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Development of Propyl Paraben-Loaded Microsponge for Enhanced Preservation in Skin Creams

Pooja Rani[1], Sonu Goyat[2], Sourav Phalswal[2], Sudeep Ahlawat[2], Sumit Chahal[2], Sunil Hooda[2], Suryakant Sharma[2], Rimmy Nandal*[2]

[1]Chandigarh Group of Colleges, Jhajeri, Mohali, Chandigarh Pharmacy College-Jhanjeri, Mohali (140307), Punjab, India,

[2]Shri Baba Mast Nath Institute of Pharmaceutical Sciences and Research, Baba Mast Nath University, Rohtak-124021

***Corresponding Author:**

Dr. Rimmy Nandal,

[2]Shri Baba Mast Nath Institute of Pharmaceutical Sciences and Research, Baba Mast Nath University, Rohtak-124021

Email ID: nandalrimmy17@gmail.com

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ABSTRACT

This study emphasizes developing a microsponge-based delivery system for propylparaben, a broadly used preservative in skin creams. The microsponge technology was employed to control the release of propylparaben, thereby reducing the risk of skin irritation and other adverse effects. The optimized microsponge formulation was incorporated into a cold cream and evaluated for its physical properties, in vitro release profile, and preservative efficacy. The results reveal that the microsponge-loaded propyl paraben provided sustained release and improved preservative activity, ultimately extending the shelf life of the cold cream. This innovative formulation offers a promising approach to enhancing the safety and effectiveness of skin creams. Particle size analysis showed that as the amount of polymer in the formulation increased, the particle size range of the batches also grew. Differential Scanning Calorimetry studies of the pure drug, ethyl cellulose, and propyl paraben-loaded microsponges revealed no interactions between the drug and the excipients. Similarly, Infrared spectroscopy analysis confirmed the absence of any interactions. Antimicrobial preservative testing conducted in a microbiology lab revealed the diameter of the zone of inhibition for the prepared microsponges, cold cream with the microsponges, and plain cream, demonstrating the antimicrobial potential of the microsponge-based formulation.

Keywords: *Microsponge, Propylparaben, cold cream, antimicrobial preservatives effectiveness testing, zone of inhibition*

1. INTRODUCTION

Microsponges are innovative, polymeric delivery systems consisting of porous, spherical particles with a non-collapsible structure and large porous surface (Jadhav *et al*., 2013, Singhvi *et al*., 2019). These tiny, sponge-like particles have a diameter ranging from 5 to 300µm and contain numerous interconnecting voids that can entrap active ingredients. By doing so, microsponges act as reservoirs, controlling the delivery rate of the entrapped substances. The microsponge technology offers a versatile platform for the controlled delivery of various substances, including emollients, fragrances, anti-inflammatory agents, sunscreens, antifungal agents, and antimicrobial agents (Jelvehgari *et al*., 2006, Moin *et al*., 2016). This delivery system provides numerous benefits, including enhanced efficacy of topical active agents, extended product stability, improved safety, and reduced side effects. Overall, microsponges offer an efficient and effective means of delivering a wide range of substances, making them an attractive option for various applications (Amrutiya *et al*., 2009). Microbial contamination of topical products can originate from various sources, including raw materials, manufacturing, storage, and patient use. This contamination can not only spoil the product but also pose a significant health risk to patients (Kaity *et al*., 2010). To mitigate this risk, the use of suitable preservatives is essential. Preservatives are chemical agents with antimicrobial properties that control the growth and survival of microorganisms. Propyl paraben, a compound derived from parahydroxybenzoic acid, is a commonly used preservative in the pharmaceutical and cosmetics industries (Soni *et al*., 2001, Shin *et al*., 2019). However, its use has been associated with several problems, including skin irritancy, allergy, contact dermatitis, and toxicity. To address these issues, the present study aimed to develop a controlled release system for propylparaben using a Microsponge Drug Delivery System (MDDS), which can help minimize the adverse effects associated

with propylparaben (Vandecasteele *et al*., 2011, Pollock *et al*., 2017, Ioannidi *et al*., 2018). The Preservative Effectiveness Test is a critical evaluation that assesses the ability of antimicrobial agents, used as preservatives or additives, to inhibit the growth of pathogenic organisms. These organisms include E. coli, Aspergillus niger, Candida albicans, Pseudomonas aeruginosa, and Staphylococcus aureus (Kadam *et al*., 2016, Maskare *et al*., 2023). The Antimicrobial Effectiveness Test is a standardized method that demonstrates the effectiveness of a preservative system in a product. The test involves inoculating a product with a controlled quantity of specific microorganisms and then comparing the level of microorganisms found on a control sample versus the test sample over 28 days (Amrutiya *et al*., 2009

2. EXPERIMENTAL

2.1 Materials and Methods

The ethyl cellulose, polyvinyl alcohol (PVA), and mineral oil were received from Hi-Media Laboratories Pvt. Ltd. (Mumbai, India). White beeswax, and borax, were purchased from MP Biomedicals, and other chemicals were analytical-grade used during the study.

