FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF MICROSPONGE DRUG DELIVERY SYSTEM

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ABSTRACT

Microsponge Drug Delivery Systems (MDS) have emerged as a promising strategy for controlled and targeted drug delivery, offering improved drug stability, reduced dosing frequency, and enhanced patient compliance. The present study focuses on the formulation, optimization, and characterization of Econazole Nitrate-loaded microsponges using Eudragit RS-100 and Ethyl Cellulose as polymers through the quasi-emulsion solvent diffusion method. A series of formulations (F1–F9) were developed by varying drug-to-polymer ratios and stabilizer concentrations to assess their influence on microsponge properties. Among them, batch F2 demonstrated superior performance with the highest drug entrapment efficiency (80.58%), production yield (82.75%), and sustained drug release profile (up to 84.17% over 8 hours). These microsponges were spherical, porous, and uniformly sized (600–700 nm), as confirmed through Motic microscopy and particle size analysis. The optimized formulation was incorporated into a gel using Carbopol 934 and evaluated for pH, viscosity, spreadability, drug content, and in-vitro diffusion studies. The microsponge gel exhibited favorable physicochemical properties and demonstrated a controlled drug release profile over 10 hours, achieving 93.53% release. Kinetic modeling revealed that the drug release followed Zero-order and Higuchi models, indicating a diffusion-controlled mechanism. Stability studies conducted over one month showed minimal changes in drug content and formulation characteristics, confirming the formulation's robustness. Thus, the developed microsponge-based topical gel of Econazole Nitrate presents a promising alternative to conventional formulations for effective antifungal therapy with enhanced therapeutic efficacy and patient compliance.

KEYWORDS: Microsponge, Econazole Nitrate, Controlled Drug Release, Quasi-emulsion Solvent Diffusion, Eudragit RS-100, Topical Gel, Drug Entrapment Efficiency, Antifungal Therapy.

INTRODUCTION

In recent years, there has been a paradigm shift in pharmaceutical sciences from conventional dosage forms to novel drug delivery systems (NDDS) aimed at improving therapeutic efficacy, minimizing side effects, and achieving controlled or targeted drug release. Among these NDDS, microsponge drug delivery systems (MDS) have garnered significant attention due to their unique architecture and versatility. Microsponges are highly porous, polymeric microspheres ranging in size from 5 to 300 μm that can encapsulate a wide range of pharmaceutical agents, enabling sustained drug release, enhanced drug stability, and reduced dosing frequency [1,2].The concept of microsponge technology was originally developed to address the limitations associated with conventional topical formulations, such as greasiness, uncontrolled release, and drug degradation. However, over time, its applications have expanded to include oral, ophthalmic, and transdermal delivery routes [3]. Microsponges function as reservoirs that release the drug at a predetermined rate, making them suitable for both systemic and localized therapies. The porous structure allows not only high drug loading but also facilitates diffusion-controlled release, which is beneficial for drugs with short half-lives or narrow therapeutic indices [4].

Formulation of microsponges typically involves techniques such as quasi-emulsion solvent diffusion, liquid–liquid suspension polymerization, and emulsion solvent evaporation. The choice of polymer—commonly ethylcellulose, polymethyl methacrylate, or Eudragit variants—plays a pivotal role in determining the characteristics of the resulting microsponge, including porosity, surface morphology, drug entrapment efficiency, and release kinetics [5]. Furthermore, drug–polymer compatibility and formulation stability are assessed through sophisticated characterization techniques such as Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and in-vitro drug release studies [6,7].

The development of curcumin-loaded Eudragit microsponges, for instance, demonstrated enhanced anti-inflammatory activity and sustained release in colonic therapy, exemplifying the potential of this system for site-specific drug delivery [1]. Similarly, formulations incorporating methotrexate or clobetasol have shown improved therapeutic performance in treating dermatological and cancer conditions when delivered via microsponges [2,8]. Furthermore, the incorporation of design of experiment (DoE) methodologies such as Box–Behnken and central composite designs has enabled researchers to optimize formulation variables efficiently and understand their influence on critical quality attributes [9,10].

As the field progresses, microsponge systems are being integrated into hydrogels, gels, and even nanocomposites to address specific therapeutic goals such as enhancing bioavailability, providing a controlled release mechanism, and minimizing systemic exposure [11]. The future of microsponge technology lies in its adaptability across diverse drug classes and routes of administration, further enhanced by advances in nanotechnology and material sciences. The present study focuses on the formulation, development, and physicochemical characterization of microsponge-based drug delivery systems, aiming to investigate the formulation parameters that influence drug release, stability, and therapeutic efficacy.

2. MATERIAL AND METHODS

2.1. Materials

Econazole Nitrate was selected as the active pharmaceutical ingredient. Eudragit RS100, Ethyl Cellulose, and Carbopol 934 were employed as polymers and gelling agents. Other excipients included Polyvinyl Alcohol (PVA), Propylene Glycol (PG), and solvents such as ethanol and distilled water. All reagents and chemicals used were of analytical grade. FTIR studies and particle size analysis were performed at Dadasaheb Balpande College of Pharmacy, Nagpur.

Table no 1: List of Reagents and Chemicals

Sr. no	Chemicals Name	Manufacture
1.	Econazole nitrate	Dhamtec pharmaand consultant Navi Mumbai
2.	Eudragit RS-100	Ozone International, INDIA
3.	Ethyle cellulose	Ozone International, INDIA
4.	Poly Vinyl Alcohol	Unico concept new delhi
5.	Carbapol 934	Oryn health care

6.	Ethanol	Lobachem, Mumbai
7.	Dichloromethane	Purosolv navi Mumbai
8.	Triethanolamine	Arihant Hyderabad
9.	Propylene glycol	Thomas baker chemical, Mumbai
10.	Sodium benzoate	Meru Chem pvt, Mumbai

2.2. METHODOLOGY

Preparation of Microsponges

Microsponges were formulated using the quasi-emulsion solvent diffusion technique. The inner phase was prepared by dissolving the polymer (Eudragit RS100 or Ethyl Cellulose) in ethanol. Econazole Nitrate was added and dissolved under ultrasonication at 35°C. This solution was then poured into an aqueous PVA solution (outer phase) and stirred for 60 minutes to allow diffusion and formation of microsponges. The microsponges formed were collected by filtration, dried at 40°C for 12 hours, and weighed to determine production yield.

Preformulation study of drug [12].

Preformulation study is one of the important prerequisites in development of any drug delivery system. It gives the information needed to define the nature of the drug release is either dissolution or diffusion. Hence, Preformulation studies on the obtained sample of drug for identification including solubility analysis, melting point determination, FTIR study of drug. Determination of ג-max and development of calibration curve and its assay.

Description

The drug was analyzed for color ,odour ,and taste .

Solubility Analysis: [13]

Solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug. The solubility was done by adding the solute in small incremental amounts to the fixed volume of solvents, after each addition, the system was vigorously shaken and examined visually for the un-dissolved solute particles. When some amount of the solute remains un dissolved, the total amount added up to the point served as a good and rapid estimate of solubility.

Physical appearance and melting point determination[14]

The melting point determination of the obtained sample was done as it is a good first indication of the purity of the sample. Melting point of drug sample was performed by using Thieles tube method. A fine powder of Econazole nitrate was filled in a capillary tube, previously sealed at one end and the capillary tube was tied to the bottom of the thermometer. The thermometer and capillary tube were immersed in to liquid paraffin taken in the tube. Bottom of the tube was heated gently by means of burner. When the sample starts to melt the reading was recorded.

Purity of Drug

FTIR Spectroscopy:[15]

IR study was carried out to check purity of drug. It was determined by Fourier Transform Infrared spectrophotometer (FTIR-Shimadzu). The sample was scanned over wavelength region of 4000 to 400 cm-1 at resolution of 4 cm-1 by dispersing sample in KBr and compressing into disc by applying pressure of 5 tons for 5 minutes in hydraulic press. The pellet was placed in light path and the spectrum was obtained.

λmax Determination in Methanol:[16]

Accurately weighed 100 mg of the drug was dissolved in 100 ml of methanol to form stock-I (1000µg/ml). Then the aliquots of 1 ml from stock-I was withdrawn in triplicate, and added to three 10 ml volumetric flasks respectively. The volume was adjusted to 10 ml using methanol). The UV spectrum was recorded in the range of 200- 400 nm using UV spectrophotometer (Dynamica,Model:Halo DB-20) at 1 cm. slit width. The λmax was determined by scanning solutions of 100µg/ml in triplicate, against a blank .

λmax Determination in phosphate buffer pH7.4:

Accurately weighed 100 mg of the drug was dissolved in 0.5 ml of methanol then make volume using phosphate bufferpH7.4 From stock-I (1000µg/ml). Then the aliquots of 1 ml from stock-I was withdrawn in triplicate, and added to three 10 ml volumetric flasks respectively. The volume was adjusted to 10 ml using phosphate buffer pH7.4. The UV spectrumwa recorded in the range of 200-400 nm using UV spectrophotometer (Dynamica,Model:Halo DB-20) at 1 cm. slit width. The λmax was determined by scanning solutions of 100µg/ml in triplicate, against a blank .

