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Formulation and Evaluation of Nanosponge Based Topical Gel Preparation of Fluconazole

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HUMAN

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ABSTRACT

The main objective of the present work is to formulate nanosponges of fluconazole for topical delivery in the form of a gel. Nanosponges were formulated successfully using ethyl cellulose and eudragit RS100 as polymer, polyvinyl acetate as the surfactant, and dichloromethane as solvent by use of emulsion solvent diffusion method. The obtained nanosponges were in the formulated of the topical gel by use of agents like Carbopol 934 and HPMC K4M. The prepared nanosponges and gel were evaluated by various tests like production yield, drug entrapment efficiency, FTIR, DSC, SEM, spreadability, pH, viscosity, and *in-vitro* drug release. Among various formulation of nanosponges, nanosponges made with ethyl cellulose showed good properties and further converted into gel form. The formed gel showed drug release for up to 12 hours. Overall, the emulsion solvent diffusion method was effectively used for the formulation of nanosponges.

INTRODUCTION:

For obtaining topical or systemic effect topical preparations are applied over the surface of the skin. Topically applied dermal and transdermal delivery systems may replace needles required to administer several medicaments with several benefits like avoiding first-pass hepatic metabolism, gastric degradation, and frequent dosing (1). The Global Burden of Disease project has revealed that skin diseases endure being the 4th principal reason for nonfatal disease burden throughout the world (2).

The present work is aimed at the production of nanosponge containing the topical gel of antifungal drug fluconazole. Nanosponge belongs to the new class of nanoscale sponge having the size of the virus which is filled with therapeutic agents with specific linkers (5). Nanosponges are spongy polymeric delivery systems that are tiny sphere-shaped particles with a great porous surface. Passive targeting of drug molecules as well as cosmetics can be achieved by nanosponge. There are several benefits of nanosponge such as dose reduction, avoidance of the first-pass metabolism, prolong retention of drugs on the skin, retention of dosage form on the skin, and avoidance of systemic absorption (6).

Fluconazole is an antifungal drug and belongs to BCS class II. IUPAC name of fluconazole is 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol. It is a triazole derivative and used in the treatment of various fungal infections such as candidiasis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and pityriasis. Fluconazole favorably hinders fungal cytochrome P-450 sterol C-14 alpha-demethylation, causing the accumulation of fungal 14-alpha-methyl sterols. Due to the loss of normal fungal sterols, it shows fungistatic activity.

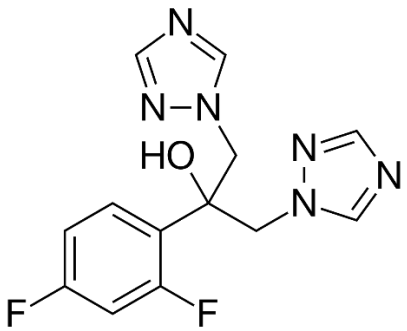

Figure No. 1: Structure of fluconazole

MATERIALS AND METHOD:

MATERIAL:

Fluconazole was obtained as a gift sample from Virupaksha Organics Limited, Hyderabad, Telangana, India. Other excipients like ethyl cellulose, Eudragit RS 100, Dichloromethane (DCM), polyvinyl alcohol (PVA), Carbopol 934, Hydroxy Propyl Methyl Cellulose K4M, Methylparaben, Propylparaben, and Propylene glycol were procured from Modern science lab, Nashik, Maharashtra, India. All the chemicals used were analytical grade and were used as obtained.

METHOD:

Preparation of Fluconazole nanosponge: Trial batches for drug strength determination

Nanosponges were prepared by using the emulsion solvent diffusion method. Drug, polymer, and cross-linker were taken in different molar ratios (Table 1). For each ratio the disperse phase having drug and polymer were weighed accurately and dissolved in DCM. The mixture was added in an aqueous phase (a mixture of PVA+ distilled water) followed by two-hour continuous stirring at 5000 RPM. Nanosponges were collected by the process of filtration and kept for drying in an oven at 40 °C for 24 hours. The Amount of drug strength is a very crucial parameter to be determined. For determination of dose strength of drug to be incorporated, there was only a way i.e. to prepare trial batches of nanosponges with different strength of drug (30, 60, 100, 140mg). The percent entrapment efficiency was evaluated and based on entrapment efficiency, the strength of the drug was selected.