2.2 Preparation of Propyl Paraben Microsponges

The microsponges were prepared using a quasi-emulsion solvent diffusion method, which involves two main steps: preparation of the inner phase and preparation of the outer phase. In the first step, the inner phase was prepared by dissolving ethyl cellulose in ethanol, followed by the addition of propyl paraben as a preservative to the solution. In the second step, the outer phase was prepared by dissolving polyvinyl alcohol in distilled water. The inner phase was then slowly added to the outer phase at room temperature, and emulsification was carried out. The mixture was stirred continuously for 5-6h at 2000 rpm to ensure proper emulsification. After emulsification, the micro sponges were separated by filtration. The collected microsponges were then dried in an oven at 40°C for 12h. Finally, the dried microsponges were stored in a vacuum desiccator (Kaity *et al*., 2010)**.**

2.3. Design of experiment

During preliminary trials, it was observed that the homogenization speed, and amount of PVA had a significant effect on the critical properties of micro- sponges. The central composite design was used to investigate the extent of the effect of change in independent variables on key product characteristics. The homogenization speed, and amount of PVA were selected as an independent variable whereas particle size (Y_1), % production yield (Y_2), % drug loading efficiency (Y_3), % entrapment efficiency (Y_4), were selected as response variables. The coded value and transformed values for designed batches are given in Table 1.

Table 1: Different batches of formulation of Microsponges.

	Coded value			**Transformed value**		
Batches	**Homengenization speed (X_1)**	**Ethyl cellulose (mg) (X_2)**	**Polyvinyl alcohol(mg) (X_3)**	**Homengenization speed (X_1)**	**Ethyl cellulose and Propyl paraben (mg) (X_2)**	**Polyvinyl alcohol(mg) (X_3)**
B1	-1	-1	-1	500	1:1	0.05
B2	1	-1	-1	1000	1:1	0.05
B3	-1	1	-1	500	2:1	0.05
B4	1	1	-1	1000	2:1	0.05
B5	-1	-1	1	500	1:1	0.12
B6	1	-1	1	1000	1:1	0.12
B7	-1	1	1	500	2:1	0.12
B8	1	1	1	1000	2:1	0.12

B9	-1.654	0	0	250	1:5	0.1
B10	1..654	0	0	1000	1:5	0.1
B11	0	0	0	700	1:5	0.1
B12	0	0	0	700	1:5	0.1
B13	0	-1.654	1..654	700	1:5	0.05
B14	0	1..654	1..654	700	1:5	0.14
B15	0	0	0	700	1:5	0.1

3. CHARACTERIZATION OF MICROSPONGES

1. Particle size determination: The particle size of the prepared microsponges was determined using Malvern Zetasizer Nano ZS 90. which was equipped with a hydro dispersing unit. Particle size measurements were performed through laser light diffractometry, ensuring accurate and precise characterization of the microsponge's size distribution (Aloorkar *et al*., 2012).

2. Production yield: The microsponges from all batches were accurately weighed, and the percentage yield was calculated using the following equation:

$$\%\text{Yield} = (\text{Total weight of product})/\text{Actual weight of product}) \times 100$$

3. Encapsulation efficiency:

The prepared microsponges can be evaluated by the proportion of the active ingredient that has been successfully incorporated into the microsponges (Rani *et al*., 2024). It is typically calculated using the following equation:

Loading Efficiency = [Actual drug content/Theoretical drug content] *100

4. Scanning Electron Microscopy (SEM):

The surface morphology and appearance of the prepared microsponges were analyzed by using Scanning Electron Microscopy (7610F Plus/JEOL). A small amount of the microsponges was mounted on a metal stub using double-sided adhesive tape. The samples were then coated with a thin layer of gold to make them electrically conductive. This study utilized various magnifications to observe the size, shape, and surface structure of the microsponges (Tiwari *et al*., 2022).

5. Fourier Transform Infrared Spectroscopy (FT-IR):

The FT-IR was used to assess the chemical composition and identify functional groups present in the propylparaben, The Physical mixture of propylparaben and ethyl cellulose and microsponge formulation propyl paraben were recorded using a FTIR Alpha, Bluker Spectrometer. The samples were first ground into a fine powder and mixed with potassium bromide (KBr) to form a thin pellet. The FTIR spectra were recorded in the range of 4000 to 400 cm^{-1}. By analyzing the absorption bands in the FTIR spectra, the presence of specific functional groups in the polymers, preservatives, or other components used in the formulation was confirmed. This technique helped in verifying the chemical integrity of the sample and in identifying any interactions between the components during the preparation process (Kumar *et al*., 2011, Nandal *et al*., 2022).