Calibration Curve of Econazole nitrate in Methanol:[17]

Accurately weighed 100 mg was taken, transferred to a 100 ml volumetric flask and volume was made to 100 ml with methanol (stock-I). The final dilutions of stock-I were then prepared in Methanol .From the stock-I solution, aliquots of 0.7, 0.8, 0.9, 1, 1.2 were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with methanol to prepare solution in the concentration range of 70-120µg/ml. The absorbance values of these solutions were measured at 261 nm using double beam UV spectrophotometer against a blank of methanol.

Calibration Curve of Econazole nitrate in Phosphate Buffer pH 7.4:[18]

Accurately weighed 100 mg Econazole nitrate was taken, transferred to a 100 ml volumetric flask and volume was made to 100 ml with phosphate buffer pH 7.4 (stock-I). The final dilutions of stock-I were then prepared in phosphate buffer pH 7.4. From the stock-I solution, aliquots of 0.7, 0.8, 0.9, 1, 1.1, 1.2 were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with phosphate buffer pH 7.4 to prepare solution in the concentration range of 70-120µg/ml. The absorbance values of these solutions were measured at 260 nm using double beam UV spectrophotometer against a blank of phosphate buffer pH 7.4.

Drug Excipient Interaction Study: [19]

Drug-excipient interaction study was performed by FTIR and DSC studies. IR study was carried out to check purity of drug. It was determined by Fourier Transform Infrared spectrophotometer (FTIR-Shimadzu). The spectra were scanned over wavelength region of 4000 to 400 cm-1 at resolution of 4 cm-1. The procedure consisted of dispersing sample in KBr and compressing into disc by applying pressure of 5 tons for 5 min in hydraulic press. The pellet was placed in light path and the spectrum was obtained.

DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and other compounds . Thermal analysis using DSC(PerkinElmer 4000) study was carried out on drug Econazole nitrate, physical mixture of drug and Eudragit RS-100,Ethyl cellulose, and Carbopol 934. Indium was used as a standard to calibrate the DSC temperature and enthalpy scale. Accurately weighed samples were used for the DSC study. Heating was done at a rate of 10°C/min.

Formulation Development of Microsponges .

Optimization of Formulation Parameters and Process Factors [20,21]

For optimizing the preparation method, selection of stabilizer, type and volume of organic solvent and volume of aqueous phase, stirring time and stirring speeds were changed, and the characteristics of the prepared Microsponges were evaluated.

Table.No.2. Formula for Econazole Nitrate Microsponge

Sr.No.	Ingredient	Use
1	Econazole Nitrate	API
2	Eudragit RS-100	Polymer
3	Ethyle cellulose	Polymer
4	Polyvinyl alcohol	Stabilizer
5	Dichloromethane	Solvent
6	Ethanol	Solvent
7	Water	Vehicle

Batches were designed for different drug: polymer ratios and for different concentrations of polyvinyl alcohol at stirring speed of1000-1500 rpm.

Preparation of Econazole nitrate Microsponges

The microsponge containing Econazole nitrate were prepared by quasi-emulsion solvent diffusion method using Eudragit RS-100,Ethyle cellulose as polymer. The processing flow chart is presented in Fig.No.6 To prepare the inner phase, Polymer is dissolved in ethyl alcohol. Drug can be added to dichloromethane . Polymer solution and drug solution dissolved under ultrasonication at 35ºC.This solution made inner phase. The inner phase was poured into the PVA solution in water (external phase). Following 120 min stirring at 1500rpm, the mixture is filtered to separate the microsponges.The microsponges are dried in an air-heated oven at 40 ºC for 12 hrs and weighed to determine production yield (PY).

Table No.3: Composition of Econazole nitrate Microsponges

Ingredient	B1	B2	B3	B4	B5	B6	B7	B8	B9
Econazole Nitrate(mg)	100	**100**	100	100	100	100	100	100	100
Eudragit RS100(mg)	100	**200**	300	400	-	-	-	-	-
Ethyle cellulose (mg)	-	**-**	-	-	100	200	300	400	
Eudragit-RS100(mg) & Ethyle cellulose(mg)	-	**-**	-	-	-	-	-	-	200
Ethanol (ml)	5	**5**	5	5	5	5	5	5	5
Dichloromethane (ml)	5	**5**	5	5	5	5	5	5	5
PVA (mg)	50	**50**	50	50	50	50	50	50	50
Water (ml)	100	**100**	100	100	100	100	100	100	100

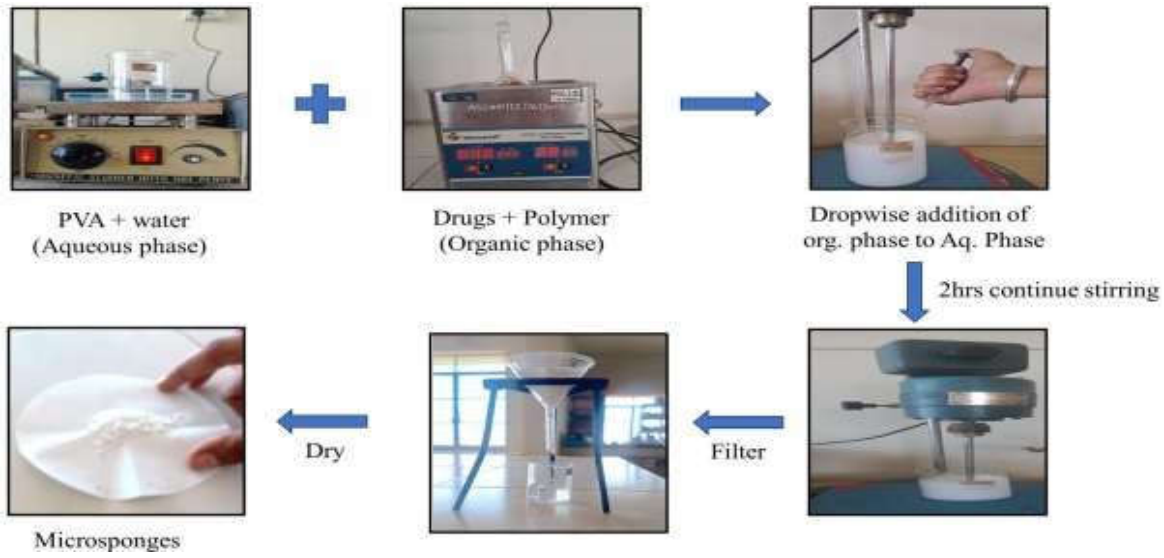

Fig.No.01.Preparation method of Microsponges

Preparation of Econazole nitrate microsponge Gel [22]

Preparation of Gel base: Accurately weighed amount of carbopol 934 was taken and dissolved in water using propeller. Microsponge formulation containing Econazole nitrate was added to the above solution with constant stirring. This final solution was neutralized slowly adding triethanolamine with constant stirring until the gel is formed . The formulation component for microsponge gel are given in TableNo.18.

Table No. 04: Composition of Gel Base

Sr.No	Ingredients	Quantity
1	Microsponge	1 % W/W
2	Carbopol 934	35 mg
3	Triethanolamine	q.s.
4	Sodium benzoate	50 mg
5	Propylene glycol	5 ml
6.	Water	q.s

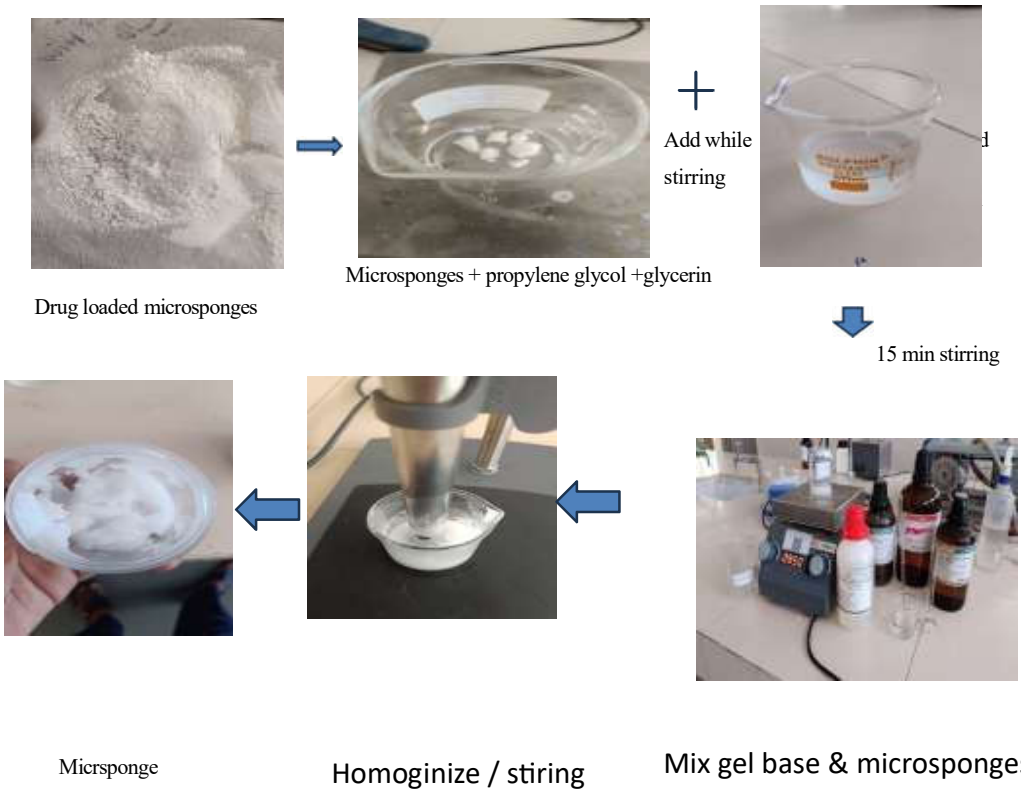

Fig.No.02:Prepration method of microsponge loaded gel

Evaluation parameters of Formulations :

Evaluation of Econazole nitrate microsponges :[23,24]

Determination of Production Yield:

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained.

$$\% \text{ production yield} = \frac{\text{Practical mass of Microsponge}}{\text{Theorotical mass(polymer + Drug)}} X100 \ldots . \text{Eqn(1)}$$

Actual Drug Content and Encapsulation Efficiency:

A sample of dried microsponges equivalent to 10 mg was taken in to mortar and pestle and add little amount of phosphate buffer of pH 7.4 and allowed to stand for 24 hours. Then transfer content in to 100 ml volumetric flask and make up volume to 100 ml with phosphate buffer of pH 7.4. The solution was filtered through whatman filter paper (No. 41). From the resulting solution take 1 ml in to 10 ml volumetric flask and then make up volume to 10 ml with phosphate buffer of pH 7.4. Drug content was determined by UV spectrophotometer (Dynamica ,Halo DB-20) at 261 nm.

