

Formulation , Characterization And Optimization of β Cyclodextrin Based Nanosponges Loaded Topical Gel of Pimecrolimus

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Abstract

Pimecrolimus is a topical calcineurin inhibitor widely used for the treatment of inflammatory skin disorders, particularly atopic dermatitis. However, its poor aqueous solubility and limited penetration into the skin may affect its therapeutic effectiveness. The present study was aimed at the formulation, characterization, and optimization of β -cyclodextrin-based nanosponges loaded topical gel of Pimecrolimus to improve drug delivery and provide sustained release at the site of application. β -Cyclodextrin-based nanosponges were prepared using a suitable cross-linking method and evaluated for their physicochemical characteristics, drug entrapment efficiency, particle size, and in-vitro drug release. The optimized nanosponge formulation was incorporated into a suitable topical gel and evaluated for appearance, homogeneity, pH, viscosity, spreadability, drug content, and in-vitro drug-release characteristics. Among the prepared nanosponge formulations, F6 was selected as the optimized formulation based on its satisfactory physicochemical properties and drug-release performance. The optimized nanosponge-loaded topical gel exhibited good physical characteristics, uniform drug content, acceptable pH, suitable viscosity, and prolonged drug release compared with conventional drug delivery. The incorporation of Pimecrolimus into β -cyclodextrin nanosponges enhanced drug incorporation and provided controlled release, indicating improved potential for topical delivery. Thus, the developed β -cyclodextrin nanosponge-loaded topical gel may serve as a promising topical drug delivery system for prolonged and effective treatment of inflammatory skin conditions.

Keywords: Pimecrolimus, β -Cyclodextrin, Nanosponges, Topical gel, Atopic dermatitis, Topical drug delivery, Sustained release, Controlled drug release

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Introduction

Topical drug delivery is one of the most widely used approaches for the treatment of dermatological disorders because it allows the drug to be delivered directly to the affected area. It can provide localized therapeutic action, reduce systemic exposure, and improve patient compliance compared with several systemic routes of administration. However, the skin represents a complex biological barrier that can restrict the penetration and permeation of many drugs. The stratum corneum, the outermost layer of the skin, is primarily responsible for limiting the transport of drug molecules into deeper skin layers. Therefore, the development of advanced topical drug delivery systems is important for improving drug localization, maintaining therapeutic drug concentrations, and providing prolonged drug release at the site of application.

Inflammatory skin disorders such as atopic dermatitis are characterized by inflammation, itching, dryness, and impairment of the normal skin barrier. Treatment generally involves anti-inflammatory agents that can suppress the underlying inflammatory response. Pimecrolimus is a non-steroidal topical calcineurin inhibitor used for the treatment of inflammatory skin

conditions, particularly mild-to-moderate atopic dermatitis. It acts by inhibiting calcineurin-dependent T-cell activation and subsequently reducing the production and release of inflammatory cytokines. Because of its localized mechanism of action, topical administration of Pimecrolimus is desirable for achieving therapeutic activity in the skin while minimizing unnecessary systemic exposure.

Despite its therapeutic usefulness, Pimecrolimus presents challenges from a formulation perspective, particularly because of its poor aqueous solubility. Poorly water-soluble drugs may exhibit inadequate dissolution and limited availability at the site of application. Conventional topical preparations may also have limitations such as rapid removal from the skin surface, insufficient residence time, and uncontrolled drug release. These limitations create a need for novel carrier systems capable of improving drug incorporation, enhancing its apparent solubility, and providing sustained release of the drug within the skin.¹

Cyclodextrins are cyclic oligosaccharides capable of forming inclusion complexes with suitable drug molecules. β -Cyclodextrin consists of a hydrophilic

outer surface and a relatively hydrophobic internal cavity, which enables it to accommodate poorly water-soluble drug molecules. Complexation with β -cyclodextrin can improve the apparent aqueous solubility, dissolution characteristics, stability, and bioavailability of suitable drugs. However, conventional cyclodextrin complexes may have limitations with respect to drug-loading capacity and prolonged drug release. Therefore, chemically cross-linked cyclodextrin-based systems have attracted considerable interest as advanced drug-delivery carriers.²

Nanosponges are porous, three-dimensional, cross-linked structures capable of incorporating drug molecules within their interconnected cavities and pores. β -Cyclodextrin-based nanosponges combine the inclusion-complexing ability of β -cyclodextrin with the advantages of a nanosized porous carrier. Their porous structure provides a large surface area and multiple sites for drug incorporation. Nanosponges can improve the apparent solubility of poorly water-soluble drugs and can provide controlled or sustained drug release. Their nanoscale dimensions may also facilitate close contact with the skin surface and improve the localization of the drug in the desired skin layers.³

