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Research Article

Formulation And Evaluation of Spanlastic Gel Containing Econazole Nitrate

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ABSTRACT

The present study aimed to develop a spanlastic gel of Econazole nitrate (ECN) to improve its solubility and enhance skin permeation. Econazole nitrate, an imidazole antifungal agent, was confirmed pure through preformulation studies, and UV analysis was used for estimation. FT-IR and DSC results indicated no significant drug–excipient interactions, confirming compatibility. Spanlastic vesicles were prepared by the ethanol injection method using Span 60 as the primary surfactant and Tween 60 or Tween 80 as edge activators. A 2^3 full factorial design was applied to study the influence of formulation variables on entrapment efficiency, particle size, and in vitro drug release. The optimized formulation showed a particle size of 178.3 ± 14.6 nm, entrapment efficiency of 91.24 ± 0.93%, and in vitro drug release of 85.49 ± 2.56% after 8 hours. When incorporated into a topical gel, it exhibited a pH of 6.04 ± 0.08, viscosity of 26,419 ± 2.30cps, drug content of 95.00 ± 0.93%, and a zone of inhibition of 26.50 ± 0.03 mm. Overall, the spanlastic gel effectively enhanced ECN penetration and provided sustained antifungal activity, demonstrating its potential as a superior topical delivery system.

INTRODUCTION

Superficial fungal infections are widespread across India, showing a relatively uniform epidemiological and fungal distribution throughout different regions. Dermatophytes are the leading cause, with their prevalence ranging from 23.6% to 100% in various studies. Candida species have been reported in 10% to 53% of cases, while non-dermatophyte moulds account for 10% to 61.6%. Notably, Candida infections appear more frequently in the eastern and northeastern regions (about 62.5%) compared to northern India (approximately 33.3%).

Despite differences in geography and infection rates, the most affected group comprises males aged 21 to 40 years. Higher incidence rates have been observed among people living in rural

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settings, especially those engaged in occupations with frequent exposure to water (such as homemakers and manual labourers) or soil (including farmers and field workers)[1].

Limited drug penetration into the skin, nails and cornea often results in reduced local drug availability and therapeutic effectiveness. Although the structural characteristics of the stratum corneum, corneal tissue, mucosa and nails vary, they all function as barriers that significantly restrict drug absorption[2]. Thus, the demand raised for the development of formulation that increased the permeation of active ingredient across the stratum corneum without causing any disruption and systemic adverse effects. This led to formulation of Spanlastics and incorporation of these vesicles into gel to ease their application and improve patient compliance.

Spanlastics are a type of nanovesicular drug delivery system composed of a non-ionic surfactant (such as Span) that forms the bilayer membrane and an edge activator (EA) that enhances the flexibility and elasticity of the vesicle structure. Spanlastics are capable of deep skin penetration, thanks to their flexible and deformable nature, along with their nanoscale size, drug-carrying capacity and affinity for skin lipids. They can deliver both water-soluble and lipid-soluble drugs effectively, maintaining therapeutic levels over an extended period[3].

Econazole nitrate is an antifungal medication related to imidazole antifungal category. Econazole nitrate prevents fungal organisms by interacting with 14 – alpha demethylase, a vital substance required for the growth and function. Half-life of this drug is 4 hours and is soluble in methanol, sparingly soluble in dichloromethane, slightly soluble in ethanol (95 percent), very slightly soluble in water and practically insoluble in ether.

Topically applied econazole nitrate exhibits minimal systemic absorption, with approximately 90% retained in the skin[4,5]. Hence, Spanlastic vesicles containing Econazole nitrate is formulated and incorporated into gel dosage form. Formulation of spanlastics provides advantage of sustained release and thus it provides better opportunity for the formulator to design a biocompatible, site specific drug delivery system with sustained drug release and with better patient compliance.

MATERIALS AND METHODS

Drug and chemicals

Econazole nitrate was obtained as gift sample from Mahrshee laboratories, Gujarat, India, Span 60 and Triethanolamine was purchased from Thomas baker chemicals Pvt.ltd. Tween 80 and Tween 60 was purchased from Himedia laboratories pvt.Ltd. Ethanol and Methanol from S D fine chem limited, Maharastra, India. Propylene glycol, Methyl paraben, Sodium hydroxide and Potassium dihydrogen phosphate from Spectrochem pvt. Ltd, Banglore,India.

Methodology

Preformulation Studies

Preformulation are the studies that focus on the physicochemical properties of a drug candidate that could affect the drug performance and the development of a dosage form.

The main aim of preformulation study is to develop the safe , effective and stable dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico-chemical parameter of new drug substances [6].

1.Organoleptic properties:

The color, nature and odor of the drug was determined by visual examination.

2.Melting Point Determination:

A few quantities of econazole nitrate are taken and placed in a thin walled capillary tube about 8-10 cm long and 1mm inside diameter and closed at one end and then it is placed in Digital melting point apparatus. The apparatus is heated slowly, the temperature at which the sample is observed to be melt is taken as the melting point. This process is repeated in thrice (n=3) and average is taken[7].

3.Determination of solubility:

The solubility study of econazole nitrate was performed by dissolving an excess quantity of the drug in 10 ml of different solvents like methanol, water, ethanol and Phosphate buffer pH 6.8. The mixtures were agitated for 24 hours at 37± 0.5°C in a shaker. The samples taken from each solvent system were filtered and diluted appropriately. The concentration of econazole nitrate in each solution was determined by using UV spectrophotometer. The measurements were taken in triplicate[8].

Analytical methods

UV Spectroscopic method for estimation of Econazole nitrate

The UV visible spectrophotometer was used as a simple precise sensitive and accurate method for estimating ECN.

Preparation of standard curve of Econazole nitrate

The absorption maxima (λ_{max}) for Econazole nitrate in methanol was determined by scanning the drug solution in the range of 200 nm to 400 nm using a UV visible spectrophotometer.

Preparation of standard solution:

Stock A -100 mg of the ECN was weighed accurately into 100 ml volumetric flask which was dissolved and made up to the mark with methanol to get 1000µg/ml solution and was used as a standard stock solution (SS-I).

Stock B - 10ml from above SS-I was measured and transferred into 100ml volumetric flask and dissolved and made up to the mark with methanol to get final concentration of 100 µg/ml (SS-II).

Preparation of the working standards:

From stock B 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0ml were taken in 10ml volumetric flask and made up to 10ml using methanol to get 5,10,15, 20, 25, 30, 35, 40, 45, 50µg/ml concentrations respectively. The beers range of econazole nitrate was found to be 0 - 50µg/ml.The absorbance of the resulting solutions were measured at screened wavelength by UV spectrophotometer. The calibration curve was plotted against concentration versus absorbance[7,9,10].

Preparation of calibration curve of Econazole nitrate in Phospate buffer 7.4

The absorption maxima (λ_{max}) for Econazole nitrate in methanol was determined by scanning the drug solution in the range of 200 nm to 400 nm using a UV visible spectrophotometer.

Preparation of standard solution:

Stock A - It was prepared according to the procedure described above(SS-I)

Stock B - 10ml from above SS-I was measured and transferred into 100ml volumetric flask and dissolved and made up to the mark with Phospate

buffer of pH 7.4 to get final concentration of 100 µg/ml (SS -I).

From stock B 1, 2, 3, 4, 5ml were taken in 10ml volumetric flask and made up to 10ml using buffer and absorbance of the resulting solutions were measured using UV spectrophotometer.

Compatibility studies

Fourier transform infrared spectroscopy (FT-IR)

The use of Fourier transform infrared (FTIR) spectroscopy has been considered to be one of the most effective techniques to study and understand the compatibility between drug and excipients. FT-IR spectra of pure econazole nitrate, ECZ with Span 60 were obtained using FT IR spectrometer using ATR method. FT-IR spectra were recorded within the spectral region of 4000 and 400 cm−1 using the instrument FTIR-ATR Thermo scientific Nicolet SummitX (compact). The IR spectra of the pure drug and excipients were interpreted for any appearance or disappearance of the peak.

Differential scanning calorimetry (DSC)

The thermogram of econazole nitrate was recorded using a Shimadzu DSC- 60 instrument equipped with an intercooler. Prior to analysis, the system was calibrated for both temperature and enthalpy using indium as the standard. The powder sample was sealed in an aluminium pan and subjected to heating at a rate of 10 °C/min across a temperature range of 30–300 °C, under a continuous nitrogen purge maintained at 20 mL/min.

Experimental design

A three factor, 2 level (2^3) factorial design was to optimize spanlastic gel formulations where the three factors were evaluated based on the previous lab experiments performed each at two different levels (low, high) and experimental trails were performed using all possible combinations using the Design-Expert® software version 13.0. The independent variables selected for experiment were ratio of Span 60 : tween, type of edge activator i.e, tween 60 or tween 80 and sonication time. Percentage cumulative drug release , Particle size and entrapment efficiency were chosen as dependent variables. The amount of ECN was maintained consistently across all batches based on literature survey. Formulation parameters that influence the properties of the spanlastic gel were selected based on a review of the literature and preliminary laboratory studies. Various factors like, the concentration of span 60, concentration of edge activators such as tween 60 and tween 80 for preparation of the spanlastic gel were recognized as critical formulation parameters that affect the cumulative drug release, viscosity, particle size, entrapment efficiency and *in-vitro* antifungal activity. To decide the level of formulation variables that influence the properties of spanlastic gel initial screening studies was performed.

Table No .01: Selected Independent Variables for Optimization

SI.No	Independent variable	Units	Low	High
1	Ratio of span 60 : edge activator		50:50	80:20
2	Types of edge activator		Tween 60	Tween 80
3	Sonication time	mins	5	15

Table No.02: Selected Dependent Variables For Optimization

SI. No	Dependent variable	Units	Goal
1	Particle size	nm	Minimize
2	Entrapment efficiency	%	Maximize
3	Percentage cumulative drug release	%	Maximize

Table No.03: Formulation Table for Preparation of Spanlastics

SI. No	Formulation code	Type of edge activator	Span 60:Edge activator	Sonication time (Mins)
1	F1	Tween 80	50:50	5
2	F2	Tween 80	65:35	10
3	F3	Tween 80	50:50	15
4	F4	Tween 80	80:20	15
5	F5	Tween 60	50:50	5
6	F6	Tween 80	80:20	5
7	F7	Tween 60	50:50	15
8	F8	Tween 60	80:20	15
9	F9	Tween 60	65:35	10
10	F10	Tween 60	80:20	5

Preparation of spanlastic gel:

Step 1: Formulation of spanlastic

Spanlastic vesicles were prepared using the ethanol injection method. Initially, a measured amount of Tween 80 was dissolved in 50 ml of distilled water and heated to 70°C. In a separate step, Span 60 was accurately weighed and dissolved in 10 ml of ethanol, followed by the incorporation of econazole nitrate into the same solution. This organic mixture was then gradually introduced into the aqueous Tween 80 phase at a controlled rate of 1 ml/min using a 30-gauge syringe. The injection process was carried out under continuous stirring at 1000 rpm with the temperature maintained at 70°C. Stirring was continued for 1 hour to ensure thorough mixing and complete evaporation of the organic solvent, resulting in the formation of econazole-loaded spanlastic vesicles. After allowing the mixture to cool to room temperature, a homogenous milky suspension was formed without any visible particles. The formulation was then sonicated in a beaker to reduce the vesicle size and subsequently stored at 4°C until further use[11].