The drug content and encapsulation efficiency were calculated using the following formula.

$$\%\text{Encapsulation Efficiency} = \frac{\text{Actual drug content in Microsponge}}{\text{Theorotical drug content}} \text{X100. . Eqn(2)}$$

$$\%\text{Actual drug content} = \frac{\text{Nact}}{\text{Nms}} \text{X100 … . Eqn(3)}$$

Where Nact is the actual oxiconazole nitrate content in weighed quantity of microsponges, Nms is the weighed quantity of powder of microsponges and Nthe is the theoretical amount of oxiconazole nitrate microsponges calculated from the quantity added in the process.

Motic Digital Microscopy: [25]

For morphology and surface topography, prepared microsponges can be placed on glassslide at room temperature and then the surface morphology of the microsponges can be studied by Motic Digital Microscopy(B1 advanced series) . Motic Digital Microscopy of a fractured microsponge particle can also be taken to illustrate its ultrastructure.The morphology of Oxiconazole nitrate microsponge was examined with a Motic Digital Microscopy . The samples were mounted on a glass slide and observed under 10X object.

Particle Size Analysis: [26]

Particle size analysis of prepared microsponges was carried out by using Motic digital microscope particle size analyzer [B1 advanced series]. Microsponges were dispersed on slide before running sample in the instrument, to ensure that the light scattering signal, particle size was measured , which is within instrument's sensitivity range.

Infrared Spectroscopy: [27]

It was determined by Fourier Transform Infrared Spectrophotometer (FTIR- Shimadzu) using KBr pellet method. FTIR spectra of Oxiconazole nitrate, physical mixture(s) of Oxiconazole nitrate and Eudragit S-100, Eudragit L-100, carbopol 934 and microsponge formulation were recorded in the wavelength range of 4000 to 400 cm-1.

In- vitro drug release study:[27]

Dissolution profile of Microsponges can be studied by use of dissolution apparatus USP(Type I) with a modified basket consisted of 5µm stainless steel mesh. A sample equivalent to 100mg of Oxiconazole nitrate was taken in the basket. The speed of the rotation is 100 rpm and temperature of 37±0.5˚C was maintained throughout experiment. The dissolution medium is phosphate buffer pH 7.4 while considering solubility of actives to ensure sink conditions. At fixed intervals, aliquots were withdrawn and replaced with fresh dissolution medium. Samples from the dissolution medium can be analyzed by UV spectrophotometer (Dynamica ,Halo DB-

20) at 261 nm at various intervals. The concentration of drug released at different time intervals was determined by measuring absorbance.

Process parameters for In –Vitro Drug Release Studies :

Table 5: Dissolution Parameters Used for In-Vitro Drug Release Study of Microsponge Gel Formulation

Parameter	Specification
Dissolution Test Apparatus	USP Type-I
Dissolution Medium	Phosphate Buffer (pH 7.4)
Temperature	37 ± 0.5°C
RPM (Revolutions per Minute)	100 rpm
Volume of Sample Withdrawn	5 ml
Total Volume of Dissolution Medium	900 ml
λmax (Detection Wavelength)	261 nm

Evaluation of Econazole nitrate Gel: [28]

Visual Inspection:

The prepared gel formulation of microsponges were inspected visually for their color, texture and appearance.

pH Measurement:

The pH of gel formulation was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of formulation was done.

Spreadability Studies:

One of the criteria for a gel to meet the ideal qualities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends

upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability.

Spreadability was determined by glass slides and a wooden block, which was provided by a pulley at one end. By this method, spreadability was measured on the basis of Slip and Drag characteristics of gels. A ground glass slide was fixed on this block. An excess of gel (about 1gm) of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 20gms, lesser the time taken for separation of two slides better the spreadability .

Spreadability was then calculated using the following
formula: $S = M \times L / T$ ….Eqn (4)

Where, S = is the spreadability, M = is the weight in the pan (tied to the upper slide), L = is the length moved by the glass slide T = represents the time taken to separate the slide completely from each other.

Fig.No. 03: Spreadability Measurement Instrument

Viscosity Measurement:

The viscosity of the different gel formulations was determined using a Brookfield viscometer with spindle no. 64 at 100 rpm at temperature 25˚C. The viscosity of the optimized formulation was determined as such without dilution using Brookfield Viscometer (Model -LVDV-E) . Brookfield Viscometer consist of a cup, which is stationary and a spindle which is rotating. Different sized rotating spindles are used and immersed in test material. For liquids with low viscosity, large size spindles (large diameter and surface area) are used while for higher

viscosity liquids small spindles (small diameter and surface area) are used. Rotate the spindle in the microsponge gel till we get a constant dial reading on the display of the viscometer. This procedure is repeated three times for reproducible results.

Drug content:

1gm of Econazole nitrate microsponge gel was accurately weighed dissolved using methanol, sonicated for a period of 10- 15 mins and made up to the mark in 100 ml volumetric flask with methanol. From this 10 ml was pipetted out and diluted to 100 ml with methanol and the final dilution was made using distilled water to get a concentration within Beer's range. The absorbance was measured by UVspectrophotometer (Dynamica, Halo DB-20) at 260 nm against blank gel treated in the same manner as sample.

In-vitro Diffusion Study: [29]

In-vitro studies of the gel were carried out across the egg membrane extracted by using the concentrated HCl. The receptor compartments were filled with phosphate buffered saline (PBS) pH 7.4, Study was carried out using excised egg membrane. Franz diffusion cell with 30ml receptor compartment and effective area 4.52cm² was placed on a thermostatic magnetic stirrer and the temperature was maintained at 37˚C throughout the study. Selected batche of drug microsponge gel (MGI,M.F.) were used for the diffusion study using diffusion cell. Aliquots, each of 1 ml volume were withdrawn at specific intervals and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium .Release studies were carried out over a period of 12 hrs at regular intervals. Samples were withdrawn and analyzed by UV spectrophotometer (Dynamica ,Halo DB-20) at 261 nm. Calculations were done by following formulae:

Determination of concentration of diffused drug (µg/ml) :

Slope and intercept were determined by using graph of absorbance versus concentration. Y = mX + c …. Eqn (5)

Where, Y = Absorbance, m = Slope, X = Concentration and c = Intercept.

Cumulative amount of drug diffused (CADD) :

[Concentration (µg/ml)* Volume of diffusion medium* Dilution factor] / 1000

Surface area (A) of egg membrane (cm2) :

A = πr2 ….Eqn (6)

Cumulative amount of drug diffused per unit area (CADD/cm2):

CADD/cm2 = CADD/ Area of membrane ….Eqn (7)

Flux (Jss) : Slope of linear portion of amount of drug diffused per unit area versus time.

Permeability Coefficient (Kp): Jss/Cv ….Eqn (8)

In-vitro Drug Release Kinetic Study: [69,70]

To determine the drug release mechanism and to compare the release profile differences among microsponge gel formulations, the data obtained from drug released amount and time was used. The release data was analyzed with the following mathematical models:

Zero Order Kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be presented by the following equation:

Q = K0t …. Eqn (9)

Where Q is the amount of drug released at time t, K0 is the zero-order rate constant expressed in units of concentration/time and t-is the time in hours.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time. This model represents an ideal release profile in order to achieve the prolonged pharmacological action

Higuchi Matrix model :

This model is used to study the release of water soluble and low soluble drugs incorporated in semisolid and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. It describes drug release as a diffusion process based on the Fick's law, square root time dependent [43].

$Q = KH\ t^{1/2}$…. Eqn (11)

Where Q is the amount of drug release in time t, KH is the Higuchi dissolution constant.

Korsmeyer-Peppas model:

Korsmeyer developed a simple, empirical model, relating exponentially the drug release to the elapsed time (t).

$ft = a.t^n$…. Eqn (12)

Where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism and function of t is Mt/M∞ (fractional release of drug)

Hixson-Crowell model:

Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation:

$W0\ 1/3 - Wt\ 1/3 = \kappa\ t$ …. Eqn (13)

where W0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets . To study the release kinetics, data obtained from in vitro drug release studies were plotted as cube root of drug percentage remaining in matrix versus time.

