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Formulation, evaluation and optimization of herbal nanogel containing Alium cepa extract for skin diseases

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Abstract:

The present study focuses on the formulation, evaluation, and optimization of a herbal nanogel containing Allium cepa extract for the treatment of skin diseases. Nanogels were prepared using Pluronic F127 and polyethyleneimine (PEI) via an emulsification and solvent evaporation technique. Compatibility studies using FT-IR confirmed the absence of any significant interaction between drug and excipients. A 3^2 full factorial design was employed to optimize formulation variables, namely concentration of Pluronic F127 (X1) and PEI (X2), and their effects on particle size, entrapment efficiency, and drug release. The optimized formulation (F2) exhibited a particle size of 81.97 nm, entrapment efficiency of 76.67%, and drug release of 96.42% over 12 hours. Ex-vivo studies demonstrated sustained drug permeation through the skin. Stability studies revealed that the formulation remained stable under refrigerated conditions but showed degradation at elevated temperature and humidity. The developed nanogel system proved to be a promising carrier for topical delivery of Allium cepa extract with enhanced stability and controlled release properties.

Keywords: Allium cepa, Nanogel, Pluronic F127, Polyethyleneimine (PEI), drug release

Introduction:

Herbal medicines have gained considerable attention due to their safety, efficacy, and minimal side effects compared to synthetic drugs. Allium cepa (onion) is well known for its therapeutic properties such as anti-inflammatory, antimicrobial, antioxidant, and wound healing activities, primarily attributed to the presence of allicin. However, conventional topical formulations of herbal extracts suffer from poor stability, low skin permeability, and rapid drug degradation. [1]

Nanotechnology-based drug delivery systems, particularly nanogels, have emerged as promising carriers for enhancing the bioavailability and therapeutic efficacy of herbal drugs. Nanogels are three-dimensional hydrophilic polymer networks capable of encapsulating bioactive compounds and providing controlled drug release. Pluronic F127, a triblock

copolymer, and polyethyleneimine (PEI), a cationic polymer, are widely used for nanogel formulation due to their biocompatibility and ability to form stable nanosystems.

The present study aims to develop and optimize a nanogel formulation of Allium cepa extract using Pluronic F127 and PEI. A factorial design approach was employed to systematically evaluate the influence of formulation variables on critical quality attributes such as particle size, entrapment efficiency, and drug release. The optimized formulation was further evaluated for physicochemical properties, in-vitro and ex-vivo performance, and stability. [2]

Materials and method

Allium cepa used for the extraction of Allium cepa powder was purchased from the local market. Authentication of crude drug was done from senior botanist. Rests of the materials for synthesis of nanogels, and characterization, analysis, etc. were purchased from different vendors.

Extraction and Preparation of Allium cepa Powder

Preparation of Allium cepa powder was done by temperature-controlled extraction process as described by British Pharmacopoeia (2009) and from the book 'Allicin – The Heart of Allium cepa' by Peter Josling. Allium cepa heads were splitted into slices and freeze dried.

FT-IR Study for Drug-Excipients Interaction:

Fourier Transform Infrared Spectroscopy was carried out for solid samples to detect if any interactions were present between the drug and polymers. The samples were prepared by the potassium bromide disc method. Powders were triturated in a small size mortar and pestle until the powder mixture was fine and uniform. Pure KBr powder was used as background and for baseline correction. Samples were placed in a sample holder. Afterwards, the sample was transferred to sample compartment. Samples were scanned in the region of 4000-400 cm-1 using a Brucker FTIR spectrometer. The results of FT-IR spectra obtain were analyzed as per the method described by Li et al. (2011). [3]

Preparation of Drug-Loaded F127/PEI Nanogel

Preparation of drug-loaded Pluronic F127/PEI nanogel was done as per the method given by Li et al. (2011) which is a 3-step process:

- Activation of Pluronic F127 by 1,1 – carbonyl diimidazole,
- Preparation of F127/PEI nanogel,
- Drug- loaded F127/PEI nanogel

Preparation of CDI-activated Pluronic F127

Drop-by-drop for two hours, a solution of Pluronic F127 (1.25 g, 0.1 mmol) in anhydrous THF (15 mL) was added to an excess of CDI (0.81 g, 5 mmol) in THF (15 mL) at room temperature with nitrogen gas. The mixture was stirred for a further six hours after the addition. To obtain CDI-activated Pluronic F127, the solution was concentrated to a small volume under vacuum and put into ethyl ether (150 mL). The precipitate was then collected by filtering. To get rid of the unreacted CDI, this procedure was repeated three times. After 12 hours of drying under vacuum at room temperature, the CDI-activated Pluronic F127 was produced as a white powder. [4]

