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Advancing Topical Drug Delivery: Formulation and Evaluation of Microsponge Loaded Topical Gel of Ibuprofen

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ABSTRACT:
This review article provides an overview of the formulation and evaluation of a microsponge based topical delivery system for ibuprofen.Ibuprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) known for its analgesic and anti-inflammatory properties. While oral ibuprofen tablets are commonly used for systemic relief, the development of topical formulations, such as microsponge-based gels, offers localized pain relief with reduced systemic side effects. This comprehensive review explores the advancements in ibuprofen formulations and the utilization of microsponges in topical gel delivery systems. Microsponges have emerged as a promising approach due to their unique structure and controlled release properties.[1]
The article highlights the importance of topical drug delivery systems and discusses the formulation of the microsponge loaded topical gel with ibuprofen along with it's ingredients, preparation method, and evaluation parameters. In conclusion, this study provides evidence of the effectiveness of microsponge loaded topical gel of ibuprofen.
The aim of this review article is to study about the ethyl cellulose facilitated microsponges for the controlled delivery of ibuprofen to the skin.

KEYWORDS: Ethyl cellulose, microsponges, topical gel, controlled delivery, topical drug delivery system, ibuprofen, quasi emulsion technique.

I. INTRODUCTION

Topical dosage forms offer a significant area for drug application, particularly on the skin. The selection and formulation of topical drugs depend on the specific characteristics of the drug itself. Topical administration provides numerous advantages, including the avoidance of first-pass metabolism. Moreover, it offers enhanced patient compliance due to its ease of application directly on the skin without external assistance. The versatility of topical administration allows for customized formulations tailored to individual body conditions. Furthermore, the release of drugs can be modified to achieve sustained or controlled release, and pH-responsive formulations can be designed to optimize therapeutic benefits. These advantages make topical administration an attractive route for drug delivery, with the potential for improved therapeutic outcomes and patient convenience.[2]

Topical delivery system refers to a substance that facilitates the application of a specific drug onto the skin and enables its penetration through the skin barrier. The main challenge in topical drug delivery lies in effectively transporting the drug across the skin barrier. Topical delivery encompasses two primary types of products: external topicals, which are spread, sprayed, or dispersed onto the skin surface to cover the affected area, and internal topicals, which are applied orally, vaginally, or rectally to mucous membranes for local effects. Topical preparations are primarily used for their localized effects at the site of application, achieved through the penetration of drugs into the underlying layers of the skin or mucous membranes. Overcoming the barriers of skin penetration and achieving effective drug delivery is crucial for optimizing the therapeutic benefits of topical formulations.[3]

Microsponges have emerged as a novel and controlled pharmaceutical product with versatile applications. They possess the ability to encapsulate a wide range of drugs, whether in solid or liquid form. One of the key advantages of microsponges is their high entrapment efficiency, allowing them to absorb more than six times their own weight. These microsponges exhibit exceptional stability, even at elevated temperatures and within a broad pH range of 1 to 11. Furthermore, they demonstrate excellent compatibility when suspended in various vehicles and incorporated into liquid or semi-solid dosage

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forms. By providing controlled release of the drug, microsponges contribute to the elegance of the product, ensuring stability and non-irritating characteristics that improve patient compliance. Overall, microsponges offer a promising approach in pharmaceutical formulations, enhancing drug delivery outcomes and patient satisfaction.[4]

Microsponges provide a valuable advantage in the delivery of dermatological agents by leveraging the unique structure and physiology of human skin. They offer enhanced efficacy while minimizing local adverse effects. The size of microsponges, typically ranging from 5 to 300 µm, plays a critical role in their topical application. This characteristic size is strategically designed to impede their passage through the stratum corneum, the outermost layer of the skin. By preventing excessive penetration, microsponges ensure controlled and localized drug delivery, optimizing the therapeutic outcomes while reducing the risk of adverse reactions. The tailored size of microsponges enables their precise targeting to the desired skin layers, enhancing the effectiveness of dermatological treatments.[5]

Advantages of Topical drug delivery system: [6, 7]

Topical drug delivery systems offer numerous advantages in comparison to other routes of drug administration.

