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FORMULATION AND EVALUATION OF GRISEOFULVIN-LOADED NANOSPONGES INCORPORATED IN HYDROGEL

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ABSTRACT

Griseofulvin, a BCS Class II drug with poor aqueous solubility, is widely used to treat dermatophytic infections. To improve its solubility and topical delivery, Griseofulvin-loaded nanosponges were formulated and incorporated into a hydrogel. The nanosponges were prepared using the emulsion solvent diffusion method with ethyl cellulose, polyvinyl alcohol, and dichloromethane. The optimized nanosponge formulation (F4) was then incorporated into a hydrogel base using Carbopol 934, propylene glycol, and triethanolamine. Various physicochemical and in vitro evaluations confirmed the effectiveness and stability of the final formulation.

Keywords: Griseofulvin; BCS Class II; Nanosponges; Hydrogel; Carbopol 934; Propylene glycol

INTRODUCTION

Topical drug delivery offers significant advantages for localized treatment, especially in the management of skin infections. It allows for direct drug application at the site of action, thereby minimizing systemic side effects and improving patient compliance. However, the efficacy of many antifungal drugs in topical formulations is often limited by their poor aqueous solubility and low permeability through the skin **[1, 2]**. To overcome these limitations, advanced drug delivery systems such as nanosponges have emerged as a promising strategy.

Griseofulvin, a fungistatic agent belonging to the Biopharmaceutical Classification System (BCS) Class II, is widely used for the treatment of superficial fungal infections

such as dermatophytoses caused by Microsporum, Trichophyton, and Epidermophyton species. Griseofulvin acts by binding to the fungal microtubules (tubulin), interfering with mitosis and inhibiting fungal cell division. Despite its effectiveness, Griseofulvin suffers from poor water solubility and limited bioavailability, which restricts its formulation into effective topical delivery systems. Currently, no topical Griseofulvin products are commercially available, which highlights the need for novel formulation approaches **[3-5]**.

Nanosponges, a relatively new class of carrier systems, offer unique structural features that make them suitable for drug delivery. These porous, nanoscale particles can encapsulate both hydrophilic and lipophilic drugs, enhancing solubility, stability, and controlled release. When incorporated into hydrogels, nanosponges can further improve drug retention on the skin, increase permeation, and sustain drug release over time **[6-7]**. This makes nanosponge-loaded hydrogels ideal candidates for topical application.

The present study focuses on the formulation and evaluation of Griseofulvin-loaded nanosponges incorporated into hydrogel for enhanced topical delivery. The nanosponges were prepared using ethylcellulose and polyvinyl alcohol via the emulsion solvent diffusion method, while Carbopol 930 was used as the gelling agent in hydrogel formulation. Propylene glycol was used as a penetration enhancer, and triethanolamine was employed to adjust the pH of the gel. The prepared formulations were evaluated for preformulation characteristics, entrapment efficiency, in vitro drug release, permeability, and various physicochemical properties including pH, spreadability, viscosity, and stability **[8]**.

This investigation aims to develop a stable and effective topical formulation of Griseofulvin with improved therapeutic efficacy, enhanced patient compliance, and potential for commercial development.

MATERIALS AND METHODS

Materials

Griseofulvin was obtained as a gift sample from a reputed pharmaceutical company. Ethyl cellulose and polyvinyl alcohol (PVA) were procured from Sigma Aldrich. Dichloromethane (DCM), methanol, ethanol, and acetone were of analytical grade and purchased from Merck India. Carbopol 934, triethanolamine, and propylene glycol were used for hydrogel formulation and were obtained from Loba Chemie, Mumbai. All chemicals used were of analytical grade.

Methods

Preformulation Studies

Preformulation studies were conducted to determine the physicochemical properties of the drug including physical appearance,

melting point, solubility, pH, partition coefficient, identification tests, and FTIR spectroscopy **[9-11]**.

Physical Appearance:

The physical appearance of Griseofulvin was observed visually and recorded in terms of color and odor.

Identification Test:

The drug was subjected to a color reaction test as per Indian Pharmacopoeia standards where a wine red color indicates positive identification.

FTIR Spectroscopy:

FTIR analysis was performed to confirm the drug identity and to evaluate compatibility with excipients. The spectra were recorded using KBr pellet method and analyzed for characteristic peaks.

Melting Point Determination:

Melting point was determined using the capillary tube method and compared with the standard.

Solubility Studies:

Solubility was assessed in various solvents including water, ethanol, methanol, acetone, PBS pH 6.8, and PBS pH 7.4.

pH Determination:

The pH of a 1% w/v aqueous solution of the drug was measured using a digital pH meter.

Partition Coefficient:

The log P value was determined using the shake flask method with n-octanol and water.