Preparation of F127/PEI nanogel

A technique involving emulsification and solvent evaporation was used to create the F127/PEI nanogel. Chloroform was used to dissolve the activated Pluronic F127 before

being added drop by drop while stirring to an aqueous PEI solution. After being sonicated for three minutes, the mixture underwent rotational vacuum evaporation at 50°C for 45 minutes to remove the organic solvent present in the emulsion. To get rid of adhesive pieces, the residual solution was centrifuged at 3000 rpm for 30 minutes. The solution was dialyzed in a dialysis bag with a 14,000–16,000 Da molecular weight cut-off against water at pH 4.0 after being neutralized with hydrochloric acid. To create F127/PEI nanogel, the pure nanogel samples were freeze dried. [5]

Drug loading

Separately, the medication and the lyophilized empty nanogels were dissolved in a 1:1 mixture of methanol and water. After both were combined, the solvent was then removed using rotary vacuum evaporation. To further hydrate the produced film, an appropriate volume of phosphate-buffer saline solution with a pH of 7.4 was added.

Screening Studies of Process Variables

The effects of following independent variables were studied by trial-and-error method (Table 7).

- Concentration of Pluronic F127 (mg)
- Concentration of Polyethyleneimine (PEI) (mg)

The effects on the following dependent variables by the change in independent variable were studied by trial-and-error method and the results of screening study are shown below.

- Particle size (nm)
- Entrapment efficiency (%)
- Cumulative drug release (%)

Table 1: Optimization of polymer concentration

Sr. No.	Concentration of Pluronic F127 (mg)	Concentration of PEI (mg)	Ratio (PF127/PEI)
1	200	50	4:1
2	300	100	3:1
3	200	100	2:1
4	100	100	1:1
5	100	200	1:2
6	100	300	1:3

Optimization [6]

For the present work, factorial design was applied to obtain optimized formulation. The optimization was done by using Design Expert software (version - 8.0.7.1)

3^2 Full Factorial Design

In this experiment, the concentration of Pluronic F127 and concentration of PEI may have impact on the quality of nanogel and hence were selected as independent variables.

In this design, two factors were evaluated each at three level in such a way that low level was **-1**, medium level **0** and high level **+1**.

Table 2: 3^2 Factorial Design Layout

Batch Code	Coded Value (X1)	Actual Value X1: Pluronic F127 (mg)	Coded Value (X2)	Actual Value X2: PEI (mg)
F1	-1	100	-1	100
F2	0	200	-1	100
F3	1	300	-1	100
F4	-1	100	0	200
F5	0	200	0	200
F6	1	300	0	200
F7	-1	100	1	300
F8	0	200	1	300
F9	1	300	1	300

Table 3: Formulation Table

Batch	Concentration of Pluronic F127 (mg)	Concentration of PEI (mg)	Water (ml)	Chloroform (ml)
F1	100	100	20	2
F2	200	100	20	2
F3	300	100	20	2
F4	100	200	20	2
F5	200	200	20	2
F6	300	200	20	2
F7	100	300	20	2
F8	200	300	20	2
F9	300	300	20	2

Note: *Each batch of nanogel formulation contains ~1% of active allicin in the form of crude drug.

Evaluation

Particle size

The droplet size of the nanogel loaded with Allium cepa powder was measured by using Malvern zeta sizer according to the method described by Singka et al. (2010). The nanogel (1-1.5 ml) was transferred to a disposable polystyrene cuvette and the droplet size of the nanogel was determined at an angle of 90° at 25°C.

Drug entrapment efficiency

Measurement of drug entrapped into the prepared nanogel was done by the method described by Azadi et al. (2012). To determine drug loaded amount, the nanogels were centrifuged at 12,000 rpm for 10 min. The supernatant was analyzed by HPLC after suitable dilution and 20 µl injected. The % entrapment efficiency of drug in nanogels was calculated as per following expression:

% Entrapment efficiency = (Drug loading /Theoretical drug loading) x 100

In-vitro release study

Using a Franz diffusion cell and a dialysis membrane 50, an in vitro drug release analysis of the produced nanogels was carried out in accordance with the methodology described by Azadi et al. (2012). 25 ml of diffusion medium with a pH 7.4 phosphate buffer was placed in the receptor compartment. The donor

compartment was positioned so that it barely touches the receptor compartment's diffusion medium. The donor compartment received the 5 ml of nanogel. The jars were double jacketed with water moving between the jacket walls during the investigation to maintain the temperature 37±0.5°C, and the entire assembly was mounted on a magnetic stirrer. This was done to ensure uniform dispersion of penetrating solutes for later collection. At predefined intervals, 2 ml samples of the receptor fluid were removed and promptly replaced with the same volume of new diffusion media. Using HPLC, the samples were examined for drug that diffused from the membrane at 254 nm.

pH

According to the procedure outlined in the Indian Pharmacopoeia, the pH of the nanogel formulation was assessed using a digital pH meter (2007). The pH meter was calibrated with the phosphate buffer pH 4.0, 7.0, and 9.0 before measuring the pH of the improved formulation. After that, the pH of the nanogel was measured by dipping the electrode of a pH meter into it for a minute. Each formulation's pH was measured three times, with the means being computed.