- Avoidance of First Pass Metabolism
- Convenient and easy to apply
- Avoidance of absorption challenges
- Easy termination of medication if necessary
- Avoidance of gastrointestinal incompatibility
- Improved patient compliance
- Suitability for self-medication
- Consistent drug release
- Site specific drug release.

Disadvantages of topical drug delivery system: [8, 9, 10]

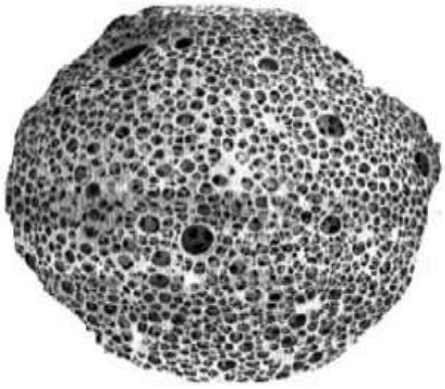
- Skin irritation or dermatitis may occurs due to the drug or excipient and this can leads to discomfort and adverse reactions.
- Drugs with larger particles sizes may face difficulties in being absorbed through the skin.
- There is a potential risk of allergic reactions occurring with topical drug delivery systems.
- Topical drug delivery is not suitable for the drugs that have potential to irritate or sensitize the skin.

MICROSPONGES:

Microsponges are porous polymeric delivery systems that enhance stability, reduce side effects, and provide controlled drug release. They consist of tiny spherical particles with a large porous surface, allowing for the controlled release of active ingredients. The size of microsponges ranges from 5-300µm in diameter, with each particle containing numerous interconnecting voids. These voids enable the retention of a significant amount of drug within the microsponge.

Compared to other technologies like microencapsulation and liposomes, microsponges offer several advantages. Microcapsules lack the ability to control the release rate of actives, as the contained actives are released once the capsule wall is ruptured. Liposomes have limitations in terms of payload, formulation challenges, limited chemical stability, and microbial instability.

In contrast, the Microsponge Drug Delivery System is a patented, highly cross-linked, and porous polymeric microsponge technology capable of entrapping a wide range of actives and releasing them at desired rates. These microsponges, typically 10-25 microns in diameter, possess the strength to withstand the high shear forces encountered during the manufacturing of creams, gels, lotions, and powders. Their unique characteristic is the ability to adsorb a high degree of active materials both within the particle and on its surface. Microsponges provide a controlled release mechanism for topically applied drugs. They offer advantages over other technologies, such as improved control over release rates, enhanced stability, reduced side effects, and the ability to load a high concentration of active ingredients. [11]



Pic: Microsponge

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(Reference:https://www.researchgate.net/figure/Highly-porous-nature-of-a-Microsponge_fig1_235945631)

Characteristics of microsponges:

- Porous structure
- Spherical shape
- Large surface area
- Controlled drug release
- High degree of cross-linking
- Insoluble and inert
- Ability to withstand high shear forces
- High drug loading capacity
- Stable at varying temperature and pH levels. [12]

Preparation method of Microsponges:

The drug loading process in microsponges drug delivery systems can be achieved through two methods: a one-step process or a two-step process. These methods namely:

1. **Liquid-LiquidSuspension Polymerization:** This method involves the one-step process of drug loading in microsponge drug delivery systems. If the drug is an inert, non-polar material, it acts as a porogen and helps create the porous structure. The drug, which does not interfere with polymerization and remains stable to free radicals, is entrapped in the microsponges.
2. **Quasi-Emulsion Solvent Diffusion Method:** This method also involves a two-step process for drug loading in microsponges. The physicochemical properties of the drug determine its suitability for this method. In this approach, a quasi-emulsion is formed by dissolving the drug in a suitable solvent, followed by diffusion of this drug-containing solvent into a non-solvent to form microsponges.