Preparation of Nanosponges

Nanosponges were prepared using the emulsion solvent diffusion method. Ethyl cellulose was dissolved in dichloromethane to form the organic phase. The drug Griseofulvin was added to this solution. Separately, an aqueous phase of polyvinyl alcohol (PVA) was prepared. The organic phase was added dropwise into the aqueous phase under continuous stirring at 1000 rpm for 2–3 hours. The resultant nanosponges were collected by filtration, washed with distilled water, and dried at room temperature.

Evaluation of Nanosponges [12-16]

Scanning Electron Microscopy (SEM):

SEM was used to determine the surface morphology, shape, and size of the nanosponges.

Entrapment Efficiency:

Entrapment efficiency was determined by centrifuging the nanosponge suspension and measuring the amount of unentrapped drug in the supernatant using UV spectroscopy at a suitable wavelength.

In Vitro Drug Release:

The in vitro release was studied using a Franz diffusion cell with phosphate buffer saline as receptor medium. Samples were withdrawn at predefined intervals and analyzed spectrophotometrically.

Preparation of Nanosponge Hydrogel

The optimized nanosponge formulation (F4) was incorporated into hydrogel. Carbopol

934 was used as a gelling agent, which was dispersed in water and allowed to swell overnight. Propylene glycol was added as a penetration enhancer and triethanolamine was used to adjust the pH. The nanosponge suspension was then added slowly under gentle stirring to obtain a uniform gel.

Evaluation of Nanosponge Hydrogel

Physical Appearance, Clarity, and Homogeneity:

Formulations were visually inspected for color, transparency, and presence of lumps.

pH Measurement:

pH was measured using a calibrated digital pH meter.

Viscosity Measurement:

Viscosity was measured using a Brookfield viscometer.

Spreadability:

Spreadability was evaluated using a glass slide method and calculated in terms of g·cm/min.

Extrudability:

Extrudability was assessed based on the quantity of gel extruded through a collapsible tube on application of weight.

Drug Content:

Drug content was determined by dissolving an accurately weighed quantity of gel in methanol and analyzing by UV spectrophotometry.

Drug Permeability Study: Performed using Franz diffusion cells with synthetic membranes. Samples were withdrawn at intervals and analyzed.

Drug Release Kinetics:

Data from in vitro release studies were fitted to zero-order and first-order kinetic models to determine the release mechanism.

Stability Studies:

Stability study of the optimized formulation (F4) was conducted over 30 days. Samples were evaluated at intervals for physical appearance, clarity, drug content, and homogeneity **[12-16]**.

3. RESULTS AND DISCUSSION

Preformulation Studies

Physical Appearance: The griseofulvin was found to be white powder (Specification – White powder). The result is given in **Table 1**.

Identification test

A wine red colour observed according to I.P.

FT-IR spectra: - The comparison of the IR spectrum revealed that there are no changes in the position of absorption bands of groups and bonds **(Figure 1 and 2, Table 2)**.

Calibration curve

A calibration curve of the drug was developed using the methanol. It was observed that a perfect linearity between the concentration of the drug and absorbance was obtained in the range. **Table 3 and Figure 3** show the calibration of griseofulvin using methanol.

Determination of pH (1% W/V solution in water) The pH of griseofulvin was found to be acidic

Partition coefficient: - If the value of log p of a compound is greater than 1 it considers as lipophilic but if the value is less than 1 it considers as hydrophilic in nature. Partition coefficient of griseofulvin was found to be 2.30 so the drug Griseofulvin is lipophilic in nature.

Solubility determination: - The following are the solubility profile for Griseofulvin Drug shown in **Table 4**.

Melting point

Melting point was found to be in range between 216-223^{O}C. (Specification 217^{O}C - 224^{O}C).

Drug Excipient compatibility

Drug and excipient chemical changes determined by IR analysis. It was used to ensure that no chemical interaction occurred between the drug and excipients, no changes are observed in the position of the bands in the spectra. This clearly suggests that the Drug remains in the same form even in its formulations indicating that there is no interaction between the drug and the polymer used for the study **(Figure 4, 5 and 6, Table 5)**.

Evaluation of Nanosponge

Vesicle shape and size

The scanning electron microscopy images show that the surface of prepared Nanosponges was spherical in shape, uniform in size and its surface was porous in nature **(Figure 7)**.

The entrapment efficiency was determined for all nanosponge formulations as listed in **Table 6**. The variation in entrapment efficiency was due to the change in the polymer concentration and difference in degree of cross linking. The entrapment efficiency was highest for F3 the formulation having least particle size and high entrapment efficiency was found **(Figure 8)**. ***In vitro*** **drug release of Nanosponge Formulation**

The in vitro drug release is given in the **Table 7 and Figure 9**.