6. Differential Scanning Calorimetry (DSC):

The DSC was used to study the thermal properties of Propylparaben, ethyl cellulose, and propyl paraben-loaded microsponges (F7) as shown in Fig The thermal behavior of the samples was analyzed by heating a small sample of the microsponges in a controlled atmosphere, typically from 0°C to 400°C, at a constant heating rate (e.g., 10°C/min). The DSC instrument measures the heat flow into or out of the sample as it undergoes phase transitions, such as melting, crystallization, or glass transition. The DSC thermograms provided information about the thermal stability, melting points, and crystallinity of the microsponges, as well as the presence of any interactions between the polymer matrix and active ingredients. Changes in the thermal properties compared to the raw materials were indicative of possible interactions or modifications during the microsponges preparation (Li *et al*., 2013).

7. In-vitro drug release studies:

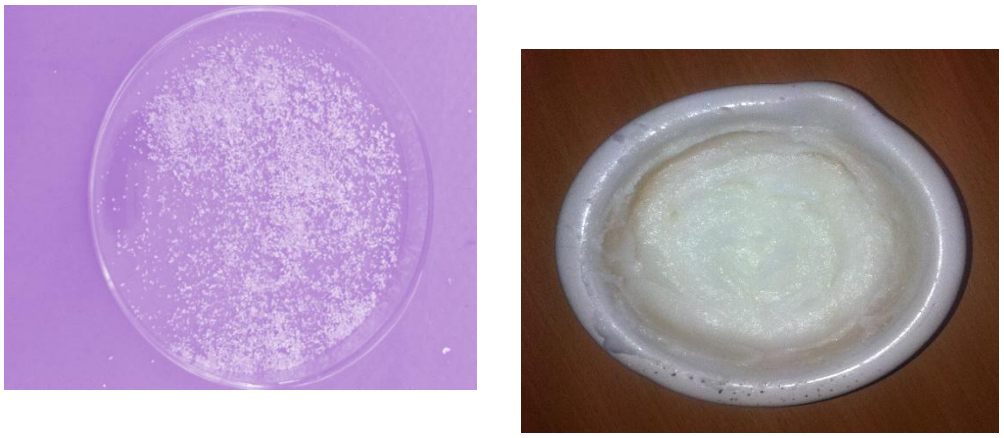
In vitro release studies of propyl paraben were conducted to evaluate the release profile of the active ingredient from the prepared microsponges. The release of propyl paraben from microsponges was investigated in pH 7.4 phosphate buffer as a dissolution medium (900 ml) using a USP (type I) apparatus. A sample of microsponge equivalent to 40 mg of propyl paraben

was taken in the basket. A speed of 100 rpm and temperature of 37 ± 1ºC was maintained throughout the experiment. At fixed intervals, aliquots (10 ml) were withdrawn and replaced with fresh dissolution media. The concentration of the drug released at different time intervals was then determined by measuring the absorbance using a spectrophotometer at 258 nm against blank. The release profile is plotted as the cumulative percentage of drugs released versus time, which provides insights into the release kinetics. The release data can be analyzed using various models (e.g., **Zero-order, First-order, Higuchi,** or **Korsmeyer-Peppas** models) to determine the release mechanism, such as diffusion-controlled or matrix degradation-controlled release. This study helps understand the drug's sustained or controlled release behavior from the microsponges, which is critical for evaluating the formulation's potential for targeted or prolonged drug delivery (Kaity *et al*., 2010, Sahu *et al*., 2016).

Table 2: In- vitro dissolution data

TIME (Hrs.)	F4	F7
1	23.94%	27.6%
2	35.81%	34.0%
4	54.67%	52.34%
6	67.0%	69.52%
8	73.32%	75.0%
10	83.72%	87.34%

Formulation of cold cream of microsponges loaded Propylparaben: Bees wax is accurately weighed and melted in a beaker using a hot plate at 70ºC. Then add white mineral oil and continue heating the mixture until it reaches 70ºC. Dissolved the sodium borate in distilled water, which had been warmed in a second beaker to 70ºC. Microsponges equivalent to 0.04% of propyl paraben were added to the oleaginous mixture. Then aqueous mixture was added gradually to the oleaginous mixture. Stirred rapidly until the mixture had congealed. Prepared cold cream was stored in an airtight container for further study (Mohiuddin and Kader, 2016).