Viscosity

The viscosity of the prepared formulations was determined using Brookfield viscometer as the method described by shah et al. (2012).166 The selected formulations were poured into the sample adaptor of the viscometer. The viscosity was measured at 10 min after the rotation of the spindle. The viscosity measurements were made in triplicate.

Ex-vivo skin permeation study

The skin permeation study was performed by using rat skin as per the method given by Singka et al. (2010) as per OECD guidelines 404.164 The diffusion area of Franz diffusion cell was 1.51 cm2 and had a receptor volume of 25 ml. The procedure of this study was same as per in-vitro diffusion study as described above except that, instead of dialysis membrane the rat skin was mounted on Franz diffusion cell. The donor and receptor chambers of a vertical Franz diffusion cell were then securely placed between the skin samples. SC was placed in the donor compartment, while the dermis was placed in the receptor compartment (50 mL of PBS pH 7.4) at 32°C. 1mL of one of the formulations was charged into the donor compartment. Samples from the receptor fluid (3 mL) were taken at predefined time intervals (0.5, 1, 2, 4, 6, 8, and 24 h) and the cell was replaced with an equal volume of freshly prepared receptor fluid. The cumulative amount of drug permeated through the skin per unit area (mg/cm2) was plotted against time (h).

The flu (Jmax) at 24hr were calculated according to the following equations -

Amount of drug permeate

J max = Time × Area of membrane

In-vivo skin irritation study

Stability study

The stability study of optimized formulation was performed as per the ICH guideline Q 1 C. The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of variety of environmental factor such as, temperature, humidity, and light, and enable recommended storage condition, re-test period and shelf-lives to be established. The optimized formulation was kept for stability study at 40 ± 2°C / 75% ± 5% RH (relative humidity) and for freezing condition at 4 ± 0.05°C as per ICH guideline for 3 months. After three months, the sample was observed for any change in globule size and % entrapment efficiency.

Results and discussion

Drug-excipients compatibility study by FT-IR

From the IR spectra of drug (Allium cepa powder), empty nanogel and drug + nanogel it was observed that the IR spectra of drug + nanogel have the same functional group as the drug and empty nanogel. Hence it can be said that there is no significant interaction between any ingredients.

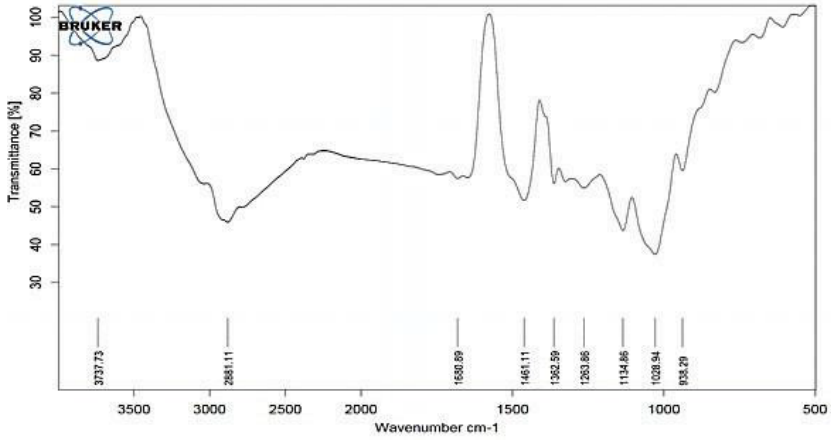

Figure 1: FT-IR Spectra of Drug (Allium cepa powder)