Evaluation of Nanosponge hydrogel

Physical appearance

All the gel formulation of Nanosponge Hydrogel was colorless **(Table 8)**.

Homogeneity

All the gel formulation of Nanosponge Hydrogel showed absence of lumps and having good homogeneity **(Table 9)**.

Clarity

All the gel formulation of Nanosponge Hydrogel was found to be transparent and no presence of particle **(Table 10)**.

Viscosity

Viscosity of the following formulation is given in **Table 11**.

Measurment pH

The pH of Nanosponge Hydrogel range between 5.6-6.8 which lies in the normal

range of pH of the skin and would not produce any skin irritation.

Spreadability

Spreadability for different Nanosponge Hydrogel formulation show good Spreadability i.e. gels is easily spreadable **Table 13**.

Extrudability

Extrudability of all Nanosponges Hydrogel formulations was satisfactory, good and excellent **Table 14**. **Drug Content for Nanosponges Hydrogel formulations**

The drug content is given in **Table 15 and Figure 10**.

Drug permeability study of Nanosponge Hydrogel formulation

The drug permeability study of nanosponge hydrogel formulation is given in **Table 16 and Figure 11**.

Drug release kinetics

The drug release kinetics is given in **Table 17 and Figure 12 and 13**.

Stability study

The following study for F4 formulation is given in **Table 18**.

Table 1: Physical Appearance of Griseofulvin

Drug	Parameters	Standard USP	Observed
Griseofulvin	Colour	White to off white powder	White Powder
	Odour	Odourless	Odourless

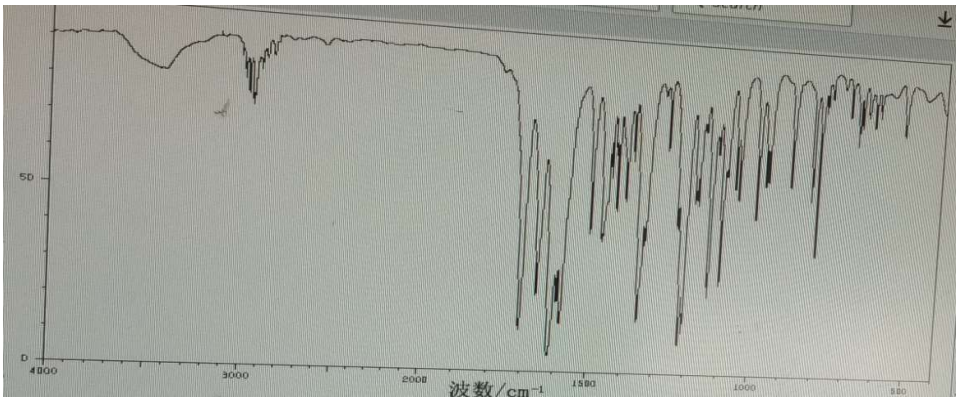

Figure 1: IR spectra Griseofulvin (standard)

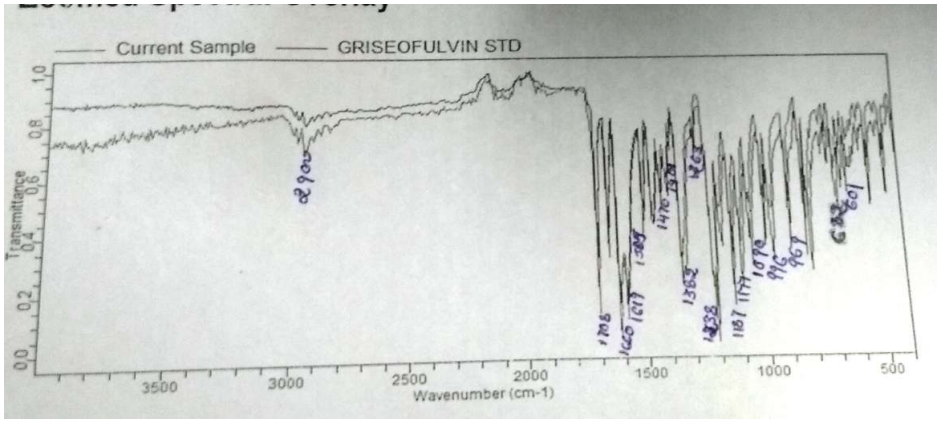

Figure 2: IR spectra Griseofulvin (sample)

Table 2: Characterization of peak in FT-IR spectrum

Band Energy(cm)	Functional group
2900-2700	C-H
770-730	-C-H
1600-1500	C=C
900-650	N-H
1200-1100	C-O-C