(a) **(b)**

Figure 1: (a) Propylparaben-loaded microsponges and (b) Propyl paraben-loaded Microsponges cold cream

4. EVALUATION OF COLD CREAM

(1) Organoleptic Characteristics: All blank formulations (i.e., those without active ingredients or preservatives) and drug-loaded formulations were assessed for physical appearance, color, texture, phase separation, and homogeneity through visual observation. To evaluate homogeneity and texture, a small amount of the formulated creams and gels was pressed between the thumb and index finger. The consistency of the formulations and the presence of coarse particles were used to assess texture and homogeneity. Additionally, the immediate skin feel, including factors such as stiffness, grittiness, and greasiness, was also evaluated (Sundar *et al*., 2020).

(2) Spreadability: The spreadability of the formulations was assessed by measuring the spreading diameter of a 1 g sample placed between two horizontal glass plates (10 cm × 20 cm) after one minute. A standard weight of 25 g was applied to the upper plate. Each formulation was tested in triplicate.

(3) pH Values: One gram of each formulation (including both the blank formulation, which contains no active ingredients or preservatives, and the drug-loaded formulation) was dispersed in 25 mL of deionized water, and the pH was measured using a pH meter (Mettler-Toledo Ingold Inc., Billerica, MA). The measurements were taken in triplicate. Before each use, the pH meter was calibrated with standard buffer solutions (pH 4, 7, and 10).

(4) Viscosity Measurement: The viscosity of the cold cream was determined using a Brookfield viscometer DV-I (Brookfield Engineering Laboratories, Middleboro, MA) with a concentric cylinder spindle #29. The measurements were conducted at 21°C, with the spindle rotating at speeds of 0, 0.5, 1, 2, 2.5, 4, 5, 10, 20, 50, and 100 rpm. All measurements were performed in triplicate.

(5) *In-vitro* drug diffusion studies: In vitro diffusion study of cream containing Propyl paraben microsponges was carried out for 10 hrs. The total amount of drug release was observed at different time intervals for a period of 10 hrs. A phosphate buffer of pH 7.4 was used as a receptor medium. The egg membrane previously soaked overnight in the dissolution medium was used in a modified Franz Diffusion Cell. The cream sample equivalent to 40mg microsponges was applied on the egg membrane and then fixed in between the donor and receptor compartment of the diffusion cell. The receptor compartment contained phosphate buffer (100 ml) of pH 7.4. The temperature of the diffusion medium was thermostatically controlled at 37ºC ± 1ºC by surrounding water in the jacket and the medium was stirred by a magnetic stirrer at 100 rpm. The sample at predetermined intervals was withdrawn and replaced by an equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 258 nm using phosphate buffer (pH 7.4) as blank (Madasamy *et al*., 2020).

(6) Antimicrobial: preservative testing is used to demonstrate the effectiveness of the preservative system in a product. Two types of microorganisms used were Staphylococcus aureus and Pseudomonas aeruginosa Method The agar well diffusion method is used for preservative testing. This method is used to determine the drug susceptibility of microbes. This method allowed the rapid determination of the efficiency of the drug by measuring the diameter of the Zone of inhibition that results from the diffusion of the agents into the well made on an agar media plate. Media used was Nutrient Agar media is used for the growth of micro-organisms. Nutrient agar media was prepared (rani et al., 2024).

Procedure: The study utilized slants of micro-organisms (Staphylococcus aureus and Pseudomonas aeruginosa) obtained from the Microbiology Lab at M.D. University, Rohtak. Nutrient agar media was prepared and used to make NA plates. The broth of micro-organism strains was then spread on each plate under sterile conditions. Three wells were bored on each agar media plate using a sterile cork borer. The wells were filled with different substances: microsponges loaded with propylparaben (Batch 7) in the first well, plane cold cream in the second well, and cold cream with microsponges loaded with propyl paraben in the third well. The plates were incubated at 37°C for 24 hours. After incubation, the diameter of the zone of inhibition was measured to assess the preservative efficacy of the substances Verma *et al*., 2016).

5. RESULT AND DISCUSSION

Particle size, percentage yield, and encapsulation efficiency of batches of microsponges are shown in Table no, and figure no shows their respective representation in graphical form. Results of compatibility studies show that no interactions were found between drug and excipients which was confirmed by FTIR and DSC studies.

FTIR: The FTIR spectrum of propyl paraben displays distinct peaks (Fig 2) that correspond to the phenolic hydroxyl group, ester functional group, aromatic ring vibrations, and the propyl side chain. These peaks serve to confirm the chemical structure and purity of propylparaben, as well as to identify any possible interactions with other excipients in formulations. In summary, the FTIR spectrum of propyl paraben typically shows a broad O-H stretch in the higher wavenumber range, a sharp C-H stretch around 2,900 cm^{-1}, a prominent C=O stretch near 1,650 cm^{-1}, and characteristic peaks for the aromatic ring and ester groups.