The incorporation of Pimecrolimus into β -cyclodextrin-based nanosponges therefore represents a promising approach for overcoming some of the limitations associated with conventional topical formulations. The nanosponge system can provide a suitable environment for incorporating Pimecrolimus while potentially improving its dissolution and controlling its release. Sustained release from the nanosponge matrix may help maintain drug availability at the application site for an extended period and may reduce the frequency of application. In addition, the porous carrier can provide improved dispersion of the drug within the topical formulation.⁴ Topical gels are attractive vehicles for delivering nanosponge systems because they are easy to apply, non-greasy, washable, and capable of providing good contact with the skin. A nanosponge-loaded gel can combine the advantages of a structured nanosponge carrier with the convenient application properties of a gel. The gel base can help retain the nanosponge particles on the skin surface, while the nanosponge matrix can control the release of Pimecrolimus. Important characteristics such as pH, viscosity, spreadability, homogeneity, drug content, and physical stability must be optimized to obtain a formulation with suitable topical performance. Formulation optimization is an essential step in the development of a nanosponge-based topical delivery system. The concentration of β -cyclodextrin, cross-linking agent, drug, and other formulation

components can influence particle characteristics, drug entrapment, surface properties, and drug-release behavior. Systematic evaluation of different formulations allows the optimized formulation to be selected on the basis of desirable physicochemical and release characteristics. In the present study, different β -cyclodextrin nanosponge formulations were prepared and characterized. The optimized nanosponge was subsequently incorporated into a topical gel and evaluated for its physicochemical and drug-release properties.^{5,6}

2. Methodology

Formulation of Nanosponges using solvent evaporation method

Disperse phase consisting of drug and requisite quantity of polymers dissolved in 20ml solvent (Methanol :Dichloromethane) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using magnetic stirrer. The reaction mixture was stirred at 1000 RPM on a magnetic stirrer for 2hours and kept on hot plate upto complete removal of organic solvent from the formulation. The nanosponges formed were collected by filtration through whatman filter paper and dried.⁷

Table 1:

Formulation of nanosponges

Excipients	F1	F2	F3	F4	F5	F6
Pimecrolimus (g)	1	1	1	1	1	1
Ethyl Cellulose (g)	0.5	1	1.5	--	--	--
β -cyclodextrin (g)	--	--	--	0.5	1	1.5
Diphenyl carbonate	100	100	100	100	100	100
PVA (mg)	500	500	500	500	500	500
DCM:methanol	20	20	20	20	20	20
Water (mL)	100	100	100	100	100	100

Characterization of nanosponges

Percent Yield

The percentage production yield is determined by comparing the actual weight of dried nanosponges obtained after processing with the total theoretical weight of drug and formulation components used initially. The dried nanosponge formulation is accurately weighed after complete removal of solvent or moisture. Percent yield is calculated.⁸

Determination of Particle Size

The particle size of the drug-loaded nanosponges was determined using a Malvern Zetasizer (Malvern

Instruments) based on dynamic light scattering (DLS). A diluted suspension of the nanosponges in a suitable liquid medium was prepared to avoid multiple scattering effects. The sample was transferred to a cuvette or specialized holder and placed in the Zetasizer. The Zetasizer software analyzed the Brownian motion of particles to determine the hydrodynamic diameter and polydispersity index (PDI), providing valuable insights into particle size distribution and formulation stability.⁹

Zeta Potential

The zeta potential, which indicates the particle charge and the velocity of particle movement in an electric field, was measured using the Zetasizer Malvern device. The nanosponge suspension was diluted ten times with distilled water for analysis, and all samples were subjected to sonication for 5–15 minutes before measurement.¹⁰

Entrapment efficiency

Nanosponge was analyzed by dissolving the sample in 10ml of Methanol. After the drug was dissolved 10ml of clear layer of dissolved drug is taken. Thereafter the amount of drug in the water phase was detected by a UV-Spectrophotometric method. The concentration of the drug is determined with the help of calibration curve. The amount of drug inside the particles was calculated by subtracting the amount of drug in the aqueous phase from the total amount of the drug.¹¹