Step 2: Formulation of econazole nitrate entrapped spanlastic gel

Carbopol 934 (0.5%w/w) was gradually dispersed in a measured amount of distilled water and stirred continuously for 30mins to allow complete swelling and uniform gel formation. Once the gel base was fully hydrated, the previously prepared spanlastic suspension was centrifuged and the sediment was added and mixed thoroughly for 30 minutes to ensure even distribution throughout the gel. Triethanolamine was then introduced dropwise while stirring to neutralize the gel and adjust its pH to the desired level. Propylene glycol was incorporated as a penetration enhancer and methyl paraben was used as a preservative to maintain formulation stability[12].

Table No.04: Formulation Table for Preparation of Spanlastic Gel

SI. No	Ingredients	Quantity
1	Econazole nitrate loaded spanlastic (%w/w)	0.5
2	Carbopol 934 (%w/w)	0.5
3	Propylene glycol (%w/w)	0.1
4	Glycerol (%w/w)	0.3
5	Methyl paraben (%w/w)	0.02
6	Triethanolamine	q.s
7	Distilled water	q.s

Evaluation of spanlastic formulation

Particle size determination

The hydrodynamic diameter and zeta potential of the resulting dispersions were measured by dynamic light scattering using a Horiba zeta sizer, Model SZ-100.

Measurement of the entrapment efficiency

The Spanlastic dispersion was centrifuged at 10,000 rpm for 30 minutes at 4^0C. The quantity of free drug in the supernatant was determined. The amount of econazole in the aqueous phase was recorded at 271 nm. Encapsulation efficiency was calculated as follows[13,14]:

$$\% \text{ Entrapment efficiency} = \frac{\text{Total drug} - \text{unentrapped drug}}{\text{Total drug}} \times 100$$

In vitro diffusion studies

In vitro release studies of the spanlastics were conducted using an cellophane membrane, which was activated with the help of zinc chloride solution. The receptor compartment of a Franz diffusion cell, having a capacity of 20 ml and an effective diffusion area of 3.142 cm^2, was filled with phosphate-buffer of pH 7.4. The apparatus was placed on a thermostatically controlled magnetic stirrer and the temperature was maintained at 37±0.5°C throughout the experiment. All batches of drug-loaded spanlastic formulation was evaluated using this setup. At predetermined time intervals, 1 ml samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh phosphate buffer to maintain sink conditions. The collected samples were suitably diluted and analyzed using a UV spectrophotometer at λ_{max} of 340.6nm. The release profile was monitored over a 8-hour period[11,15.]

Differential scanning calorimetry (DSC)

Thermal analysis was carried out to evaluate possible drug–excipient interactions within the optimised spanlastic formulation. Any alteration in the DSC thermogram was considered indicative of such interactions. The thermogram of econazole nitrate loaded spanlastics was recorded using a Shimadzu DSC- 60 instrument equipped with an intercooler.

Scanning electron microscopy

Scanning electron microscopy (SEM) offers high-resolution imaging, making it suitable for examining materials for surface irregularities such as cracks, defects, contamination and corrosion. When a focused beam of secondary electrons interacts with the atoms of the specimen, signals are generated that provide detailed information about the surface morphology. In this study, imaging of optimised formulation was carried out using a Hitachi S-3400N instrument.

Evaluation of spanlastic gel

Visual examination

All developed gel formulae were inspected for their homogeneity , color, syneresis and presence of lumps by visual inspection after the gels have been set in the container.

Spreadability test

A 0.5 g sample of formulation was placed between two standard-sized glass slides and left undisturbed for approximately 5 minutes, allowing the material to spread naturally until no further increase in diameter was observed. The diameter of the resulting spread circle was measured in centimeters and used as an indicator of spreadability. The values reported represent the mean of three independent measurements.

pH determination

The pH of the gels was determined using digital pH meter (Systronics, µ pH system 362).The readings were taken for average of 3 times.

Viscosity determination

Viscosities of the gels were measured by using Brookfield viscometer DV- III. The spindle (S 64) was rotated at 100 rpm.

Drug content determination

A measured amount of the formulated gel as well as Placebo gel was accurately transferred into a 100 ml volumetric flask and dissolved in methanol. The flask was subjected to continuous shaking on a mechanical shaker for 2 hours to ensure complete dissolution of the drug. Following appropriate dilution, the absorbance of the solution was measured at 271 nm using a UV-visible spectrophotometer (UV-1700, Shimadzu, Japan), with Placebo gel solution serving as the blank[14,15].

In vitro diffusion studies

All the procedures followed and conditions maintained were same as described above. Selected batch of drug-loaded spanlastic gel formulation was evaluated using this setup.

In vitro antifungal activity

Preparation of inoculum:

Suspension of organism was prepared as per Mc Farland standard. A 24 hr old culture was used for the preparation of fungal suspension, suspension of organism was made in a sterile isotonic solution of sodium chloride (0.9%w/v) and the turbidity was adjusted such that it contained approximately $1.5X10^8$cells/ml. It was obtained by adjusting the optical density of the fungal suspension equivalent to mixture of 0.05ml of 1.175% of barium chloride and 9.95ml of 1% sulphuric acid.

Procedure:

- The Petri plate was washed thoroughly and sterilized in Autoclave at 121°C for 20 mins.
- Sabouraud dextrose agar medium was prepared by using distilled water and subjected to sterilization in an autoclave at 121°C for 20mins.
- Approximately 40ml of the sterilized agar medium was poured into each petri plate. After pouring into petriplates, agar was allowed to solidify while maintaining aseptic conditions.
- The agar surface was inoculated by spreading the microbial inoculum evenly over the entire surface of the solidified agar plate using sterile cotton swab.
- Wells of 10mm diameter were aseptically bored using a sterile cork borer onto the solidified agar plate.
- Three wells were bored aseptically using a cork borer: 1st well for the standard (Econozole loaded gel), 2nd for the Placebo, 3rd for the spanlastic gel(0.1g) was added using sterile syringe
- The plates were then kept in Refrigerator at 4°C for pre-diffusion.
- After pre-diffusion, the plates were incubated in an incubator at 37°C±2ºC for 24 hours.
- Antifungal activity was carried out under strict aseptic condition in triplicate and zone of inhibition was measured in mm.

Drug release kinetics

To analyze the *in vitro* drug release behavior, various mathematical models were employed to assess the release kinetics. The zero-order model (Equation 1) describes a system in which the drug is released at a constant rate, independent of its concentration. Conversely, the first-order model (Equation 2) illustrates a release pattern where the rate is proportional to the concentration of the drug

remaining in the formulation. The Higuchi model (Equation 3) explains drug release from an insoluble matrix, where the release follows a diffusion-controlled mechanism and is proportional to the square root of time, aligning with Fick's law of diffusion. The Korsmeyer-Peppas model (Equation 4) is used to characterize the drug release mechanism from polymer-based systems by establishing a relationship between the fraction of drug released and time.

$$C = k_0 t \quad (1)$$

where, C is the concentration of drug at time t, t is the time and k_0 is zero-order rate constant expressed in units of concentration/time

$$\text{Log } C_0 - \text{Log } C = \frac{k_1 t}{2.303} \quad (2)$$

where, C_0 is the initial concentration of drug and k_1 is the first order rate constant.

$$C = K_H \sqrt{t} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$\frac{M_t}{M_\infty} = K_{KP} t^n \quad (4)$$

where $\frac{M_t}{M_\infty}$ is the fraction of drug released at time t, K_{KP} is the rate constant and n is the release exponent[16].

Stability studies

The stability assessment of vesicles plays a crucial role in determining the overall stability of the formulations. This study was conducted to evaluate parameters such as physical appearance, pH, viscosity and drug content under controlled conditions of $45 \pm 2°C$ with $75 \pm 5\%$ relative humidity (RH) over the period of 3 months [17].

RESULTS

Preformulation studies of the drug:

Table No.05: Pre-Formulation Study Observations of Econazole Nitrate

Properties	Observation
Color	White powder
Odour	Odourless
Nature	White crystalline powder
Melting point	161^0C

Determination of λ_{max} of econazole nitrate in methanol:

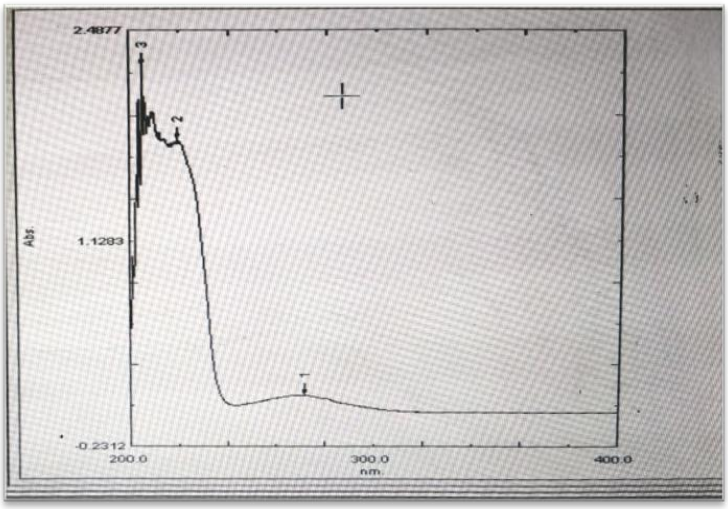


Fig No.01: Lamda Max of Econazole Nitrate Using Methanol

Scan mode: spectrum

λmax = 271.4 nm

Standard curve of Econazole nitrate

Standard calibration curve data for econazole nitrate at 271.4 nm shown in the table and standard calibration curve was plotted and shown in the below figure.

