fix container to protect it from light.
- Container: Keep the medication in its original container with the lid tightly closed to avoid exposure to air and moisture.

Handling Instructions

- Do Not Crush or Split Tablets: Febuxostat tablets should be swallowed whole to ensure proper dosing and avoid exposure to the drug's bitterness.
- Keep Out of Reach of Children: Ensure that the medication is stored in a secure place, out of reach of children and pets.
- Disposal: Dispose of expired or unused medication

Summary

- Temperature: 20°C to 25°C.
- Humidity: Protect from moisture
- Light: Protect from light by storing in original packaging
- Container: Keep tightly closed

Additional Tips

- Check Expiry Date: Always check the expiration date on the packaging before use.
- Avoid Excessive Heat or Cold: Do not store Febuxostat in extreme temperatures, such as in a car or near a heat source.
- Traveling: When traveling, keep Febuxostat in its original container and ensure it is stored at appropriate conditions. Avoid exposing it to excessive heat or moisture.

By following these storage and handling guidelines, the stability and effectiveness of Febuxostat can be maintained throughout its shelf life.

6.6 Incompatibilities of Febuxostat [8]

Incompatibilities refer to conditions or substances that may adversely affect the stability, efficacy, or safety of Febuxostat. While Febuxostat itself is a stable compound, there are several factors and substances that can affect its performance:

1. Physical Incompatibilities

Moisture: Febuxostat tablets are sensitive to moisture. Exposure to moisture can degrade the drug, reducing its efficacy.

Recommendation: Store in a dry place and keep the container tightly closed.

Light: Prolonged exposure to light can degrade Febuxostat.

Heat: Exposure to excessive heat can affect the stability of Febuxostat.

Recommendation: Store at room temperature and avoid exposing to high temperatures.

2. Chemical Incompatibilities

Strong Acids and Bases: Febuxostat may be unstable in the presence of strong acids or bases, which can lead to degradation.

Recommendation: Avoid exposing Febuxostat to environments with extreme pH levels.

Oxidizing Agents: Febuxostat may react with strong oxidizing agents, potentially leading to decomposition.

Recommendation: Keep away from oxidizing agents.

3. Pharmaceutical Incompatibilities

Concomitant Medications: Some medications can interact with Febuxostat, affecting its metabolism and efficacy.

- Azathioprine and Mercaptopurine: Concurrent use is contraindicated due to severe toxicity risks.
- Theophylline: Febuxostat may increase the plasma concentration of theophylline, leading to toxicity.
- Didanosine: Febuxostat may increase didanosine exposure, enhancing toxicity risks.
- Antacids: Antacids containing aluminum hydroxide and magnesium hydroxide can reduce the absorption of Febuxostat.

Recommendation: Administer Febuxostat at least 1 hour before or at least 2 hours after taking antacids.

4. Food Interactions

Food: While food does not significantly affect the absorption of Febuxostat, it may delay the time to reach peak plasma concentration.

Summary of Incompatibilities

- Physical: Moisture, light, heat
- Chemical: Strong acids, bases, and oxidizing agents
- Pharmaceutical: Specific medications (e.g., azathioprine, mercaptopurine, theophylline, didanosine, antacids)

- Food: can be taken any way, however taking it with meals may cause a delay in absorption.

Recommendations

- Storage: Keep the container tightly closed.
- Handling: Avoid exposure to extreme pH environments and strong oxidizing agents. Follow administration guidelines to prevent interactions.
- Medication Review: Regularly review patient medications to identify potential interactions and adjust dosing regimens accordingly.

By understanding and managing these incompatibilities, healthcare providers can ensure the safe and effective use of Febuxostat.

7. EXPERIMENTAL WORK

1. Preparation of Niosomes

Ether Injection Method for Formulating Febuxostat Nanoparticles

The ether injection method can be adapted for the formulation of Febuxostat nanoparticles to improve its solubility, bioavailability, and therapeutic efficacy. This method involves dissolving Febuxostat and appropriate lipids or polymers in an organic solvent (ether) and then injecting this solution into nanoparticles as the solvent evaporates.