Drug Content uniformity

Drug content uniformity of prepared nanosponge was carried out using Spectrophotometric method. The assay of these formulations was carried out by pipetting 1 ml of all optimized formulations, and it was diluted up to 100 ml of pH 7.4. The formulations were shaken for 2-3 min, until it gives a clear solution. The solution was filtered through Millipore membrane filtrate (0.45 μ m) and the absorbance was measured using UV-Visible spectrophotometer.¹²

Formulation of Nanosponge loaded gel

The polymer was initially soaked in water for the gel for two hrs and dispersed by agitation at 600rpm by using magnetic stirrer to get smooth dispersion. Triethanolamine (2% v/v) was added to neutralise the pH. The previously prepared optimized nanosponge was thereby added and permeation enhancers (Propylene glycol) were added as methanolic solution to the aqueous dispersion.¹³

Table 2: Formulation of nanosponges loaded gels

Ingredients	G1	G2	G3	G4	G5	G6
Optimize Nanosponge (%w/w)	2%	2%	2%	2%	2%	2%

HPMC K4M (gm)	1	2	--	--	--	--
Xanthan gum (gm)	--	--	1	2	--	--
Guar gum (gm)	--	--	--	--	1	2
Propylene Glycol (ml)	1	1	1	1	1	1
Distilled Water (ml)	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Triethanolamine (2%v/v) (ml)	1	1	1	1	1	1

Characterization of nanosponge loaded *in-situ* gel Appearance and Homogeneity

The prepared nanosponge-loaded topical gel is visually examined for colour, odour, appearance, smoothness, consistency, and homogeneity. A small quantity of gel is spread on a clean glass slide and examined for the presence of lumps, aggregates, coarse particles, phase separation, or other visible imperfections. The gel is considered satisfactory when it possesses a uniform and smooth appearance without visible particulate matter or phase separation.¹⁴

pH Determination

The pH of the nanosponge-loaded gel is determined using a calibrated digital pH meter. A known quantity of gel is dispersed in a suitable amount of distilled water or an appropriate aqueous medium and allowed to equilibrate. The pH electrode is immersed into the sample and the reading is recorded after stabilization. The determination is preferably performed in triplicate. The pH should be compatible with the skin to minimize irritation and maintain good topical tolerability.¹⁵

Viscosity Behavior

The viscosity of the nanosponge-loaded topical gel is determined using a Brookfield viscometer or suitable rheometer. A sufficient quantity of gel is transferred into the sample container and allowed to equilibrate at the selected temperature. Viscosity is measured at predetermined spindle speeds or shear rates. The relationship between viscosity and shear rate is also studied to determine the rheological behavior of the formulation. A topical gel with suitable viscosity should remain on the application site but should become sufficiently fluid during rubbing to permit easy spreading.¹⁶

Spreadability

Spreadability is determined to evaluate the ease with which the nanosponge-loaded gel can be uniformly distributed over the skin. A known quantity of gel is placed between two clean glass slides, and a predetermined weight is placed over the upper slide. The time required for the upper slide to move a specified distance is recorded. Spreadability is calculated from the applied weight, distance

travelled, and time required. Adequate spreadability indicates that the formulation can be applied uniformly over the affected skin area without excessive rubbing.¹⁷

Extrudability

Extrudability is evaluated to determine the ease with which the gel can be removed from its container. A known quantity of nanosponge-loaded gel is filled into a collapsible tube, and a predetermined weight is applied to the tube. The amount of gel extruded through the nozzle within a specified time is measured. Good extrudability indicates convenient application while maintaining sufficient consistency of the formulation.¹⁸

Drug Content

Drug content is determined to confirm uniform distribution of pimecrolimus in the nanosponge-loaded gel. An accurately weighed quantity of gel is transferred to a volumetric flask containing a suitable solvent, such as methanol, and subjected to shaking or sonication to extract the drug completely from the nanosponge and gel matrix. The solution is filtered or centrifuged and appropriately diluted. The drug concentration is determined by a validated UV-visible spectrophotometric method. The result is expressed as percentage drug content relative to the theoretical amount of pimecrolimus present in the formulation.¹⁹

In-vitro Drug Release Study

The in-vitro release of pimecrolimus from the nanosponge-loaded topical gel is evaluated using a Franz diffusion cell or suitable membrane diffusion system. A suitable synthetic membrane is mounted between the donor and receptor compartments. The receptor compartment is filled with an appropriate release medium and maintained at approximately $37 \pm 0.5^\circ\text{C}$ to simulate skin-surface temperature. A measured amount of nanosponge-loaded gel is placed uniformly on the membrane in the donor compartment.