Study of Stability: (70)

The optimized batch's short-term stability was tested using a photostability chamber for one months at 25±2°C and RH 60±5%. The goal of stability studies was to see how the quality of a formulation changes over time as a result of a variety of factors like pH, viscosity, the volume of solution released for each actuation and homogeneity of the optimized batch stayed constant

throughout the experiment. If nothing has changed before and after, then the formulation is said to be stable.

3. RESULTS AND DISCUSSION

Results:

Pre-formulation studies of Econazole nitrate:

Solubility of econazole nitrate:

Table 06: Solubility table of econazole nitrate

Sr. no	Solvents	Solubility
1.	**Distilled water**	**Insoluble**
2.	**Ethanol**	**Sparingly Soluble**
3.	**Methanol**	**Soluble**
4.	**Dichloromethane**	**Sparingly Soluble**

The solubility of pure drug in 10mg/ml of solvent was carried out and it reveals that it is insoluble in distilled water, sparingly soluble in acetone and ethanol and soluble in methanol.

Physical appearance and melting point determination

Table 07: Physical appearance and melting point

Sr.no	Test	Observation
1.	Nature	Powder form
2.	Colour	White
3.	Melting point	162°C
4.	Taste	Tasteless
5.	Odour	Odourless

The physical characters were found to be as per standard drug, so drug used in formulation was found to be pure according to Indian Pharmacopeia specification. The melting point of pure Econazole nitrate was found to be 162°C so drug.

Determination of FTIR study:

The FTIR study for the pure drug and its excipients were done on the instrument namely as FTIR spectrophotometer (Thermo Nicolet). The FTIR spectra were obtained by an FTIR spectrophotometer using the potassium bromide (KBr) disk method by means of a hydrostatic press. The procedure consisted of dispersing a sample (drug and drug carrier mixture) in KBr and compressing into disk by applying a pressure by hydraulic press. Data were collected over a spectral region from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1}. The interaction between the drug and its excipients was observed IR- spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug and the data was obtained on spectra.

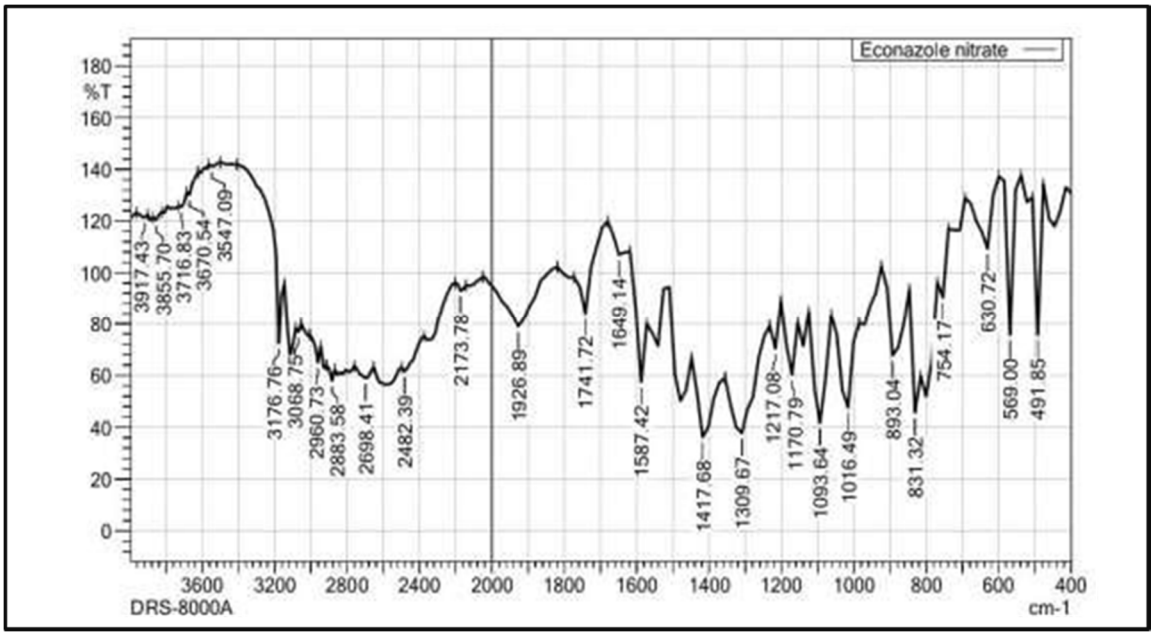

Fig 04: FTIR of Drug (Econazole Nitrate)

Identification and confirmation of pure drug (Econazole Nitrate) was carried out by observing obtained spectra. It showed characteristics peak at 3176.76 (-C-N stretching) imidazole ring; 3068.75 (-C-H stretching); 1417.68 (-C-C stretching);630.72 (-C-Cl stretching). These peaks value was in accordance with previously reported spectra of Econazole Nitrate

FT-IR OF ECONAZOLE NITRATE AND EUDRAGIT RS100:

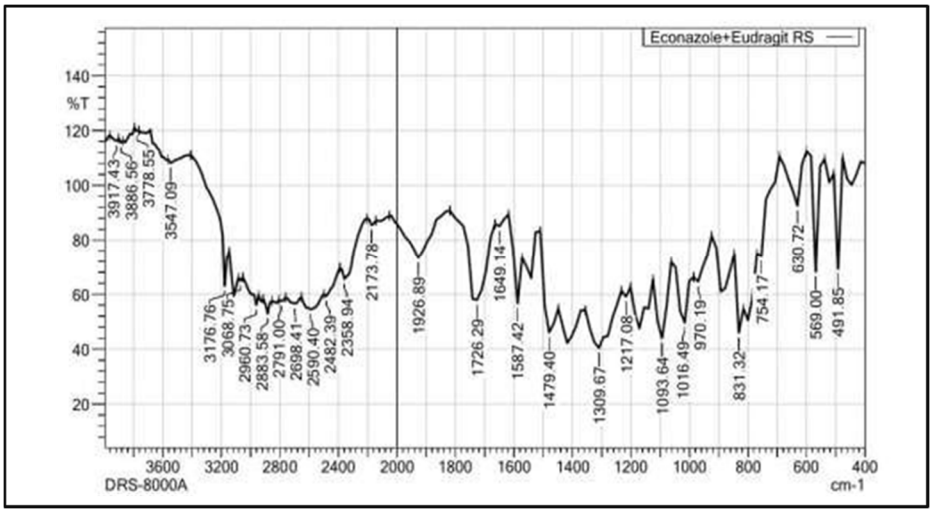

Fig 05: FT-IR Spectra of Econazole Nitrate and Eudragit RS 100:

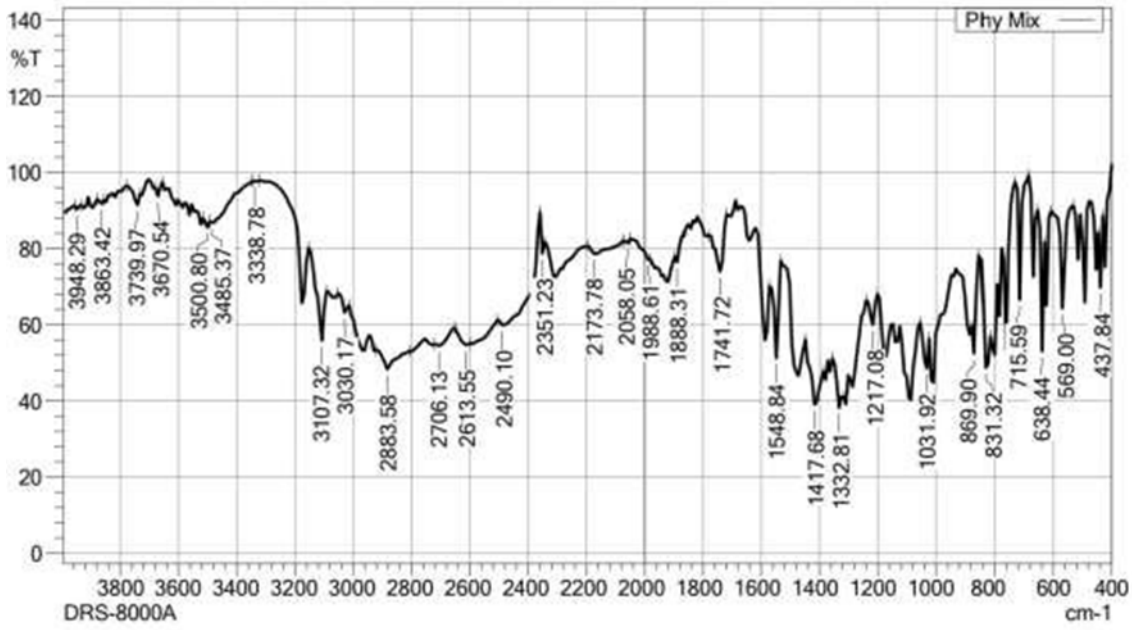

Fig 06: FT-IR Spectra of Econazole nitrate and Ethyle cellulose :

Determination of wavelength:

Econazole nitrate showed the maximum wavelength at 300 nm, which matches with the standard. Hence, drug used in formulation, was found to be pure according to Indian pharmacopeia specification.