Materials and Equipment

1. Febuxostat: Active pharmaceutical ingredient.
2. Organic Solvent: Diethyl ether or a suitable alternative.
3. Lipids/Polymers: Commonly used lipids (e.g., phosphatidylcholine, cholesterol)
4. Aqueous Phase: Typically water or a buffer solution.
5. Syringe with Fine Needle: For injecting the organic solution.
6. Magnetic Stirrer/Ultrasonic Bath: For mixing and ensuring uniform dispersion.
7. Rotary Evaporator: For solvent removal.
8. Analytical Equipment: UV, PSA, ZP.

Procedure

1. Preparation of Organic Phase:

Dissolve an appropriate amount of Febuxostat and the selected lipid or polymer in diethyl ether. The concentration should be optimized to achieve the desired nanoparticle size and drug loading efficiency.

2. Preparation of Aqueous Phase:

Prepare the aqueous phase, which could be distilled water, phosphate-buffered saline (PBS), or another suitable buffer. Ensure that the pH and ionic strength are optimized for stability and drug release.

3. Injection Process:

Using a fine needle or syringe, slowly inject the organic solution containing Febuxostat and lipid/polymer into the aqueous phase under constant stirring. Maintain a consistent injection rate to promote uniform nanoparticle formation.

4. Stirring and Solvent Evaporation:

Continue stirring the mixture to ensure thorough mixing. Allow the ether to evaporate, which can be facilitated by Rotary Evaporator. This step results in the formation of Febuxostat-loaded nanoparticles.

5. Collection and Purification:

After complete solvent evaporation, collect the nanoparticle suspension. Purify the nanoparticles by centrifugation, dialysis, or filtration to remove any residual solvent, unencapsulated drug, and other impurities.

6. Characterization:

Particle Size and Distribution: Use DLS to gauge the nanoparticles' size and dispersion.

Drug Loading and Encapsulation Efficiency: Febuxostat using HPLC or another suitable analytical technique.

Stability Studies: Under various storage conditions (e.g., temperature, light, humidity).

Optimization and Considerations

1. Injection Rate:
   - A slower injection rate typically results in smaller and more uniform nanoparticles. Optimize the rate based on preliminary experiments.
2. Stirring Speed:

- Adequate stirring is crucial to ensure uniform distribution and prevent aggregation. Optimize

2. Characterization of Niosomes

1. PSA: DLS.
2. ZP Measurement: To determine the surface charge.
3. Encapsulation Efficiency: Centrifuge the niosomal suspension and measure the drug concentration in the supernatant using UV spectroscopy.

3. Preparation of Niosomal Gel

1. Gel Base Preparation: Disperse Carbopol 940 or HPMC in distilled water and allow it to hydrate.
2. Neutralization: Add triethanolamine dropwise to the hydrated gel base to obtain the desired viscosity and pH.
3. Incorporation of Niosomes: Mix the niosomal suspension with the prepared gel base under gentle stirring to ensure even distribution.



Fig No 05-Niosomal gel of Febuxostat

4. EVALUATION OF NIOSOMAL GEL

Physical Characterization:

- Appearance: Observe color, consistency, and homogeneity.
- pH Measurement: Utilizing a digital pH meter, measure. pH. A digital pH meter that has been calibrated was used in triplicate to measure the pH of the manufactured gel composition. Before each usage, the pH meter was calibrated using standard phosphate buffer solutions with a molarity of 100 mM and pH values of 4 and 7. The formulations were kept at a temperature of 25 °C.

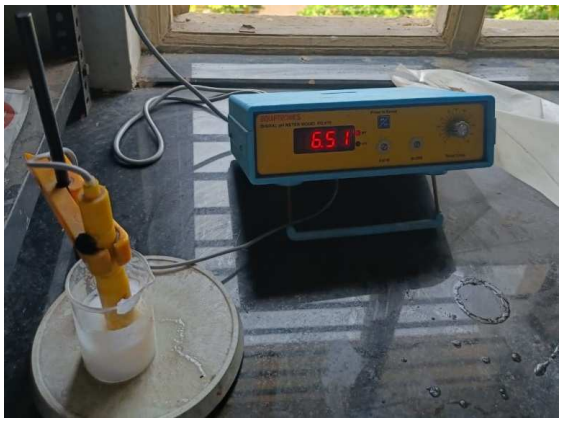


Fig No 06- pH meter

Spreadability: Assess by measuring the diameter of the gel spread between two glass slides under a specified weight. Spreadability. Following Knorst's (1991) approach, this treatment was carried out in triplicate on samples at time zero and after 90 days. This technique involves a glass mold plate that is circular in shape (20 cm in diameter and 0.2 cm in breadth) and has a 1.2 cm diameter central aperture. The glass mold plate is set on top of a glass support plate (20 cm x 20 cm) that is placed on top of millimetric graph paper. After inserting each sample into the die plate's aperture, a spatula was used to level the surface. After the plaque mold was carefully taken out, the sample was covered with a glass plate that was known to be heavy. Using the graph paper scale, the diameter in the opposite positions (as covered by the sample) was measured after a minute.