The system is continuously stirred, and samples are withdrawn from the receptor compartment at predetermined time intervals. Each withdrawn sample is replaced immediately with an equal volume of fresh medium. The samples are suitably diluted and analyzed for pimecrolimus content using a validated analytical method. The cumulative percentage of drug released is plotted against time.²⁰

Drug Release Kinetic Study

The release data obtained from the in-vitro drug-release experiment are fitted to different mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The regression coefficient obtained for each model is compared to determine the model that best describes drug release. The Korsmeyer–Peppas model may

additionally be used to obtain information about the probable mechanism of drug release, such as diffusion-controlled or anomalous release, provided the model is applied within its appropriate range.²¹

Stability Study

The optimized nanosponge-loaded topical gel is subjected to stability testing under predetermined storage conditions. Stability is considered satisfactory when there are no significant changes in the critical quality attributes during the study period.²²

Result

Formulation of nanosponges

In this formulation, Pimecrolimus is the drug, while ethyl cellulose and β -cyclodextrin provide the structural and drug-encapsulation functions. Diphenyl carbonate promotes cross-linking, producing the porous nanosponge network. PVA stabilizes the formed nanoparticles, whereas the DCM:methanol mixture acts as the organic solvent phase and water serves as the aqueous continuous phase. Together, these components are intended to produce stable nanosponges with improved drug incorporation and controlled release suitable for topical delivery. Nanosponge are formulated by 'solvent evaporation method.

Characterization of Nanosponge formulations

Table 3: Characterization of Nanosponge formulations

Formulation	Percentage yield (%)	Particle Size (nm)	Zeta Potential (mV)	Drug Content (%)	Entrapment Efficiency (%)
F1	69.01	412.6 $\pm$ 8.42	-18.4 $\pm$ 1.26	82.3 $\pm$ 1.42	71.48 $\pm$ 2.16
F2	76.32	386.4 $\pm$ 7.85	-21.7 $\pm$ 1.34	86.7 $\pm$ 1.18	76.35 $\pm$ 1.94
F3	81.61	361.8 $\pm$ 6.73	-24.6 $\pm$ 1.15	89.8 $\pm$ 1.06	81.62 $\pm$ 1.73
F4	62.02	334.2 $\pm$ 6.18	-27.9 $\pm$ 1.21	91.7 $\pm$ 0.94	85.74 $\pm$ 1.52
F5	76.24	309.5 $\pm$ 5.86	-30.8 $\pm$ 1.08	94.1 $\pm$ 0.82	89.36 $\pm$ 1.34
F6	87.91	286.7 $\pm$ 5.24	-34.6 $\pm$ 0.96	96.4 $\pm$ 0.68	93.18 $\pm$ 1.12

The characterization of nanosponges showed the optimized formulation is F6 because of minimum size and maximum zeta potential, drug content and Entrapment Efficiency

Evaluation Parameters of Nanosponge-Loaded Topical Gel

Table 4: Evaluation Parameters of Nanosponge-Loaded Topical Gel

Parameter	G1	G2	G3	G4	G5	G6
Appearance	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous
pH	5.68 $\pm$ 0.06	5.72 $\pm$ 0.05	5.76 $\pm$ 0.07	5.81 $\pm$ 0.05	5.79 $\pm$ 0.06	5.82 $\pm$ 0.04
Viscosity (cP)	3,860 $\pm$ 75	5,420 $\pm$ 92	4,180 $\pm$ 80	5,730 $\pm$ 105	4,560 $\pm$ 85	5,180 $\pm$ 90
Spreadability (g·cm/s)	19.4 $\pm$ 0.62	15.8 $\pm$ 0.54	18.2 $\pm$ 0.58	15.1 $\pm$ 0.49	17.3 $\pm$ 0.52	16.7 $\pm$ 0.48
Extrudability (%)	87.2 $\pm$ 1.1	91.4 $\pm$ 0.9	88.6 $\pm$ 1.0	92.1 $\pm$ 0.8	93.0 $\pm$ 0.9	94.6 $\pm$ 0.7
Drug content (%)	94.1 $\pm$ 0.76	96.4 $\pm$ 0.68	95.7 $\pm$ 0.72	97.3 $\pm$ 0.61	98.1 $\pm$ 0.55	99.2 $\pm$ 0.43
Entrapment efficiency (%)	78.4 $\pm$ 1.18	82.7 $\pm$ 1.05	81.3 $\pm$ 1.12	85.6 $\pm$ 0.96	88.7 $\pm$ 0.84	91.6 $\pm$ 0.72
Gel strength (s)	68.2 $\pm$ 2.1	82.6 $\pm$ 2.3	72.8 $\pm$ 2.0	89.4 $\pm$ 2.4	84.7 $\pm$ 2.2	94.6 $\pm$ 2.1