The method described is commonly employed for the preparation of oral and topical microsponges. It involves the preparation of two phases: an inner organic phase and an outer aqueous phase. In the inner organic phase, a polymer is dissolved in ethyl alcohol, and the drug is dissolved in this solution using ultra-sonication at room temperature. The outer phase consists of a polyvinyl alcohol (PVA) solution in water. The solution is stirred and filtered for subsequent use. The inner phase is then added dropwise to the outer phase under mechanical stirring. Stirring leads to the formation of quasi-emulsion droplets, which further undergo solvent evaporation, resulting in the formation of solid microsponge cages. The prepared microsponges are subsequently filtered and dried in an oven for a duration of 12 hours. [13]

FORMULATION OF IBUPROFEN MICROSPONGES:[14, 15, 16]

Microsponges containing the anti-inflammatory and antipyretic drug "Ibuprofen" were prepared using the Quasi emulsion method. Different combinations of the drug and polymers shall be mixed with an organic solvent (e.g. dichloromethane) in a magnetic stirrer for 15 minutes to obtain a uniform polymer solution. This solution then slowly added to a dispersion medium consisting of 100 ml of 0.5% PVA solution and 1 ml of glycerol. The entire system then stirred at a constant speed using a mechanical stirrer with a three-blade propeller at room temperature. The stirring process should be continued for 2-3 hours.

Once the stirring is completed, the formed microsponges shall be separated by filtration using Whatmann filter paper and then air dried for 48 hours. The dried microsponges then stored in an airtight container for further evaluation.

Table:Formulation of Ibuprofen Microsponges:

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ibuprofen(gm)	1	1	1	1	1	1
Ethyl cellulose(gm)	0.5	1	1.5	2	2.5	3
PVA (gm)	0.5	0.5	0.5	0.5	0.5	0.5
Dichloromethane(ml)	10	10	10	10	10	10
Glycerol(ml)	1	1	1	1	1	1
Water(ml)	100	100	100	100	100	100
Drug: polymer	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3

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EVALUATION OF IBUPROFEN MICROSPONGES:

Percentage yield:

The microsponges obtained from various formulations shouldbe collected and weighed. Here, the actual weight of the microsponges will be divided by the total weight of the drug and polymer used in the preparation process. This calculation allows for an assessment of the percentage of drug encapsulated within the microsponges, providing insight into the efficiency of the formulation.[17]

The percentage yield is calculated using the following formula:

% Yield= (Actual weight of microsponges/Total weight of Drug and Polymer) x 100

Drug entrapment efficiency:

Microsponges equivalent to 100mg of Ibuprofen from each batch should be carefully weighed and crushed. The resulting powder then placed in a 100ml volumetric flask and pH 7.4 phosphate buffer should be added to bring it up to the mark. The solution then filtered using Whatmann filter paper No.44. After filtration, an accurate quantity of the solution (1ml) should be taken and diluted up to 10ml with pH 7.4 phosphate buffer. From this diluted solution, an accurate volume (1ml) should be pipetted out and further diluted up to 10ml with pH 7.4 phosphate buffer.

The absorbance of this final solution should be measured at 264 nm using a spectrophotometer. This measurement allows for the quantification of Ibuprofen present in the microsponges, as the absorbance at 264 nm is specific to Ibuprofen. [18, 19]

The drug entrapment efficiency should be calculated by using formula:

%Drug Entrapment Efficiency= (Practical drug content/ Theoretical drug content) x 100

Particle size analysis:

The size of the Ibuprofen microsponges are determined using the optical microscopy method. To calibrate the eyepiece micrometer, a standard stage micrometer should utilized.

From each batch, the size of 200 microsponges are measured individually. This extensive measurement allowed for a more accurate representation of the particle size distribution within the batch. The measurements should be recorded, and the average particle size then calculated by taking the mean value of the measured sizes. This approach provides valuable information regarding the size characteristics of the microsponges in each batch. [20]

Calibration of eyepiece micrometer:

One division of the stage micrometer = 0.01mm = 10µm

$\therefore \mu=(SM/EM) \times 10$

Where, µ= correction factor

SM= Reading of stage micrometer which overlap with the reading of eyepiece micrometer (EM)

Shape and surface morphology:

The shape and surface characteristics of the prepared microsponges should be examined using scanning electron microscopy (SEM). For SEM analysis, samples of the microsponges prepared by carefully sprinkling them onto a double-sided adhesive tape that should be attached to an aluminum stub. To enhance conductivity and imaging quality, the stubs containing the samples should be coated with a 30nm thick layer of gold using a sputter coater operating under high vacuum and high voltage conditions.