Table 3: Calibration curve by UV

S. No.	CONC.	ABSORBANCE
1	1	0.16 ±0.87
2	2	0.31±0.53
3	3	0.41±0.45
4	4	0.61±0.43
5	5	0.70±0.35

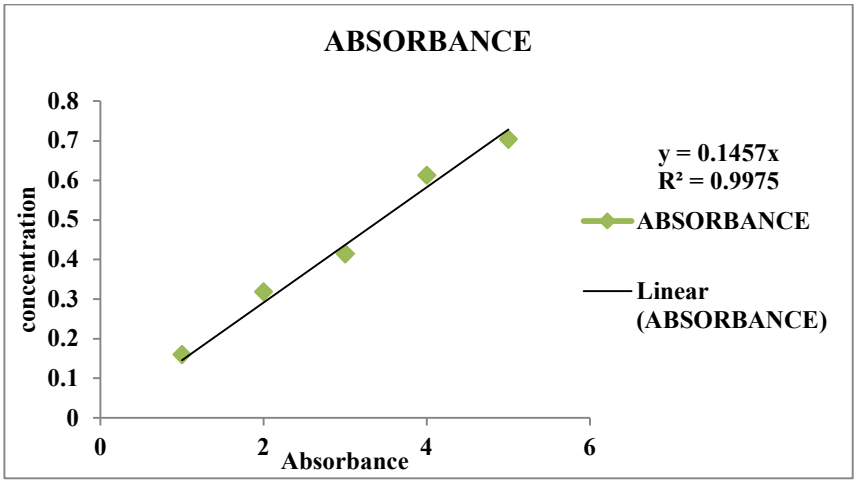

Figure 3: Calibration curve of griseofulvin by UV

Table 4: Solublity of griseofulvin in various solvent

S. No.	Solvent	Solublity
1	Water	Poorly soluble
2	Ethanol	Soluble
3	Methanol	Soluble
4	Acetone	Soluble
5	PBS (6.8)	Soluble
6	PBS (7.4)	Soluble

