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FORMULATION AND EVALUATION OF MICROSPONGE-BASED NOVELDRUG DELIVERY SYSTEM FOR ACUTE GOUT FLARES

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ABSTRACT

Objective: Acute gouty flares cause joint pain and inflammation, necessitating effective treatment. Colchicine is a key treatment, but its low oral bioavailability and gastrointestinal side effects make it unsafe. This research aimed to develop a microsponge-based drugdelivery system that enhances colchicine's bioavailability and therapeutic efficacy whilereducing side effects in acute gout flares.

Method: The synthesized colchicine-loaded microsponges were characterized by FTIR spectroscopy, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction. The formulated microsponge gel was evaluated for spreadability, pH, and viscosity properties to find out their suitability for topical application. In vitro drug release and drug content of the microsponge gel were analyzed by UV spectrophotometry, in vitro ischemic diffusion using Franz diffusion cells, and ex vivo diffusion using albino rat skin. Drug-excipient interactions are evaluated through FTIR and DSC studies.

Findings: The developed microsponge formulations had desired features like porous and spherical morphology and high drug encapsulation efficiency. In-vitro and ex-vivo studies revealed the

controlled and sustained drug release. From all the formulations, F4 showed a maximum percentage of drug release over a period of 24 hours. Topical gels have proper spreadability, viscosity, and pH. Drug-excipient compatibility studies showed no significant interaction.

Novelty: Microsponge-based delivery systems in colchicine provide hope for the application-oriented treatment of acute gout flares through controlled drug release and have great potential to increase therapeutic outcomes while reducing the incidence of side effects.

Keywords: Colchicine, Gout, Drug Release, microsponges, UV spectrophotometry

1. INTRODUCTION

A Drug Delivery System (DDS) controls drug release timing, location, and rate to improve therapeutic compound effectiveness and safety **[1]**. Due to the rise in newdiseases and drugs, advanced drug delivery systems are needed to deliver proteins, immunomodulatory agents like DNA, and peptides directly to target sites. One of the most plausible candidates is microsponge technology, a well-known agent that may modulate medication lifetime to match the desired therapeutic index and release rate while minimizing negative effects. Norbert and microsponge drug delivery systems are the current drug discovery targets for effective, low-cost infectious illness treatment **[2]**. Microsponge technology evolves with porous, cross-linked, polymeric microspheres ranging from 5 to 300μm in size. Lalita and Twinkle Garg described microsponges as non-toxic, indestructible spherical microns that absorb antidrugs and do not penetrate the skin in 2023 **[3]**. This microsphere's bigger interface lets drugs penetrate through epidermal layers during topical or transdermal usage **[4]**. Their design captures and releases bioactive substances to resist germs and cure. Drug development now focuses on nanotechnological and microsponge drug delivery systems to produce cost-efficient and effective medications. Micro-sponge technology is legitimate, however, research should be expanded **[5]**. Several studies demonstrate its controlled drug release and stability, however further research is needed on gel compositions and drug release kinetics particularly inductions such as NSAIDs for inflammatory conditions. Gout is caused by uric acid crystals and causes severe, inflammatory arthritis. Oral colchicine, the principal treatment, has significant gastrointestinal adverse effects. MSU deposits in joints, periarticular tissues, and synovial fluid indicate gout, according to Dehlin *et al*. 2020 **[6]** and Dalbeth *et al*. 2021 **[7]**. Demographic data from 2016 indicates a 6.8%

increase in gout incidence from <1%. In that year, Dalbeth *et al*. **[8]** described four stages of gout pathologies: radiographic erosions, lattice with acute gout episodes, elevated uric acid levels, severe tophi, and long-lasting gouty arthritis. According to Neogi (2016) **[9]**, Gout flare-ups are indicated by nocturnal joint volume, heat, discomfort, and erythema. In 2019 and 2020, Gao J. *et al*. **[10]** studied medication formulations' physico-chemical properties and self-control system release. In separate studies, Kaity S. *et al*. **[11]** and Tiwari A. *et al*. **[12]** showed that micro-sponge drug delivery was becoming more popular due to the small group's better skin crevices and skin secretions that accumulate where the drug is dispensed. Thus, gout sufferers may benefit from such delivery methods.

Medication delivery methods incorporating micro-sponges offer controlled medication release and stability, according to studies. The management of acute gout flares is seldom studied. Since most research is preclinical or focused on other inflammatory conditions, clinical trials are few. Acute gout flares need drug release optimization for fast onset and sustained release. Micro-sponge-based devices have not been extensively compared to other advanced delivery methods. Patient-centered outcomes research lacks quality of life, user-friendliness, and treatment adherence. The subject's long-term safety and efficacy are unknown. Addressing these shortcomings might accelerate micro-sponge-based acute gout flare treatments. Better patient outcomes and more therapeutic options would ensue.