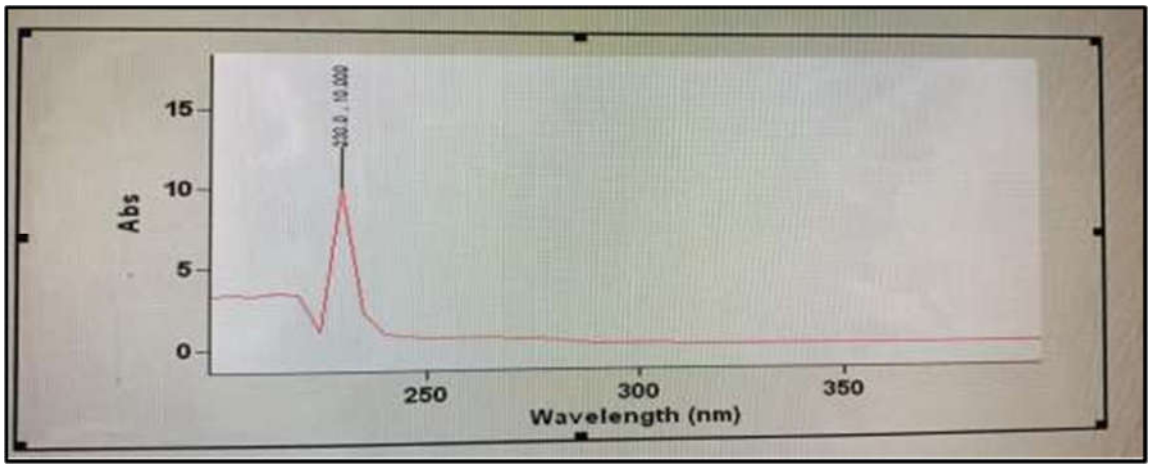

Fig 07: Wave length of Econazole nitrate

The wavelength of the Econazole nitrate was found to be 230 nm.

Calibration curve of Econazole nitrate:

The absorbance of the solutions was measured at 230 nm by using UV visible spectrophotometer.

Table 8: Calibration curve Absorbance

Sr. no	Concentration(µg/ml)	Absorbance
0.	0	0
1.	2	0.0075
2.	4	0.0102
3.	6	0.0121
4.	8	0.0152
5.	10	0.0181
6.	12	0.0209

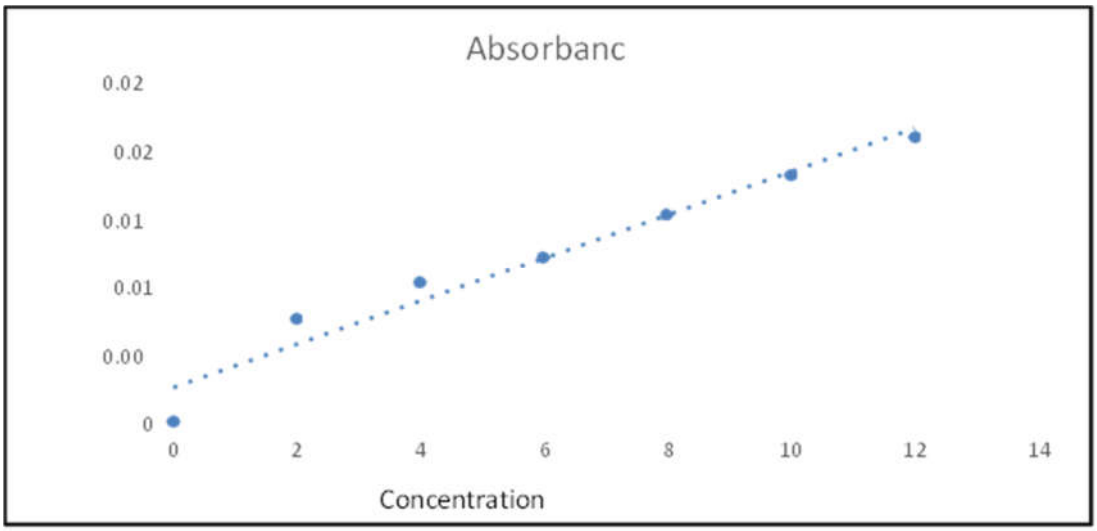

Fig 08. Graph 1: Calibration Curve of Econazole

From the above equation of line of calibration curve of econazole nitrate in phosphate buffer (pH 7.4), the slope was found to be 0.0076 and the correlation coefficient(R2) was found to be 0.9535. the value indicates that the calibration curve of pure econazole found to be linear.

Assay of Econazole nitrate:

By titrimetric method the percent purity of econazole nitrate was found to be 98% is acceptable as per the IP standard.

Solubility of Econazole nitrate in solvents:

Table 9: Solubility study of drug in different vehicles

Sr. no	Names of vehicles	Solubility (mg/ml)
1.	DCM	95.4
2.	Ethanol	68.7
3.	Acetone	65.2
4.	Propylene Glycol	59.8
5.	PEG 400	78.2
6.	Isopropyl Alcohol	54.3
7.	Water	<1 (very slightly soluble)

EVALUATION OF FORMULATION

Evaluation of Econazole nitrate Microsponges:

Optimization of Quasi-Emulsion Solvent Diffusion Method:

The preparation methods of microsponges are limited in the means of complexity and cost. The suspension polymerization is the known process to prepare the commercially available microsponges. Quasi-emulsion solvent diffusion method serves an alternative way for preparing microsponges. This method seems to be promising for the preparation of Econazole nitrate microsponges with being easy, reproducible and rapid and also has an advantage of avoiding solvent toxicity. In quasi-emulsion solvent diffusion method, the parameters optimized were inner phase solvents, stabilizer in aqueous phase, and drug: polymer ratio, stirring speed and stirring time.

Selection of Inner Phase Solvent:

Ethanol and methanol was selected as an inner phase solvent as it is the good solvent for polymer and drug respectively. Solvents in a volume of less than 5 ml was found to be insufficient to dissolve polymer and drug while microsponges were failed to be formed on increasing the volume of internal phase by more than 10 ml as milky phase was obtained. So 10ml inner phase solvent volume was decided to be used for experimental design.

Selection of Stabilizer in External Phase:

It was observed that at least one stabilizer was necessary for the microsponge formation. For this polyvinyl alcohol (PVA) was tried as stabilizer. When concentration of PVA was increased, the mean particle size of microsponges was also found to be increased. This could be attributed to an increase in apparent viscosity at increased emulsifier concentration.

Selection of Stirring Speed and Stirring Time:

The optimum stirring speed was selected as 1500 rpm. At the stirring speed of less than 1300 rpm, fibrous aggregates were formed while above 1500 rpm; turbulence of external phase was observed due to which polymer stucked around the paddle of stirrer and the vessel. So, 1500 rpmwas selected as optimum speed. The stirring time had significant effect on the formation of microsponges. It was found that the solidification of microsponges was not enough in 1hr of stirring. 2 hrs stirring was appropriate for the preparation and additional stirring time did not affect the formation of microsponges. In this respect, the optimum stirring time was selected as2 hrs. Microsponge production parameters are given in Table No .10.

Table No.10: Parameters for microsponge formulation

Sr. No	Parameters	Optimum Values
1	Drug	100mg
2	Polymer	100,200,300,400,mg
3	Polyvinyl alcohol	0.5-0.75% w/v
4	Amount of Inner Phase Solvent	10 ml
5	Amount of Water in outer Phase	100 ml
6	Stirring rate	1000-1500 rpm
7	Stirring time	2 hrs

Table no; 11. Determination of Production Yield and Entrapment Efficiency, Actual drug content:

Batches	Production Yield(%)	Entrapment Efficiency(%)	Actual Drug Content (%)
F1	81.53	78.5	90.21
F2	82.75	80.58	89.45
F3	70.2	68.73	81.23
F4	74.25	79.31	79.04
F5	77.79	72.64	89.23
F6	70.35	66.11	84.40
F7	71.50	68.13	81.63
F8	64.89	73.78	77.20
F9	70.61	63.2	88.12

Evaluation of econazole nitrate of microsponge formulations

The production yield of all batches was ranged from 64.89% to 82.75%. It was found that production yield was greatly affected by drug: polymer ratio as well as by concentration of polyvinyl alcohol. It was indicated that increasing polymer concentration ,increased production yield while increasing polyvinyl alcohol concentration ,decreased production yield.

Use of the higher amounts of PVA while preparing microsponges at higher drug: polymer ratios caused slightly an increased viscosity of the dispersed phase. When solvents in inner phase were diffused out, nearly all of the dispersed phase was converted to the form of solid microsponges and separated particles appeared. The highest drug loading efficiency of these formulations could be explained through the fact that the amount of polymer to per unit drug was greater than that in other formulations.

Motic Digital Microscopy:

The morphology of the microsponges prepared by quasi emulsion solvent diffusion method and entrapment method was investigated by Motic Digital microscope (B1 Advanced series). The representative motic microscopic images of the microsponges are shown in Fig. No.16. Images showed the microsponges to be porous and were having predominantly spherical shape and not much entire. Econazolee nitrate crystals were observed visually.