Viscosity: Determine using a Brookfield viscometer. Using the Brookfield Digital Viscometer LVDV-II + PRO Brookfield at 25°C, the viscosity of NEG-IS was ascertained. Spindle number 62 was used for the experiments, and the sample was rotated at 5, 10, 50, and 100 rpm. The viscosity was determined ten minutes after the spindle was rotated.



Fig No 07- Magnetic stirrer

- Syringeability: A 20-gauge needle was used to put each prepared formulation into an identical 1-milliliter syringe, maintaining a consistent volume of 1 milliliter. Solutions that came out of the syringe easily were called passes, and those that were harder to pass were called fails.
- Gelling Time: Using the test tube inversion method, the gelling time of the produced gel formulation was determined. Using this procedure, a 10 ml glass test tube held 2 ml of the mixture. The gelling time was recorded while the test tube was submerged in a water bath at 37 ± 2 °C.
- Gelation Temperature: Two milliliters of the formulations were put into paraffin-sealed test tubes, which were then submerged in a 4°C water bath. The bath's temperature was raised by 1°C at a time. Gelation was determined by looking at the samples; at 90°C, the meniscus was thought to have stopped moving. Every measurement was done three times.

Table no. 02- Evaluation test of gel

Formulations	Syringeability	pH	Spreadability (g.cm)	Gelling Time (Sec)	Gelation Temp (0C)	Gel Clarity
Gel	Pass	6.86	14.58	127	24.7	+

5. Drug Content Uniformity:

Procedure: Take a known quantity of the gel, dissolve in an appropriate solvent, and measure the drug concentration using UV spectroscopy.

6. In Vitro Drug Release Studies:

Activity:

In-vitro

Diffusion

assay

Experimental Procedure

- Skin membrane was used to accumulate the

Franz Diffusion cell.

- The receptor hollow was loaded with the buffer 6.9 and donor chamber was filled with the test gel.
- The diffusion cell was adjusted for optimum temperature and constant stirring byusing stir bar.
- The cell was kept for skin permeation
- After a set amount of time, the sample was removed and the same volume was replaced with brand-new PBS. The absorbance of the extracted material was determined via UV spectroscopy at 392 nm.



Fig No 08- Franz Diffusion cell

8. RESULTS AND DISCUSSION

1. Preformulation of Febuxostat [1, 4]

Preformulation studies are essential in drug development as they help to describe the properties of a drug, guiding the formulation and manufacturing process. For Febuxostat, preformulation studies would focus on its solubility, stability, polymorphism, and compatibility with excipients.

1. Physical Properties

1. Appearance: Febuxostat is a white to off-white crystalline powder.
2. MP: The MP of Febuxostat is approximately 238-242°C.
3. Particle Size: Particle size distribution affects drug dissolution and bioavailability. Optimizing particle size is crucial for ensuring consistent drug release and absorption.
4. Polymorphism: Febuxostat can exist in multiple polymorphic forms, which can affect its solubility, stability, and bioavailability. Identifying and controlling the polymorphic form used in the formulation is essential.

2. Chemical Properties

1. Solubility: Febuxostat water insoluble but DMSO soluble, methanol, and slightly in ethanol soluble. Improving solubility is a key challenge in formulating Febuxostat.
2. pKa: The pKa value of Febuxostat is approximately 4.1, indicating that it is weakly acidic. This affects its ionization and, consequently, its solubility and absorption at different pH levels.
3. Partition Coefficient (Log P): Febuxostat has a log P value of around 2.8, indicating moderate lipophilicity, which influences its absorption and distribution.

3. Stability

1. Thermal Stability: Febuxostat should be evaluated for stability under various temperature conditions to understand its behavior during manufacturing and storage.
2. Photostability: Exposure to light can degrade Febuxostat. Photostability studies help to determine the need for light-protective packaging.
3. Chemical Stability: Febuxostat's stability in different pH environments, and its degradation profile should be characterized. Stability in the presence of oxidizing agents and other potential degradants is also important.