This study aims to formulate a colchicine-loaded micro-sponge gel for gout treatment and evaluate its physicochemical properties and pharmacokinetics. By using Carbopol® 934 polymer and the quasi-emulsion solvent diffusion approach, the study aims to maximize colchicine's therapeutic effectiveness while reducing its adverse effects, thereby contributing to the field of topical drug delivery systems.

2. MATERIAL AND METHOD:

The chemicals required for the research work were procured from different pharma and biological companies. The Organoleptic properties of the colchicine drug were studied forthe characterization and purity of the drug obtained as described below:

2.1 Evaluation of Micro-sponge Loaded with Colchicine

- **FTIR Spectroscopy**

FTIR study was conducted and verified by FTIR BRUKER in the wavelength range of 4000-400cm-1 at resolutions as explained by Kumar *et al*. 2015 **[13]**. In the present study,

the 5mg sample was placed on the probe and the spectra visualized were recorded and then compared with standard colchicine.

❖ **Scanning Electron Microscopy (SEM)**

SEM helped to visualize the surface topography, and external and internal morphology of the micro-sponge at room temperature by coating it with gold-palladium under an argon atmosphere. On the metal grid, 5mg of prepared micro-sponge was mounted with the help of double adhesive tape and coated with gold under vacuum, then analyzed with SEM.

❖ **DSC (Differential Scanning Calorimetry)**

Thermograms of colchicine micro-sponge formulation and pure colchicine were obtained by DSC 4000. On the hermetically Aluminium fixed samples were placed and the heat was given at a temperature range of 10-200^0 C and the inert nitrogen gas at 10ml/min flow rate.

❖ **Spreadability Studies**

A weighted 0.5gm gel was placed on a pre-marked glass plate, and another plate was placed on top of it along with a 500gm weight that was left on for five minutes. This measurement of the diameter of the gel was made between the two glass plates of determined weight. It was observed that the gel's diameter had grown.

❖ **Drug Content**

The drug content was measured by the following steps:

- 1gm accurately weighed micro-sponge gel was dissolved in pH 4.0 phosphate buffer.
- The solution was filtered and 100ml solution was prepared in buffer solution.
- The resulting solution was diluted ten times with phosphate buffer to assess the drug concentration. A UV spectrophotometer was used to detect absorbance at 260 nm.

❖ **Drug Release Studies**

In the first step, the same amount of the micro-sponge was placed in a capsule with phosphate buffer pH 6.8 and rotated at 50 rpm then spectrophotometrically examined at 258nm.

❖ **In vitro drug release micro-sponge gel**

Franz diffusion cells were covered and a soaked cellophane diffusion membrane was put between the recipient and donor with the lower region having PBS pH 7.4 at a temperature 371^0 C.

Franz diffusion cells were used to accomplish the in vitro gel diffusion. A diffusion membrane that had been previously soaked and put between the donor and recipient compartments was placed over it. PBS at pH 7.4 was thermostatically maintained at 371 °C while stirring, and 20 ml of diffusion medium was located in the bottom area. With

the use of a UV spectrophotometer, the formulations were examined at 248 nm, and the cumulative drug release percentage was determined.

❖ **Ex vivo Diffusion Study**

Ex vivo diffusion studies were conducted by the institution's ethical committee and the procedure adopted was as mentioned below:

- Animals selected -male albino rats with a weight of 200-250gm
- The skin was removed more than the surface area of diffusion cells after sacrificing them with xylazine and ketamine dose
- The skin was put in normal saline i.e. 0.94%w/v and fixed
- The skin was fixed in the compartments of Franz diffusion cell as epidermal skin wastowards the donor and dermal towards the recipient compartment.
- Colchicine Micro-sponge gel sample was prepared with 2.32 %w/w gel or 50mg ofcolchicine is equal to 2.5 gm of the gel rubbed on the epidermal skin.
- 3ml of the sample was taken and UV-visible spectrophotometer analysis was carried outat 275nm.
- The drug diffusion was calculated as cumulative against time.

❖ **Drug Excipient Studies**

FTIR and DSC examination and spectra lead to identify drug-excipient interaction and functional groups. Further, it helped to evaluate the sample's physical properties as amorphous or crystalline and identify the interaction between the excipient and drug. Colchicine gel was optimized and subjected to thermal analysis.