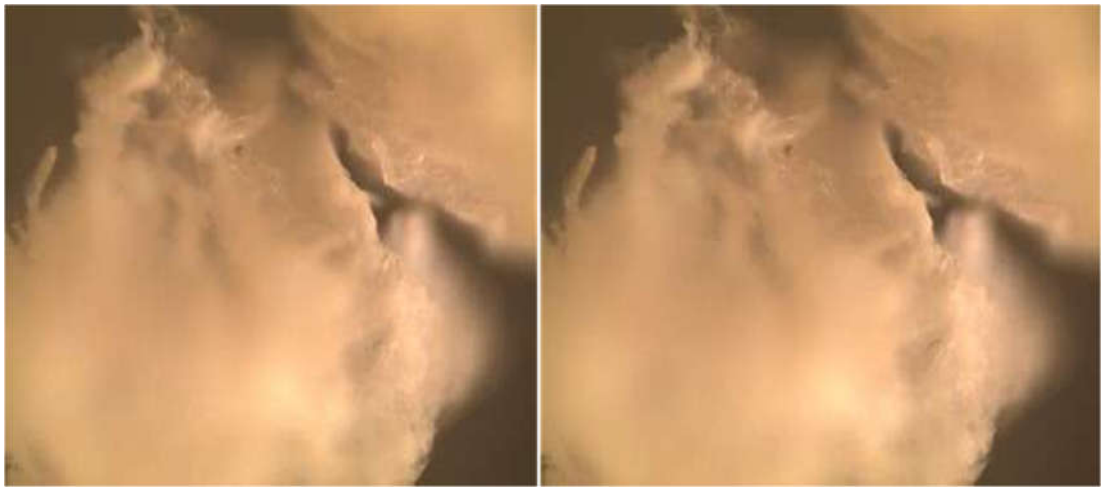

Fig.No.09: Images of Econazole nitrate microsponges

The pores were induced by the diffusion of the solvent from the surface of the microsponges. The appearance of the particles was such that they were termed as microsponges.From Fig. No.16 it was revealed that the characteristic internal structure was a spherical cavity enclosed

by a rigid shell constructed from drug and polymer. The inner structure consisted of void spaces.

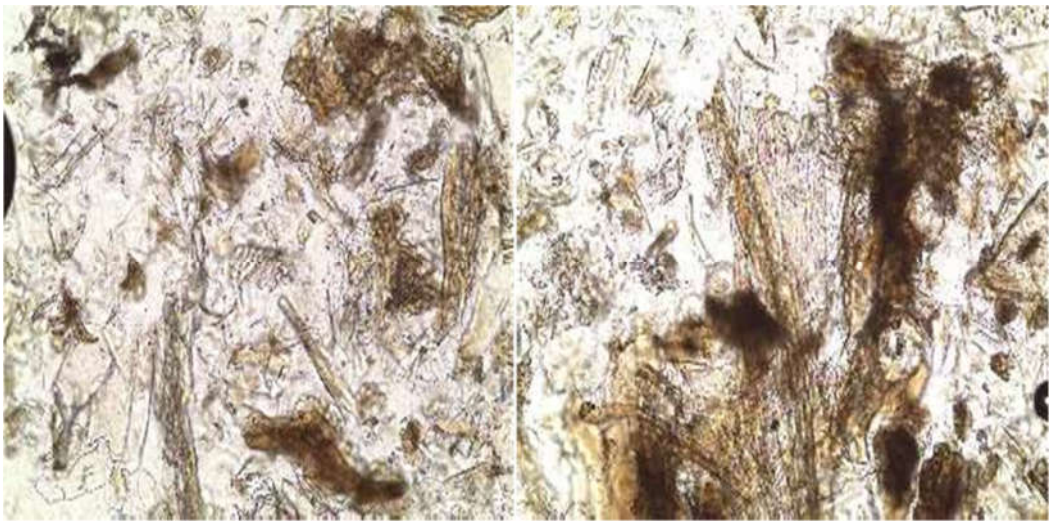

Fig.No .10: Images of Econazole nitrate microsponge gel

Microsponge gel image by Motic Digital microscope (B1 Advanced series) showed that microsponge are entrapped uniformly in three dimensional cross-linked network within the liquid.

Particle Size Analysis:

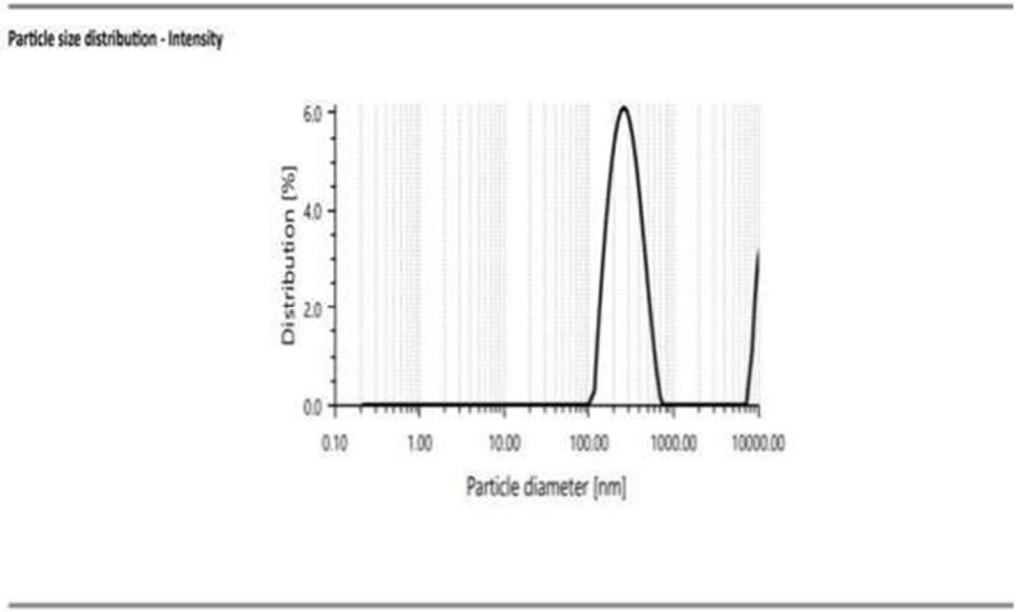

Fig.No.11:Image of particle size of Microsponge (F3)

Particle size analysis of optimized batch : The results indicate that the majority of microsponges exhibited a particle size in the range of approximately 200–1000 nm, with a prominent peak around 600–700 nm, suggesting a uniform distribution

Evaluation of Econazole nitrate microsponge Gel:

Visual Inspection:

The prepared gel formulations of Econazole nitrate microsponges were inspected visually for their color, texture and appearance. All prepared formulations were pearl white, viscous preparations with a smooth texture and showed good homogeneity with absence of any lumps and syneresis as shown in Figure given below.

Fig.No.12: Econazole nitrate Microsponge gel formulation

pH Measurement:

The pH values of all prepared formulations were found to be in the range of 6.7 to 6.8, which were considered to be acceptable to avoid the risk of irritation upon application to the skin.

Table No.12: $P^H$of microsponge gel formulation

Formulation	PH
F1	6.47±001

(Mean ± SD; n=3)

Spreadability Study:

The values of spreadability indicated that the gel was easily spreadable by small amount of shear.

(Mean ± SD; n=3)

Table No. 13: Spreadability of microsponge gel formulation

Formulation	Spreadability (g.cm/sec)
F1	16.5±0.3

(Mean ± SD; n=3)

Spreadability of microsponge gel was found to be16.5g.cm/sec; indicating that spreadability of drug loaded microsponge gel was good.

Viscosity Studies:

The viscosities studies for microsponge formulations was carried out. The viscosities of all formulations are shown in table No.19.

Table No. 14: Viscosities of microsponge gel formulation

Formulation	Viscosity (cps)
MGI	18,500cp

Drug content Studies:

Drug content studies for microsponge formulations was carried out. Drug content of all formulations are shown in Table No.20

Table No.15:Drug content of microsponge gel formulation

Formulation	Drug content (%)
MGI	93.1

In-vitro Drug Release Study:

The cumulative percent drug release (% CDR) for all formulations was calculated out. The cumulative percent drug release of all formulations was as quoted in Table No. 21 and 22.

Table No.16: In vitro drug release profile of F7- F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1hr	2.37	4.46	3.36	3.77	2.74	2.01	2.5	3.53	3.36
2hr	14.8	12.75	8.14	14.21	5.68	7.37	9.41	8.35	8.14
3hr	25.22	21.56	15.56	24.37	10.67	14.38	14.66	18.43	15.56
4hr	33.36	25.63	27.99	30.7	15.22	19.44	21.97	21.85	27.9
5hr	48.2	38.51	45.68	39.27	28.59	23.68	29.72	29.56	45.68
6hr	57.11	43.51	56.7	48.4	39.93	37.69	35.67	35.47	56.70
7hr	69.03	62.57	68.79	57.37	53.44	59.42	49.25	48.99	68.79
8hr	80.44	84.17	77.37	64.28	76.19	72.39	60.87	61.51	79.10

The drug release was found to be decreased in the range of 84.17 % to 60.87% for eudragit RS-100 as the drug: polymer ratio was changed. The drug release was found to be decreased in the range of 84.17 % to 60.87% for ethyle cellulose- as the drug: polymer ratio was changed. The reason behind is as drug: polymer ratio was increased, the amount of polymer available per microsponge to encapsulate the drug becomes more, thus increasing the thickness of the polymer matrix wall which might led to longer diffusion path and ultimately to decreased drug release. The highest drug release i.e. 84.17 % was found for the formulation F2, while the lowest 60.28% for F5 76.19 of drug relese of ethyle cellulose and F9 eudragit rs- 100 and ethyle cellulose drug release is 79.10% . The highest drug release i.e. 84.17% was found for the formulation F2, while the lowest 60.87% for F8 for Ethyle cellulose .It has been reported that

with same amount of PVA from batches F1-F9,the drug release went on descrasing.It might be due to fact that the polymer amount matrix releases drug after complete swelling and time required for swelling of polymer is directly proportional to stabilizer concentration. Graphical presentation of all batches (F1_F9) are shown in Figure below respectively.