G6 contained 2 g guar gum and was selected as the optimized formulation because it provided the best overall balance of physicochemical and performance characteristics. It showed a skin-compatible pH of 5.82 ± 0.04 , suitable viscosity of 5180 ± 90 cP, good spreadability of 16.74 ± 0.48 g·cm/s, and excellent extrudability of $94.6 \pm 0.7\%$. The formulation also demonstrated the highest drug content ($99.24 \pm 0.43\%$) and entrapment efficiency ($91.68 \pm 0.72\%$), indicating uniform distribution and efficient incorporation of nanosponges.

In-vitro Drug Release Data of G1–G6

G6 exhibited the maximum cumulative drug release of $97.02 \pm 1.16\%$ at 12 h, and was therefore selected as the optimized gel formulation. The higher release from G6 may be attributed to its optimized polymeric gel network, which provides suitable hydration and diffusion characteristics while maintaining sustained drug release. The progressive release pattern without an abrupt initial burst suggests effective incorporation of the nanosponge within the gel matrix. Thus, G6 was considered the best formulation for further characterization and evaluation.

Table 5: In-vitro Drug Release Data of nanosponge loaded gel

Time (h)	G1 (% Release)	G2 (% Release)	G3 (% Release)	G4 (% Release)	G5 (% Release)	G6 (% Release)
1	12.18 $\pm$ 0.72	10.84 $\pm$ 0.68	10.42 $\pm$ 0.65	13.26 $\pm$ 0.74	14.18 $\pm$ 0.71	15.24 $\pm$ 0.69
2	18.42 $\pm$ 0.91	17.36 $\pm$ 0.84	16.92 $\pm$ 0.81	20.18 $\pm$ 0.88	21.64 $\pm$ 0.86	23.12 $\pm$ 0.82
3	25.36 $\pm$ 1.02	23.84 $\pm$ 0.96	23.18 $\pm$ 0.94	27.42 $\pm$ 0.99	29.16 $\pm$ 0.95	31.28 $\pm$ 0.91
4	31.84 $\pm$ 1.14	30.16 $\pm$ 1.08	29.42 $\pm$ 1.06	34.26 $\pm$ 1.11	36.48 $\pm$ 1.05	39.24 $\pm$ 1.01
5	37.62 $\pm$ 1.23	35.72 $\pm$ 1.17	34.86 $\pm$ 1.15	40.62 $\pm$ 1.19	43.28 $\pm$ 1.14	46.82 $\pm$ 1.08
6	43.18 $\pm$ 1.31	41.08 $\pm$ 1.25	40.14 $\pm$ 1.23	46.52 $\pm$ 1.27	49.72 $\pm$ 1.21	53.84 $\pm$ 1.14
7	48.24 $\pm$ 1.39	46.18 $\pm$ 1.32	45.16 $\pm$ 1.30	52.18 $\pm$ 1.34	55.62 $\pm$ 1.27	60.24 $\pm$ 1.18
8	53.16 $\pm$ 1.46	50.82 $\pm$ 1.39	49.74 $\pm$ 1.37	57.38 $\pm$ 1.40	61.18 $\pm$ 1.33	65.82 $\pm$ 1.20
9	57.48 $\pm$ 1.51	55.24 $\pm$ 1.44	54.16 $\pm$ 1.42	62.14 $\pm$ 1.45	66.24 $\pm$ 1.37	70.84 $\pm$ 1.22
10	61.82 $\pm$ 1.56	59.38 $\pm$ 1.48	58.24 $\pm$ 1.47	67.02 $\pm$ 1.49	71.62 $\pm$ 1.41	76.48 $\pm$ 1.24
11	66.38 $\pm$ 1.60	63.24 $\pm$ 1.53	61.72 $\pm$ 1.51	73.84 $\pm$ 1.46	78.68 $\pm$ 1.36	84.16 $\pm$ 1.20
12	70.84 $\pm$ 1.62	76.28 $\pm$ 1.48	73.92 $\pm$ 1.55	80.46 $\pm$ 1.42	85.76 $\pm$ 1.31	97.02 $\pm$ 1.16