Subsequently, the samples were subjected to imaging using a scanning electron microscope with a 20KV electron beam. This imaging technique allowed for a detailed examination of the microsponge's morphology, surface features, and overall structure at a high resolution. [21]

FORMULATION OF IBUPROFEN MICROSPONGES:

Table: Formulation of gel containing Ibuprofen microsponges

SL No.	Ingredients	Quantity (mg/ml)
01	Ibuprofen microsponges	5 %
02	Carbopol 934	35
03	Triethanolamine	2
04	Methyl paraben	3
05	Propyl paraben	1
06	Distilled water	q.s.

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Procedure:

1. A clear dispersion of carbopol (35 mg) is prepared in water (q.s) using moderate agitation.
2.Triethanolamine (1-2 drops) is used to neutralise the formulation and subsequently preservatives Methyl paraben (3 mg) and Propyl paraben (1 mg) was added to resist the microbial growth.
3. And then volume was maintained with water. Gel prepared were degassed with ultrasonication.

EVALUATION OF IBUPROFEN MICROSPONGES GEL:

Visual inspection

The gel containing microsponges underwent visual inspection to assess its organoleptic properties, including color, texture, consistency, homogeneity, and overall physical appearance. This evaluation was conducted through direct visual observation, without the use of any analytical instruments. [22]

Spreadability studies:

Spreadability refers to the ability of the gel to readily spread over a larger area of the skin or affected area. It plays a crucial role in determining the therapeutic efficacy of the formulation. The spreadability of a gel is typically measured by the time it takes for two slides to separate from the gel placed in between them under a specific load.

The spreadability of a gel is expressed in terms of the time taken (in seconds) for the slides to slip off from the gel surface. A shorter time required for the separation of the slides indicates better spreadability, implying that the gel can effectively cover a larger area with ease. This property is crucial for ensuring optimal therapeutic outcomes, as it allows for better coverage and absorption of the active ingredients into the skin or affected area. [23]

It can be calculated by:

S = ML/T

Where, M = weight attached to upper slide (in gm)
L = length of glass slides (in cm)
T = time taken to separate the slides.

pH measurement:

The pH of the gel formulation is determined using a digital pH meter. A quantity of 5 g of the gel is dispersed in 45 ml of distilled water at a temperature of 27°C. The resulting solution then subjected to pH measurement using a digital pH meter. This measurement provided information about the acidity or alkalinity of the gel formulation, which is an important parameter for assessing its stability, compatibility with the skin, and potential therapeutic effects.

Viscosity measurement:

The viscosity of the gel formulation is determined using a Brookfield viscometer equipped with a spindle number 7. The measurement is performed at a rotational speed of 50 rpm. To ensure accuracy, three readings should betaken, and the average value is calculated. [24]

IN-VITRO DRUG DIFFUSION STUDIES:

In vitro diffusion studies shall be conducted for all formulations using a France diffusion cell apparatus at a temperature of 37°C. The release medium will be carefully selected to ensure a sink condition, considering the properties of the active ingredients. At predetermined time intervals, samples should withdrawn from the release medium, and their analysis should performed using a suitable analytical method.

To conduct the diffusion studies, an egg membrane shall fitted at the donor site of the diffusion cell. A predetermined quantity of the gel formulation should be mounted on the membrane. Samples then collected from the release medium at specific time intervals and analyzed using an appropriate assay method. [25, 26]

IN-VITRO DRUG RELEASE KINETICS:

The cumulative amount of Ibuprofen released at various time intervals from the different formulations of microsponges was analyzed using different kinetic models to characterize the mechanism of drug release. The different models were applied like zero-order kinetics, first-order kinetics, Hixson-Crowell kinetics, Higuchi's model and Korsmeyer-Peppas model to characterize mechanism of drug release. [27, 28]

STABILITY STUDIES:

Stability of a drug refers to the ability to maintain its desired physical, chemical, therapeutic, and toxicological properties over a specific period. It can be defined as the duration from the manufacturing & packaging date of the formulation until the chemical or biological activity of the drug remains above a predetermined level of labeled potency, and its physical characteristics remain relatively unchanged.

