World Journal of Pharmaceutical and Life Sciences

www.wjpls.org

Impact Factor: 7.409 Coden USA: WJPLA7

FORMULATION AND EVALUATION OF MICROSPHERE CONTAINING COMBINATION OF ANTI-PIGMENTATION DRUGS CREAM FORMULATION AND ITS ANTI-MICROBIAL ACTIVITY

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DOI: https://doi.org/10.5281/zenodo.17748022

How to cite this Article: Amandeep Singh*, Pinky Singh, Hemant Agarwal. (2025). Formulation And Evaluation Of Microsphere Containing Combination Of Anti-Pigmentation Drugs Cream Formulation And Its Anti-Microbial Activity. World Journal of Pharmaceutical and Life Science, 11(12), 18–25.
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Article Received on 20/10/2025 **Article Revised on 10/11/2025** **Article Published on 01/12/2025**

ABSTRACT

The present study focuses on the formulation and evaluation of a microsphere-based cream containing mometasone furoate and hydroquinone for topical application. Mometasone furoate appeared as an odorless off-white solid powder, while hydroquinone was identified as a white, odorless crystalline powder. Solubility studies indicated that both drugs dissolved readily in ethanol, dimethyl sulfoxide, and methanol. The pH of mometasone furoate and hydroquinone was found to be 4.4 and 3.8, respectively, with melting points of 173°C and 221°C. UV spectrophotometric analysis revealed λmax values of 250 nm for mometasone furoate and 293 nm for hydroquinone, within specification limits. Microspheres were prepared and characterized by particle size, zeta potential, drug entrapment efficiency, and morphology. The average particle size ranged between 150.4 and 217.8 nm, with zeta potential values of 0.3–9.1 mV, indicating good stability. Drug entrapment efficiency ranged from 77.03% to 95.86%, with the F1 formulation showing the highest entrapment. Scanning electron microscopy confirmed spherical microspheres with smooth surface morphology. The optimized microspheres were incorporated into a cream base, which demonstrated favorable physicochemical properties including viscosity (4823±0.31 cps), spreadability (12.70 g·cm/s), and skin-compatible pH (6.6). Antimicrobial testing showed significant inhibition of bacterial growth, confirming the formulation's effectiveness against microbial skin conditions. Overall, the developed microsphere-based cream improved the solubility, stability, and skin penetration of mometasone furoate and hydroquinone while demonstrating notable antimicrobial activity. These findings suggest that the formulation holds strong potential as an effective and patient-compliant topical treatment for inflammatory and microbial-associated skin disorders.

KEYWORDS: Mometasone furoate, Hydroquinone, Microspheres, Topical cream, Antimicrobial activity, Skin disorders.

1. INTRODUCTION

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered **(Gao *et al.*, 2023).** Hence, the combination of both sustained release and control release properties in a delivery system would further enhance therapeutic efficacy. Drug delivery is the technique of administering the drug or pharmaceutical product, in order to obtain desired therapeutic impact. Novel drug delivery system (NDDS) includes combining polymer science, pharmaceutics and molecular biology. Novel drug delivery systems can consist of those

primarily based totally on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms additionally referred as managed drug delivery systems consist of osmosis, diffusion, erosion, dissolution and electro transport **(Stockwell *et al.*, 2014).**

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature **(Gavali *et al.*, 2019).** Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug disperse or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products **(Lengyel *et al.*, 2019).**

Skin disorders such as hyperpigmentation, melasma, and inflammatory dermatoses present significant therapeutic challenges and often require combination therapy to achieve effective management. Hydroquinone, one of the most widely used depigmenting agents, acts by inhibiting tyrosinase, the key enzyme involved in melanin synthesis. This reduces excess pigmentation, making it highly effective in conditions like melasma and post-inflammatory hyperpigmentation. However, hydroquinone is associated with stability concerns, limited penetration, and potential irritation when used alone **(Draelos *et al.*, 2020).**

Mometasone furoate, a potent topical corticosteroid, is frequently prescribed for its strong anti-inflammatory, antipruritic, and vasoconstrictive properties. It helps reduce erythema, swelling, and itching associated with inflammatory skin conditions. When combined with hydroquinone, mometasone furoate not only improves therapeutic outcomes but also reduces skin irritation caused by hydroquinone, thereby enhancing patient compliance **(Spada *et al.*, 2018).**

The present study focuses on the formulation and evaluation of microsphere-loaded cream containing mometasone furoate and hydroquinone, with particular emphasis on physicochemical properties, antimicrobial activity, and skin applicability.