Table No. 1: Trial formulation batches for drug strength determination

Sr. No.	Ingredients	Formulation Code							
		TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8
1)	Drug (mg)	30	60	100	140	30	60	100	140
2)	Polyvinyl alcohol (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3)	Ethyl cellulose (mg)	60	90	120	150	-	-	-	-
4)	Eudragit RS100 (mg)	-	-	-	-	60	90	120	150
5)	Dichloromethane (ml)	30	30	30	30	30	30	30	30
6)	Distilled water (ml)	100	100	100	100	100	100	100	100

Preparation of Fluconazole loaded nanosponges by using Emulsion Solvent Diffusion method (7, 8, 9):

Two different polymers, Ethylcellulose and Eudragit RS100 with different ratios were used for formulation. A total of eight formulations were prepared for the further optimization process. Two phases were used, one is organic and the other is the aqueous phase. The organic phase, containing drug and polymer mixture in 30 ml DCM and the aqueous phase containing PVA and in 100 ml distilled water. The aqueous phase was added in a dropwise manner in the organic phase on a magnetic stirrer at 5000 rpm. After two hours of stirring, nanosponges were collected by filtration method and dried in an oven at 40 °C for 24 hours. Nanosponges are stored in a vacuum desiccator for removal of moisture.

Table No. 2: Formulation of fluconazole Nanosponges

Sr. No.	Ingredients	Formulation Code							
		F1	F2	F3	F4	F5	F6	F7	F8
1)	Drug (mg)	100	100	100	100	100	100	100	100
2)	Polyvinyl alcohol (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3)	Ethyl cellulose (mg)	60	90	120	150	-	-	-	-
4)	Eudragit RS100 (mg)	-	-	-	-	60	90	120	150
5)	Dichloromethane (ml)	30	30	30	30	30	30	30	30
6)	Distilled water (ml)	100	100	100	100	100	100	100	100

Preparation of Fluconazole nanosponge topical gel (10, 11, 12):

Different amount of gelling agents like Carbopol 934, HPMC K4M was dissolved and soaked over-night insufficient quantity of water to get good dispersion. After 24 hours, to this remaining ingredient i.e. propylene glycol as a penetration enhancer, methyl and propylparaben as a preservative was added. In another beaker fluconazole equivalent, nanosponges were dispersed in water. This was added to the previous beaker containing other excipients. Triethanolamine was added drop by drop to neutralize the pH of the formulation. The composition of nanosponge gel is shown in table 3.

Table No. 3: Composition of Fluconazole Nanosponge Gel

Sr. No.	Ingredients	Formulation Code							
		C1	C2	C3	C4	C5	C6	C7	C8
1)	Nanosponges (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
2)	Carbopol 934 (gm)	0.25	0.5	0.75	1	-	-	-	-
3)	HPMC-K4M (gm)	-	-	-	-	0.25	0.5	0.75	1
4)	Propylene glycol (ml)	10	10	10	10	10	10	10	10
5)	Methyl paraben (gm)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
6)	Propyl paraben (gm)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
7)	Triethanolamine (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8)	Distilled water (ml)	Up to 20							

Evaluation:

Evaluation of nanosponge:

Production yield (13):

Production yield can be determined by calculating the initial weight of raw material and the final weight of drug-loaded nanosponges. The production yield was determined by the following formula.

$$\text{Production yield} = \frac{\text{Practical mass of nanosponge}}{\text{Theoretical mass of nanosponge}} * 100$$

Drug entrapment efficiency (14):

Accurately weighed 10 mg of nanosponges were suspended in 100 ml of phosphate pH 7.4 buffer solution. After that, the solution was filtered through filter paper and after appropriate dilution, absorbance was measured at 264 nm by using a UV-visible spectrophotometer (Shimadzu UV-2600). The entrapment efficiency was calculated by the following formula.

$$\text{Drug entrapment efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} * 100$$

Fourier Transform Infrared spectroscopy (FTIR) (15,16):

FTIR study was performed to override the possibility of interaction between drug and polymer. FTIR studies were performed on the optimized nanosponges F2 formulation. The nanosponges were mix with potassium bromide (KBr) in 1:90 ratios, compressed in the form of the pellet by 15 tonnes pressure. The FTIR spectrum of Fluconazole nanosponges formulation batch was recorded in the wavelength range of 4000 to 400 cm^{-1}. The changes in the principal peaks of spectra of optimized nanosponges were recorded.