The stability of a drug formulation is crucial to ensure its efficacy, safety, and quality

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throughout its intended shelf-life, allowing patients to receive consistent and reliable medications.

METHODS:

The optimized formulation of microsponges underwent stability studies for a duration of 3 months. The microsponges should be packaged in amber-colored screw-capped containers and stored at room temperature. After the 3-month stability period, samples shouldbe taken from the stored formulation and subjected to various analyses.

The samples then analyzed to determine the drug content, percentage of drug entrapment efficiency, any changes in appearance, pH, and the in-vitro diffusion profile. A comparison should be thenmade between the in-vitro drug release profiles obtained at the beginning of the stability study (0 month) and after the 3-month period. This comparison provided insights into any changes or alterations in the drug release behavior of the microsponges during the stability study. [29]

II. LITERATURE REVIEW:

Sheefali Mahant and co-workers (2020) studied about Microsponges for dermatological application and found that the utilization of advanced drug delivery systems has revolutized the field of dermatology. Among the various innovative approaches, Microsponges have emerged as a promising technology for dermatological applications. Their unique properties allow for controlled and targeted release of APIs, resulting in improved efficacy and patient outcomes. While challenges exist, continued research and technological advancements are expected to overcome these barriers, paving the way for the widespread adoption of microsponges in dermatology. Overall, this literature review provides valuable insights into the perspectives and challenges associated with microsponges as a drug delivery system for dermatological applications, highlighting the potential of this technology to revolutionize dermatological treatments. [30]

Sailesh Sharma et al. (2020) conducted a study on microsponges for topical drug delivery and concluded that the microsponges delivery system is a unique technology that enables controlled release of macro porous beads containing an active agent. This system has the potential to reduce side effects while maintaining therapeutic efficacy. The drug delivery system utilizing microsponges offers the ability to encapsulate ingredients, leading to potential benefits such as decreased side effects, enhanced stability, improved formulation flexibility, and increased aesthetic appeal. Extensive research has consistently demonstrated that microsponges systems are characterized by their non-irritating, non-mutagenic, non-allergenic, and non-toxic properties. Currently, this technology is being employed in various products such as cosmetics, over-the-counter skincare, sunscreens, and prescription medications. The utilization of microsponges-based drug delivery technology holds the promise of advancing our understanding of disease healing processes. Therefore, it is anticipated that microsponges-based drug delivery matrices will play a crucial role in diverse therapeutic applications in the future. [31]

Sreejan Manna et al (2019) did researched on **Ibuprofen controlled release matrix tablets using its solid dispersion** with an objective to enhance the dissolution rate and evaluate the impact of combining of hydrophilic and hydrophobic polymers on drug release. They concluded that **in-vitro**drug release study conducted in phosphate buffer pH 7.2 demonstrated a release range of 68.76±3.04% to 95.33±2.34% over 8 hours. Additionally, the swelling index of the formulated tablets ranged from 90±5.43 to 137±6.41, falling within acceptable limits. This formulation technique was considered highly promising for Ibuprofen, as it achieved controlled release from the polymer matrix, enabling improved drug absorption, reduced side effects, increased dissolution rate, and potential dose reduction. [32]

Pradeep Kumar Bolla and co-workers (2019) conducted research on the impact of formulation parameters on the permeation of Ibuprofen from topical formulations using the Strat-M® membrane. The results clearly demonstrated that a clear non-aqueous gel containing 3% w/w ibuprofen exhibited the highest permeation rate compared to other formulations tested. This finding highlights the importance of considering critical formulation factors during the early stages of developing topical drug products to meet the predetermined Quality Target Product Profile (QTPP). Moreover, since many nonsteroidal anti-inflammatory drugs (NSAIDs) share similar physicochemical properties, this article serves as a valuable reference for formulation scientists in