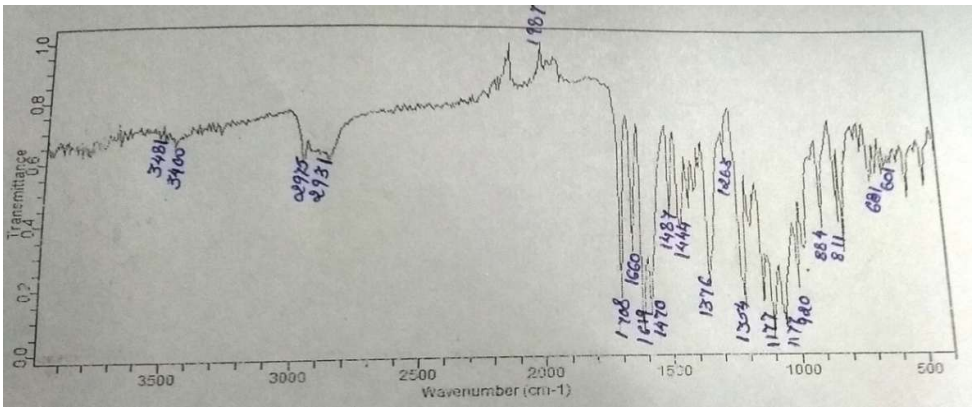

Figure 4: IR spectra Ethylcellulose and drug

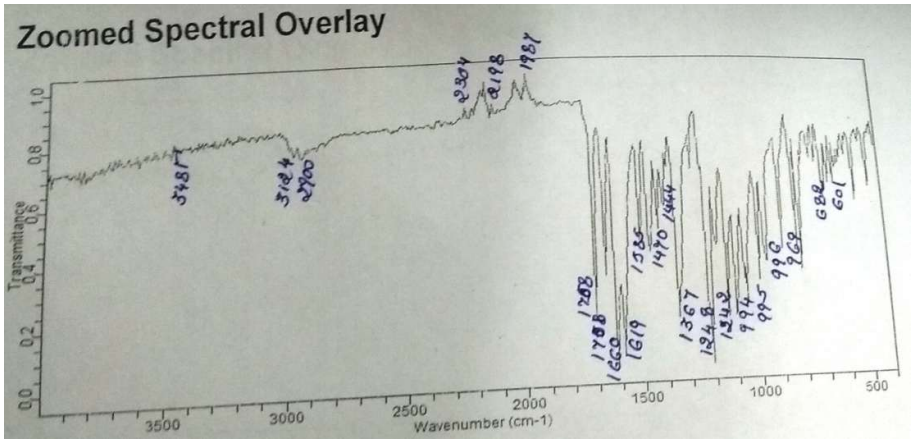

Figure 5: IR spectra Ethylcellulose, drug and Dichloromethane

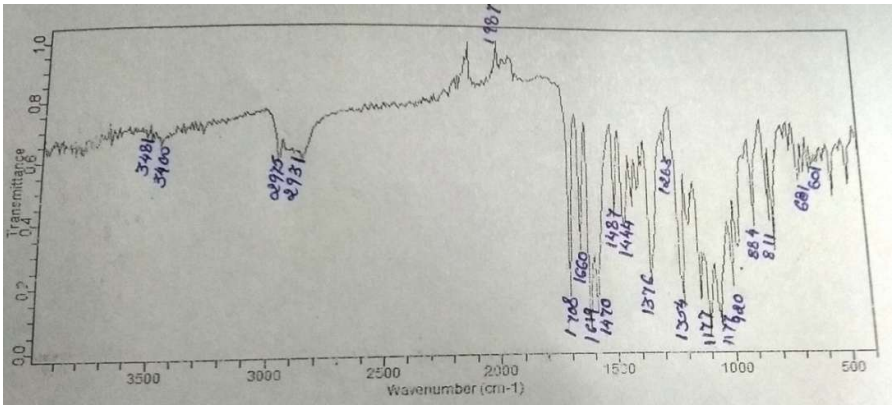

Figure 6: IR spectra Ethylcellulose, drug and Dichloromethane

Table 5: Characterization of peak in FT-IR spectrum

Band Energy(cm)	Functional group
1708	Aldheyde (CHO)
1619-1680	Alkene (C=C)
1500-1570	Nitro Compound
1750-1700	C=O
1200-1100	C-O-C
3100-3074	=CH-H

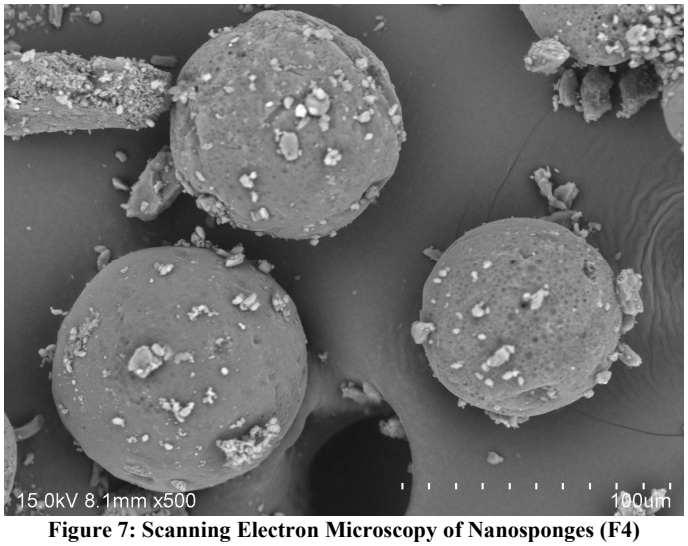

Figure 7: Scanning Electron Microscopy of Nanosponges (F4)

Table 6: Entrapment efficiency

Formulation	EE%
F1	45.81 0.42
F2	85.43 0.44
F3	88.12 0.54
F4	81.56 0.52

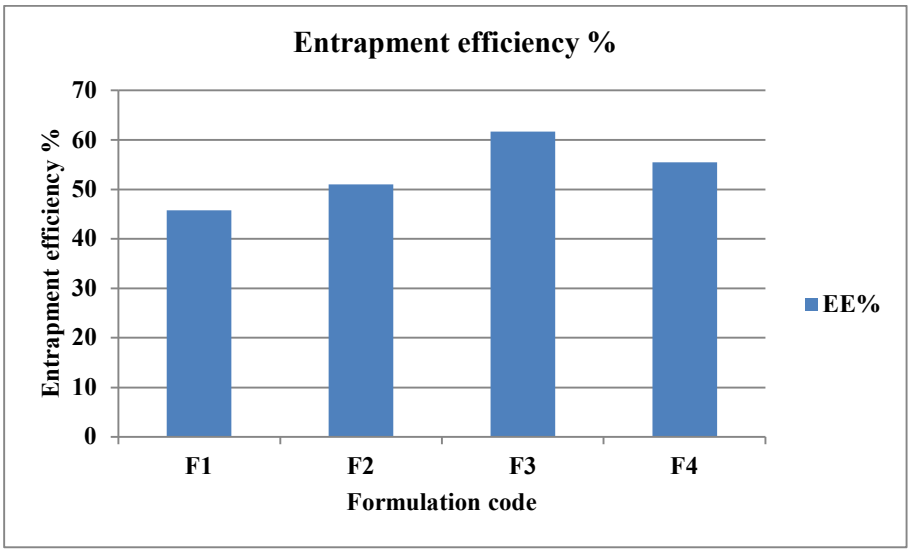

Figure 8: Entrapment efficiency plot for various Nanosponge Hydrogel

Table 7: *In vitro* drug release

Time (Hours)	F1	F2	F3	F4
0	0	0	0	0
1	10.021	07.216	12.344	09.216
2	19.547	17.387	25.746	19.387
3	32.177	25.510	39.804	20.510
4	43.223	34.679	55.344	30.679
5	56.222	47.276	60.585	47.276
6	63.622	64.063	68.269	64.063
7	70.080	70.093	74.950	75.093
8	79.306	82.963	85.474	82.963