2. MATERIAL AND METHODS

2.1 Chemicals

Conc. HCl, Conc. H_2SO_4, Nitroprusside, and Petroleum ether were obtained from Merck, a reputable supplier of analytical reagents. *Sigma*-Aldrich provided the Mometasone Furoate, and Krishna Chem Industry provided the Hydroquinone. Loba chem provided the Propylene glycol, Methyl paraben and Triethanolamine. Carboxymethyl cellulose were obtained from Narang chemical while Glacial Acetic Acid supplied by Researchlab. All other solvents, Chemicals and reagents used were of analytical (AR) grade and purchased from Fizmerck**,** Molychem, Clorofiltind, Himedia and Rankem.

2.2 Pre-formulation study of Mometasone furoate and Hydroquinone

Pre-formulation study focuses on those physiochemical properties of the new drug performance and development of an efficacious dosage form. The pre-formulation investigation confirms that there are no significant barriers to the compounds development **(Ahirwar and Shukla 2023).**

2.2.1 Organoleptic evaluation

Organoleptic properties of Mometasone furoate and Hydroquinone were observed by visual observation. The organoleptic studies of Mometasone furoate and Hydroquinone general appearance like color, odor, state, etc. were observed/ performed (**Smitha, 2006).**

2.2.2 Solubility study

The solubility study of a drug involves assessing its ability to dissolve in a specific solvent under defined conditions, such as temperature, pH, and agitation. Solubility is a critical parameter in drug development as it directly influences the drug's bioavailability, absorption, and therapeutic efficacy **(Avdeef *et al.*, 2016).**

2.2.3 Melting point

To determine the melting point of Mometasone furoate and Hydroquinone using a melting point apparatus **(Pal *et al.*, 2021).**

2.2.4 Determination of pH

Determine the pH of Mometasone furoate and Hydroquinone drug using a digital pH meter **(Thakur *et al.*, 2012).**

2.2.5 Determination of Maximum Wavelength (λ max)

2.2.5.1 Preparation of Mometasone furoate and Hydroquinone standard stock solution in methanol

Standard solution of Mometasone furoate and Hydroquinone was prepared by dissolving accurately weighed 10 mg of Mometasone furoate with 5 ml of methanol solvent, in a 10 ml volumetric flask. The volume was made up to 10 ml with methanol to obtain a stock solution of 1000 µg/ml. 1ml of this stock solution was taken and then diluted up to 10 ml using respective solvent (methanol) to obtain a solution that has a concentration 100 µg/ml which is standard stock solution **(Kumbhar and Salunkhe 2016).**

2.2.5.2 Lambda max

Stock solution 2 ml of Mometasone furoate and Hydroquinone was transferred into a 10 ml volumetric flask and the volume was made up to mark with methanol to prepare a concentration of 20 µg/ml. The working standard solution of the drug was scanned in the UV range

of 200 to 400 nm in normal mode, using distilled water as blank. Then obtained peaks were noted and the absorption maxima were determined **(Sheliya *et al.*, 2014).**

2.2.5.3 Linearity and Calibration Curve

From the working standard solution of 100 µg/mL, dilutions were made in the range of 10, 15, 20, 25, 30, 35, and 40 µg/mL. After precisely transferring the Mometasone furoate and Hydroquinone working standard stock solution into a series of 5 mL calibrated flasks, the volume was adjusted with methanol. At Mometasone furoate and Hydroquinone 247.00 nm, the absorbance of the resultant solutions was measured in comparison to a blank of methanol. A calibration curve was created by graphing the drug's absorbance against concentration. A seven-point calibration curve was produced for Mometasone furoate and Hydroquinone concentrations ranging from 10 to 40 µg/ml **(Patidar and Ramteke 2024).**

2.3 Formulation of microspheres by Solvent Evaporation method

Microspheres containing Mometasone furoate and Hydroquinone as a core material were prepared by Solvent Evaporation method. Mometasone furoate and Hydroquinone HPMC and EC were dissolved in a mixture of ethanol and dichloromethane (1:1) at room temperature (As in table 6). This was poured into 250 mL water containing 0.01% Tween-80 maintained at a temperature of 30–40 °C and subsequently stirred at 300 rpm agitation speed for 45 minutes to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried in oven at 37°C **(Fartyal *et al.*, 2011).**

Table 1: Composition of microsphere formulation.