***n=3 Table No.06: Standard Calibration Curve Data for Econazole Nitrate.**

SI.No	Volume of stock-B pipetted ml	Volume made upto ml	Concentration µg/mL	Absorbance at 271.4 nm	Average absorbance ±SD	SI.No	Volume of stock-B pipetted ml
				1	2		
1	0.5	10	5	0.07	0.05	1	0.5
2	1.0	10	10	0.11	0.11	2	1.0
3	1.5	10	15	0.16	0.16	3	1.5
4	2.0	10	20	0.24	0.22	4	2.0
5	2.5	10	25	0.29	0.29	5	2.5
6	3.0	10	30	0.35	0.33	6	3.0
7	3.5	10	35	0.40	0.38	7	3.5
8	4.0	10	40	0.47	0.46	8	4.0
9	4.5	10	45	0.51	0.53	9	4.5

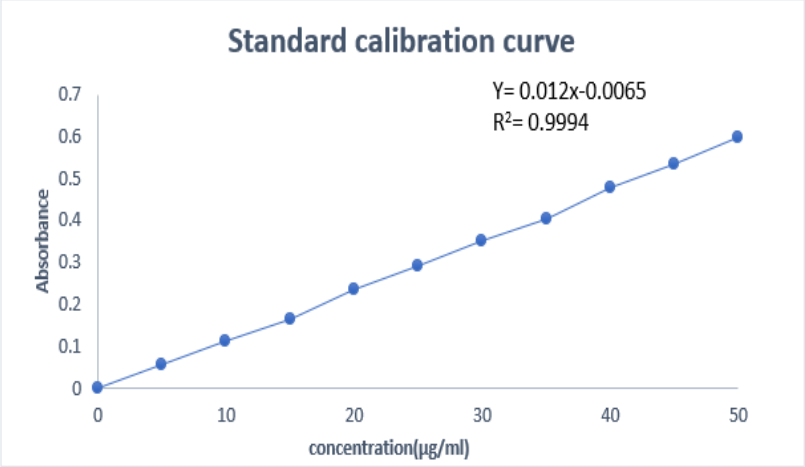


Fig No.02: Standard Calibration Curve of ECN Using Methanol

Determination of λ_{max} of econazole nitrate in Phosphate buffer 7.4:

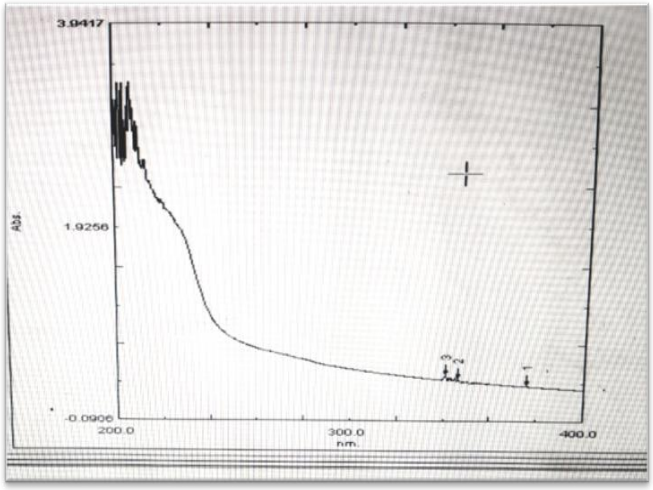


Fig No.03: Lamda Max of Econazole Nitrate Using Phosphate Buffer 7.4

Scan mode: spectrum

Λmax = 340.6nm

N=3 Table No.07: Standard Calibration Curve Data for Econazole Nitrate Using Buffer

SI. No	Volume of stock- B pipetted ml	Volume made up to ml	Concentration µg/mL	Absorbance at 340.6 nm			Average absorbance ±SD
				1	2	3	
1	1	10	10	0.01	0.01	0.01	0.01±0.01
2	2	10	20	0.02	0.02	0.02	0.02±0.08
3	3	10	30	0.03	0.03	0.03	0.03±0.02
4	4	10	40	0.04	0.04	0.04	0.04±0.09
5	5	10	50	0.05	0.05	0.05	0.05±0.01

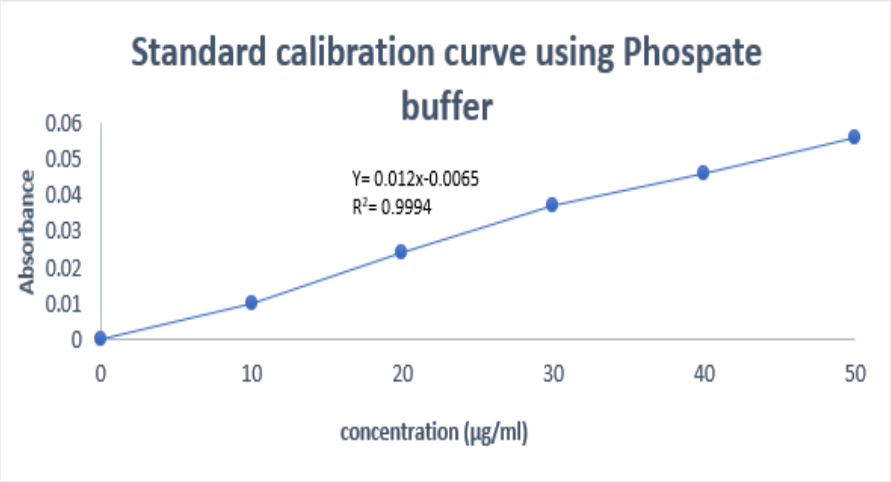


Fig No.04: ST Calibration Curve of ECN Using Phosphate Buffer 7.4

Regression analysis:

Slope:0.012

Regression coefficient:0.9994

The R^2 values confirms the linearity of concentration with change in absorbance.

Compatibility studies:

Fourier transform infrared spectroscopy:

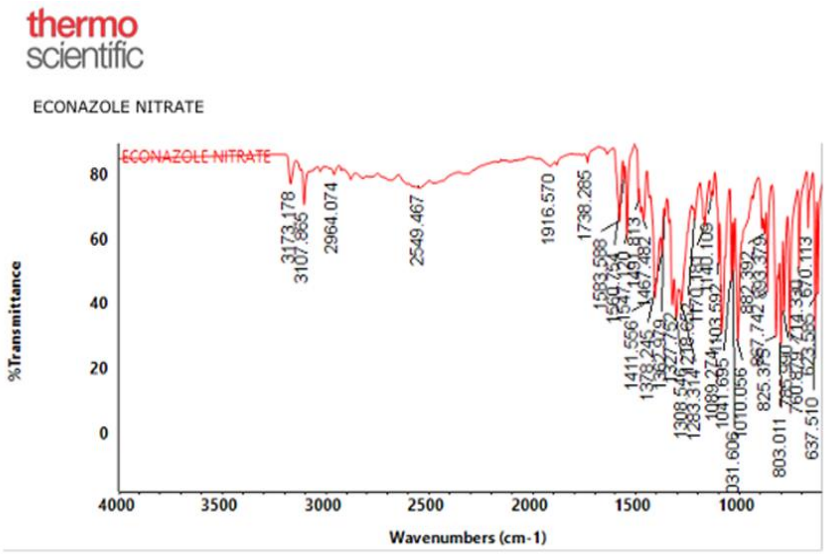


Fig No.05: FTIR Spectra of ECN

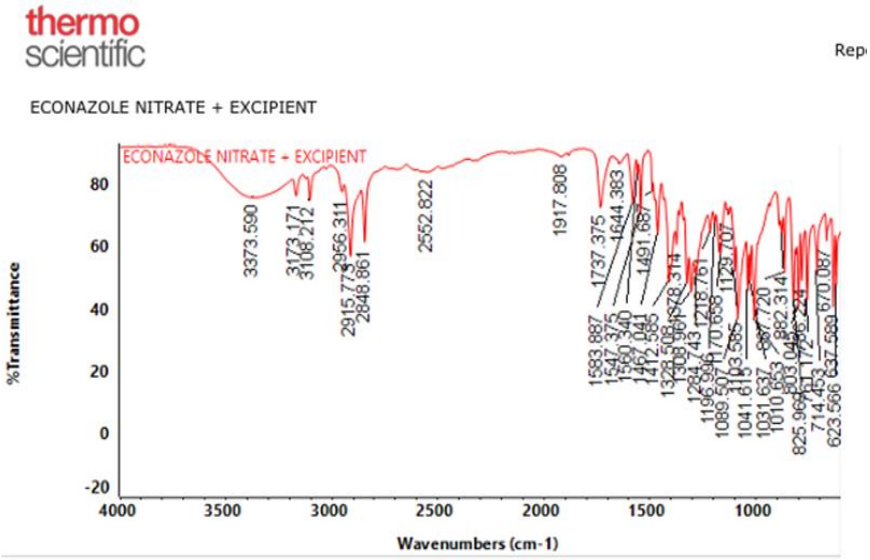


Fig No.06: FTIR Spectra of ECN + Span60

Table No.08: FTIR Spectral Data of ECN And ECN+ Span 60.

Econazole nitrate(cm^{-1})	ECN + SPAN 60(cm^{-1})	Type of vibration
3173.18	3173.17	Aromatic C–H stretch
2964.07	2956.31	Aliphatic C–H stretch
1738.29	1737.38	C=O stretch (carbonyl)
1583.59	1583.89	Aromatic C=C / C=N stretch
1491.81	1491.69	Aromatic C–C stretch
1327.75	1328.51	C–N stretch
1283.31	1284.74	Aromatic C–O stretch
1218.65	1218.76	C–O stretch
882.39	882.31	Aromatic C–H bend
825.38	825.97	Aromatic C–H bend
714.33	714.45	Aromatic C–H bend
882.39	882.31	Aromatic C–H bend

Differential scanning calorimetry

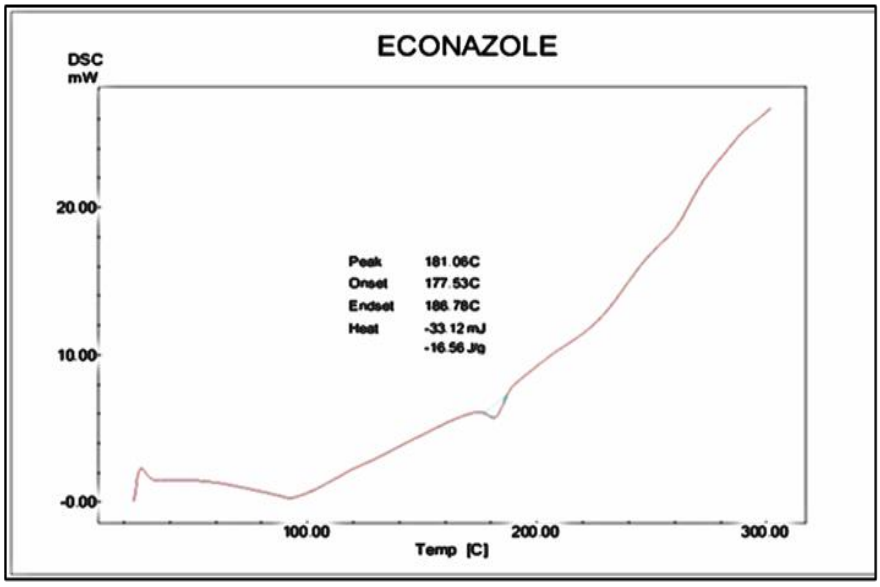


Fig No.07: DSC Report Of ECZ

Preparation and characterization of econazole nitrate spanlastic:

1. Particle size analysis:

The Horiba zeta sizer SZ-100 was used to assess the particle size of spanlastic formulation. The results of the study were shown in below table.