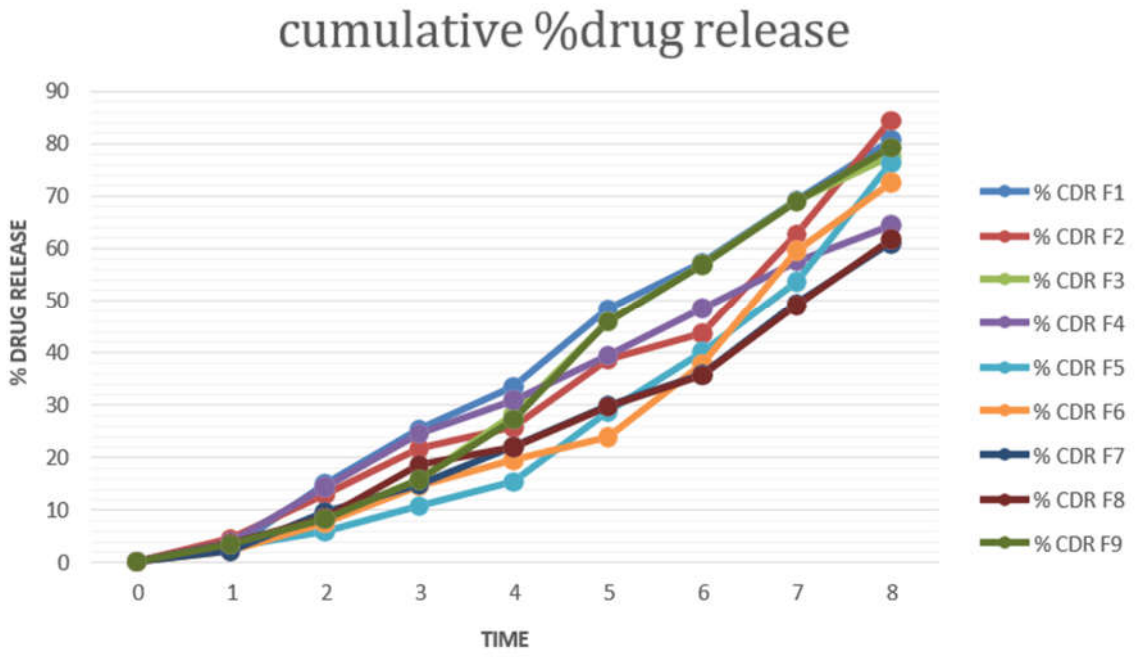

Fig .no.13 :% Drug release of formulated drug loaded microsponges of F1-F9

In-vitro Diffusion Study:

The in-vitro diffusion studies were carried out for all formulations using PBS (pH 7.4). In-vitro diffusion of formulation F2 . is shown in Table No.31

Table No.17: Amount of drug diffused per unit area of microsponge gel formulations

Time (hrs)	Formulations (% drug release) cm^2)
	F2
0	0
1	0.95
2	5.73

3	11.42
4	21.06
5	30.42
6	39.65
7	48.99
8	67.99
9	82.53
10	93.53

It was observed that the formulation (F2) showed higher amount of drug diffused at the end of 10 hrs the end of 10 hrs .The results indicated that the Q value (cumulative amount of drug permeated per unit skin surface area) was controlled for 10 hrs at F2 drug: polymer ratio and at 0.5% w/v PVA. The cumulative amount of drug permeated per unit skin surface area (Q) from the microsponge loaded gel formulations were plotted against time and are as shown in Figure below .

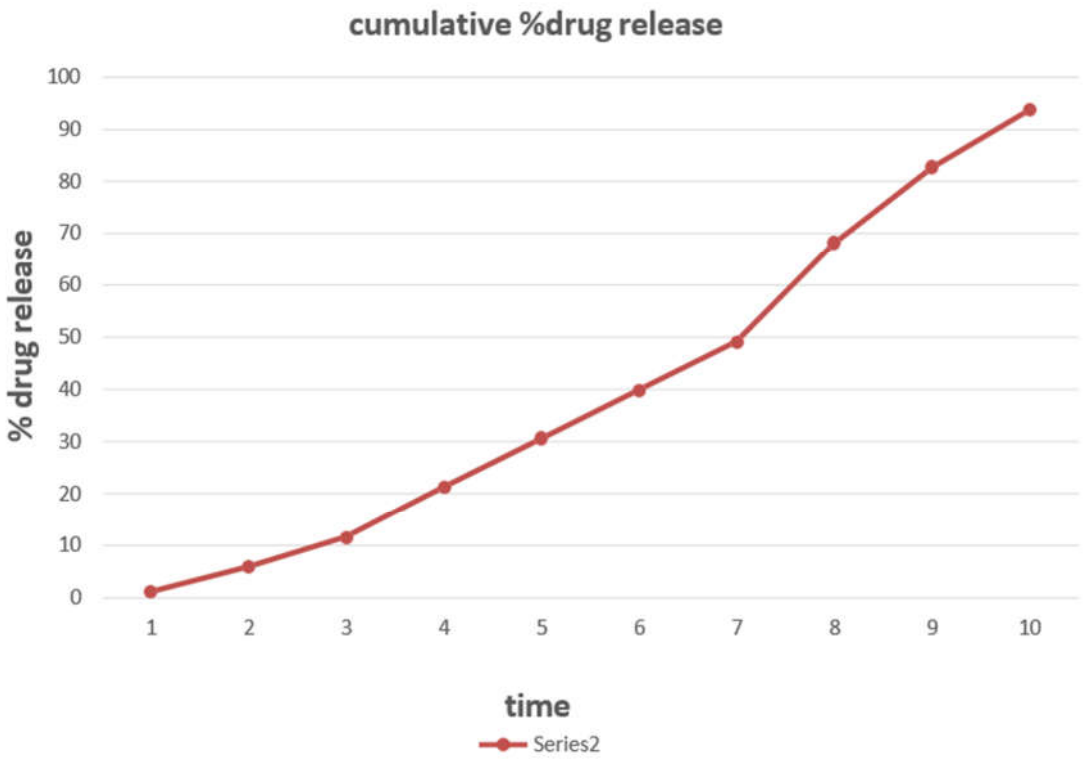

Fig.No.14: In-vitro Diffusion Study of Formulations (F2)

Drug release kinetic study of optimized formulation (F2):

To determine the kinetics of release ,drug diffusion data was treated with different kinetic equations. Obtained drug diffusion data was fitted to Zero order, First order, Higuchi –matrix model, Hixson crowell model and Korsmeyer-peppas model.

The mathematical models are used to evaluate the kinetics and mechanism of the drug. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The in vitro drug release data of microsponge gel formulation and the drug was subjected to the goodness of fit test by linear regression analysis. The optimized batch follows the Zero order and Higuchi model.

Table No.18 :Release kinetics of optimized formulation(F2)

Model	Zero order	Higuchi plot
R2 value	**0.9562**	**0.9434**
Slope	9.768	8.7951
Intercept	12.27	7.9126

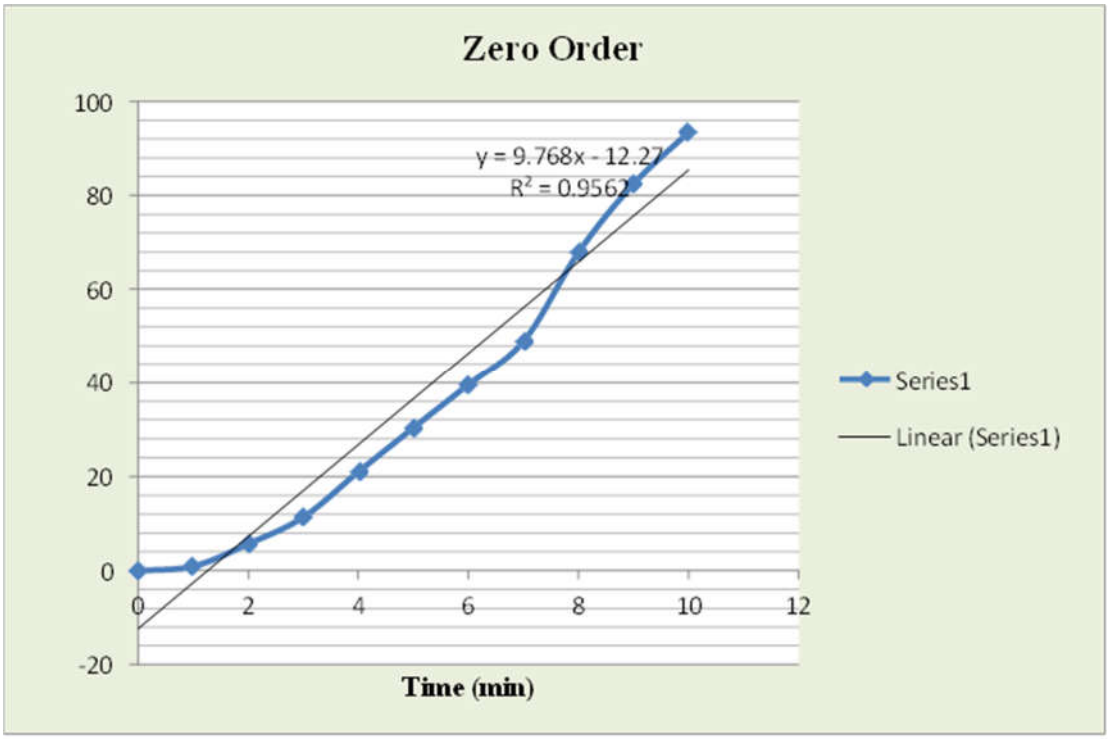

Fig.No.15: Release Kinetics graph of optimized Formulation (F2)