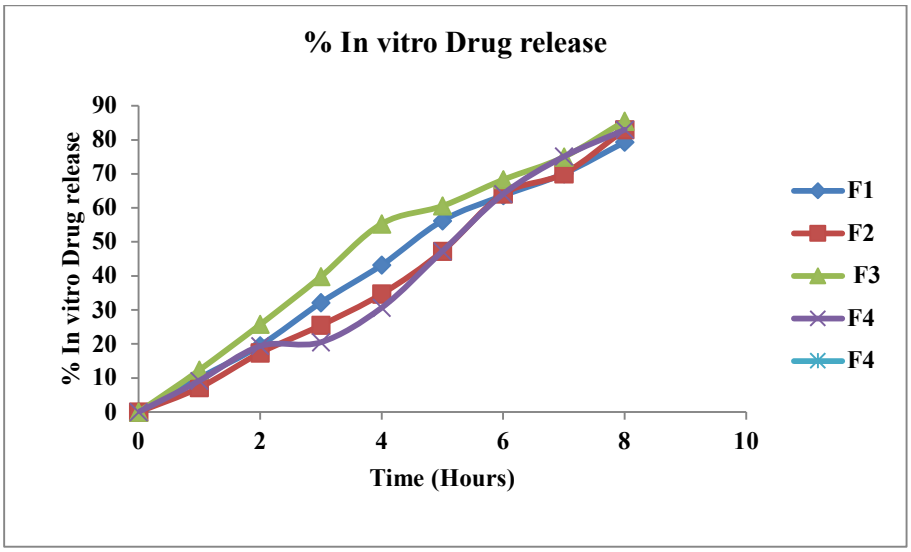

Figure 9: *In vitro* Drug release of Nanosponges Formulation

Table 8: Physical appearance

Formulation	Physical appearance
F1	Colorless
F2	Colorless
F3	Colorless
F4	Colorless
F5	Colorless
F6	Colorless
F7	Colorless
F8	Colorless
F9	Colorless

Table 9: Homogeneity

Formulation	Physical appearance
F1	Good
F2	Good
F3	Good
F4	Good
F5	Good
F6	Good
F7	Good
F8	Good
F9	Good

Table 10: Clarity

Formulation	Physical appearance
F1	Good
F2	Good
F3	Good
F4	Good
F5	Good
F6	Good
F7	Good
F8	Good
F9	Good

Table 11: Viscosity

Formulation	Viscosity(cps)
F1	10340±0.26
F2	10410±0.29
F3	10224±0.25
F4	10511±0.36
F5	10380±0.40
F6	10344±0.35
F7	10529±0.25
F8	10091±0.29
F9	10190±0.26

Table 12: pH

Formulation	pH
F1	5.7 ±0.03
F2	5.8 ±0.02
F3	5.7 ±0.02
F4	5.6 ±0.05
F5	5.8 ±0.04
F6	5.9± 0.06
F7	6.0 ±0.06
F8	6.2 ±0.06
F9	5.8 ±0.07

Table 13: Spreadability

Formulation	Spreadability(g-cm/min)
F1	9.81±0.07
F2	9.30±0.06
F3	9.20±0.05
F4	8.82±0.08
F5	9.37±0.07
F6	9.82±0.10
F7	9.81±0.11
F8	9.33±0.05
F9	9.82±0.06

Table 14: Extrudability

Formulation	Extrudability
F1	++
F2	++
F3	++
F4	+++
F5	++
F6	+++
F7	+
F8	+
F9	+

Note: + Satisfactory, ++ Good, +++Excellent

Table 15: Drug content

Formulation	% Drug content
F1	90.26 ±0.12
F2	90.40± 0.11
F3	91.94 ±0.16
F4	90.45±0.12
F5	90.75±0.15
F6	90.12 ±0.10
F7	91.34± 0.13
F8	91.34±0.14
F9	92.27±0.15