Formulations (Code)	Polymer HPMC (mg)	Polymer Ethyl cellulose (mg)	Hydroquinone and Mometasone Furoate (mg)	Temp °C	Solvent ratio (1:1) ethanol/DCM
MSF1	300	50	400: 100	30-40°C	5ml:5ml
MSF2	250	100	400: 100	30-40°C	5ml:5ml
MSF3	200	150	400: 100	30-40°C	5ml:5ml
MSF4	150	200	400: 100	30-40°C	5ml:5ml
MSF5	100	250	400: 100	30-40°C	5ml:5ml

2.4 Evaluation parameter of drug loaded Microspheres formulation

2.4.1 Physical properties

The physical properties of the material, including its color, odor, appearance, and homogeneity, were carefully evaluated to ensure suitability for its intended application.

2.4.2 Entrapment Efficiency (EE)

Per cent entrapment efficiency (% EE) was estimated by collecting the filtrate from the dispersion after REMI Ultra Centrifuge was used to centrifuge drug-loaded microsphere for 30 minutes. The supernatant was collected, filtered and analysed by UV at 247 nm to determine the Mometasone furoate and Hydroquinone concentrations. The % EE of Mometasone furoate loaded NS were calculated by using following equations **(Khattab and Nattouf 2021).**

$$\%EE = \frac{(\text{Initial amount of drug added - Drug amount in supernatant}) \times 100}{\text{Initial amount of drug added}}$$

2.4.3 Determination of Particle size

The particle size determination of drug-loaded microspheres using a Malvern Zetasizer (Malvern Instruments) is a precise analytical method based on dynamic light scattering (DLS). **(Jabar et al., 2021)**

2.4.4 Zeta potential

The microsphere was diluted ten times with distilled water for the current study, and Zetasizer Malvern devices were used for analysis **(Volić *et al.*, 2022).**

2.4.5 SEM analysis

Scanning electron microscopy (SEM) was used to assess the exterior properties of the prepared microspheres. The microspheres were spread out on a double-sided adhesive tape that was adhered to a metal slab and put under a scanning electron microscope to show the microspheres' spongy structure. Following that, photomicrographs were obtained and the samples of produced microspheres were scanned at an acceleration voltage of 15.00 kV (**Dora *et al.*, 2016).**

2.5 Preparation of Microspheres Cream Formulations

Preparation of Herbal Face Cream- Heat liquid paraffin and beeswax in a china dish at 75^0 C and maintain that heating temperature (Oil phase). In another china dish dissolve borax, methyl paraben in distilled water and heat this beaker to 75^0 C to dissolve borax and methyl paraben and to get a clear solution (Aqueous phase). Then slowly add this aqueous phase to the oily phase in a mortar and pestle and stir in a single direction to avoid lumps. Then add the microsphere formulation to the cream base and mix it. Add few drops of Lavender oil as a fragrance to impart the aroma and mix all the ingredients properly **(Badwaik et al., 2022).**

Table 2: Composition of cream formulation.

Ingredients	Quantity	Use
Microsphere	1.0 gm	Pigmentation and Scar healing
Bees wax	3.0ml	Emulsifier, thickener
Liquid Paraffin	4.0 gm	Moisturizing agent, Skin softener
Methyl Paraben	20 ml	Anti- bacterial agent, preservative
Essential oil	0.05 gm	Fragrance, Glowing Skin
Borax	0.4gm	Buffering agent, Preservative

2.6 Evaluation parameter of microspheres cream formulation

2.6.1 Physical properties of creams

This includes checking the appearance and color for uniformity, measuring the pH to ensure compatibility with skin, and assessing the texture and consistency using instruments like viscometers **(Al-Smadi *et al.*, 2025).**

2.6.2 Determination of the pH

The formulated cream was subjected to pH measurement using a digital pH meter **(Priya Pa *et al.*, 2025).**

2.6.3 Viscosity Determination

The rheological characteristics of the prepared Mometasone furoate and Hydroquinone microspheres embedded cream were measured at 37°C ± 2°C 27 at a speed of 100 rpm using a Brookfield viscometer DV- III Programmable with spindle no. S- 6 **(Dipakkumar, 2012).**