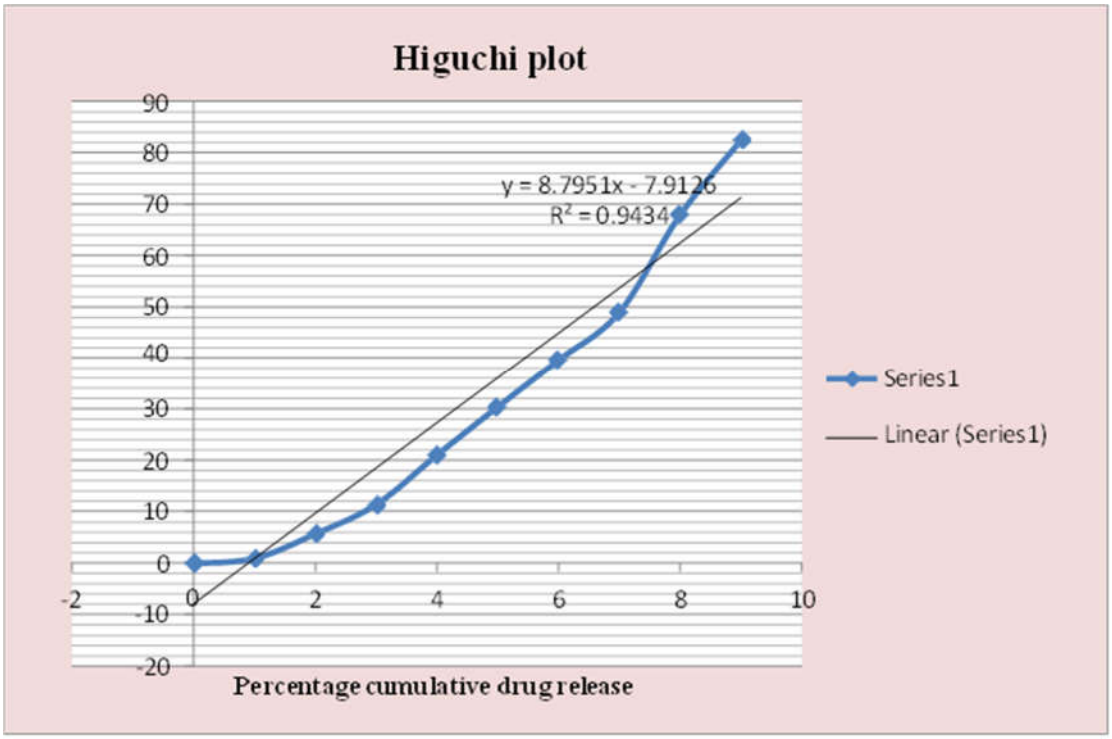

Fig.No.16: Release Kinetics graph of optimized Formulation [F2]

- As the kinetics release profile shown that the value which we get R2 in Zero order and Higuchi order
- Constant and sustained release microsponge shows zero order.
- Porous polymeric matris strutures of microsponges shows Higuchi model .

From the result best fit model for optimized formulation F2 is Zero order model and Higuchi model .

Particle size analysis of optimized batch of microsponge gel. F2

Particle Size AnalysisThe particle size distribution of the optimized batch of Econazole Nitrate-loaded microsponge gel was determined using dynamic light scattering. The results indicated that the average particle size was approximately 150 nm, with a narrow size distribution. This small particle size enhances the surface area, enabling better drug release and penetration through the skin. Avg size (10-300) which is equal to 10000to 300000 nm.

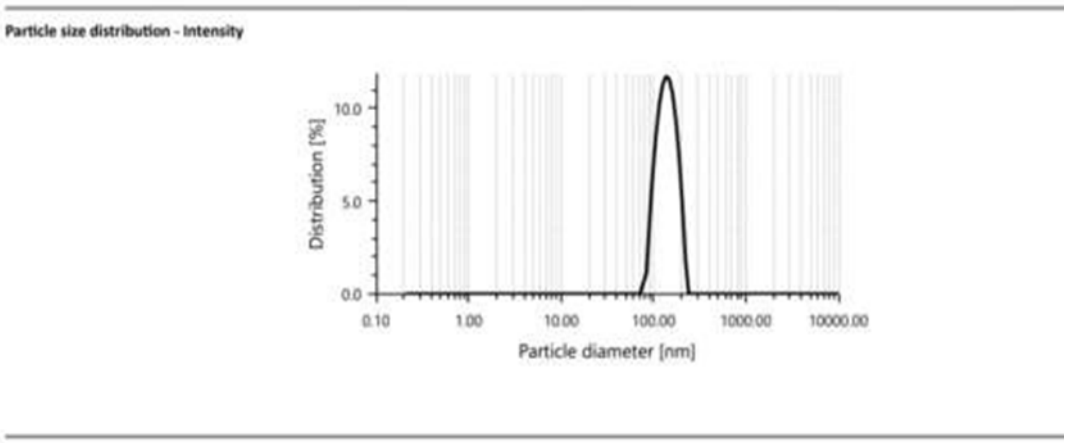

Fig.No.17: partical size analysis of microsponge gel [F2]

Stability Study:

The optimized batch's short-term stability was tested using a photostability chamber for one months at 25±2°C and RH 60±5%. The goal of stability studies was to see how the quality of a formulation changes over time as a result of a variety of factors like pH, viscosity, the volume of solution released for each actuation and homogeneity of the optimized batch stayed constant throughout the experiment. If nothing has changed before and after, then the formulation is said to be stable.

Stability study of microsponge loaded gel

On the basis of stability data, it concluded that there were no significant changes in result obtained during stability studies, thus indicating that formulation is stable under specified temperature and humidity condition. Stability studies were carried out for microsponge gel showed that was no significant changes in drug content, in vitro drug release after 1 months of the prepared formulation indicating the prepared econazole nitrate microsponge gel is stable.

Table No.19:stability study of (F2) batch

Sr. no	Parameter	Day 0	Day 30
1.	Colour	white	white
2.	Phase separation	No change	No change
3.	pH	6.47	6.3
4.	Viscosity (cps)	18500	1700-1800

5.	Spreadability	16.5g.cm\sec	16.2g.cm\sec
6.	Drug content (%)	93.1	92.2
7.	Drug release for 10 hours (%)	93.1	91.03

DISCUSSION

The study aimed to develop a controlled release topical gel of Econazole Nitrate using a microsponge delivery system. This approach addresses the limitations of conventional creams, such as frequent application and poor drug retention.Microsponges were prepared using the quasi-emulsion solvent diffusion method with Eudragit RS-100 and ethyle cellulose as polymers. Ethanol and DCM were used as solvents, and PVA served as a stabilizer. Nine batches (F1–F9) were formulated with varying drug-to-polymer ratios.Among all, the F2 batch was optimized due to its high entrapment efficiency, good production yield, and controlled in vitro drug release over 8 hours. The microsponges were spherical and porous, suitable for sustained release.The optimized microsponges were incorporated into a gel base and evaluated. The F2 microsponge gel showed appropriate pH, viscosity, spreadability, and extrudability, making it ideal for topical use.In vitro studies confirmed that the F2 gel provided controlled and sustained drug release, superior to conventional gel. Eudragit RS-100 supported release at skin pH, while enhanced gel performance.In conclusion, the F2 microsponge gel was found to be an effective and promising formulation for topical antifungal therapy, with better patient compliance and therapeutic results.

CONCLUSION

The present research focused on the formulation, development, and characterization of a microsponge-based drug delivery system for Econazole Nitrate, aimed at enhancing topical antifungal therapy. The quasi-emulsion solvent diffusion method was successfully employed using Eudragit RS-100 and ethyl cellulose polymers, where optimization of formulation parameters such as drug-to-polymer ratio, stabilizer concentration, and stirring conditions yielded microsponges with desirable characteristics. The optimized batch (F2) demonstrated high production yield, significant entrapment efficiency, and a uniform spherical morphology, as confirmed through Motic Digital Microscopy and particle size analysis.These microsponges were further incorporated into a gel formulation and evaluated for pharmaceutical attributes

including pH, viscosity, spreadability, drug content, and in-vitro diffusion behavior. The F2 microsponge gel showed excellent physicochemical stability, spreadability, and prolonged drug release, maintaining a steady therapeutic concentration over a 10-hour period. The drug release kinetics followed Zero Order and Higuchi models, indicating a diffusion-controlled and sustained release pattern.The incorporation of Econazole Nitrate into microsponges embedded in a topical gel matrix significantly improved the drug's performance, offering reduced frequency of application and enhanced patient compliance. The final formulation demonstrated stability under accelerated conditions, confirming its suitability for long-term storage and commercial viability. Overall, the study confirms that microsponge technology is an effective and promising strategy for delivering antifungal agents like Econazole Nitrate. It offers considerable advantages over conventional dosage forms in terms of controlled release, skin compatibility, and formulation stability—making it a robust platform for future pharmaceutical applications.

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