Differential scanning calorimetry (DSC) (16, 17):

The optimized nanosponges batch F2 was selected for DSC. Nanosponges samples were kept in an aluminum pan, sealed, and heated at a constant rate of 10 °C/min over a temperature range of 40 to 400 °C. By purging nitrogen with a flow rate of 100 ml/min.

Particle size (18):

The average particle size of optimized nanosponge formulation was determined by a dynamic light scattering analyzer by using Malvern Zetasizer, (Malvern Instrument Ltd.).

Polydispersibility index (19):

The Polydispersity index (PDI) is an index showing the particle size distribution range. PDI can be determined by a dynamic light scattering instrument. Lower PDI values are observed in the monodisperse sample, whereas higher PDI values indicate wide particle size distribution and the polydisperse nature of the sample.

Zeta potential (20):

The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, nanosponges were diluted 10 times with distilled water and analyzed by Malvern Zetasizer, (Malvern Instrument Ltd.).

Scanning electron microscopy (SEM) (19):

SEM is used for detailed morphological structure characterization of nanosponges. The sample was kept on a glass slide under a vacuum. The samples were coated with a thin gold/palladium layer using a sputter coater unit of scanning electron microscopy (Carl Zeiss,

Germany). The scanning electron microscope was operated at an acceleration voltage of 15kV.

Evaluation of gel:

pH:

The pH of the formulation was measured using a digital pH meter (Lab India, 6E404). The pH of the topical gel formulation should be between 3 to 9.

Drug content (21):

1 gm of the gel was dissolved in 100 ml of phosphate buffer pH 7.4, a sample (5ml) was taken from this solution and diluted to 25 ml. Fluconazole concentration was determined by measuring the absorbance at 264 nm using UV-visible Spectrophotometer (Shimadzu, UV-2600).

Viscosity (16):

The viscosity of prepared gel was measured using Brookfield viscometer (Brookfield Engineering, spindle LV6) at different RPM viscosity. The measurement was made over a whole range of speed settings from 5-100 rpm with 10 seconds between two successive speeds.

Spreadability test (21):

The spreadability of the gel formulation was determined by using a sliding plate apparatus and by measuring the diameter of 1 gm of gel between horizontal plates after 1 minute. The standardized weight tied on the upper plate was 125 gm. An excess of gel is placed between two glass slides and a 1000 gm weight is placed on them for 5 minutes, to compress the sample to a uniform thickness. The bottom slide is anchored to the apparatus and weights are placed in the pan. The time in seconds needed to separate the two slides is taken as a measure of spreadability. A shorter time interval indicates better spreadability. Spreadability was determined by using a formula.

$$S = M*L/ T$$

S = Spreadbility.

M = weight tied to the upper slide.

L = length of a glass slide.

T = Time taken to separate two slides (sec).

***In-vitro* drug release study (22):**

In-vitro diffusion study of nanosponge formulation was performed through the cellulose membrane by using Franz diffusion cell. The receptor compartment was filled with 7.4 pH phosphate buffer and kept at 32 ± 0.5 °C with continuous stirring with help of a magnetic stirrer. 100 mg of the gel was placed over the cellulose membrane. An interval of 1, 2, 3, 4, 5, 6, 7, and 8-hour 1 ml sample was withdrawn and suitably diluted. The withdrawn sample was replaced with the same amount of 7.4 pH phosphate buffer to maintain the sink condition. Diluted samples were analyzed for fluconazole content with help of UV at 264 nm.

RESULTS AND DISCUSSION:

Preparation of Fluconazole nanosponge: Trial batches for drug strength determination:

From the literature survey, it was concluded that PVA is a suitable polymer and emulsifier. Hence, PVA was a suitable emulsifier for further formulation study. From the literature survey and polymer compatibility study, it was concluded that ethylcellulose and Eudragit RS100 polymer are suitable for the formulation of the nanosponges. The dichloromethane is a good crosslinking agent from a literature survey and hence used further for batch optimization study.

The different batches were evaluated for the appropriate concentration of drug Fluconazole. Based on entrapment efficiency, the strength of the drug was selected. From these, it was observed that a maximum of 100 mg of the drug (formulation TF3 and TF7) can load into the formed nanosponges. So, this concentration of drug was used for further batch optimization. The different batches were evaluated for the appropriate concentration of Ethylcellulose and Eudragit RS100. From this, it is observed that the formulation from Drug and EC, Drug, and Eudragit RS100 in solvent DCM were formed the more proper nanosponges.