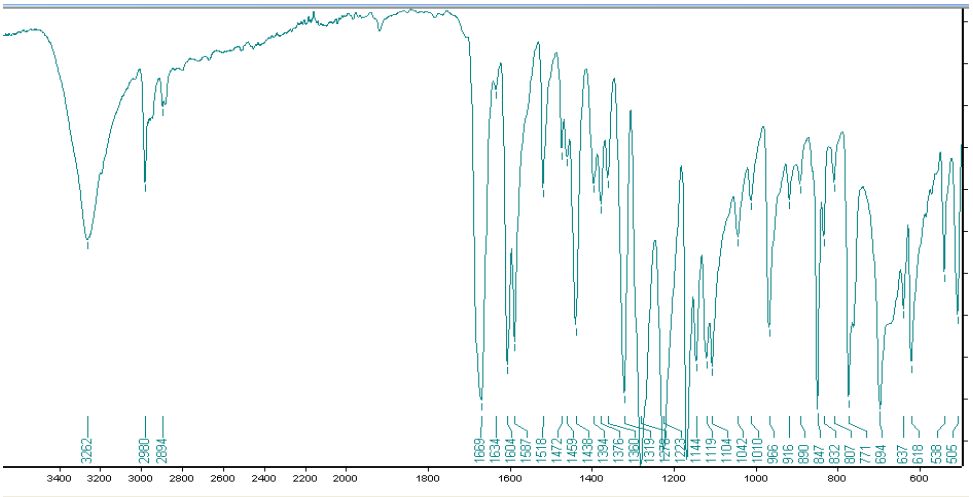


Fig: 2 (a) FTIR of Propyl paraben

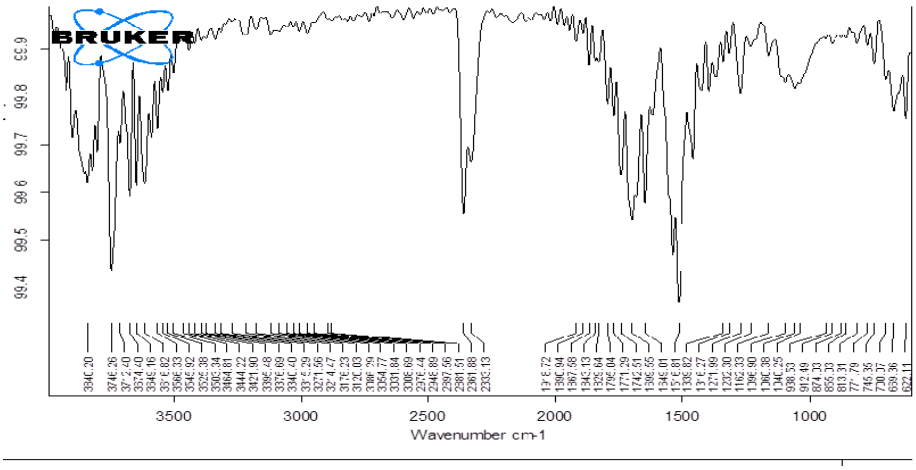


Fig: 2 (b) FTIR of physical mixture of drug & polymer

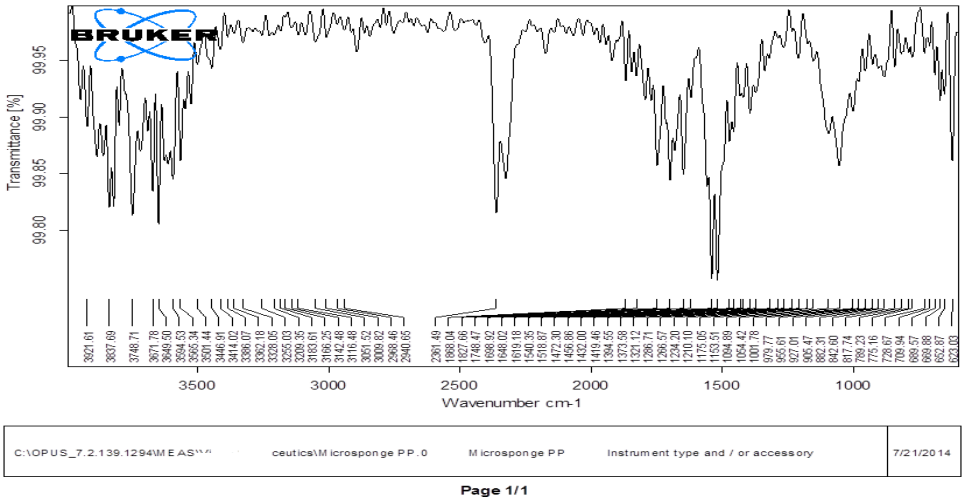


Fig 2 (c): FTIR of propyl paraben loaded microsponge (batch no.7)