3. RESULTS

3.1 Evaluation of the Micro-sponge Loaded Colchicine

- **Scanning Electron Microscopy (SEM), DSC, FTIR, and X-ray diffraction**

The study found that all formulations, except F3, F5, and F10, were porous and perfectly spherical, entrapping medication without crystals. The thermograms showed an endothermic peak at 144.250 C and a melting point of 1430 C, similar to pure form. The data imply no polymer-drug interaction, as reported by prior studies. Polymorphs were visualized using XPRD, indicating two crystal forms have the same internal structure. SEM scans showed spherical, porous crystals, and solvent diffusion showed a rigidpolymer and drug shell with a characteristic interior spherical hollow. Binocular PPL showed spherical micro-sponge in every entity or group with a porous nature. X-ray diffraction investigations detect drug crystal structure by seeing crystal modification patterns, making micro-sponge stable.

3.2 Evaluation Results of Colchicine Micro-sponge

The micro-sponge was evaluated for percentage yield, drug entrapment, and particle size to visualize which micro-sponge formulation has better drug yield, etc., and can be used for gel and drug delivery. **Table 1** shows the results of the percentage yield ranging from 85.620 ± 0.139 to 94.960 ± 0.507, Percentage Drug Entrapment ranging from 55.52 ± 0.101 to 81.0 ± 0.101%, and particle size range varied between 15.7 and 27.7 microns. The percentage of Drug loading was calculated by drug weight divided by micro-sponge weight multiplied by 100.

Table 1: Colchicine Microsponge (F1-F10) Evaluation

Sr. No.	Formulation Code	% Yield	% EE	Particle Size (µm)
1	F1	90.22 ± 0.166	68.47 ± 0.144	15.7 ± 0.577
2	F2	85.62 ± 0.139	55.52 ± 0.116	16.7±0.577
3	F3	90.96 ± 0.753	52.37 ± 0.121	18 ± 0.000
4	F4	89 .46± 0.420	67.64 ± 0.101	21 ± 0.000
5	F5	93.28 ± 0.507	70.51 ± 0.058	26.7 ± 0.577
6	F6	91.64 ± 0.567	81 ± 0.101	23.7 ± 0.577
7	F7	93.28 ± 0.507	71.52 ± 0.116	20.7 ± 0.577
8	F8	89.96 ± 0.753	65.52 ± 0.116	17.7 ± 0.577
9	F9	92.28 ± 0.507	58.32 ± 0.116	19.7 ± 0.577
10	F10	94.96 ± 0.753	67.52 ± 0.116	27.7 ± 0.577

3.3 Evaluation of Colchicine Loaded Micro-sponge Gel

The viscosity of formulated gel loaded with colchicine was noted as 1003± 0.46 to 1023.637 ± 0.52 rotated at optimum speed. The values indicated that the gel is viscous in nature. The results are shown in **Table 2**. pH in all the Formulated gels from F1-F8 was normal within the range of 6.6-6.9

❖ **Spread ability Studies and Drug Content**

The formulated gel spreads easily by applying a small amount of shear thus it was concluded that the formulated were better than the market with the Spreadability range of 33.832 ± 0.23 and 35.435 ± 0.32 as shown in **Table 2**.

The most important factor for drug delivery is drug content and its retention as per the requirement for the therapy. In almost all the gel formulations drug concentration was in the range of 92.475 ± 0.101 to 98.096 ± 0.101%. F5 and F8 were not included for further evaluation as visual characteristics were not as per standard.

Table 2: Drug-loaded micro-sponge gel Evaluation					
S. No.	**Formulation No.**	**pH**	**viscosity**	**Spreadability**	**Drug Concentration (%)**
1	**F1**	**6.65 ± 0.01**	**1003.33± 0.51**	**35.244 ± 0.22**	**92.475 ± 0.101**
2	**F2**	**6.70 ± 0.01**	**1012.33 ± 0.51**	**33.822 ± 0.22**	**97.296 ± 0.101**
3	**F3**	**6.90 ± 0.01**	**1016.67 ± 0.51**	**34.460 ± 0.22**	**96.296 ± 0.101**
4	**F4**	**6.80 ± 0.01**	**1021.67 ± 0.51**	**35.160 ± 0.22**	**94.596 ± 0.101**
5	**F6**	**6.85 ± 0.01**	**1022.67 ± 0.51**	**35.435 ± 0.22**	**98.096 ± 0.101**
6	**F7**	**6.89 ± 0.01**	**1023.637±0.51**	**33.760 ± 0.22**	**94.2596 ± 0.101**

❖ Drug Release Studies

In vitro drug release

The drug release cumulative percentage was noticed to reduce with an increase in drug: polymer ratio as it increases the thickness therefore the formulations F1-F4 were best with optimized formulations and characteristics etc. The drug release percentage exhibits that F4 has maximum drug release in 24 hrs which has 1.75% Carbopol 934 thus it could be selected for the drug delivery in the treatment of Acute Gout Flares for pain relief topically or transdermal **(Table 3)**.