4. Excipient Compatibility

1. Compatibility with Excipients: Febuxostat's compatibility with common pharmaceutical excipients (e.g., lactose, microcrystalline cellulose, magnesium stearate) needs to be assessed. Incompatible excipients can affect the drug's stability and efficacy.
2. Formulation Strategy: Strategies to improve solubility and bioavailability include the use of solubilizing agents, complexation with cyclodextrins, solid dispersions, and nano-formulations.

6. Formulation Considerations

1. Tablet Formulation: Given Febuxostat's poor water solubility, techniques like wet granulation or hot-melt extrusion can be used to enhance its solubility and compressibility.
2. Coating: Film coating can be used to protect the drug from light and moisture, as well as to improve the tablet's appearance and taste masking.
3. Bioavailability Enhancement: Techniques such as micronization, nanocrystallization, or the use of surfactants and cosolvents can be employed to enhance bioavailability.

2. UV Visible Spectrometer

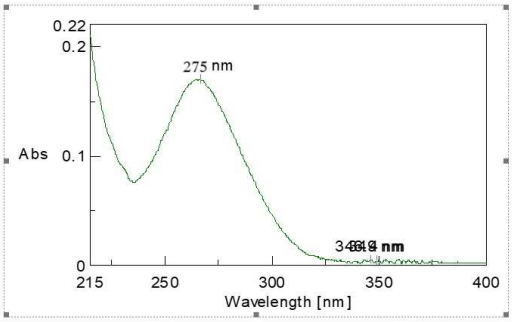


Fig No 09- Calibration curve

Table No.03- Absorbance of drug

Sr. No.	Concentrate (microgram/ml)	Absorbance
1	0	0
2	0.2	0.1648
3	0.4	0.3562
4	0.6	0.4674
5	0.8	0.792
6	10	0.8411

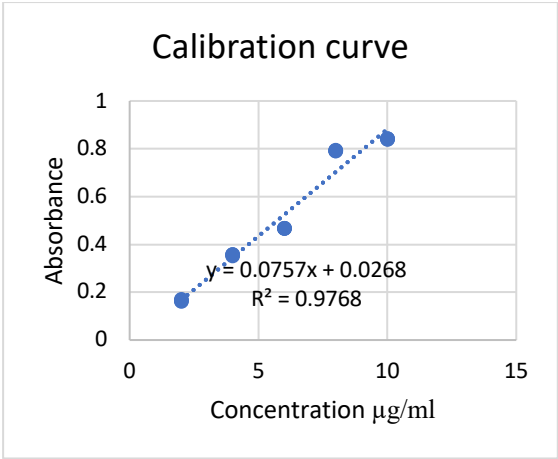


Fig No 10- Abs curve λmax

3. Particle Size Analyzers for Febuxostat Nanoparticles [3, 4]

To ensure optimal performance, stability, and bioavailability of Febuxostat nanoparticles, accurate particle size analysis is essential. Here are several commonly used particle size analysis techniques and instruments suitable for analyzing Febuxostat nanoparticles.

Procedure:

1. Disperse the Febuxostat nanoparticles in a suitable solvent to create a suspension.
2. Load the suspension into the DLS instrument.
3. The instrument measures the scattering of light as it passes through the suspension.
4. The software calculates the particle size distribution based on the light scattering data.

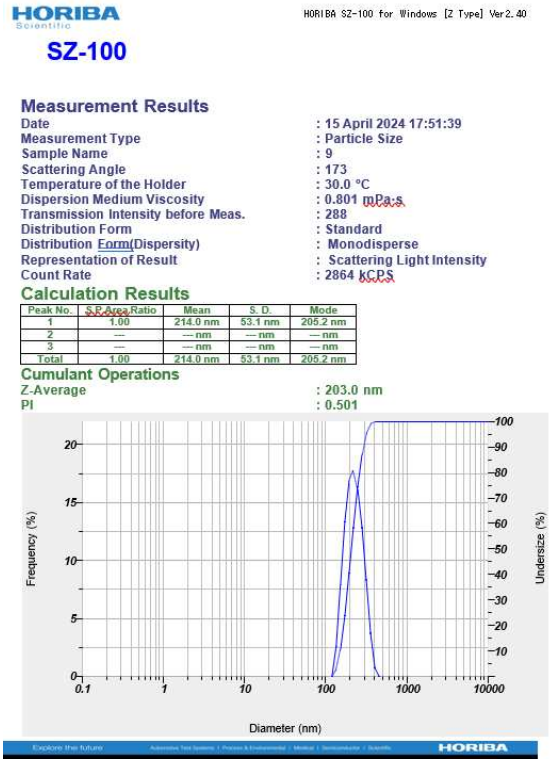


Fig No 11- particle size

Discussion:

1. The particle size of 150 nm is within the optimal range for drug delivery applications, ensuring good bioavailability and cellular uptake.
2. A PDI of 0.2 suggests that the nanoparticles are uniformly sized, which is crucial for consistent drug release and performance.
3. The lipid/polymer content, the ether infusion rate, and the speed at which the slurry is stirred can all be changed to control the size.

4. Zeta Potential Analysis for Febuxostat Nanoparticles [1, 2]

Zeta potential is a critical parameter for understanding the stability and surface charge of nanoparticles. It provides insight into the colloidal stability of the nanoparticle suspension, which is essential for ensuring consistent drug delivery and therapeutic efficacy. Here's an overview of zeta potential analysis for Febuxostat nanoparticles:

Materials and Equipment

1. Febuxostat Nanoparticles: The nanoparticles to be analyzed.
2. Dispersing Medium: A suitable aqueous medium, typically water or a buffer solution.
3. Zeta Potential Analyzer: An instrument designed to measure the zeta potential of nanoparticles.

Procedure

1. Preparation of Sample:
   - Disperse the Febuxostat nanoparticles in a suitable dispersing medium. Ensure the concentration is appropriate for the instrument being used (typically a few milligrams per milliliter).
2. Sample Loading:
   - Load the nanoparticle suspension into the zeta potential analyzer's sample cell. Ensure there are no bubbles or particles that could interfere with the measurement.
3. Measurement:
   - The instrument measures the velocity of the particles and calculates the zeta potential using the Smoluchowski or Huckel equations, depending on the particle size and medium.

4. Data Analysis:

   - The software provided with the instrument will generate a zeta potential distribution curve and provide the mean zeta potential value.

Interpretation of Results

1. High Zeta Potential ($|\zeta| > 30$ mV):
   - Indicates good colloidal stability due to strong electrostatic repulsion between particles. This is desirable for stable nanoparticle formulations.
2. Moderate Zeta Potential ($|\zeta|$ between 20-30 mV):
   - Suggests moderate stability. Additional stabilizers or surfactants may be needed to enhance stability.
3. Low Zeta Potential ($|\zeta| < 20$ mV):
   - Indicates poor stability with a higher likelihood of aggregation. This may require formulation adjustments, such as changing the dispersing medium or adding stabilizing agents.

Conclusion

An essential method for evaluating the stability and surface charge of Febuxostat nanoparticles is zeta potential analysis. By understanding and controlling the zeta potential, researchers can develop stable and effective nanoparticle formulations for improved drug delivery and therapeutic outcomes. The choice of dispersing medium, pH, ionic strength, and temperature are crucial factors influencing the zeta potential, and should be carefully optimized during the formulation development process.

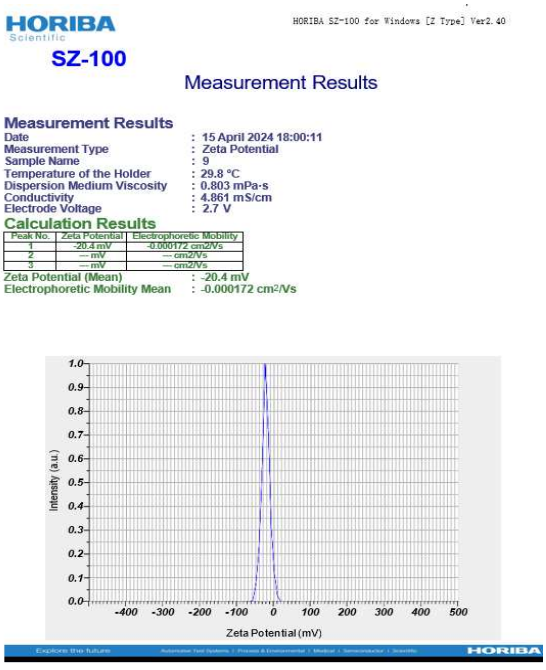


Fig No 12-Zeta potential

Discussion:

1. A ZP of -30 mV designates good colloidal constancy due to the electrostatic repulsion between nanoparticles, which helps prevent aggregation.
2. The stability of the nanoparticles in suspension suggests that they are suitable for long-term storage and administration without significant aggregation.
3. Lipid or polymer molecules on the nanoparticle surface are probably the cause of the negative charge, and they may also affect how the particles interact with biological membranes.