Table No.09: Particle Size of F1 – F10 Formulations

Formulation Code	Particle Size In NM
F1	181.4
F2	392.8
F3	122.1
F4	441
F5	260.8
F6	487.5
F7	193.9
F8	559.1
F9	394.8
F10	597.8

Response 1: Particle size

ANOVA for selected factorial model

Table No.10: Anova Model for Particle size

Source	Sum of Squares	DF	Mean Square	F-value	p-value	
Model	240,300	3	80110.19	70.79	< 0.0001	significant
A-Span 60	220,200	1	220,200	194.56	< 0.0001	
B-Type of EA	14561.86	1	14561.86	12.87	0.0115	
C-Sonication time	5586.24	1	5586.24	4.94	0.0680	
Residual	6790.08	6	1131.68			
Cor Total	247,100	9				

The Model F-value of 70.79 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

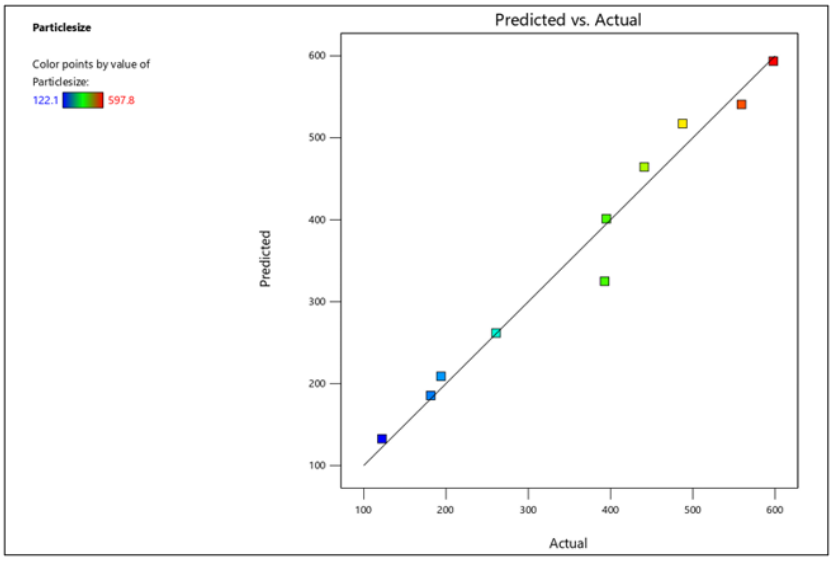


Fig No.08: Predicted VS Actual Correlation of Particle Size

Fit statistics

Table No.11: Fit Statistics Data for Particle size

Std dev	33.64	**R²**	0.9725
Mean	363.12	**Adjusted R²**	0.9588
CV%	9.26	**Predicted R²**	0.9419
		Adeq Precision	21.6661

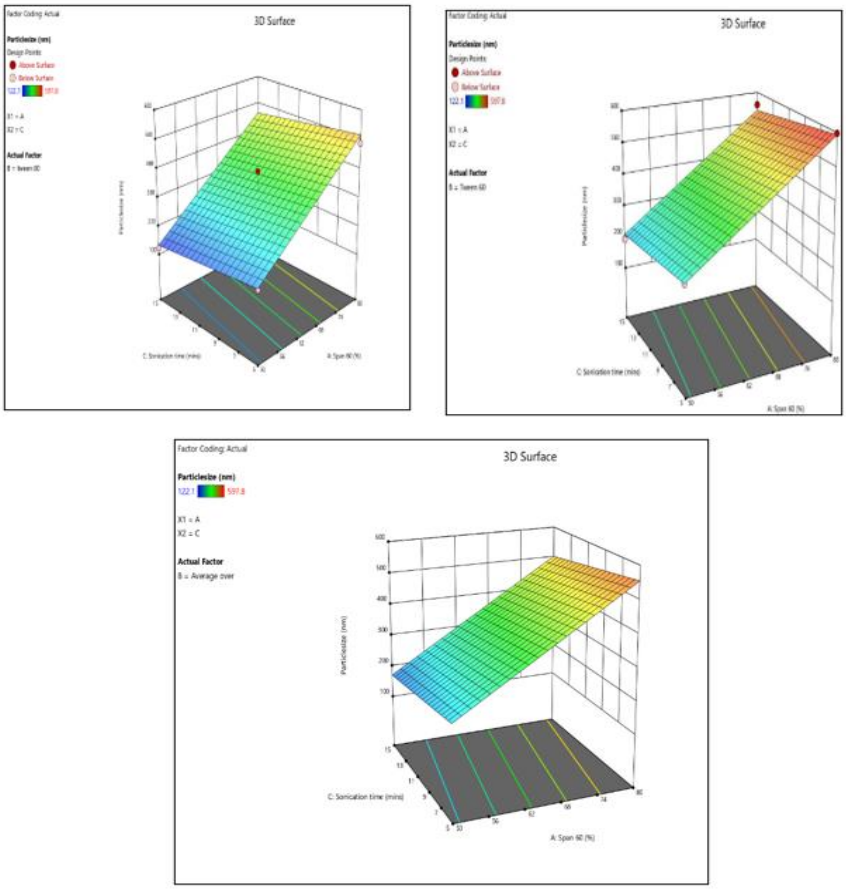


Fig No.09: 3D Response Surface Graph of Particle Size

2. Determination of %Entrapment efficiency:

The results of % Entrapment efficiency is shown in the below table.

Table No. 12: % Entrapment Efficiency of Econazole Nitrate Spanlastic Formulation

Formulation code	% Entrapment efficiency
F1	89.30
F2	91.15
F3	90.98
F4	97.55
F5	92.33
F6	97.42
F7	89.45
F8	87.4
F9	89.63
F10	85.00

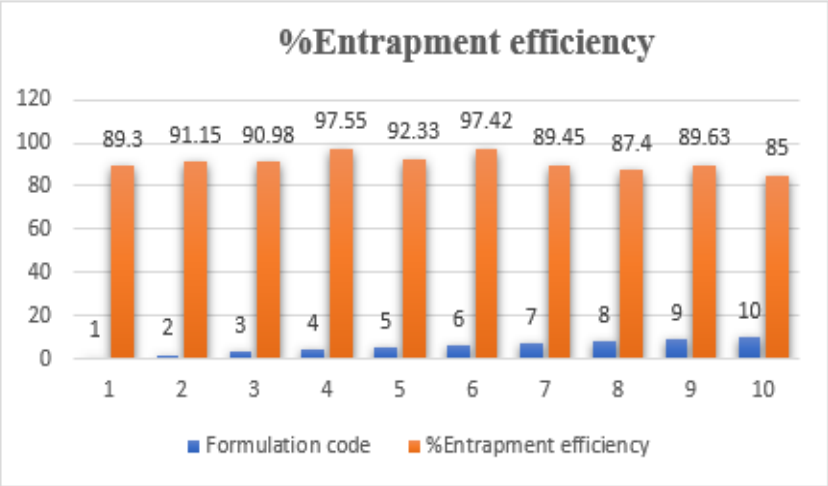


Fig No.10: %Entrapment Efficiency of Spanlastic Formulation(F1-F10)

Response 2: Entrapment efficiency

Table No.13: Anova Model for Entrapment Efficiency

Source	Sum of Squares	DF	Mean Square	F-value	p-value	
Model	126.98	3	42.33	16.86	0.0025	significant
A-Span 60	3.52	1	3.52	1.40	0.2808	
B-Type of EA	51.03	1	51.03	20.33	0.0041	
AB	72.42	1	72.42	28.85	0.0017	
Residual	15.06	6	2.51			
Cor Total	142.04	9				

Factor coding is Coded.

Sum of squares is Type III - Partial the Model F-value of 16.86 implies the model is significant. There is only a 0.25% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B, AB are significant model terms.

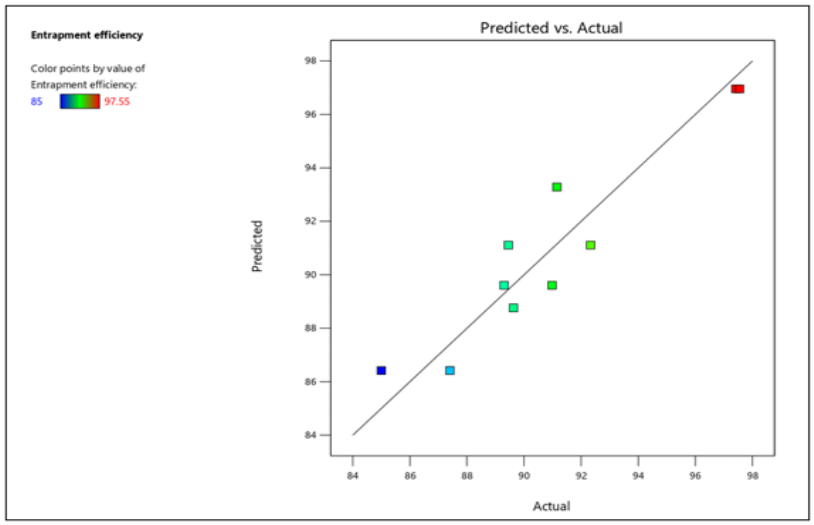


Fig No.11: Predicted Vs Actual Correlation of Entrapment Efficiency

Fit statistics

Table No.14: Fit Statistics Data for Entrapment Efficiency

Std dev	1.58	**R^2**	0.8940
Mean	91.02	Adjusted R^2	0.8410
CV%	1.74	Predicted R^2	0.7144
		Adeq Precision	10.5146

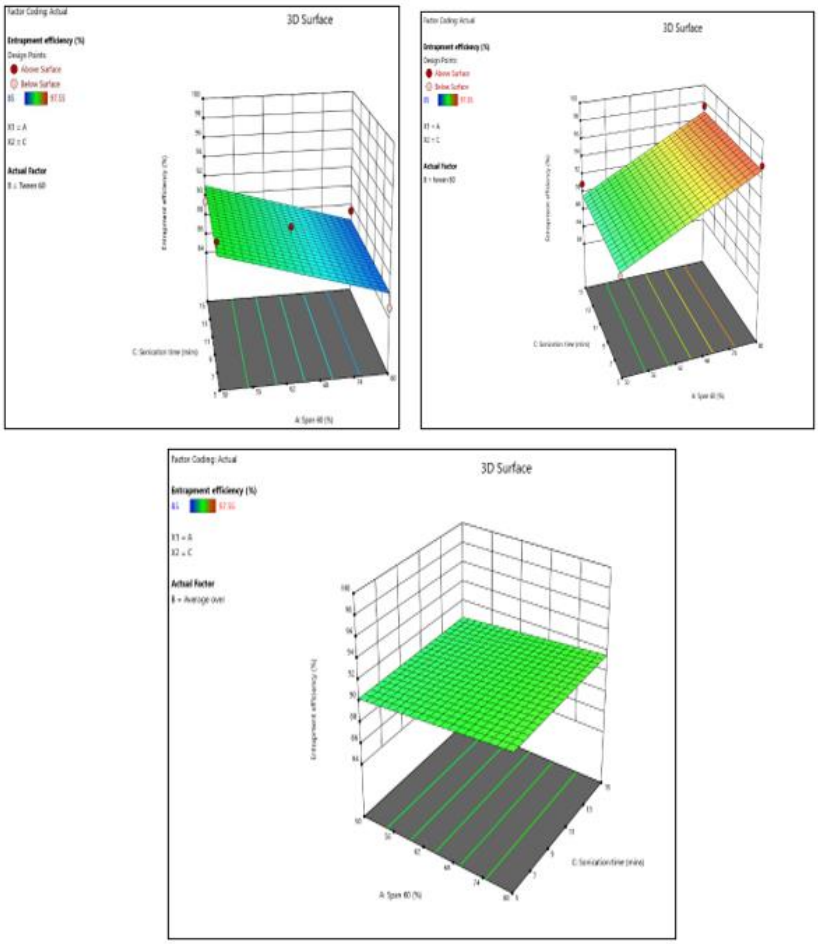


Fig No.12: 3D Response Surface Graph of Entrapment Efficiency

3. *In-vitro* release studies:

Response 3: % Cumulative drug release

Table No.15: Anova Model For %Cumulative Drug Release

Source	**Sum of Squares**	**DF**	**Mean Square**	**F-value**	**p-value**	
Model	2268.12	4	567.03	5.30	0.0481	significant
A-Span 60	2038.09	1	2038.09	19.04	0.0073	
B-Type of EA	152.33	1	152.33	1.42	0.2864	
C-Sonication time	48.86	1	48.86	0.4565	0.5292	
AB	28.84	1	28.84	0.2695	0.6258	
Residual	535.12	5	107.02			

Cor Total	2803.25	9				

The Model F-value of 5.30 implies the model is significant. There is only a 4.81% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term.