2.6.4 Determination of Spreadibility

Using the horizontal slide method, the spread ability of the prepared Mometasone furoate and Hydroquinone microspheres cream was ascertained and quantified in terms of time in seconds. A glass slide that was adhered to a wooden surface was covered with 1 gram of cream. The cream was sandwiched between two slides by placing a second slide of the same dimensions on top of the fixed slide. For five minutes, a 125 g weight was placed over the upper slide in order to remove extra cream and provide a consistent layer of cream between the slides. After that, spread ability was determined using equation 04 and noted in Table (**Baibhav *et al.*, 2012).**

2.6.5 Test for skin irritancy

The 0.5 g prepared microsphere cream was applied to the skin for four hours, during which time the skin was checked for signs of erythema and oedema. The reactions were then recorded at four, eight, and twelve hours showed in table (**Bothiraja *et al.*, 2014).**

2.6.6 *In vitro* antimicrobial activity

- **Culture collection**

The microbial strains were obtained from Pinnacle Biomedical Research Institute, Bhopal. The pure cultures were preserving on nutrient agar for growth. Cultures were stored at 4°C in refrigerator for further use**.**

- **Preparation of microspheres cream dilutions**

Weigh out 2mg, 4mg, and 8mg of the microspheres gel separately. Transfer each weighed amount into three separate clean and dry test tubes. To each test tube, add 1mL of double-distilled water. Mix thoroughly until the microspheres cream was completely dispersed or dissolved in the water. If necessary, use gentle agitation, such as stirring or vortex, to ensure uniform dispersion of the microspheres cream in the solution. Label each test tube appropriately based on the respective concentration for subsequent use.

- **Agar well diffusion method**

Preparation of media

The Agar well diffusion method is used to evaluate the antimicrobial activity of a substance. To prepare 100 mL of nutrient agar media first 2.8 grams nutrient agar media dissolved in 100 mL of distilled water in a clean flask. Sterilize the media by autoclaving at 121°C for 15-20 minutes to eliminate any potential microbial contamination. After autoclaving, allow the nutrient agar to cool slightly (but not solidify) then poured it into sterile Petri dishes.

- **Culture inoculation and well preparation**

Lawn culture of bacteria *E. coli* was spread on the Nutrient Agar Media using spreader. Using a sterile cork borer, create four wells in the agar plate. Then, add the drug- loaded cream in a different concentration, into the wells. The plate is incubated at 37 °C temperature for 24 hours. After incubation, the zone of inhibition around each well is measured. A larger zone indicates stronger antimicrobial activity, while the absence of a zone suggests no antimicrobial effect **(Bauer 1996).**

2.6.7 *In-vitro* drug release

The dialysis bag diffusion method was used to evaluate the in-vitro drug release of microsphere cream formulations. Cream loaded with Microsphere was distributed into a dialysis bag, which was subsequently placed in a goblet containing 100 milliliters of pH 7.4 phosphate buffer. The experiment involved keeping the assembly's temperature at 37 ± 2 °C while the beaker was put over a magnetic stirrer. RPM was kept constant at 100 rpm throughout the experiment. At certain times, a small number of samples (2 ml) were removed and replaced with corresponding volumes of brand-new pH 7.4 phosphate buffers. Following appropriate dilutions, the samples were examined with UV-Visible spectrophotometer **(Rai and Ravikumar 2016).**

3. RESULTS

3.1 Organoleptic properties

Table 3: Organoleptic properties of Mometasone furoate and Hydroquinone.

Drug	Organoleptic properties	Observation of Mometasone furoate	Observation of Hydroquinone
Mometasone furoate and Hydroquinone	Color	Off- white	White
	Odor	Odorless	Odorless
	Appearance	Powder	Crystalline powder
	State	Solid powder	Solid powder

3.2 Solubility study

Table 4: Solubility study of Mometasone furoate.

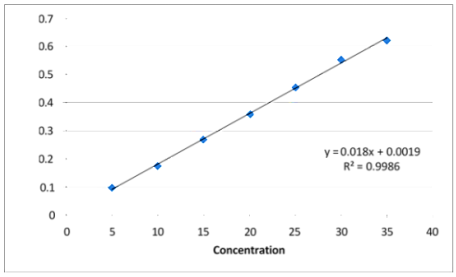
Drug	Solvents	Observation of Mometasone furoate	Observation of Hydroquinone
Mometasone furoate and Hydroquinone	Water	Insoluble	Soluble
	Ethanol	Freely soluble	Freely soluble
	Methanol	Freely soluble	Freely soluble
	Chloroform	Soluble	Soluble

3.3 PH determination

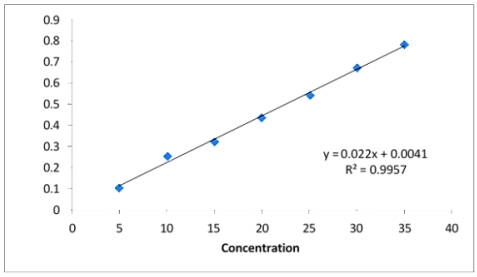
Table 5: pH of Mometasone furoate and Hydroquinone.