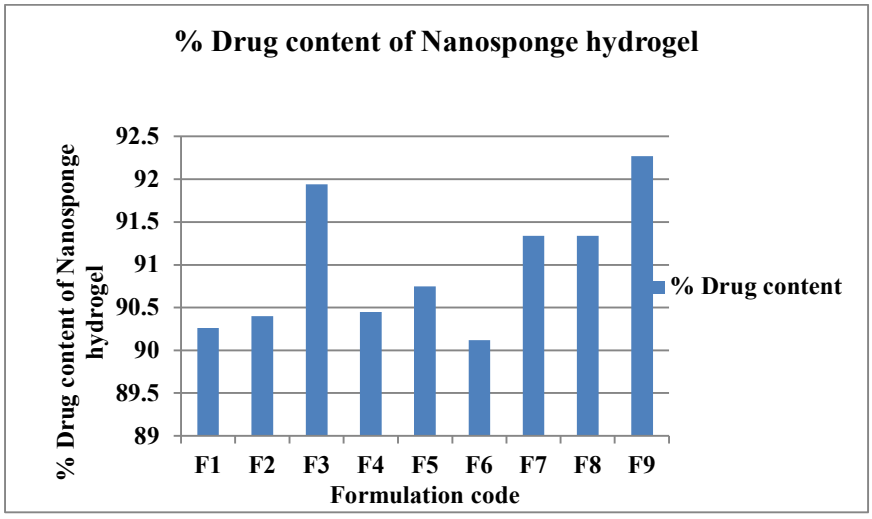

Figure 10: Drug content for various Nanosponge Hydrogel formulations

Table 16: Drug permeability study of Nanosponge Hydrogel formulation

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.16± 0.63	14.064± 0.11	15.225± 0.21	6.408± 0.41	8.107± 0.32	9.397± 0.11	7.216±0. 25	10.021±0 .16	12.344±0 .21
2	23.431± 0.36	29.261± 0.12	34.263± 0.45	13.848±0 .45	17.038±0 .32	19.034±0 .23	17.387±0 .21	19.547±0 .16	25.746±0 .11
3	30.422± 0.10	32.251± 0.37	42.231± 0.26	20.256±0 .31	21.526±0 .15	22.256±0 .10	20.546±0 .13	25.562±0 .25	32.564±0 .25
4	38.931± 0.55	49.899± 0.23	48.834± 0.45	24.178±0 .11	29.607±0 .32	27.431±0 .21	25.512±0 .10	32.177±0 .35	39.804±0 .13
5	47.811± 0.24	55.794± 0.51	57.658± 0.36	34,789±0 .23	37.877±0 .23	41.145±0 .15	34.679±0 .16	43.223±0 .26	55.344±0 .25
6	52.364± 0.31	62.294± 0.13	65.536± 0.56	47.989±0 .26	51.359±0 .23	52.614±0 .25	47.276±0 .20	56.222±0 .35	60.585±0 .19
7	61.844± 0.18	70.061± 036	69.062± 0.25	58.042±0 .56	64.551±0 .23	61.578±0 .26	64.063±0 .50	63.622±0 .26	68.269±0 .15
8	69.012± 0.33	75.716± 0.36	72.555± 0.56	63.676±0 .23	67.527±0 .33	69.589±0 .32	70.093±0 .16	70.084±0 .29	74.951±0 .50
9	74.724± 0.19	80.937± 0.54	75.632± 0.32	83.168±0 .56	76.219±0 .25	78.216±0 .24	82.963±0 .19	79.306±0 .30	80.474±0 .19