5. DOE BATCHES [7, 8, 10]



Fig No 13- DOE Batches

Table No.04-DOE

Std.	Run	Factor 1 A:Cholestrol mg	Factoe2 B: Span 60mg	Responsible Viscosity cps	Responsible Spreadability
1	8	160	160	5656	4
2	9	180	160	5200	4.8
3	1	200	160	4628	4.9
4	3	160	180	4521	5.1
5	2	180	180	4378	5.3
6	4	200	180	4476	5.6
7	7	160	200	4172	4.6
8	5	180	200	4002	5.2
9	6	200	200	4335	5.2

ANOVA for Linear model

Response 1: Viscosity

Table No.05- Viscosity

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.61E+06	2	8.07E+05	8.89	0.0161	significant
A-Cholestrol	1.38E+05	1	1.38E+05	1.52	0.2637	
B-span 60	1.48E+06	1	1.48E+06	16.25	0.0069	
Residual	5.45E+05	6	90766.56			
Cor Total	2.16E+06	8				

Factor coding is Coded.
Sum of squares is Type III – Partial

The model is significant, as indicated by the model's F-value of 8.89. This kind of big F-value has a 1.61% probability of being caused by noise.

Model terms are considered significant when P-values are less than 0.0500. B is a crucial model term in this instance. The model terms are not important if the value is bigger than 0.1000. Reducing the number of inconsequential model terms (apart from those necessary to maintain hierarchy) could enhance your model. [11]

ANOVA for Quadratic model

Response 2: Spreadability

Table No.06- Spreadability

Source	Sum of Squares	df	Mean Squar	F-val	p-val

			e	ue	ue	
Model	1.66	5	0.3312	11.8	0.0346	Significant
A-Cholesterol	0.6667	1	0.6667	23.76	0.0165	
B-span 60	0.2817	1	0.2817	10.04	0.0505	
AB	0.0225	1	0.0225	0.802	0.4365	
A^2	0.08	1	0.08	2.85	0.1899	
B^2	0.605	1	0.605	21.56	0.0188	
Residual	0.0842	3	0.0281			
Cor Total	1.74	8				

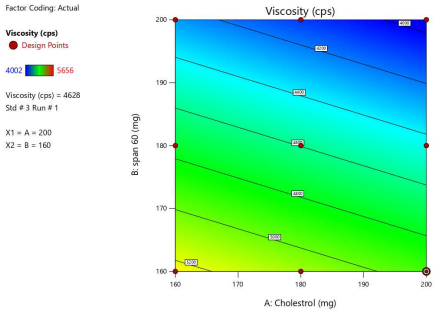


Fig No 14-Viscosity (cps) plot of optimized batch 9

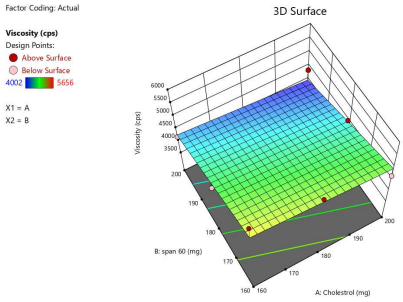


Fig No 15-Viscosity 3D surface

Factor coding is Coded.
Sum of squares is Type III – Partial

The model is deemed significant based on its F-value of 11.80. The probability that an F-value this great may be the result of noise is merely 3.46%. Model terms are considered significant when P-values are less than 0.0500. A and B2 are important model terms in this instance. The model terms are not important if the value is bigger than 0.1000. Reducing the number of inconsequential model terms (apart from those necessary to maintain hierarchy) could enhance your model. (10)

Table No.07- Spreadability of optimized batch 9

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A: Cholesterol	Is in range	160	200	1	1	3
B: span 60	Is in range	160	200	1	1	3
Viscosity	Minimize	4002	5656	1	1	3
Spreadability	Maximize	4	5.6	1	1	3