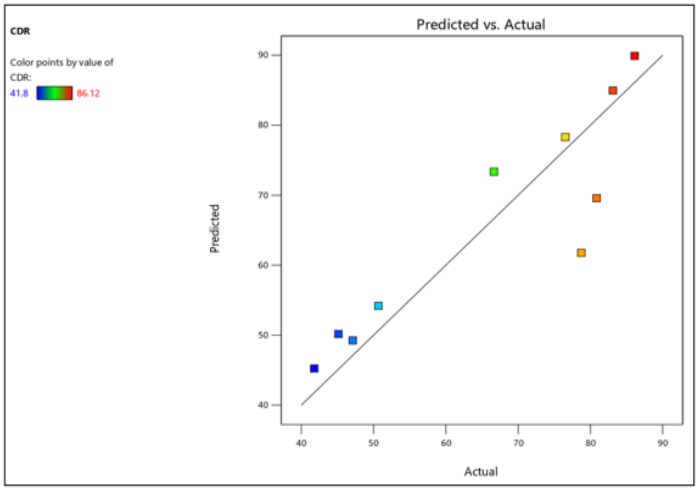


Fig No.13: Predicted VS Actual Correlation Of %Cumulative Drug Release At 8 Hour

Fit statistics

Table No.16: Fit Statistics Data For %CDR

Std dev	10.35	**R²**	0.8091
Mean	65.68	**Adjusted R²**	0.6564
CV%	15.75	**Predicted R²**	0.5316
		Adeq Precision	6.1066

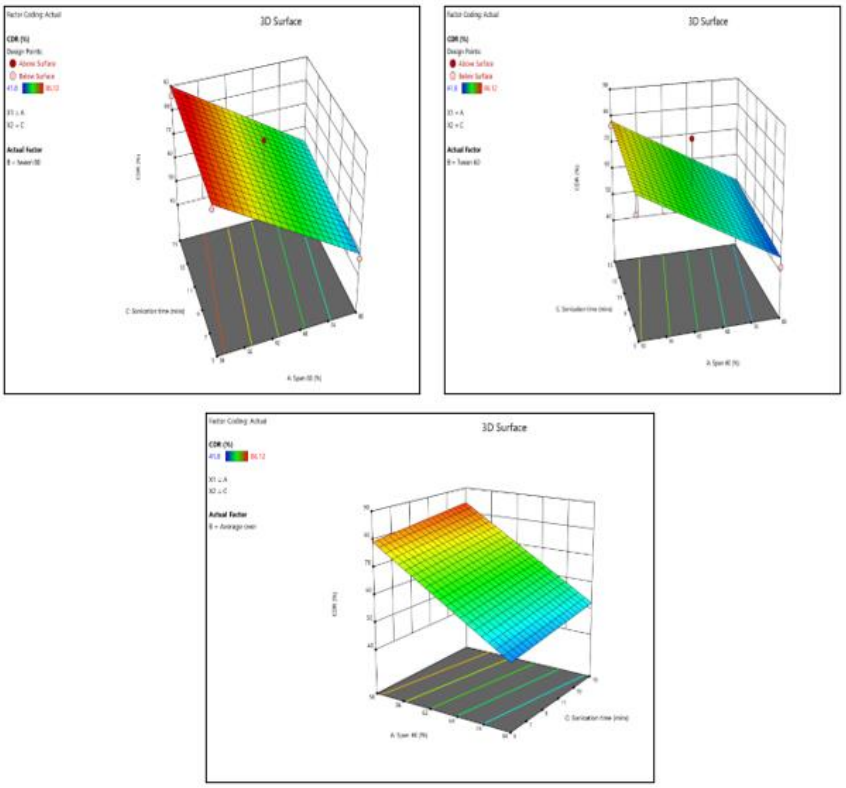


Fig No.14: 3d Response Surface Graph Of *In Vitro* Drug Release

The results of in vitro release studies is given as follows:

Table No.17: *In Vitro* Drug Release Data of Formulation F1-F6

Time In Hours	Formulation Code				
	F1	F2	F3	F4	F5
1	11.05±0.64	18.31±1.02	12.17±0.66	15.38±1.20	20.83±0.58
2	25.04±1.32	26.55±0.78	20.27±0.62	18.72±1.14	31.87±1.20
3	38.21±1.39	29.67±1.33	37.17±1.32	23.03±0.60	35.92±1.26
4	46.45±2.71	45.69±0.97	40.82±0.33	26.67±0.45	45.08±0.55
5	51.33±2.36	53.29±2.67	49.25±0.29	29.57±0.54	51.29±0.53
6	60.04±1.35	57.50±1.16	60.81±2.94	37.69±1.23	55.21±0.53
7	74.58±1.39	61.81±2.19	71.91±2.35	46.15±2.65	60.04±1.32
8	83.28±3.56	80.86±0.81	86.23±1.92	50.68±1.84	66.67±2.82

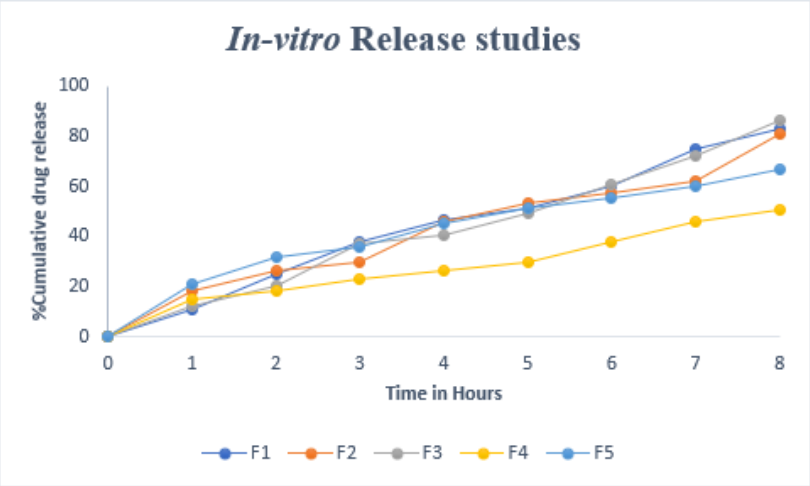


Fig No.15: *In Vitro* Drug Release Profile of F1-F5

Table No.18: *In Vitro* Drug Release Data of Formulation F6-F10

Time In Hours	Formulation Code				
	F6	F7	F8	F9	F10
1	11.17±1.82	15.32±0.67	13.72±2.07	9.80±0.63	8.42±0.66
2	17.74±1.30	22.79±0.64	16.37±0.79	20.99±0.59	10.72±1.37
3	23.75±0.45	36.35±1.35	20.09±0.83	32.71±0.63	14.04±0.76
4	27.45±0.85	44.78±1.28	23.97±1.21	44.96±1.22	17.51±0.13
5	31.27±0.36	52.58±1.35	28.97±0.58	57.75±1.92	22.98±0.79
6	36.08±2.30	57.81±0.74	33.18±0.06	63.95±0.75	29.63±0.49
7	41.92±1.45	67.00±1.93	40.49±0.76	72.10±1.41	34.69±2.11
8	47.12±1.79	76.53±1.35	45.15±0.10	78.74±0.22	41.81±1.55

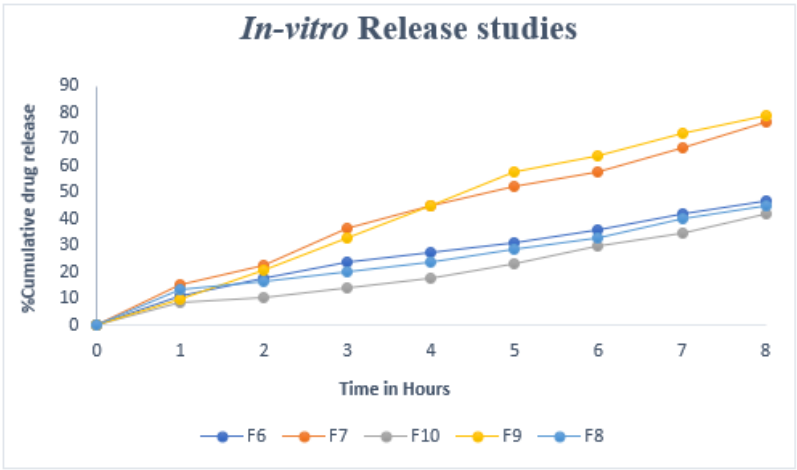


Fig No.16: *In Vitro* Drug Release Profile of F6-F10

Optimization **Factors**

Table No.19: Factors Selected for Optimization

Factors	Name	Units	Type	Minimum	Maximum	Coded low (-1)	Coded high (+1)
A	Span 60	%	Numeric	50.00	80.00	50	80
B	Type of edge activator		Categoric	Tween 60	Tween 80		
C	Sonication time	mins	Numeric	5	15	5	15

Response

Table No. 20: Responses Selected for Optimization

Responses	Name	Units	Observations	Min	Max	Mean	Std	Ratio
R1	Particle size	nm	10.0	122.1	597.8	363.12	165.70	4.90
R2	Entrapment efficiency	%	10.0	85	97.55	91.02	3.97	1.15
R3	Cumulative drug release	%	10.0	41.8	86.12	65.68	17.65	2.06

Solution for optimized formulation given by design expert

Table No.21: Solution For Optimized Formulation Given by Doe

Span 60 (%w/v)	53.184
Type of Edge activator	Tween 80
Sonication time (mins)	15
Particle size	167.851nm
Entrapment efficiency	90.387%
% Cumulative drug release	86.120