Table No. 4: Percentage Entrapment efficiency for determination of drug strength

Formulation Code	Drug Strength (mg)	Ethyl Cellulose (mg)	Eudragit RS 100 (mg)	Drug Entrapment
TF1	30	60	-	48.56%
TF2	60	90	-	56.52%
TF3	100	120	-	79.53%
TF4	140	150	-	68.42%
TF5	30	-	60	40.98%
TF6	60	-	90	51.56%
TF7	100	-	120	75.13%
TF8	140	-	150	73.91%

An increase in the concentration of ethyl cellulose increased entrapment efficiency. Ethylcellulose increases the viscosity of the internal phase and reduces drug mobility outside the formed droplets, hence an increase in entrapment efficiency of nanosponges is observed.

By using 100 mg drug, PVA, DCM, distilled water, and different concentration of ethyl cellulose and Eudragit RS100 nanosponge optimization was done.

Production yield:

The percentage production yield of F1 to F8 batches was observed in a wide range from 27.69% to 64.21%. From this, F1, F2, F6 batch F8 batch have good % production yield (52.09%, 64.21%, 51.87%, 48.52%). It was concluded that ethylcellulose concentration and cross-linking time affects the production yield of nanosponges. The production yield may vary due to the change in polymer concentration. The percentage production yield of eight batches of nanosponges is listed in Table No. 5.

Entrapment efficiency:

The percentage Entrapment efficiency of batches F1 to F8 was in the range from 66.55±0.45 to 80.32±0.58%. Highest % entrapment efficiency shown in F1, F2, F5 and F4 batch was 71.01%, 80.32%, 78.96% and 75.54% respectively. From this, it was concluded as ethyl cellulose concentration increases, percentage entrapment efficiency increases.

Table No. 5: Percent of production yield and percent entrapment efficiency

Formulation Code	Percent of Production Yield	Percent Entrapment Efficiency
F1	52.09±0.13	74.52±0.10%
F2	**64.21±0.54**	**82.33±0.47**
F3	45.12±0.87	72.55±0.59
F4	39.22±0.06	74.69±0.35
F5	33.85±0.56	79.40±0.21
F6	51.87±0.5	68.4±0.78
F7	27.69±0.04	73.2±0.78
F8	48.52±0.14	71.8±0.94

Result expressed in mean (n=3) ± SD (Standard Deviation).

Fourier Transform Infrared spectroscopy:

The FTIR studies are performed to observe any interaction between drug and polymers in the formulation. FTIR study of optimized nanosponges (F2 batch) was carried out. The FTIR spectra of optimized nanosponges were shown in Figure 1. The FTIR spectra indicate that there is no interaction between ethyl cellulose & drug within nanosponges. The spectrum of optimized nanosponges was found to be similar to pure Fluconazole drug. FT-IR spectra of prepared formulation showed there are significant changes in the fingerprint region i.e. 600 to 1500 cm-1. This confirmed the formation of a bond between ethyl cellulose and Fluconazole. There is a significant change in the downshift and upshift in the formulation due to cross-linking, seen in a condition such as S-O, and C-N stretching. Thus, it can be concluded that no major chemical interaction is taking place between the drug and carrier.

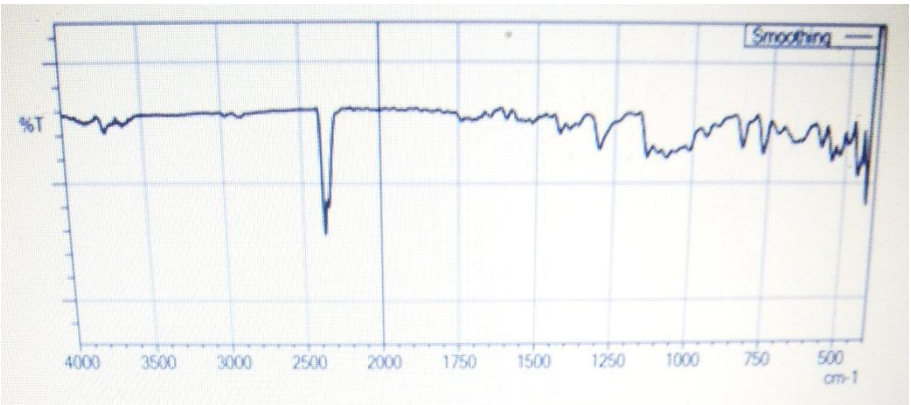

Figure No. 2: FTIR of F2 formulation

Table 6 represents the interpretation FTIR spectrum of optimized nanosponges batch F2.