Ex vivo Diffusion Percentage

The cumulative percentage of drug release was fit into kinetic models such as zero-order, Peppas, etc. to obtain the highest values for the formulations. Zero-order was best at0.930-0,980 for all formulations. Drug release was regulated by thickening the polymer matrix wall to extend the diffusion channel and reduce drug release.

In ex vivo diffusion trials, increasing polymer concentration inhibits drug transport on rat skin. Drug release from the biological membrane was higher for the first hour and then sustained, as in previous studies. Due to diffusion via microsponge and gel matrix, drug release in Flurbiprofen-loaded gel formulations decreased slowly. After 8 hours, drug diffusion was minimal in F1 and maximal in F4, with increased diffusion in the first hour.

Table 3: Drug Release Percentage in Different Formulations and Ex vivo Diffusion Percentage		
Drug Release Percentage in Different Formulations		
Formulation No.	**Time in hrs.**	**Drug Release Percentage**
Control	**4**	**99.091 ± 0.909%.**
F1	**24hrs**	**71.152 ± 0.052%,**
F2	**24hrs**	**82.939 ± 0.105%,**
F3	**24hrs**	**67.125 ± 0.091%**
F4	**24hrs**	**83.339 ± 0.105%,**
Ex vivo Diffusion Percentage		
Formulation No.	**Time in hrs.**	**Diffusion Percentage**
Control	**4**	**99.091 ± 0.909%.**
F1	**8hrs**	**63.152 ± 0.052%,**
F2	**8hrs**	**68.939 ± 0.105%,**
F3	**8hrs**	**65.125 ± 0.091%**
F4	**8hrs**	**70.52 ± 0.105%,**

- **Drug Excipient Studies**

The interaction between the pure drug and the colchicine gel loaded with microsponges was detected using FTIR by looking for changes in any of the drug's characteristics, suchas position or absence. According to FTIR spectra, the colchicine's distinctive characteristics and interaction with any excipient were unaltered. The addition of excipients in microsponge gel formulations does not cause an interaction or structural change, as demonstrated by Differential Scanning Calorimetry (DSC) peaks at 1500 C. Gout and inflammatory diseases can be effectively treated with colchicine. Its oral bioavailability is restricted, its therapeutic range is narrow, and it may have serious adverse effects on the gastrointestinal tract. Consequently, researchers have been focusing on creating the Microsponge Drug Delivery System. The spherical porous structure of the microsponge makes it suitable for use as a drug delivery device, dispensing precise dosages of medicines at the intended spot.

4. DISCUSSION

This study showed the prepared colchicine-loaded microsponges with spherical and porous morphology in SEM images, DSC, FTIR, and X-ray diffraction, with high drug encapsulation (55.52 ± 0.101 to 81.0 ± 0.101%) as well as high yielding (85.620 ± 0.139 to 94. The developed gel was found to have high drug content, good spreadability, high viscosity, and normal pH. The amount of drug released in 24 hours was highest with the F4 formulation, which can be suitably used in the elaboration of transdermal or topical application in acute flare-ups of gout. No interactions between the drug and excipients are Indicated by FTIR and DSC, ensuring the stability of the formulation. Studies on NSAID-loaded microsponges by Sharma *et al*., (2022) **[14]** and microsponge formulations foracne treatment by Kumari A *et al*. (2016) **[15]** showed similar results regarding its structural integrity, drug entrapment efficiency, and controlled drug release. Moreover, Garg A. *et al*. (2020) **[16]** worked out microsponges for antifungal drugs with high entrapment studying a similar in vitro release profile as current research. Furthermore, Bhatia M and Sania M *et al*., (2018) **[17]** analyzed the curcumin microsponges and reported that microsponges possessed good spreadability and stability. Even though the repeatability of these investigations proves the potentiality and efficiency of microsponge technology, the high percentage drug release in 24 hours can be on account of formulation specific differences in drug polymer interactions and the release kinetics.

5. CONCLUSION

Colchicine, a topical drug, was administered to acute gout flares using a transdermal microsponge gel. The gel regulated and sustained colchicine release to increase therapeutic efficacy and reduce adverse effects. The FDA approved colchicine as a topical drug with a controlled dose, and various formulations of microsponge gels were prepared in 10 batches. The optimal polymer concentration was between 1% and 1.75%, with microsponge wall thickness delayed release. The most successful formulations were F1, F2, F3, and F4. Studies with microsponge drug delivery systems (MDDSs) have reported better repeatability, minimized side effects, and increased efficacy in treating gout patients. This study uses microsponge gel technology to release colchicine slowly for acute gout flares, and the efficacy and safety of these formulations may be confirmed through clinical trials. The most promising formulations should be tested in vivo to confirm their safety and efficacy in a clinical setting, optimize the formulation process forscalability and consistency, assess patient compliance and satisfaction, and determine if microsponge technology can be used for other controlled treatments.

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