Characterisation of optimised formulation:

Table No.22: Actual And Predicted Values of Optimized Formulation

Variables	Actual value	Predicted value
Particle size	178.3± 14.6nm	167.851nm
%Entrapment efficiency	91.24±0.93%	90.387%
%CDR	85.49±2.56%	86.120%

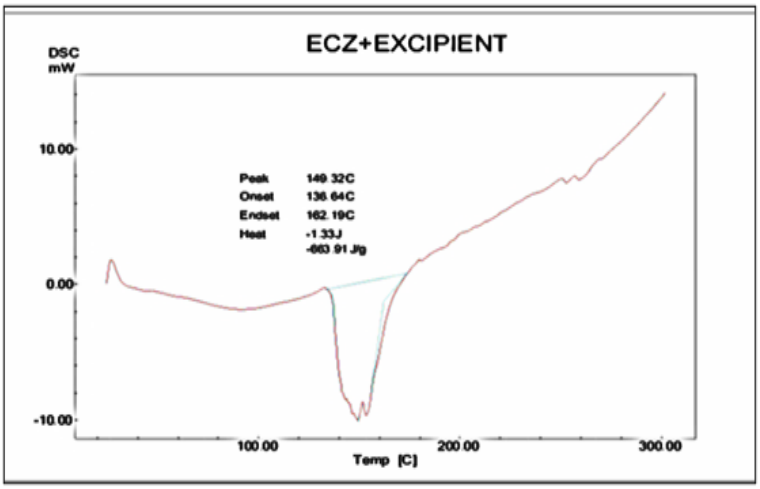


Fig No.17: DSC Report of Optimized Formulation

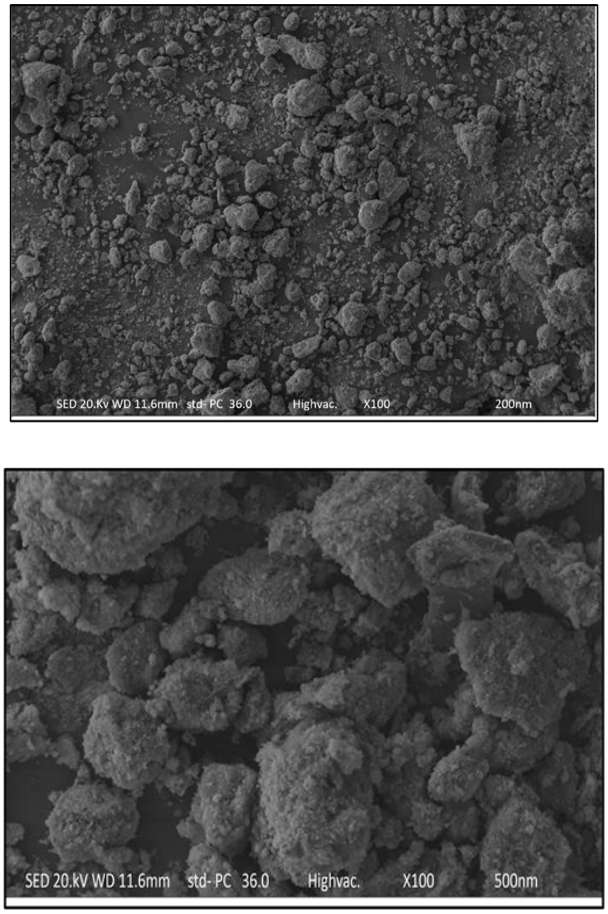
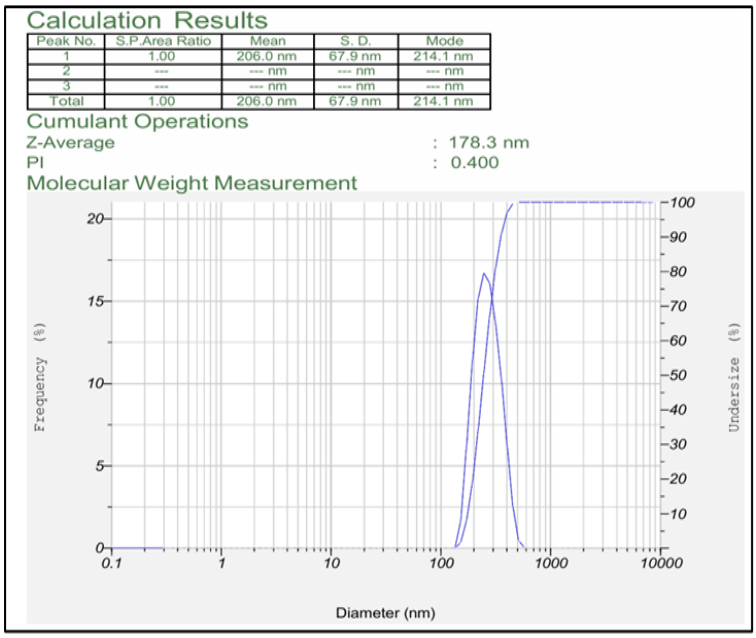


Fig No.18: Sem Images of Optimised Spanlastic Formulation



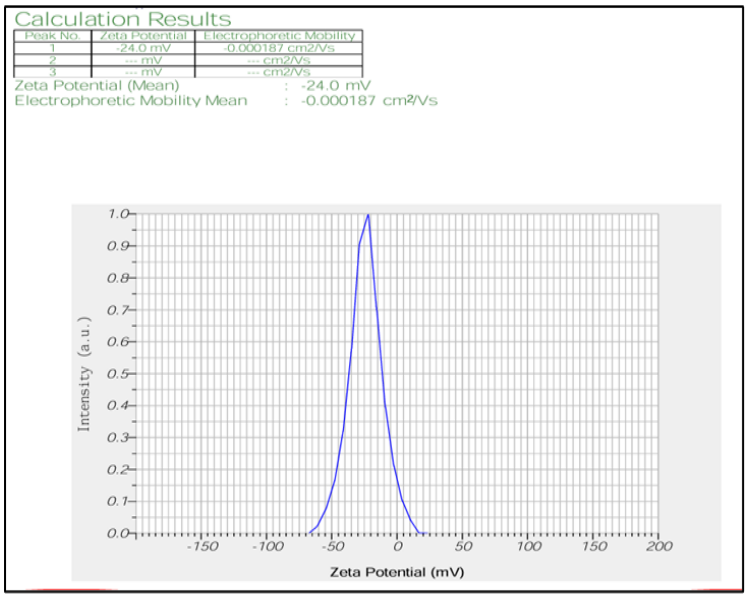


Fig No.19: Particle Size and Zeta Potential Report of Optimised Formulation

***In – vitro* drug release from optimized spanlastic formulation**

Table No.23: *In Vitro* Drug Release Data of Optimised Formulation For 8 Hours

Time in Hours	%CDR (n=3)
1	25.53±0.78
2	30.89±2.01
3	42.59±1.40
4	49.69±1.65
5	64.19±0.98
6	69.10±1.70
7	77.17±1.14
8	85.49±2.56

Drug release kinetics for optimized spanlastic formulation:

Fig No.20: Zero Order Drug Release Kinetics

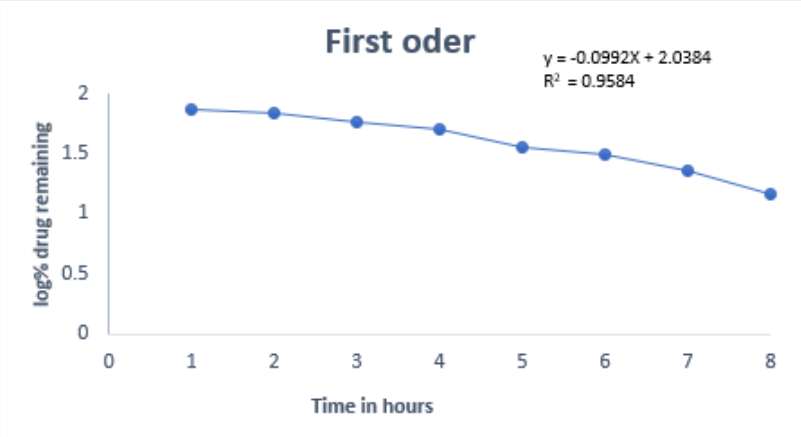


Fig No.21: First Order Drug Release Kinetics

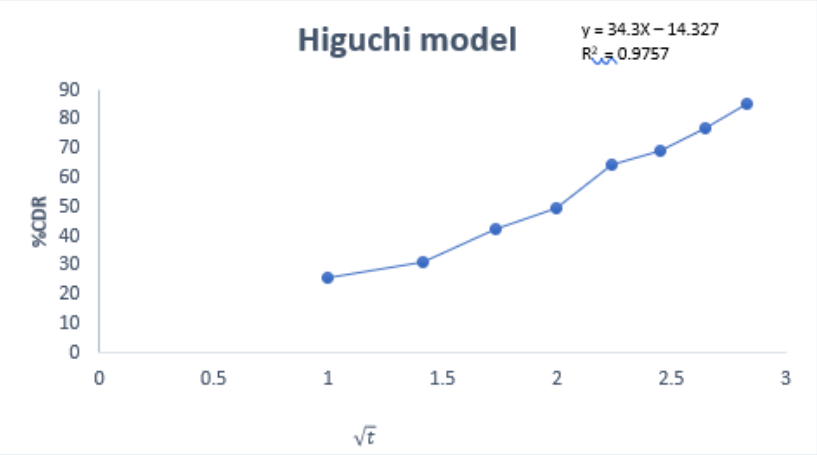


Fig No.22: Higuchi Model of Drug Release Kinetics

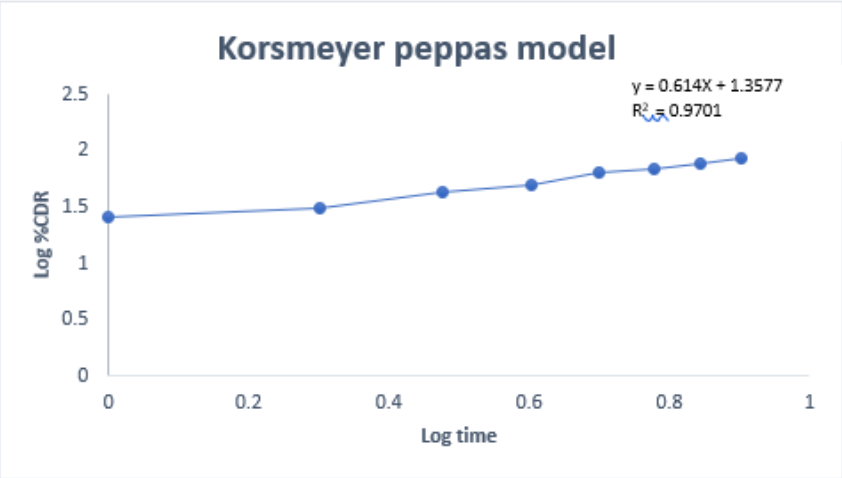


Fig No.23: Korsmeyer Peppas Model of Drug Release Kinetics

Table No.24: *In – Vitro* Drug Release Kinetics Data of Optimised Spanlastic Formulation