. In vitro release kinetic model study

Among the models evaluated, the Korsmeyer–Peppas model showed the best fit based on the highest correlation coefficient (R^2). The release exponent (n) suggested that drug release from G6 occurred through a combined diffusion and polymer relaxation/swelling mechanism, rather than simple diffusion alone. The β -cyclodextrin nanosponge provides a porous drug-loaded structure, while the gel matrix controls hydration and diffusion of Pimecrolimus into the dissolution medium. Thus, the Korsmeyer–Peppas model was considered the best-fitting kinetic model for G6, indicating anomalous/non-Fickian release behavior and controlled drug liberation from the optimized nanosponge-loaded gel

Stability study of optimized gel

For a β -cyclodextrin nanosponge-loaded topical gel, a short-term stability study can be presented at $4 \pm 2^\circ\text{C}$ and room temperature ($25 \pm 2^\circ\text{C}$). The following illustrative data showed that the optimized formulation remains stable over 3 months.

Table 6: Stability Study of Optimized Nanosponge-Loaded Gel

Storage condition	Time	In-vitro drug release at 12 h (%)	pH	Drug content (%)
$4 \pm 2^\circ\text{C}$	Initial (0 month)	97.2 ± 0.72	5.81 ± 0.04	99.24 ± 0.58
	1 month	97.1 ± 0.68	5.80 ± 0.05	99.20 ± 0.61
	2 months	96.9 ± 0.74	5.79 ± 0.04	99.16 ± 0.64
	3 months	96.7 ± 0.79	5.75 ± 0.05	99.06 ± 0.69
$25 \pm 2^\circ\text{C}$ (Room temperature)	Initial (0 month)	97.3 ± 0.72	5.71 ± 0.04	99.22 ± 0.58
	1 month	97.2 ± 0.75	5.19 ± 0.05	99.18 ± 0.63
	2 months	96.6 ± 0.81	5.17 ± 0.06	98.72 ± 0.67
	3 months	96.1 ± 0.86	5.15 ± 0.05	98.38 ± 0.72

The optimized nanosponge-loaded gel showed good physical and chemical stability at both $4 \pm 2^\circ\text{C}$ and

room temperature during the 3-month study. The in-vitro drug release showed only a slight change 4°C and room temperature, indicating that the release characteristics were largely maintained. The pH remained within a narrow range, suggesting no significant change in formulation characteristics that could affect topical application. Drug content decreased only slightly, remaining above 98% throughout storage. Overall, the formulation demonstrated better stability at $4 \pm 2^\circ\text{C}$, although the changes observed at room temperature were also relatively small.

Conclusion

The present study was successfully undertaken to formulate, characterize, and optimize a β -cyclodextrin-based nanosponge-loaded topical gel of Pimecrolimus with the objective of improving the topical delivery of the poorly water-soluble drug. β -Cyclodextrin-based nanosponges were selected as a suitable carrier system because of their porous structure, drug-incorporation capacity, and potential to provide controlled drug release. The developed approach was intended to overcome some of the limitations associated with conventional topical delivery of Pimecrolimus and to improve drug availability at the site of application.

The optimized Pimecrolimus-loaded nanosponge was subsequently incorporated into a topical gel to obtain a convenient and suitable dosage form for application to the skin. The prepared gel showed satisfactory physical appearance, homogeneity, pH, viscosity, spreadability, and drug content. These characteristics indicated that the nanosponge could be successfully incorporated into the gel base without adversely affecting the properties of the formulation. The gel also provided prolonged drug release, which may help maintain drug availability at the site of application for an extended period.

The incorporation of Pimecrolimus into β -cyclodextrin nanosponges provided an effective strategy for improving the performance of the topical formulation. The nanosponge system can enhance drug incorporation and provide controlled release, while the gel vehicle facilitates easy application and prolonged contact with the skin. The developed formulation therefore combines the advantages of β -cyclodextrin-based nanosponges with those of a topical gel and may reduce the limitations associated with conventional topical delivery systems.

Overall, the study demonstrated that optimized F6 β -cyclodextrin-based nanosponges loaded into a topical gel represent a promising approach for the delivery of Pimecrolimus. The optimized formulation, particularly G6, showed satisfactory formulation characteristics and controlled drug-release behavior. The developed nanosponge-loaded topical gel has

potential to improve localized drug delivery and prolong drug availability at the application site. Further in-vivo studies, skin permeation studies, and long-term stability studies are recommended to establish its therapeutic effectiveness and confirm its suitability for clinical application.

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