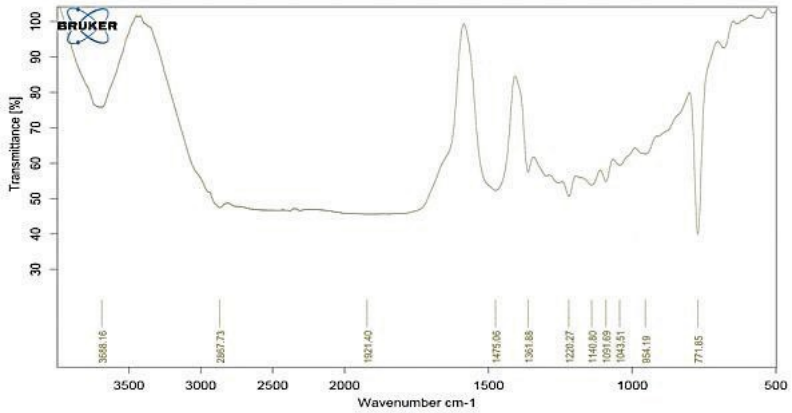

Figure 2: FT-IR Spectra of empty nanogel

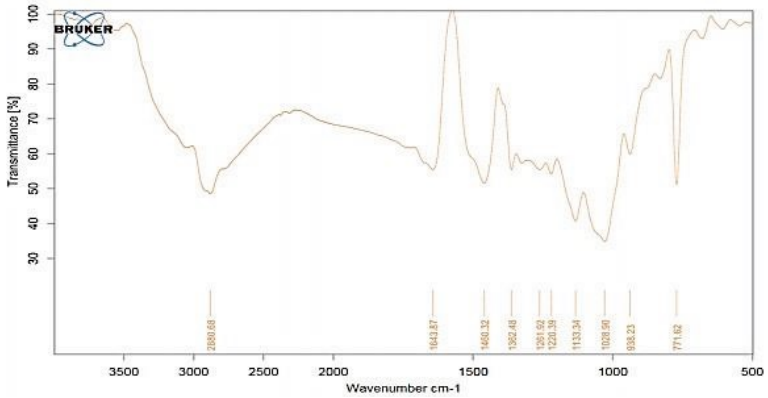

Figure 3: FT-IR Spectra of drug + nanogel

Table 4: FTIR peaks of Allium cepa powder, empty nanogel and Physical mixture

Group	Ideal FTIR Peak (cm^{-1})	Drug (cm^{-1})	Empty Nanogel (cm^{-1})	Drug + nanogel (cm^{-1})	Observation
=C–H Stretch	2800–3000	2881.11	2867.73	2880.68	No interaction
–C=H Stretch	1600–1700	1680.69	–	1643.87	No interaction
–C–H Bend	1450–1480	1461.11	1475.06	1460.32	No interaction
–C=C	3550–3700	–	3688.16	–	No interaction
S=O	1000–1150	1028.94, 1134.86	–	1028.90, 1133.34	No interaction
–C–H Bend	750–800	–	771.85	771.62	No interaction

Preparation of drug-loaded F127/PEI Nanogel

Dose calculation

Marketed formulations for most of the herbal drugs contains approximately 1% of the active constituents of the drug. So, similar strategy was followed for nanogel formulations and as per the calculation 3.82 g of Allium cepa crude powder were used to provide 180 mg of allicin which will be equivalent to the 1% of active constituent in the nanogel.

The F127/PEI nanogel was prepared by an emulsification/solvent evaporation method using different proportion of polymers as described by Li et al. (2011). The activated Pluronic F127 were dissolved in chloroform and added drop-wise to an aqueous solution of PEI under stirring. After neutralizing with hydrochloric acid empty nanogel samples were freeze dried. Then drug and lyophilized empty nanogels were dissolved separately in mixture of methanol and water, mixed it and the organic solvent was subsequently removed by rotary vacuum evaporation. The resulting film formed was further hydrated with a suitable amount of phosphate buffered saline pH 7.4 to obtain yellowish liquid nanogel formulation.

Preliminary screening

Effect of Polymer Concentration

Preliminary screening was done by measuring effect of concentration of Pluronic F127 and concentration of Polyethyleneimine (PEI) on particle size and poly dispersity index (PDI).

Table 5: Effect of Polymer Concentration

Sr. No.	Concentration of Pluronic F127 (mg)	Concentration of PEI (mg)	Ratio (PF127/PEI)	Particle Size (nm)	PDI
1	200	50	04:01	166	1
2	300	100	03:01	32.68	0.691
3	200	100	02:01	49.39	0.777
4	100	100	01:01	141.5	0.461
5	100	200	01:02	755	0.258
6	100	300	01:03	204.6	0.613

In preliminary batches, high concentration of Pluronic F127 if taken as compared to concentration of PEI gave small particles of nanogel. Concentration Pluronic F127 gave small size nanogel up to the certain concentration and afterward increases the

particle size. The ratio of concentration of Pluronic and PEI as 1:1 gave acceptable particle sizes of nanogel than higher and lesser ratio.

Effect of stirring rate

There is no significant effect of stirring was observed on particle size of nanogel formulation. At low and higher speed of stirring, nearly same particle size of nanogel was observed.

Table 6: Screening of stirring rate

Batch Code	Stirring Rate (RPM)	Particle Size (nm)
A1	1000	49.39
A2	2000	48.75
A3	3000	48.26

Optimization of formulation

Based on preliminary screening study, the following variables were selected.