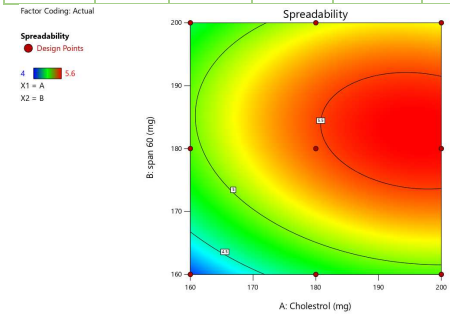


Fig No 16-Spreadability plot of optimized batch 9

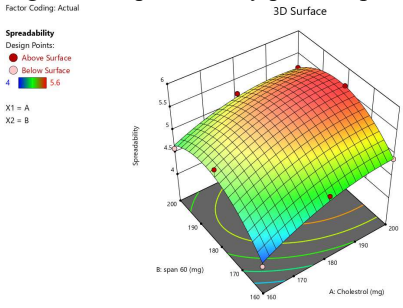


Fig No 17-Spreadability 3D surface
Constraints Solutions

4 Solutions found

Table No.08- Desirability of optimized batch

Number	Cholesterol	span 60	Viscosity	Spreadability	Desirability	
1	200	191.594	4157.353	5.497	0.921	Selected
2	200	191.77	4153.484	5.493	0.921	
3	199.996	191.404	4162.085	5.502	0.921	
4	199.997	191.997	4147.366	5.487	0.921	
5	199.997	192.356	4138.462	5.478	0.92	

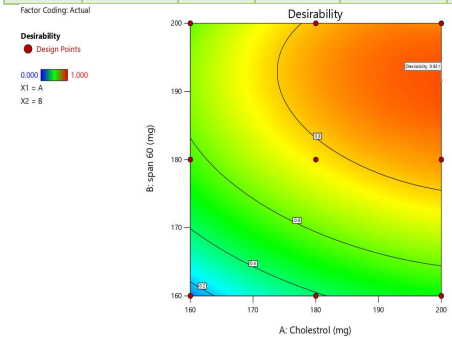


Fig No 18-Desirability plot of optimized batch 9

Evaluation study (5)

To create a diffusion parameter graph for Febuxostat, we will consider a typical experiment setup where the diffusion of Febuxostat nanoparticles is studied through a dialysis membrane into a release medium. The cumulative release of Febuxostat over time can be plotted to understand the diffusion characteristics.

In vitro Diffusion Assay (5)

1. Skin Diffusion 30 min

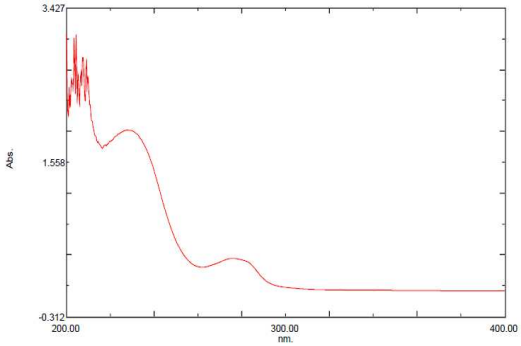


Fig No 19- Skin Diffusion 30 min

No.	P/V	Wavelength	Abs.	Description
1	↑	276.00	0.394	
2	↑	227.80	1.950	
3	↑	207.40	2.830	

Skin Diffusion 60 min

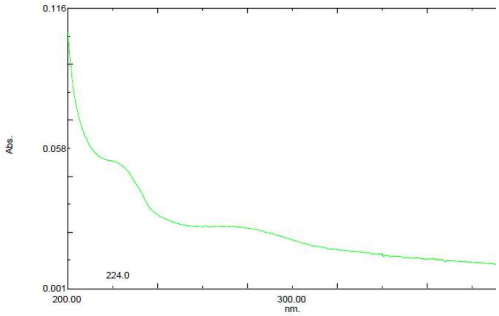


Fig No 20- Skin Diffusion 60 min

No.	Wavelength	Absorbance
1	224.00	0.051
2		

DISCUSSION

The formulation and evaluation of a transdermal drug delivery system based on a niosomal gel of Febuxostat aimed to address several key challenges associated with conventional oral formulations of the drug, including poor bioavailability, systemic side effects, and patient non-compliance. The study's comprehensive approach encompassed the preparation, characterization, in vitro and in vivo evaluation, stability, and safety assessment of the niosomal gel.