Drugs	Reference range (Melting points)	Observed (Melting points)	Observed (pH)	UV absorption maxima (Lambda max)	UV absorption maxima (Lambda max) of both drug
Mometasone furoate	216°C-222°C	221°C	4.4	250.0 nm	278.0 nm
Hydroquinone	170°C-175°C	173°C	3.8	293.0 nm	

3.5 Calibration curve of Mometasone furoate and Hydroquinone



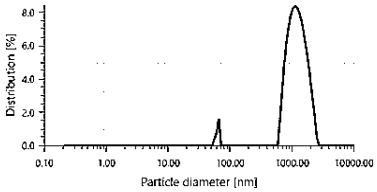
Graph 4:- Calibration curve of Mometasone furoate.



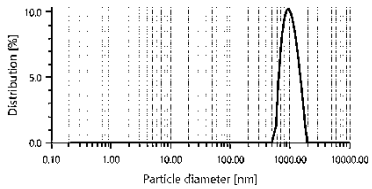
Graph 5:- Calibration curve of Hydroquinone.

3.6 Evaluation parameter of microsphere formulations

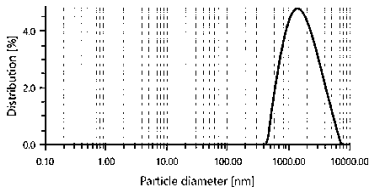
3.6.1 Particle size



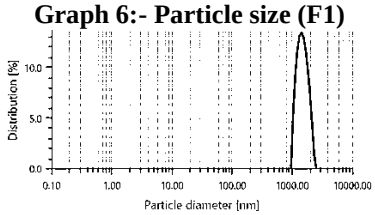
Graph 6:- Particle size (F1)



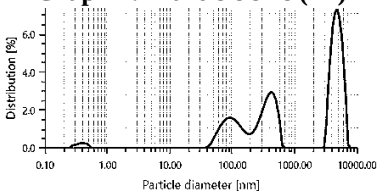
Graph 7:- Particle size (F2)



Graph 8:- Particle size (F3)



Graph 9:- Particle size (F4)

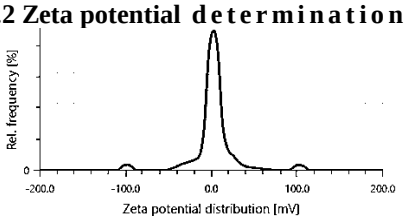


Graph 10:- Particle size (F5)

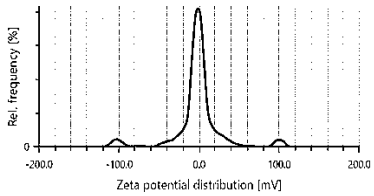
Table 6: Result of Particle size of all formulations.

Formulations	Particle size (nm)	PI Value
Microsphere (F1)	**153.4 nm**	**0.226**
Microsphere (F2)	179.5 nm	0.395
Microsphere (F3)	220.8 nm	0.446
Microsphere (F4)	154.5nm	0.318
Microsphere (F5)	154.5nm	0.213

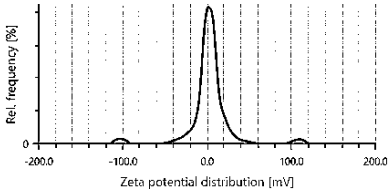
3.6.2 Zeta potential determination



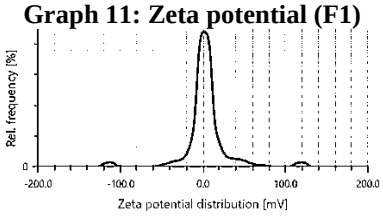
Graph 11: Zeta potential (F1)