Independent variables

- Concentration of Pluronic F127 (X1) and
- Concentration of PEI (X2)

Dependent variables

- Particle size (Y1)
- % Entrapment efficiency (Y2)
- % Cumulative drug release (% CDR) (Y3)

3-Level, 2-Factors Full Factorial Design

A 3 level 2 factors factorial design (3^2) was employed to design sustained release nanogel formulation of Allium cepa powder. The design was employed to study the effect of independent variables, i.e., concentration of Pluronic F127 (X1) and concentration of PEI (X2) on dependent variables particle size (Y1), % entrapment efficiency (Y2) and % CDR (cumulative percentage Drug Release) (Y3).

Table 7: 3^2 full factorial design

Sr. No.	Batch Code	X1: Pluronic F127 (mg)	X2: PEI (mg)	Particle Size (Y1) (nm)	% Entrapment Efficiency (Y2)	% Drug Release (Y3) (12 hr)
1	F1	100	100	131.8	70.83	95.58
2	F2	200	100	81.97	76.67	96.42
3	F3	300	100	56.18	46.38	95.84
4	F4	100	200	714.6	48.81	93.28
5	F5	200	200	711.6	67.78	94.68
6	F6	300	200	520.2	46.15	94.06
7	F7	100	300	331.3	45.07	93.24
8	F8	200	300	290.4	68.42	95.21
9	F9	300	300	144.1	58.4	95.73

Factor Influence Study and Optimization of the Formulations

Effect on particle size

From the ANOVA of particle size, the non-significant factors which having p value more than 0.5 were eliminated and the

reduced mathematical model for the particle size was as given below,

(Y1) = + 678.77 - 76.20X1 + 82.64X2 - 476.18X22 ..... **(1)**

Statistical analysis of data of particle size (Table 19) shows that factors in polynomial equation have **p value less than 0.05** (where level of significance p is less than 0.5 indicated that this factor have significant effect on particle size.

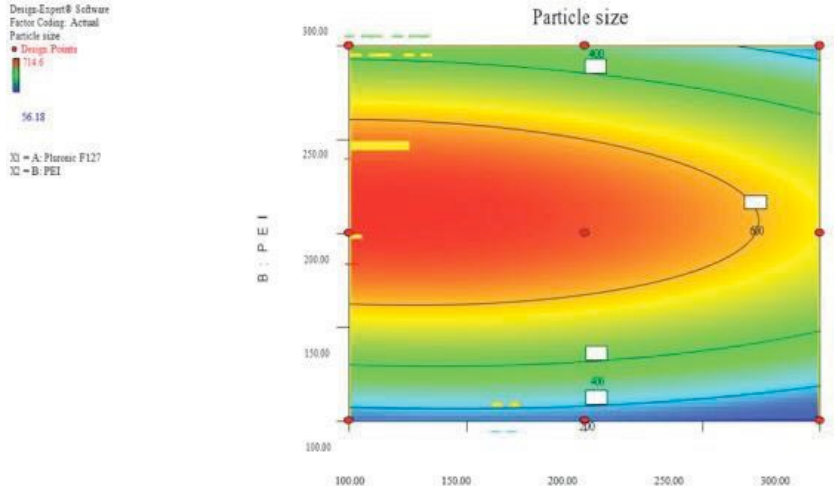

Figure 4: Contour plots (2D) for particle size of batches F1-F9

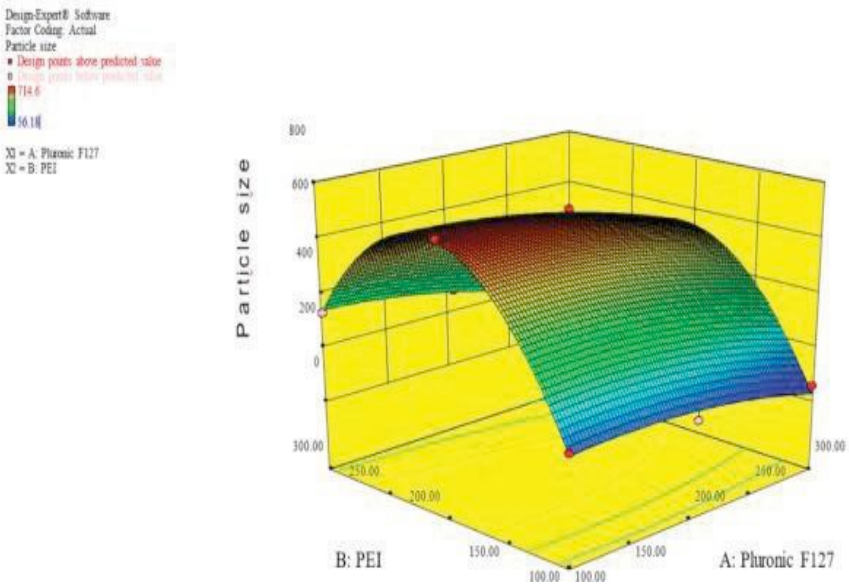

Figure 5: Response surface plots (3D) for particle size of batches F1-F9

Effect on % Entrapment efficiency

From the ANOVA of % entrapment efficiency, the non-significant factors which having p value more than 0.5 were eliminated and the reduced mathematical model for the % entrapment efficiency was as given below