	Zero order	First order	Higuchi model	Korsmeyer peppas model
K_{Slope}	8.8702	-0.0992	34.3	0.614
R^2 value	0.9914	0.9584	0.9757	0.9701

Preparation of econazole nitrate loaded spanlastic gel:

Fig No.24: Gel Loaded with Optimized Spanlastic Formulation

Evaluated parameters for prepared optimized spanlastic gel

Parameters	Results
pH	6.035±0.08
Viscosity	26419±2.30cps
Spreadability	7.00±0.1cm
%Drug content	95.00±0.93%
%CDR	75.89±1.02
In vitro antifungal activity	26.50±0.03mm

Fig No.25: Determination Of Viscosity

Fig No.26: Determination Of Spreadability

In – vitro drug release from optimized spanlastic gel

Table No.26: *In-Vitro* Drug Release Data of Optimized Spanlastic Gel

Time in Hours	%CDR (n=3)
1	19.40±1.32
2	28.54±0.76
3	31.97±1.16
4	35.49±2.65
5	41.16±1.35
6	47.03±0.98
7	56.17±1.14
8	75.89±1.47

Drug release kinetics for optimized spanlastic gel:

Fig No.27: Zero Order Drug Release Kinetics

Fig No.28: First Order Drug Release Kinetics

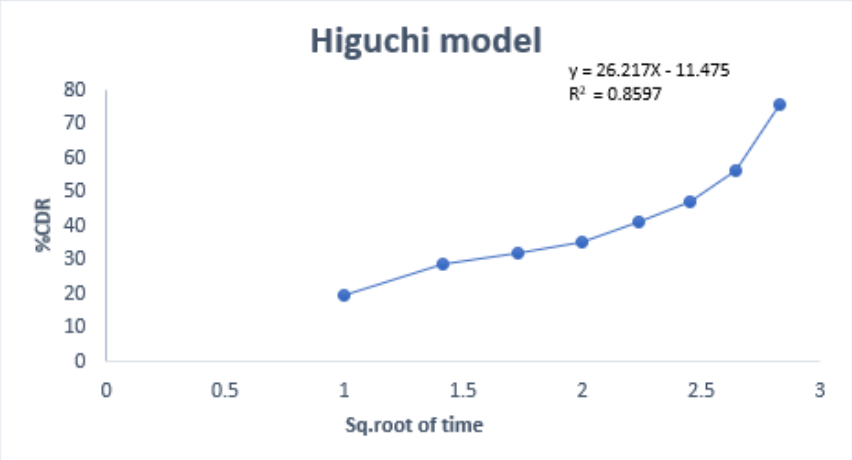


Fig No.29: Higuchi Model of Drug Release Kinetics

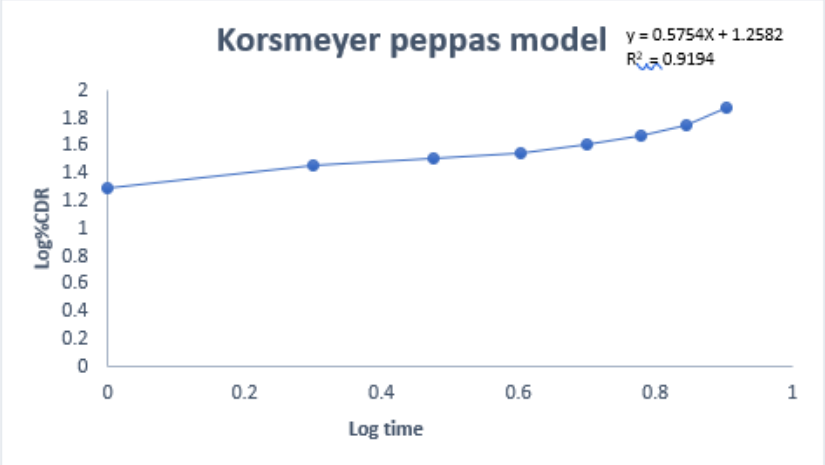


Fig No.30: Korsmeyer Peppas Model of Drug Release Kinetics

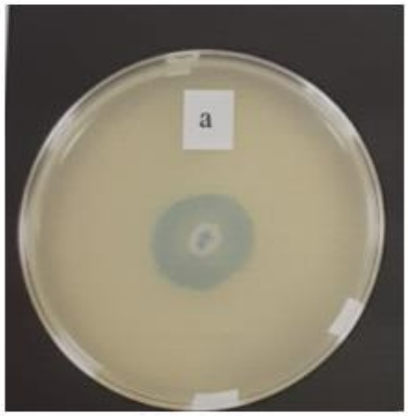
Table No.27: *In – Vitro* Drug Release Kinetics Data of Spanlastic Gel

	Zero order	First order	Higuchi model	Korsmeyer peppas model
K_{Slope}	6.9574	-0.0607	26.217	0.5754
R^2 value	0.9199	0.8014	0.8597	0.9194

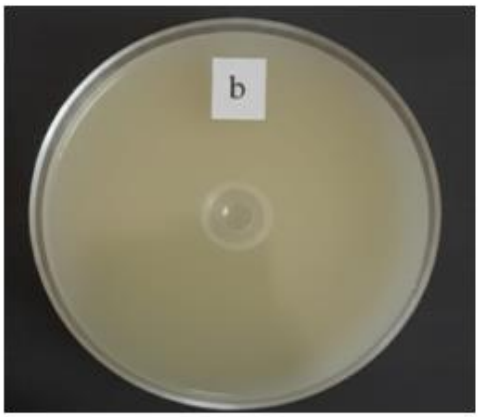
Table No.28: Stability Studies Data of Spanlastic Gel Formulation

45±0.5^{0}C and 75%±0.5 RH				
Sample type	**Sampling interval**	**Appearance**	**Drug content**	**pH**
Spanlastic gel containing econazole nitrate	0 day	White	95.00±0.93%	6.03±0.08
	90 day	White	94.07±0.65%	6.28±0.08

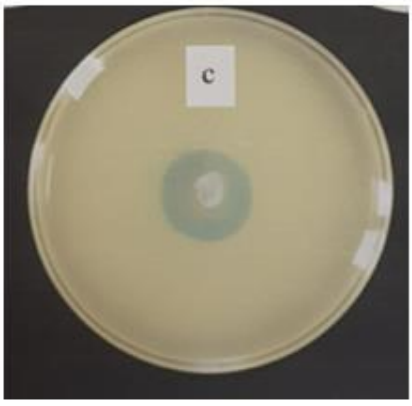
In vitro antifungal activity:



a. Standard econazole nitrate gel



b. Blank gel



c. Gel containing optimised spanlastic formulation.

Fig No.31*: In Vitro* Antifungal Activity Study Showing Zone of Inhibition

Table No.29: Zone Of Inhibition Of *In Vitro* Antifungal Activity

Products	Zone of inhibition in mm (n=3)
Standard econazole nitrate gel	27.01±0.02
Blank gel	0.00
Gel containing optimised spanlastic formulation	26.50±0.03

DISCUSSION

UV spectrophotometric method:

The absorption spectra of Econazole nitrate in Methanol showed the maximum absorption at 271.4 nm (Fig no.01) .The standard calibration curve performed using methanol at λ_{max} 271.4nm showed a linear relationship between concentration and absorbance (Fig no.02). This can be confirmed by regression coefficient value R^2= 0.9994.The Beer lambert's range was between 5- 50µg/ml. Similarly, The absorption spectra of Econazole nitrate in Phosphate buffer 7.4 showed the maximum absorption at 340.6 nm(Fig no.03) .The standard calibration curve performed using Phosphate buffer 7.4 at λ_{max} 340.6nm showed a linear relationship between concentration and absorbance(Fig no.04). This can be confirmed by regression coefficient value R^2= 0.9949. The equation obtained from the curve was used to calculate drug concentration.

Compatibility studies:

FTIR studies

The compatibility studies between pure ECN and Drug along with excipient were analysed using FTIR Spectra (Fig no.05 and 06). The graph reveals that there is no significant change in principal peaks (Table no.08) in spectra. This confirms the compatibility between the drug and the selected excipients.

DSC studies

Pure econazole displayed a sharp, well-defined endothermic melting event endset at 186.8°C (Fig no.07), confirming the purity of drug.

Design of Experiments:

To optimize the spanlastic formulation, a 2^3 full factorial design involving three independent variables at two levels each (low and high) was implemented using Design-Expert® software version 13.0. The formulation variables—Span 60 to Tween ratio, type of edge activator (Tween 60 or Tween 80) and sonication time—were selected based on insights from preliminary laboratory experiments and supporting literature. These factors were systematically varied across ten experimental runs, covering all possible combinations. Ethanol injection method was employed for the formulation of spanlastics(F1-F10). The corresponding effects on critical quality attributes, including percentage cumulative drug release, particle size and entrapment efficiency were evaluated. Throughout all batches, the concentration of econazole nitrate (ECN) was maintained constant, as established through prior experiments to ensure consistency. The resultant optimised formulation obtained from the solutions given by the software was incorporated into the gel.

Particle size

The particle size of all the prepared Spanlastic formulation (F1-F10) ranged from 122.1nm to 597.8nm (Table no.09). The nano-size range is

<1000nm, since the maximum particle size is 597.8nm, it may be concluded that the desired nanosize particles were achieved by the process. The effect of various independent variables on particle size is explained by the following polynomial equation

Particle size = 363.12+ 165.90A- 38.16B- 26.43C.

Where,

A = Span 60

B = Type of edge activator

C = Sonication time.

Thus, the results of study indicated that particle size were influenced by the concentration of span 60 and tween 80 or tween 60 . As the concentration of Span 60 increases from the ratio of 50:50 to 80: 20 it resulted in increase in the particle size range from 122 – 597nm. Increase in the concentration of edge activators used were found to decrease the particle size and aided in formation of vesicles of desired size range. The duration of sonication aided in decreasing the particle size, increased sonication time from 5- 15mins reduced particle size.

The reponse analysed by 2^3 factorial design which showed F value of 70.79 and P value < 0.0001indicating significant reponse(Table no.10). The actual and predicted values of particle size were correlated as shown in the fig.no.08. They were found to be in good correlation confirming the robustness of the process.

The Table no.11 reveals that Predicted R^2 of 0.9419 was in reasonable agreement with the Adjusted R^2 of 0.9588; i.e. the difference is less than 0.2.

Adeq Precision measures the signal to noise ratio. Here ratio was greater than 4 which was desirable. The ratio of 21.666 indicates an adequate signal. This model can be used to navigate the design space.

The Fig no.09 clearly indicates increase in the particle size with increase in span 60 concentration also Tween 80 used as edge activator provides smaller particle size in comparison to tween 60. Prolonged sonication time had decreased particle size, which is desirable.