DSC: The DSC analysis of ethyl cellulose showed in fig 3(a) reveals important thermal properties, including a glass transition temperature (Tg) typically ranging from 150–170°C, which marks the transition from a rigid, glassy state to a more flexible, rubbery state. As an amorphous polymer, ethyl cellulose does not have a distinct melting point, but an endothermic peak between 200–250°C may appear, indicating dehydration or thermal degradation. In case of propyl paraben showed in fig 3(b) has a melting point around 98–102°C, which would appear as an endothermic peak on the DSC curve, indicating the absorption of heat as the material transitions from solid to liquid. At higher temperatures, above 200°C, propyl paraben may decompose, showing an exothermic or endothermic peak due to thermal degradation. The fig 3(c) showed the propylparaben-loaded microsponges of batch 7 revealed the melting point of pure propylparaben around 98–102°C may be altered due to its encapsulation within the microsponges. If the drug is molecularly dispersed or amorphous, the characteristic melting peak of propylparaben could be diminished or absent. This analysis also provides insights into the polymer's thermal stability, showing gradual degradation at elevated temperatures, which is crucial for understanding its behavior in pharmaceutical and cosmetic applications.

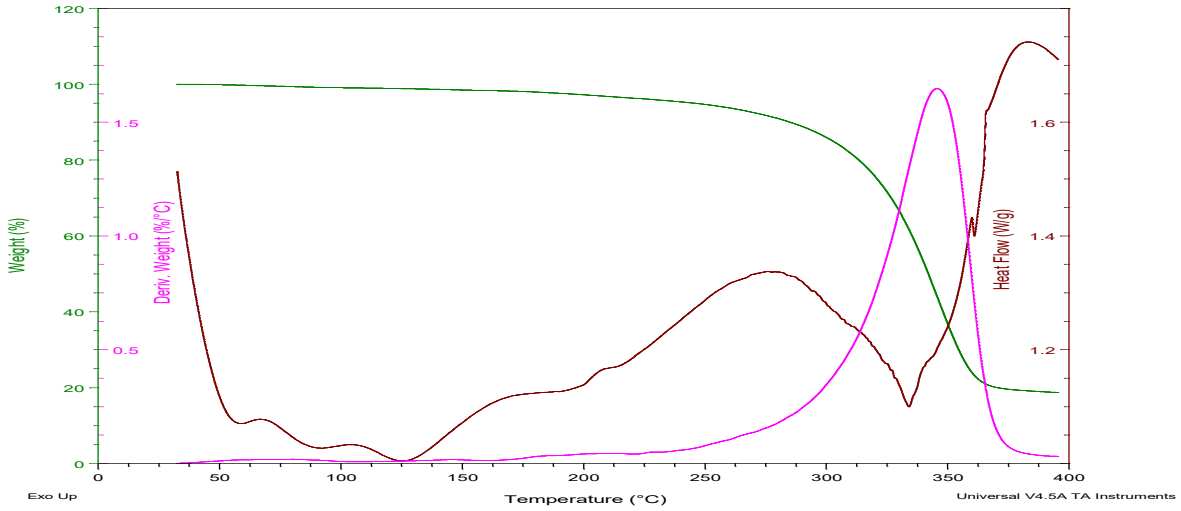


Fig 3 (a): DSC of Ethyl Cellulose

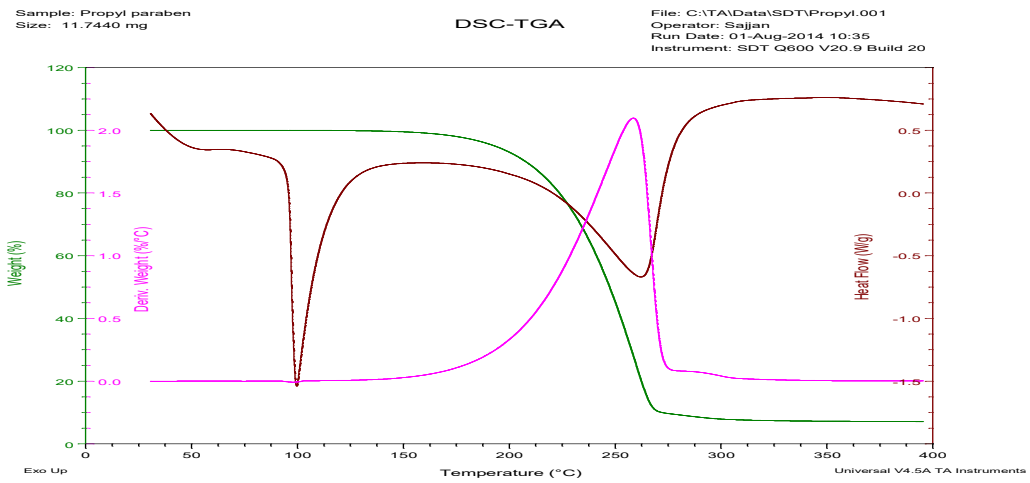


Fig 3 (b): DSC of Propyl Paraben

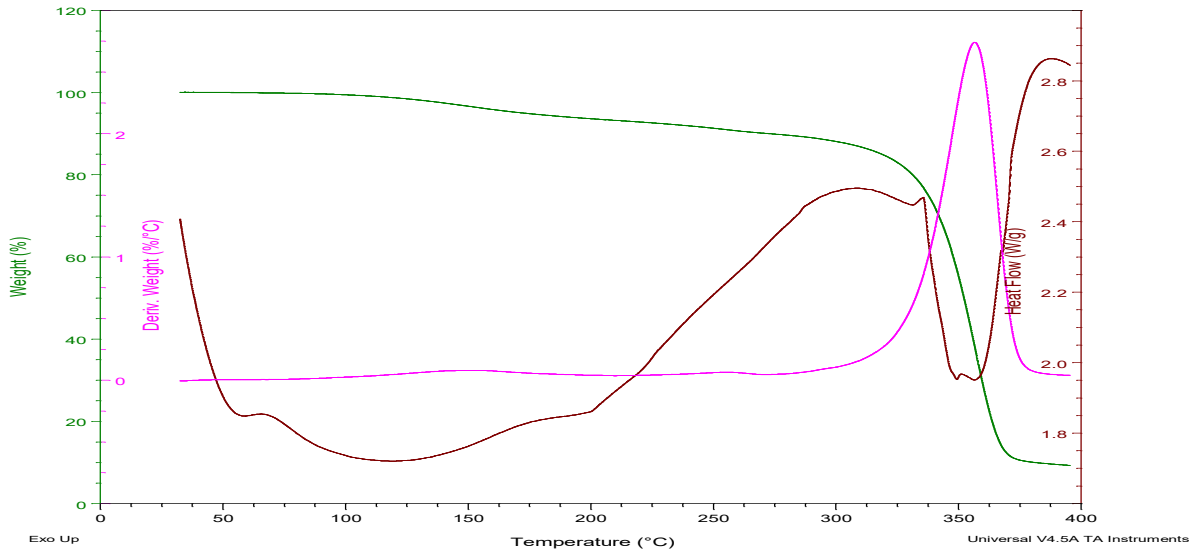


Fig 3 (c): DSC of Propylparaben loaded microsponges

SEM: SEM analysis of propyl paraben-loaded microsponges helps confirm the successful encapsulation of the drug, as well as the uniformity, porosity, and integrity of the microsponges in fig 4. These characteristics are critical for ensuring effective drug delivery and controlled release in various pharmaceutical and cosmetic applications (Kumar et al., 2025).