Table No. 6: FTIR spectra interpretation of Fluconazole nanosponges F2 batch

Functional Group	Observed Ranges cm-1	Standard Range cm^{-1}
C- N Stretching	1145	1080 - 1360
C – H Stretching Aromatic	2362	2300 - 2500
C – Cl Stretching	771	600 - 800
S-O Stretching	839	910 - 895

Differential scanning calorimetry (DSC):

DSC was also performed to check the interaction between drug and polymer. The DSC thermogram of the pure drug shows a sharp endothermic peak which corresponds to the melting point of the drug at 138.45°C. The DSC spectra of optimized nanosponges show a slight variation in endothermic peak as that of the pure drug while the intensity of peak is slightly reduced. This effect may be due to the decrease in the crystal size of the drug. The DSC thermogram of F2 at 102.14^0C shows a broad endothermic peak. From the peak broadening in the spectra, one can understand that the drug is mostly encapsulated in nanosponges.

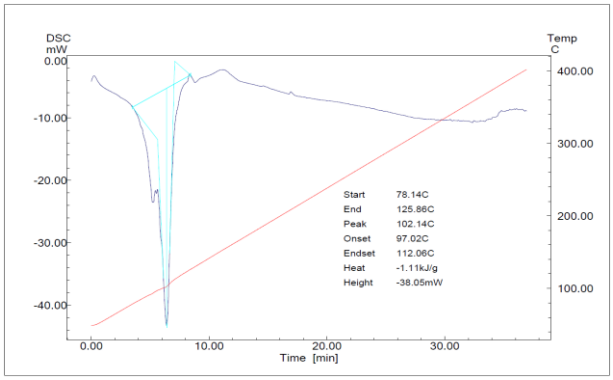

Figure No. 3: DSC of F2 formulation

Table No. 7: DSC observation table

Serial Number	Sample	Melting point	Standard Melting point	Inference
1	Fluconazole pure drug	138.19 °C	134- 138	A sharp endothermic peak was observed
2	Optimised nanosponges	102.14 °C	134- 138^0C	Broad Endothermic Peak was Observed

Particle size:

Particle size analysis was performed by zeta sizer of batch F2. The particle size was found to be between 2 nm to 95 nm which is in increasing order due to an increase in the concentration of polymer but after a certain concentration, the ratio of drug to polymer was increased the particle size decrease. This may be because of the high drug to polymer ratio, the amount of the polymer available was less. Hence it was concluded that particle size varies with the concentration of the drug-polymer ratio. The average particle size of batch F2 was observed 12.3nm. It shows that cross-linker has a significant influence on the particle size of the nanoparticle.

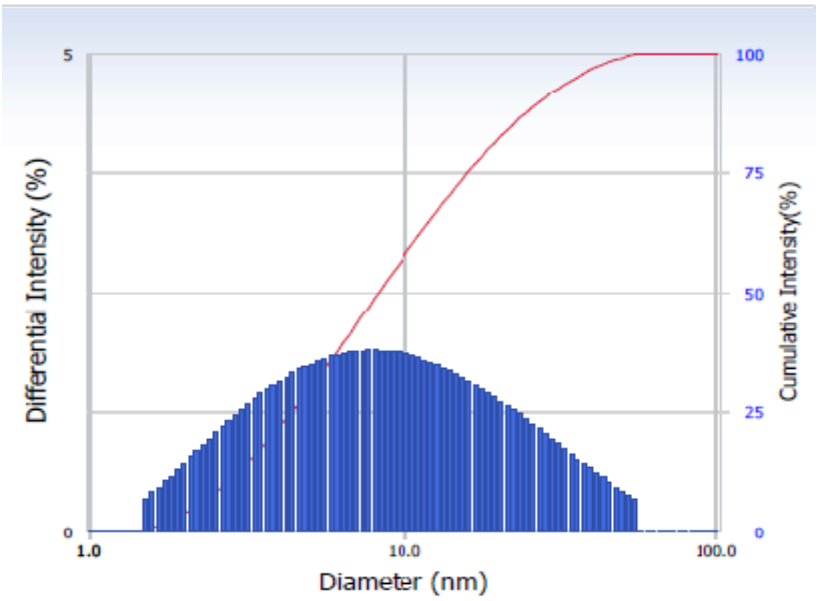

Figure No. 4: Particle size distribution analysis of F2 formulation

Poly dispersibility index (PDI):

PDI is an index of width or spread or variation within the particle size distribution. Monodisperse samples have lower PDI value, whereas PDI of the higher value indicates a wider particle size distribution and polydisperse nature of the sample. As shown in table 8, the nature of nanosponges formulation for the optimized batch shows mid-range monodisperse. The polydispersity indices of nanosponges were found to be 0.4. Therefore, it can be stated that the ethyl cellulose-based nanosponges prepared exhibited a homogeneous size distribution.