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selecting the appropriate formulation type to achieve the desired permeation profile. [33]

Vishal Yadav et al (2018) investigated on formulation and evaluation of microsponges gel for topical delivery of antifungal drug. The gel containing microsponges exhibited a viscous modulus, indicating its desirable rheological properties. The study concluded that microsponges prepared using a combination of eudragit S-100 and eudragit L-100 in a 1:10 ratio demonstrated enhanced drug release characteristics, with 87.77% and 83.24% of the drug released at the end of 8 hours. The optimized formulation of microsponges gel followed zero-order kinetics and non-Fickian diffusion, suggesting a controlled and sustained release of the drug. [34]

Bhumi Bhavsar et al (2015) formulated and evaluated microballoons encapsulating the drug Ibuprofen. The research investigated the impact of different concentrations of the polymer and stabilizing agent on the entrapment efficiency and practicality of the microballoons. The results demonstrated that the microballoons of Ibuprofen exhibited a high percentage of entrapment efficiency, specifically 96.66%, along with a maximum drug loading of 95.55. Through the optimization process, it was determined that the microballoons achieved high entrapment efficiency at a rotational speed of 1300 rpm. The study concluded that microballoons of Ibuprofen have the potential to serve as an effective drug delivery system for the treatment of inflammation.[35]

Mahaparale P.R., et al (2018) formulated microsponges of ethyl cellulose containing by using the quasi-emulsion solvent diffusion method. The morphology of the resulting microsponges was examined through scanning electron microscopy, revealing porous and spherical structures. The optimized microsponge formulation was then dispersed in Carbopol gel for further evaluation, including drug content, pH, viscosity, and in vitro drug release. The study found that the release of the drug from the microsponge gel was sustained when compared to both the marketed product and the pure drug gel. This suggests that the microsponge formulation has the potential to provide controlled and prolonged release of terbinafine hydrochloride when incorporated into a gel formulation. [36]

A. B. Suchithra and colleagues (2017) conducted research on nanoparticulate gel containing ibuprofen formulation. The combination of carbopol 934 and HPMC demonstrated favorable attributes, including good consistency, homogeneity, and low viscosity (2431 cP). The formulation exhibited high percentage yield (98.10%) and drug content (98.67 ± 0.021%). Additionally, the in vitro diffusion study showed that 93.33% of the drug was released within 4 hours. Based on these observations, it can be concluded that the developed topical gel, incorporating ibuprofen nanoparticles, has the potential to enhance the bioavailability of the drug while mitigating its side effects. [37]

Chandramouli Y. and co-workers (2012) microsponge formulation was prepared as gel in carpool and studied for pH, viscosity, spreadability, drug content, invitro release. The Microsponge formulation gel, showed viscosity 206.72 pa.s spread ability of 11.75g cm/s and drug content of 92.37%. A Microsponge acyclovir sodium gel formulations showed an appropriate drug release profile. [38]

Puligilla R.D et al (2016) researched on famotidine floating microsponges to enhance the site-specific absorption of the drug for the treatment of peptic ulcers. The microsponges were formulated using a modified quasi-emulsion solvent diffusion method. Different concentrations of Eudragit S100 and polyvinyl alcohol were utilized, and the prepared microsponges underwent evaluation for parameters such as percentage entrapment efficiency, buoyancy, and cumulative drug release. The results revealed an entrapment efficiency of 88.3%, buoyancy of 76.4%, and cumulative drug release of 86.9% for the optimized formulation. This study introduces a novel approach utilizing the floating ability of microsponges for the treatment of ulcers, offering potential benefits for site-specific drug delivery. [39]

III. CONCLUSION

In conclusion, microsponge shows a promising approach for development of topical formulation of ibuprofen. It showed that ethyl cellulose facilitated microsponges for controlled delivery of ibuprofen to the skin. The comprehensive characterization and evaluation of the formulations shows their potential as effective carriers for targeted drug delivery, offering controlled release and favorable skin application properties.

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