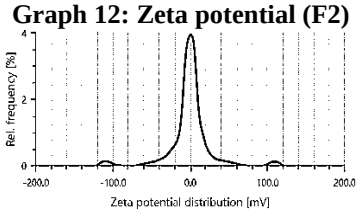
Graph 12: Zeta potential (F2)



Graph 13: Zeta potential (F3)



Graph 14: Zeta potential (F4)



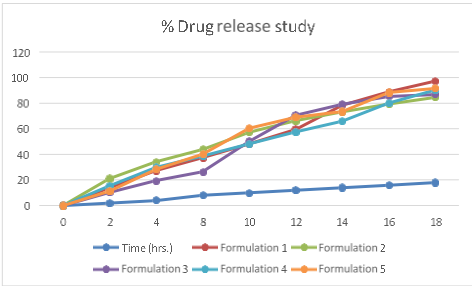
Graph 15: Zeta potential (F5)

Table 7: Result of Zeta potential and Entrapment efficacy of all form.

Formulation	Entrapment efficacy (%)	Zeta potential
Microsphere (F1)	**95.86**	0.3 mV
Microsphere (F2)	77.03	1.7 mV
Microsphere (F3)	78.32	1.9 mV
Microsphere (F4)	85.80	9.1 mV
Microsphere (F5)	87.20	8.3 mV

Table 8: Cumulative % drug released.

Cumulative % Drug Released					
Time (hrs.)	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5
0	0	0	0	0	0
2	13.86	21.08	10.36	15.33	11.20
4	27.36	34.26	19.56	29.78	28.46
8	37.46	43.86	26.33	38.66	40.30
10	48.33	57.23	50.33	48.21	60.53
12	59.62	66.35	70.63	57.63	69.22
14	78.50	73.22	79.23	66.01	73.51
16	88.85	79.32	85.36	80.05	88.36
18	95.36	84.6	86.77	90.30	91.63



Graph 16: Release study of all formulation (F1 to F5).

3.6.3 Scanning electron microscopy characterization of F1 formulation

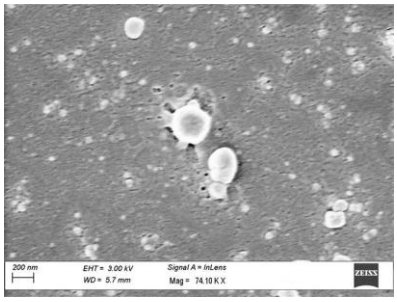


Figure 1: SEM.

3.7 Characterization of microsphere loaded Cream

3.7.1 Physical appearance

Table 9: Physical appearance.

Parameter	Result
Colour	Yellowish colour
Odour	Odourless
Appearance	Yellowish colour
Homogeneity	Homogeneous

3.7.2 Viscosity, pH, Spredability and Skin irritation study of Cream formulation

Table 10: Viscosity, pH, Spredability and Skin irritation study.

Formulation	Viscosity (cps)	pH	Spreadability (g.cm/s)	Skin Irritation
Cream	4823±0.31	6.6	12.70	Not Irritation observed

3.8 Results of antimicrobial activity of microsphere cream formulation

3.8.1 Antimicrobial activity of Formulation against *E.coli.*

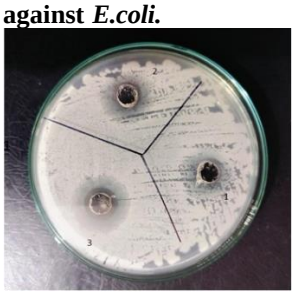


Figure 2: Antimicrobial activity.

Table 11: Antimicrobial activity of Formulation, against *E.coli.*

Sample Name	Zone of Inhibition (mm)
Microsphere Cream (0.5mg/ml)	7 mm
Microsphere Cream (1mg/ml)	10 mm
Microsphere Cream (2mg/ml)	14mm

4. CONCLUSION

The present study successfully developed a polymer-based microsphere cream formulation containing mometasone furoate and hydroquinone. Both drugs were confirmed to meet the required physicochemical specifications, including pH, melting point, and absorption maxima. The cream base was optimized to provide stability, spreadability, and skin-friendly pH, ensuring ease of application and minimizing irritation. The microsphere system improved the solubility, stability, and skin penetration of the drugs while also exhibiting notable antimicrobial activity. These findings highlight the potential of polymer-based microspheres as a promising approach for the topical delivery of mometasone furoate and hydroquinone, offering enhanced therapeutic efficacy, reduced side effects, and improved patient compliance in the management of skin and microbial-related disorders.

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