Table No. 8: Polydispersibility index according to its type of dispersion

Polydispersity index	Type of dispersity
0-0.05	Monodisperse Standard
0.05-0.08	Nearly Monodisperse
0.08-0.7	Mid- Range monodisperse
> 0.7	Very Polydisperse

Zeta potential:

Zeta potential gives the type of charge present on the surface of the nanosponges and stability of the prepared formulation. Zeta potential graph of F2 formulation is shown in Figure 5. The zeta potential of the F2 batch is 31.76. The nanosponges of the optimized batch are having moderate stability.

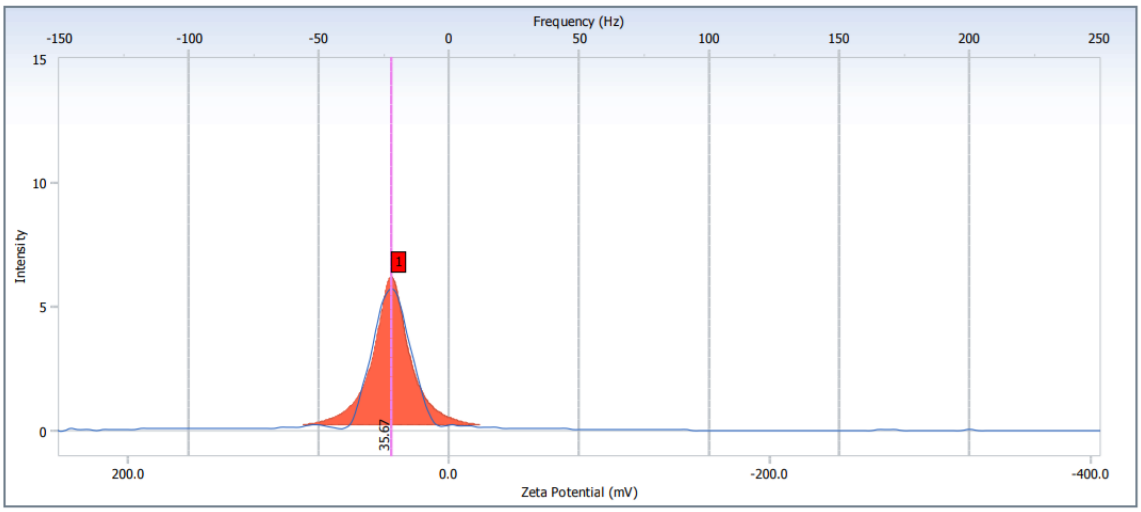

Figure No. 5: Zeta potential of F2 formulation

Table No. 9: Zeta Potential determination of F2 formulation

Determination of Optimized Batch Standard for Zeta Potential (mV)	Stability Behavior	Result obtained for Batch F2 (mV)
From 00 to ± 5	Rapid Coagulation or Flocculation	-
From 10 to ± 30	Incipient Instability	-
From 30 to ± 40	Moderate Stability	+31.76
From 40 to ± 60	Good Stability	-
More than ± 61	Excellent Stability	-

Scanning Electron Microscopy (SEM):

By Scanning electron microscopy, the surface morphology of nanosponges can be studied. The SEM images of batch F2 confirms that nanosponges were spherical in size with a porous

surface with no drug crystal on the surface of nanosponges. The sample was observed under scanning electron microscopy at 5 KX magnetic resonance.