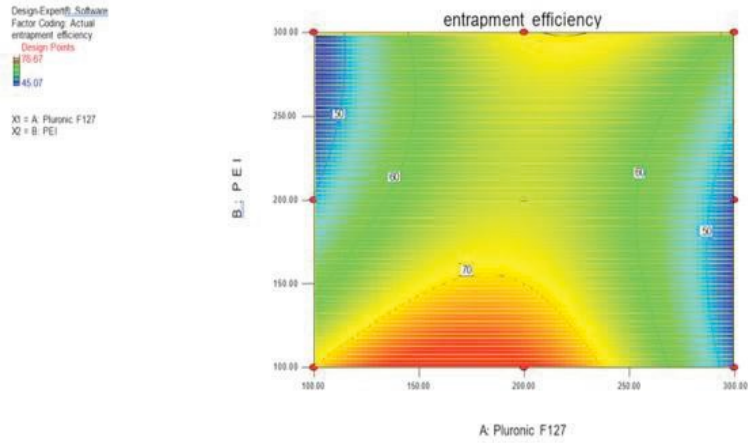

Figure 6: Contour plots (2D) for % entrapment efficiency of batches F1-F9

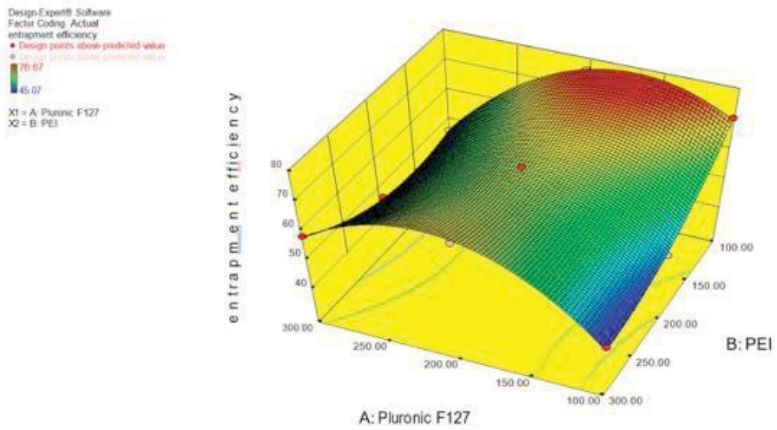

Figure 7: Response surface plots (3D) for % entrapment efficiency of batches F1- F9

Effect on % cumulative drug release

From the drug release of F1 to F9 formulations, it was found that all the formulation gave initial burst release of drug in first half hours and afterward provides sustained release of drug from the formulation up to 10 hrs. All the formulation were shown release of more than 80 % of drug in 10 hr. and more than 90 % of drug in 12 hr.

Table 8: In-vitro drug release profile of nanogel formulations of batches F1- F9

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	12.04	10.54	12.45	13.38	14.26	10.56	11.44	12.26	11.32
1	27.06	16.13	19.24	25.5	29.31	22.16	28.33	27.75	26.76
2	52.05	24.1	28.44	38.08	55.76	34.65	48.22	46.01	53.85
3	61.97	32.19	37.47	47.77	65.63	42.58	58.33	56.15	61.32
4	69.22	39.19	45.22	55.69	70.34	49.74	65.89	60.95	68.21
6	80.21	53.53	58.81	65.52	81.39	60.82	74.03	69.54	78.25
8	89.04	68.17	72.84	76.41	90.71	73.2	83.76	78.49	88.55
10	93.01	82.4	85.46	85.25	92.78	84.5	88.4	85.3	93.67
12	95.58	96.42	95.84	93.28	94.68	94.06	93.61	95.21	95.73