Entrapment efficiency

The study of % Entrapment efficiency revealed that the prepared spanlastics had good Entrapment efficiency property ranging from 85.0% - 97.55%(Table no. 12). The effect of various independent variables on particle size is explained by the following polynomial equation

Entrapment efficiency = 91.02+ 0.6637A+ 2.26B+ 3.01AB.

Where,

A = Span 60

B = Type of edge activator

AB = span 60 + EA

The equation explains that, Span 60 alone does not have a strong direct effect on Entrapment efficacy, type of edge activator significantly influences %EE. Different edge activators used like tween 60 and tween 80 strongly impact vesicle properties and thus entrapment. This means the effect of one factor depends on the level of the other.

The response was analyzed by 2^3 factorial design which showed F values of 16.86 and P value of < 0.0500 indicating a significant response(Table

no.13). The actual and predicted values of percentage drug entrapment was almost similar and had a good correlation as shown in the fig.no 11.

Table no.14 shows that Predicted R^2 of 0.7144 is in reasonable agreement with the Adjusted R^2 of 0.8410; i.e. the difference is less than 0.2.

Adequate Precision measures the signal to noise ratio. Since the ratio was 10.515 which is greater than 4, it indicates an adequate signal. This model can be used to navigate the design space.

Fig no.12 shows that with Tween 80, Span 60 concentration plays a major role in enhancing entrapment. At higher Span 60:Tween 80, vesicles are more stable and entrap more drug. From this we can conclude that as the Type of edge activator along with Span 60 exhibits noticeable effect upon percentage drug entrapment. However, sonication exhibits slight impact on entrapment, extended sonication time improved encapsulation efficiency.

In vitro drug release

In vitro drug release of F1-F10 ranged from 41.8 – 86.38% (Table no 17 and 18). The effect of various independent variables on particle size is explained by the following polynomial equation,

%CDR = 65.68- 15.96A+ 3.90B+ 2.47C- 1.90AB

Where,

A = Span 60

B = Type of edge activator

C = Sonication time.

AB = Span60 + EA.

The response was analyzed by 2^3 factorial design which showed F values of 5.30 and P value of < 0.0500 indicating a significant response(Table no.15). The actual and predicted values of percentage *In vitro* drug release was correlated as shown in the fig.no.13.

The data from Table no.16 indicates that predicted R^2 of 0.5316 is in reasonable agreement with the Adjusted R^2 of 0.6564; i.e. the difference is less than 0.2.

Adequate Precision measures the signal to noise ratio. Since the ratio obtained was 6.107 which is greater than 4 is ,indicates an adequate signal. This model can be used to navigate the design space.

Fig.no.14 explains that, among the studied factors, Span 60 concentration (A) had the significant impact , while the type of edge activator (B), sonication time (C) and interaction (AB) had minor effect upon the *in vitro* release of drug from vesicles. These findings indicate that drug release is predominantly governed by the proportion of Span 60 in the formulation, with higher concentrations resulting in more rigid vesicles and reduced release rates. Among edge activators i.e tween 60 and tween 80 , surfactant mixture containing tween 80 as edge activator showed better release in comparison to tween 60. With increase in sonication time there was increase in drug release from formulation

Design of experiments and optimisation

In the present study, three independent variables (factors) were selected for the optimization of the formulation using a systematic design of experiments (DoE) approach, as summarized in Table no.19. These included:

Span 60 concentration (A): A non-ionic surfactant used as a vesicle former, varied between 50% and 80%.

Type of edge activator (B): A categorical variable with two levels—Tween 60 and Tween 80—which serve to modulate the flexibility and permeability of the vesicle membranes.

Sonication time (C):This was varied from 5 to 15 minutes to assess its impact on particle size and drug entrapment.

Among these, Span 60 concentration and sonication time are continuous numeric factors and were coded using low (-1) and high (+1) values for statistical modeling. The type of edge activator is a qualitative categorical variable and was included to evaluate the comparative performance of the two surfactants.

The responses measured to assess the impact of these factors are presented in Table no.20:

Particle size (R1): A critical parameter affecting drug release and bioavailability, ranging from 122.1 to 597.8 nm, with a high standard deviation (165.70), indicating significant variability across formulations.

Entrapment efficiency (R2): Representing the percentage of drug successfully encapsulated within the vesicles, values ranged from 85% to 97.55%, with relatively low variability (standard deviation: 3.97).

Cumulative drug release (R3): Measuring the extent of drug release over time, values ranged from 41.8% to 86.12%, with moderate variability (standard deviation: 17.65).

The particle size (R1) exhibited the greatest variability (max/min ratio = 4.90), suggesting it is highly sensitive to changes in formulation parameters. In contrast, entrapment efficiency (R2) showed minimal variation (max/min ratio = 1.15), indicating that it was less influenced by the selected factors within the studied range. Cumulative drug release (R3) presented a moderate range of variation (ratio = 2.06), suggesting that formulation variables moderately influenced the drug release profile.

Optimised formula

Solution for optimized formulation given by design expert is given in the table no.21 which suggested 53.185w/v of span 60 , tween 80 as edge activator with 15 mins of sonication time. Drug concentration was maintained at 1%w/v. Formulation was prepared using ethanol injection method.

Characterisation studies of the optimised formulation

DSC Studies: The physical mixture (ECZ + excipient) showed a the principal endothermic event was shifted to lower temperature endset 162.2 °C (Fig no.17). This confirms the encapsulation of econazole in the spanlastics.

Scanning electron microscopic study: The shape and surface characteristics of prepared spanlastics were evaluated by means of scanning electron microscopy (SEM). The results of SEM revealed that prepared vesicles were discrete and spherical in shape with a rough outer surface(Fig no.18). The spherical structure of vesicles is due to the amphipilicity of non ionic surfactant which reduces the surface free energy and leads to formation of nanospanlastics in the aqueous dispersion medium.

Regression Analysis

The formulation was optimized using desirability method of numerical optimization. The optimum

settings for dependent and independent variables were defined. The set criteria for all independent variables and dependent variables are shown in the Table no.01 and 02 . All the response variables are subjected to the regression analysis to determine the regression coefficients and all the dependent variables were found to be significant. The optimized formulation was prepared in accordance with the predicted model and studied for responses. The results clearly indicated that all the dependent factors had an important role in the preparation of ECN spanlastic gel. The actual and predicted values of optimized formulation were compared as shown in table no.22 and are in close agreement with each other.

Particle size and zeta potential: The optimised formulation had the particle size of 178.3± 14.6nm and zeta potential of -24.0±2.41mV which is shown in Fig no.19. This shows that the prepared spanlastic vesicles were suitable for topical delivery and the zetapotential value indicates the stability of the particles over the period of time.

%Entrapment efficiency: The %entrapment efficiency was found to be 91.24±1.85% , the maximum encapsulation is due the lipophilic nature of drug as well as the non ionic surfactant used in the formulation.

In vitro drug release: The %CDR obtained was 85.49±2.56%(Table no.23), this ensures that the maximum drug concentration is delivered from the formulation by the end of 8 hour.

Kinetic modelling

Different models(Fig no.20,21,22 and 23) were adopted to study the drug release data. The result of *in-vitro* drug release data for the optimized formulation showed that it follows Zero order kinetics based on the regression coefficient value of 0.9914(Table no.24).

Formulation of spanlastic gel loaded with econazole nitrate

The optimised formulation obtained from the design expert software was incorporated into the gel. Carbopol 934 was used as gelling agent along with which triethanolamine was used to adjust pH , propylene glycol acted as permeation enhancer, glycerine as humectant and methyl paraben was used as preservative.

Evaluation of gel

Visual Examination

The formulation was white, homogenous without any gritty particles.

pH

Skin compatibility is the primary requirement for a good formulation. It was found that the pH of all the spanlastic gel formulation was 6.035 ± 0.08 (Table no.22), that suits the skin pH indicating the skin compatibility.

Spreadability

Proper spreadability ensures that the drug is evenly distributed over the application site. This is critical for localized treatment of antifungal agents. The value of spreadability of spanlastic gel formulation was 7.0±0.1cm(Table no.25). Spreadability depends on the viscosity of the gel and concentration of the polymer. The value of spreadability indicate that the gel is easily spreadable with minimal shear.

Viscosity

Viscosity plays a critical role in the performance of topical gels by influencing spreadability, drug release, residence time, stability and patient acceptability. Viscosity of spanlastic gel was

found to be 26419±2.30cps (Table no.22). Viscosity of formulation mainly depends on the type of gelling agent and its concentration.

Drug Content

The drug content of formulation was found to be 95.00±0.93% (Table no.22) which guarantees that the formulation will produce the desired therapeutic outcome.

In Vitro Drug Release

The *in vitro* drug release from plain spanlastic dispersion (85.49±2.56% in 8 h)(Table no.20) was higher compared to the gel-incorporated formulation (75.89±1.47% in 8 h)(Table no.23). This reduction can be attributed to the additional diffusion barrier created by the gel matrix, increased viscosity and possible interactions between the polymer and vesicles. Incorporation into gel thus transforms the rapid release profile of spanlastics into a more controlled and sustained release system, which is desirable for topical drug delivery.

Kinetic Modelling

Different models(Fig no.27,28,29 and 30) were adopted to study the drug release data. The result of *in-vitro* drug release data for the optimized formulation showed that it follows Zero order kinetics based on the regression coefficient value of 0.9914(Table no.27).

Stability Studies

The results of stability study(Table no.28) indicate that the spanlastic formulation proves to remain stable after storage for one month under conditions such as 40±2^{0}C and 75±5%RH. Any remarkable difference was not found in the formulation even after 3 month , Hence the prepared formulation is considered as stable.

In Vitro Antifungal Activity

The *in vitro* antifungal study comparing the standard econazole nitrate gel and the spanlastic gel showed a similar zone of inhibition(Fig no.31), indicating that incorporation of the drug into the spanlastic system did not alter or reduce its antifungal efficacy. This finding from Table no.29 confirms that the drug retained its activity after formulation and that the excipients used were compatible with the drug. Although both formulations produced comparable inhibition zones, the spanlastic gel is expected to offer additional benefits such as enhanced skin penetration, sustained release and improved local retention, which may not be reflected in the agar diffusion assay.

CONCLUSION

The study aimed to develop a spanlastic gel of Econazole nitrate (ECN) to enhance solubility and topical delivery. Spanlastics, elastic vesicular carriers of Span 60 and Tweens, enable deeper skin penetration and sustained release. ECN purity was confirmed by preformulation studies; UV, FT-IR, and DSC analyses indicated compatibility with excipients. Spanlastics were prepared by ethanol injection using a 2^3 factorial design to evaluate effects of formulation variables on particle size, entrapment efficiency and drug release. Higher Span 60 improved entrapment, while Tween 80 and sonication reduced particle size and enhanced release. Optimized vesicles were incorporated into 0.5% Carbopol gel, exhibiting desirable pH, viscosity, spreadability, stability and antifungal activity. The formulation showed zero-order drug release, confirming its potential as an effective topical antifungal system.

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