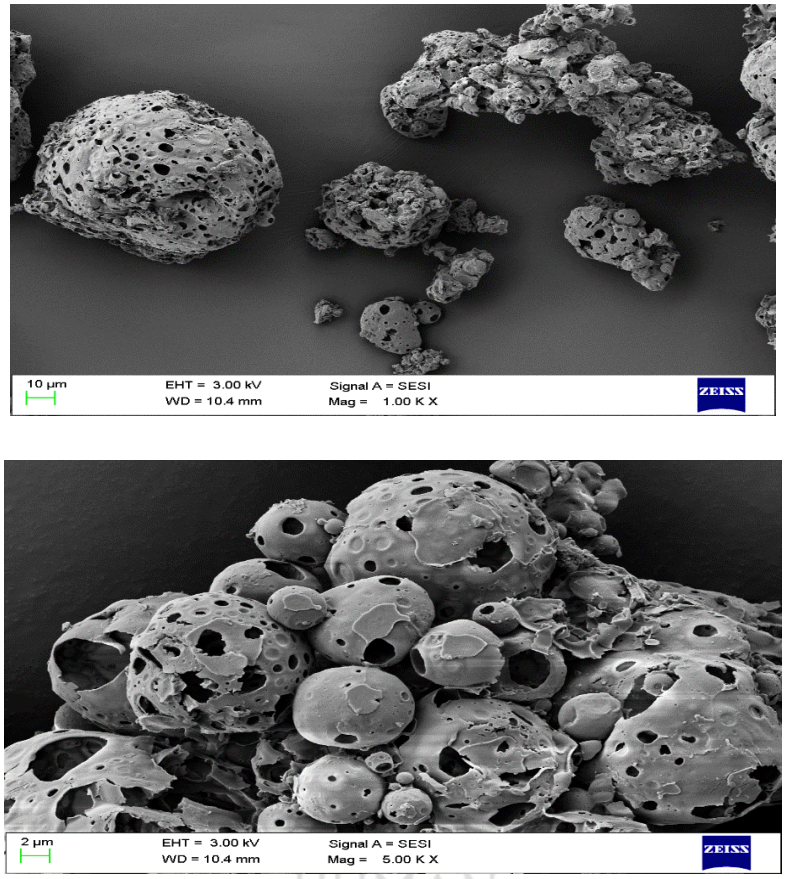

Figure No. 6: SEM image of F2 formulation

pH of gel:

The pH of gel formulation was determined by using the pH meter. The results were reported in Table 10. The pH of all formulations was in the range compatible with the normal pH range of the skin. Hence the preparation was non-irritant.

Drug content of formulated gel:

The prepared formulation was analyzed for drug content. It was observed that the drug content in the prepared nanosponges gel was satisfactory and the drug was uniformly distributed in all the formulation. The percentage of drug content was found to be between 93.56±0.85 to 67.35±0.08.

Spreadability of gel:

Spreadability is an important characteristic of topical formulation and it's responsible for correct dosage transfer to the target site. Spreadability is an important factor to consider in the formulation of gel. The viscosity and spreadability are inversely proportional to each other. The spreadability of prepared nanosponges gel formulation was in the range between 5.756±0.052 to 6.529±0.014.

Table No. 10: Actual drug content, Spreadability, and pH of the formulated gel

Formulation code	Actual Drug Content	Spreadability(gm.cm/sec)	pH
C1	87.54±0.013	5.756±0.052	6.9±0.054
C2	83.54±0.36	6.324±0.045	6.6±0.018
C3	93.56±0.85	6.352±0.012	7.3±0.09
C4	79.41±0.95	6.261±0.042	7.1±0.001
C5	85.56±0.55	6.215±0.028	6.8±0.020
C6	77.81±0.95	6.489±0.069	6.9±0.025
C7	74.26±0.26	6.529±0.014	6.2±0.024
C8	67.35±0.08	6.154±0.11	7.0±0.046

Viscosity of gel:

The viscosity of gel was measured by Brookfield viscometer with spindle LV6. The result shows a decrease in viscosity as a shear rate (RPM) is increased which indicates Gel has pseudoplastic flow. The result indicates the viscosity of gel formulation was consistent.

Table No. 11: Viscosity of the formulations

Code	Torque %	RPM	Viscosity (cp)
C1	96	5 10 20 50 100	1080 672 600 240 220
C2	96	5 10 20 50 100	1142 943 883 666 325
C3	96	5 10 20 50 100	1245 954 823 752 325
C4	96	5 10 20 50 100	1056 826 751 623 456
C5	96	5 10 20 50 100	1114 964 824 624 536
C6	96	5 10 20 50 100	1079 743 542 456 362
C7	96	5 10 20 50 100	1011 1456 524 596 584
C8	96	5 10 20 50 100	1015 715 624 574 489