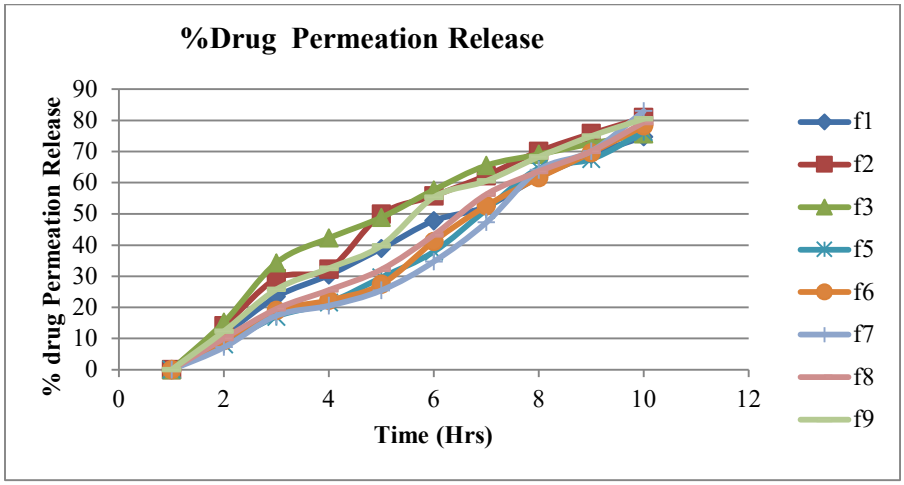

Figure 11: Drug permeation study of Nanosponge based gel formulation

Table 17: Drug release kinetics

S. No.	Kinetic model	Regression Coefficient
1	Zero order Equation	0.964
2	First order Equation	0.991

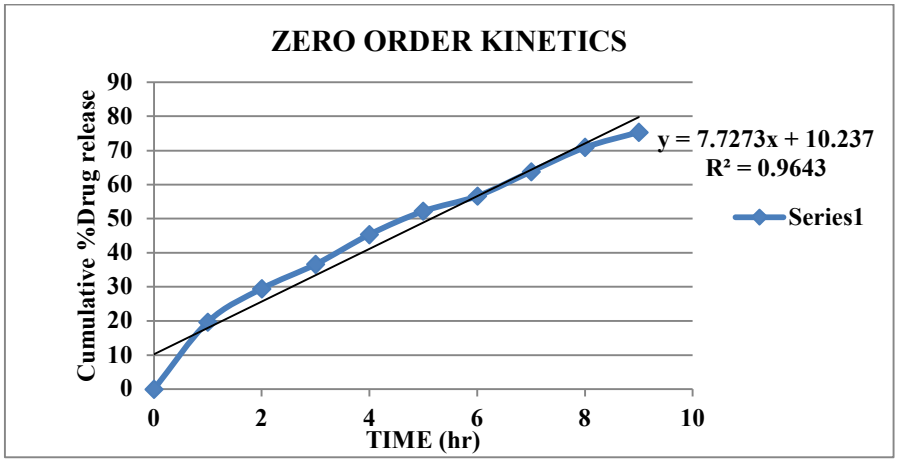

Figure 12: Zero order (%cumulative drug release vs. time)

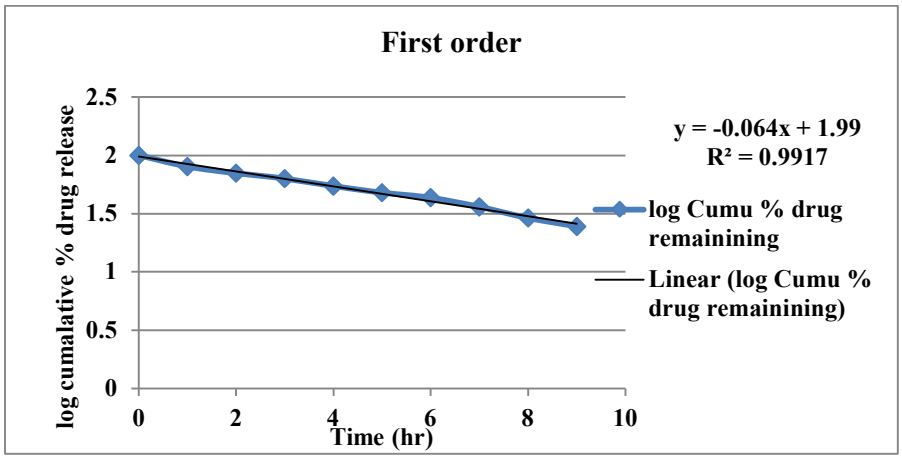

Figure 13: First order (log% cumulative drug release vs. time)

Table 18: Stability study for F4 formulation

Days Interval	Color	Clarity	%Drug content	Homogeneity
10	Colorless	Clear	91.00±0.36	Good
20	Colorless	Clear	90.98±0.25	Good
30	Colorless	Clear	90.00±0.16	Good

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of Griseofulvin-loaded nanosponges incorporated into a hydrogel for topical delivery. Griseofulvin, a BCS Class II drug with limited aqueous solubility and no existing topical formulation, was effectively encapsulated in nanosponges using ethyl cellulose and polyvinyl alcohol via the emulsion solvent diffusion method. Among the four nanosponge formulations, F4 exhibited the highest entrapment efficiency and optimal drug content, making it the most suitable for hydrogel incorporation.

Hydrogel formulations prepared using Carbopol 934, with propylene glycol and triethanolamine, were evaluated for their physicochemical properties. The F4-based hydrogel showed favorable pH (7.36), viscosity (10511 cps), excellent spreadability, extrudability, and sustained in vitro drug release. FTIR analysis confirmed compatibility between Griseofulvin and the excipients used.

Overall, the study concluded that the F4 nanosponge-loaded hydrogel formulation was stable, effective, and exhibited controlled drug release, making it a promising candidate for the topical treatment of dermatophytic fungal infections.

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