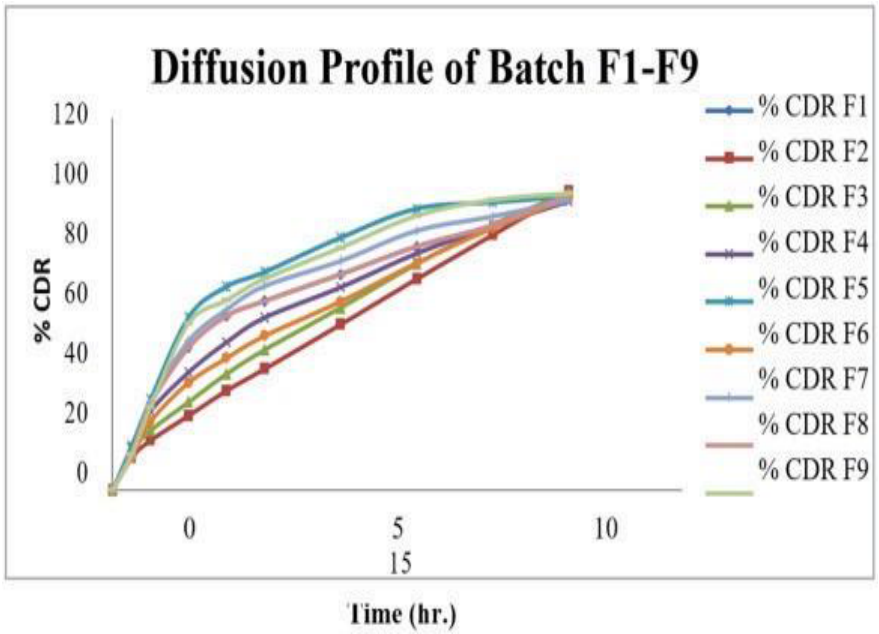

Figure 8: In-vitro drug release profile of nanogel formulation of batches F1-F9

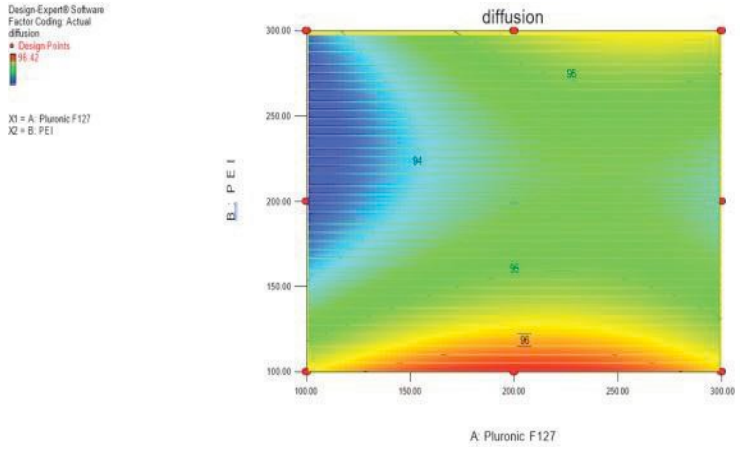

Figure 9: Contour plots (2D) for % cumulative drug release of batches F1-F9

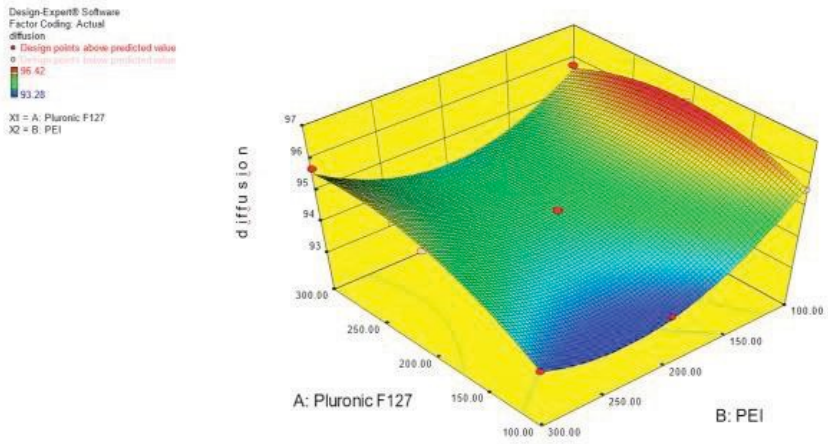

Figure 10: Response surface plots (3D) for % entrapment efficiency of batches F1- F9

Characterization of optimized nanogel formulation (F2)

pH

The pH of optimized nanogel was determined using digital pH meter. The optimized formulation of nanogel had pH **5.51 ± 0.0152 (n=3)**, which is like the pH of skin i.e., 4 – 7.

Viscosity

The viscosity of optimized nanogel was determined using Brookfield viscometer. Using spindle, no S63 at 100 rpm, the viscosity of optimized nanogel formulation was found to be

2.68 ± 0.13 (n=3). As the concentration of polymer solution increases viscosity also increases.

Particle size

The particle size of optimized nanogel was measured by using Malvern zeta sizer. Particle size of optimized nanogel was found to be **81.97 ± 0.15 nm (n=3)** which is desired for the nanogel.

Drug entrapment efficiency

Drug loaded amount of optimized nanogels was measured by HPLC after centrifugation at 12,000 rpm for 10 min. The % entrapped drug in optimized nanogel was found to be **76.67 ± 1% (n=3)**.

Ex-Vivo skin permeation study

The skin permeation study was performed by using rat skin. Samples were withdrawn and analyzed for drug diffused through the skin at 254 nm using HPLC. From skin permeation study using rat skin it was found that the optimized formulation of nanogel can pass through the skin and had a **98.51 ± 1% (n=3)** of drug release showing sustained manner in 12 hrs.