***In-vitro* drug release study:**

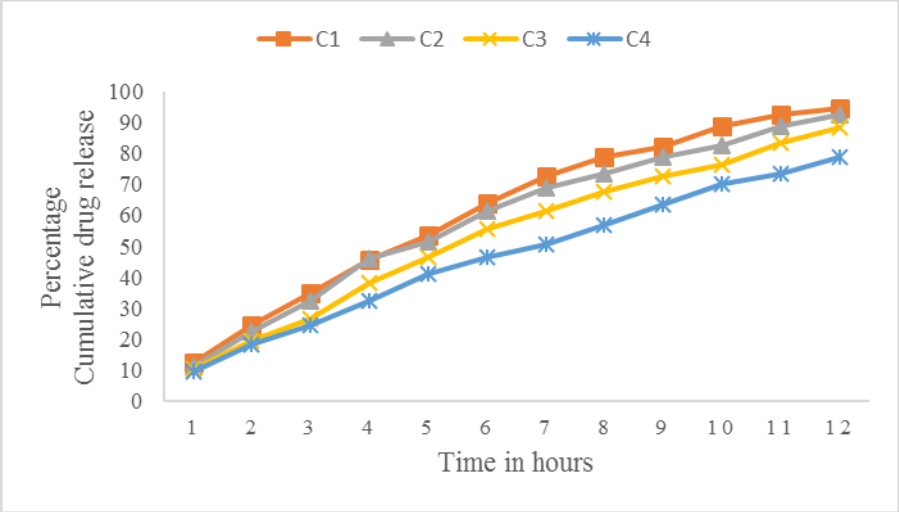

Figure No. 7: *In-vitro* drug release data of batch C1 to C4

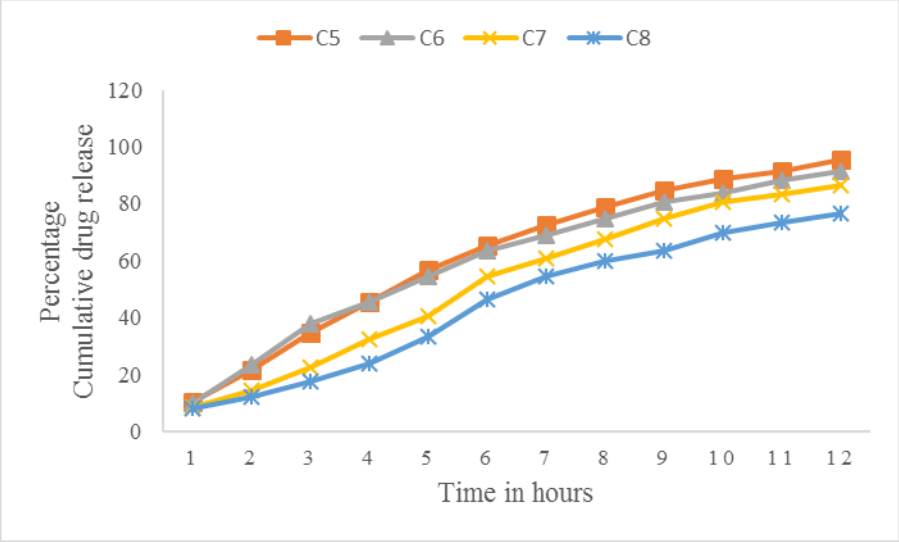

Figure No. 8: *In-vitro* drug release data of batch C5 to C8

In-vitro drug release data of formulation C1 to C4 showed that as the concentration of ethyl cellulose increased in nanosponge gel formulation drug release is decreased. Formulated nanosponge gel showed drug release over 12 hours. In formulation, C5 to C8 as the concentration of Eudragit RS100 increased drug release decreased. This may be attributed due to an increase in the thickness of nanosponges which may decrease drug release.

CONCLUSION:

From the above study, it was confirmed that nanosponges were prepared by the emulsion solvent diffusion method. Also, prepared nanosponges were successfully formulated into topical gel form. Preliminary batches showed that 100 mg of the drug can be incorporated in nanosponges successfully. Formulation F2 of nanosponges showed better results among eight nanosponge formulations. Batch F2 showed 82.33 % entrapment efficiency. FTIR spectra of F2 formulation indicated minimum interaction between drug and polymer. DSC spectra also indicated the same. PDI indicated mid-range monodispersing. Zeta potential of F2 batch is found to be 31.76, which indicated moderate stability. SEM images confirmed the formation of nanosponges. Among formulated batches of nanosponge gel batch C3 showed maximum drug content with 6.324 gm.cm/sec spreadability. In-vitro drug release showed sustain drug dissolution for up to 12 hours.

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