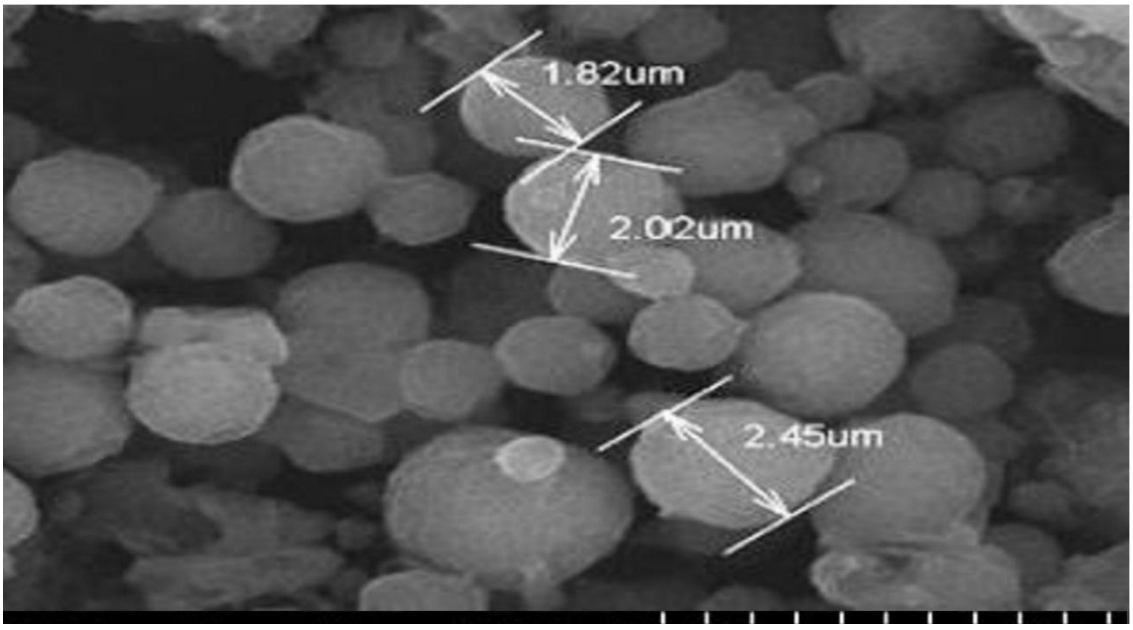


Fig 4: SEM of Miicrosponges

***In vitro* drug release:** In vitro release studies (fig 5 and 6) of propyl paraben-loaded micro sponges help demonstrate their **effectiveness** in controlled drug delivery, providing insights into the release kinetics, the efficiency of encapsulation, and the suitability of the microsponges for specific therapeutic applications.

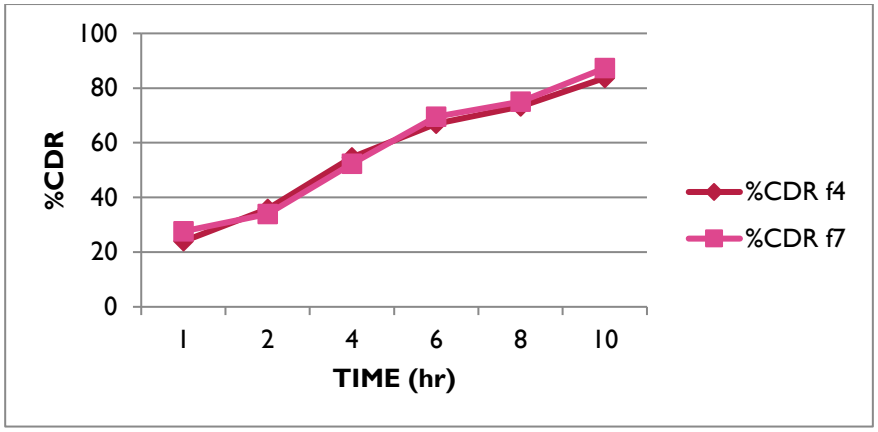


Fig 5: Cumulative Drug release plot for f4 & f7 batches of microsponges

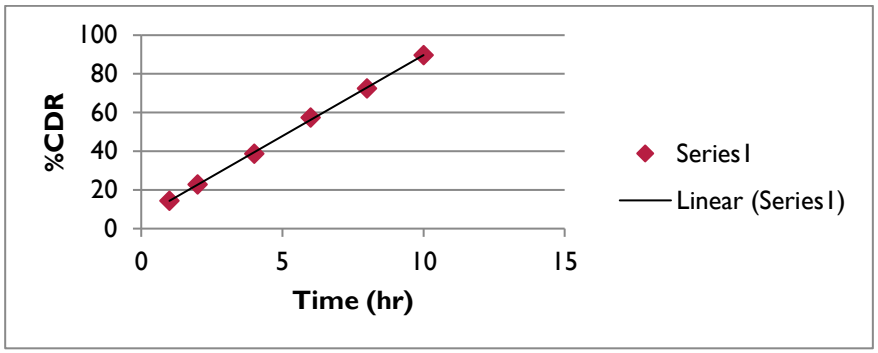


Fig 6: Drug Release profile of Propylparaben loaded Micosponge cold cream

6. CONCLUSION

Microsponges containing Propyl paraben were prepared by quasi-emulsion solvent diffusion method using ethyl cellulose and PVA. By considering the solubility study of the drug and polymer and the rate of diffusion of the solvent used, ethanol was used for the internal phase and distilled water was used for the external phase. A mixture of Ethyl cellulose and drug in ethyl alcohol served as an internal phase. The solution of PVA in water served as an external phase. The Microsponge drug delivery technology is widely applicable to dermatological drug delivery products. The microsponge drug delivery technology of a controlled release system in which active pharmaceutical ingredients are loaded in the microporous beads can initiate a reduction in side effects with improved therapeutic efficacy. The microsponge drug delivery system had properties like improved stability and increased flexibility in formulation. The result we got after performing various studies revealed that microsponge formulation loaded propylparaben is an effective drug delivery system with prolonged action.

Conflicts of Interest

The authors showed no conflicts of interest.

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