Table 9: Ex-vivo skin permeation profile of optimized nanogel formulation

Time (hr)	0.5	1	2	3	4	6	8	10	12
%CDR	7.03	13.12	21.66	29.02	35.63	47.18	61.03	75.97	90.58

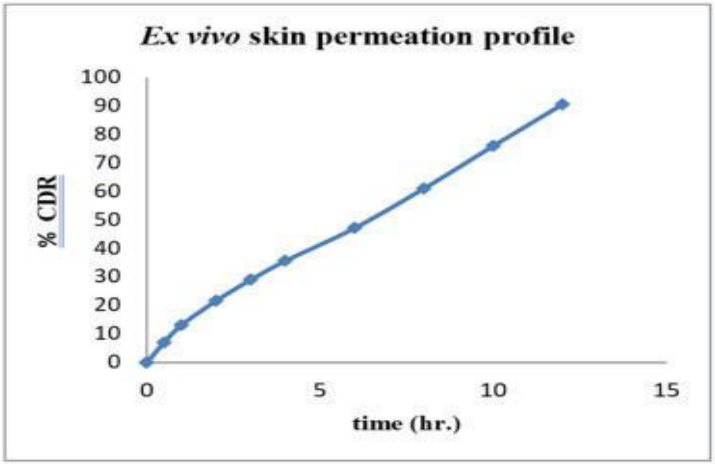

Figure 11: Ex-vivo skin permeation profile of optimized nanogel formulation

In-Vitro Drug Release profile

In-vitro drug release study of optimized nanogel was performed using Franz diffusion cell. From the release study, it was found that optimized nanogel shows initial burst release of drug in first 30 minutes and

afterward provides sustained release of drug. The optimized nanogel was shown release of more than 90 % (96.42 %) of drug in 12 hr.

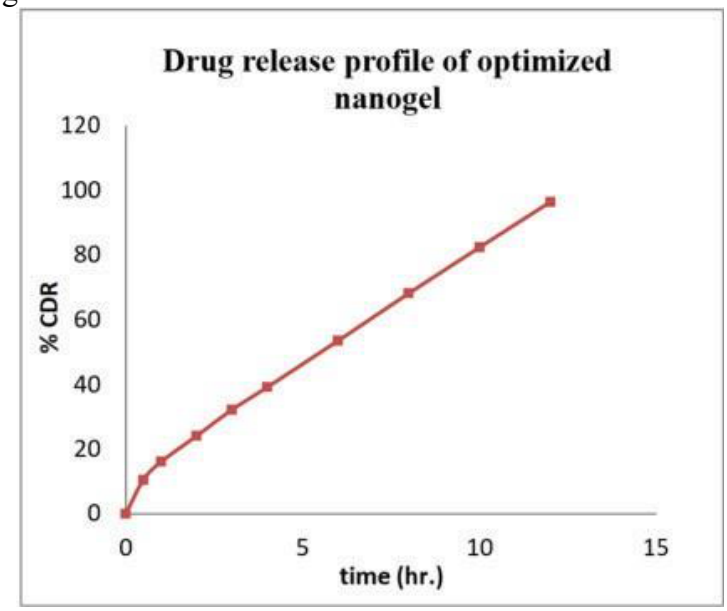

Figure 12: Drug release profile of optimized nanogel

Stability study

Stability study of the optimized nanogel was performed as per ICH guidelines Q1.170 After 3 months of stability study formulation was evaluated for its particle size and

% entrapment efficiency. From the results it was found that formulation was shown increase in particle size and decrease in % Entrapment efficiency at refrigeration condition (4±0.05°C) (Table 30). While formulation stored at 40 ± 2°C/75% ± 5% RH (relative humidity) was being precipitated and degraded. So, it was concluded that optimized nanogel formulation was stable at refrigeration condition and unstable at room temperature.

Table 10: Data of Stability study of optimized batch F2 at 4 ± 0.05°C

Parameter	Time	Before Stability	After Stability
Particle Size (nm)	3 months	81.97	96.23
% Entrapment Efficiency (%)	3 months	76.67	72.44

Conclusion

The study successfully developed a stable and effective nanogel formulation containing Allium cepa extract using Pluronic F127 and PEI. The application of factorial design enabled systematic optimization of formulation variables, resulting in an optimized batch (F2) with desirable particle size, high entrapment efficiency, and sustained drug release profile. FT-IR studies confirmed compatibility between drug and excipients, while ex-vivo studies demonstrated effective skin permeation. Stability studies indicated that the formulation is stable under refrigerated conditions but unstable at higher temperatures. Overall, the developed nanogel system offers a promising approach for topical delivery of herbal drugs in the treatment of skin diseases.

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