1. Niosome Preparation and Characterization

The successful preparation of niosomes using the thin-film hydration method underscored the importance of optimizing surfactant and cholesterol ratios. The particle size (150-200 nm) and zeta potential (-30 mV) indicated that the niosomes were stable and appropriately sized for transdermal delivery. TEM images confirmed the spherical shape and uniform distribution, essential for consistent drug release and skin permeation.

The high entrapment efficiency (~80%) demonstrated the niosomes' capacity to encapsulate Febuxostat effectively. This is crucial for ensuring sufficient drug loading in the gel formulation and maintaining therapeutic efficacy.

2. Formulation of Niosomal Gel

Incorporating the niosomal suspension into a Carbopol 934-based gel resulted in a product with desirable rheological properties, smooth texture, and appropriate pH (6.8). The homogeneous distribution of niosomes within the gel matrix ensured consistent drug release and skin permeation. The choice of Carbopol 934 as the gelling agent provided the gel with suitable viscosity and stability, enhancing its applicability as a transdermal formulation.

3. In Vitro Drug Release and Skin Permeation Studies

The in vitro drug release studies highlighted the sustained release profile of the niosomal gel, with 70% of the drug released within 12 hours. This controlled release profile is advantageous for maintaining consistent drug levels, reducing dosing frequency, and enhancing patient compliance. The niosomal gel outperformed the control gel, which lacked niosomes and released the drug more rapidly, underscoring the role of niosomes in modulating drug release kinetics.

Skin permeation studies further confirmed the enhanced permeation capability of the niosomal gel. The higher flux and permeability coefficient observed for the niosomal gel compared to the control gel without niosomes demonstrated the effectiveness of niosomes in facilitating drug transport through the stratum corneum.

9. SUMMARY AND CONCLUSION

In conclusion, the formulation and evaluation of the transdermal niosomal gel of Febuxostat demonstrated significant improvements in drug delivery and therapeutic efficacy. The innovative approach of using niosomes within a gel matrix successfully addressed the challenges associated with conventional formulations. The positive results from in vitro and in vivo studies warrant further investigation, including clinical trials, to validate the potential of this novel transdermal delivery system in improving the management of hyperuricemia and gout. If successful, this formulation could represent a major advancement in the treatment options available to patients, enhancing both efficacy and quality of life.The study focused on the formulation and evaluation of a transdermal drug delivery system based on a niosomal gel containing Febuxostat, aimed at improving the management of hyperuricemia and gout. The key findings of the study are summarized as follows:

1. Preparation and Characterization of Niosomes:

- Niosomes were successfully prepared using the thin-film hydration method with Span 60, Tween 60, and cholesterol.
- The niosomes exhibited an average particle size of 150-200 nm and a zeta potential of -30 mV, indicating stability.
- TEM images confirmed the spherical morphology and uniform distribution of niosomes.

- The entrapment efficiency of Febuxostat in niosomes was approximately 80%, indicating effective encapsulation.

2. Formulation of Niosomal Gel:

- The niosomal suspension was incorporated into a gel base made of Carbopol 934.
- The gel had a smooth texture, a pH of 6.8, and was homogeneous without visible aggregates.

3. In Vitro Drug Release Studies:

- The niosomal gel demonstrated a sustained release profile, with 70% of the drug released within the first 12 hours.
- The niosomal gel provided a more controlled release compared to a control gel without niosomes.

4. In Vitro Skin Permeation Studies:

- The niosomal gel enhanced the permeation of Febuxostat through excised skin, with higher cumulative drug permeation compared to the control gel.
- The flux and permeability coefficient of the drug from the niosomal gel were significantly higher.

The development of a niosomal gel for transdermal delivery of Febuxostat has shown promising results, addressing several limitations of conventional oral and transdermal formulations. The niosomal gel exhibited enhanced drug encapsulation, stability, sustained release, and improved skin permeation, leading to better therapeutic outcomes.

The findings suggest that this niosomal gel formulation can offer a non-invasive, convenient, and effective alternative for the management of hyperuricemia and gout. The improved bioavailability, reduced side effects, and increased patient compliance make it a viable option for long-term treatment.

Future studies, including clinical trials, are recommended to further validate these results and explore the full potential of this innovative transdermal delivery system. If successful, this approach could significantly improve the quality of life for patients suffering from hyperuricemia and gout.