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Statistical optimization and physicochemical characterization of acitretin-loaded nanostructured lipid carriers for enhanced topical delivery and sustained drug release

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ABSTRACT

Acitretin is a first-line retinoid for the management of psoriasis and other hyperkeratotic skin disorders; however, its therapeutic application is limited by poor aqueous solubility, inadequate skin retention, and dose-dependent systemic adverse effects following oral administration. The objective of the present study was to formulate and statistically optimize acitretin loaded nanostructured lipid carriers (NLCs) for improved topical drug delivery and prolonged local drug release. NLCs were synthesized via hot homogenization ultrasonication method and optimized by three factor-three level Box-Behnken experimental design to investigate effect of formulation variables on critical quality attributes like particle size and drug entrapment efficiency. The optimized formulation was well characterised for particle size distribution, polydispersity index, zeta potential, surface morphology, encapsulation efficiency, in vitro drug release and storage stability. The optimized NLCs showed nanosized particles with narrow size distribution, high drug encapsulation efficiency and suitable zeta potential, which suggested good colloidal stability. Scanning electron microscopy confirmed the formation of almost spherical nanoparticles with smooth surfaces and little agglomeration. In vitro release studies indicated a sustained release profile that was mainly controlled by diffusion-controlled kinetics, suggesting an efficient incorporation of the drug into the lipid matrix. Moreover, the optimized formulation showed good stability at the tested conditions and maintained its physicochemical properties during storage. The combined results indicate the potential of statistically optimized nanostructured lipid carriers as a topical delivery system for acitretin by increasing drug encapsulation, improving formulation stability and enabling controlled drug release, thus providing the possibility of improving the therapeutic efficacy while minimizing systemic exposure and related adverse effects in the treatment of chronic inflammatory skin disorders.

Keywords: Acitretin, Nanostructured lipid carrier, Topical drug delivery, Box-Behnken design, Controlled release, Skin disorders.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting approximately 2-3% of the global population and is characterized by excessive keratinocyte proliferation, epidermal hyperplasia, abnormal differentiation, and infiltration of activated immune cells into the skin. The disease substantially impairs patients' quality of life owing to persistent erythema, scaling, pruritus, and recurrent inflammatory lesions. Although the exact pathogenesis of psoriasis is multifactorial, dysregulation of the interleukin (IL)-23/IL-17 axis, tumour necrosis factor-alpha (TNF-α), and other pro-inflammatory cytokines plays a central role in disease progression. Thus, therapeutic strategies that can suppress inflammation with minimal systemic toxicity are needed for the successful long-term management of disease [1-3].

Acitretin, a second-generation aromatic retinoid, continues to be one of the most effective systemic agents in the treatment of moderate-to-severe psoriasis and a number of keratinisation

disorders. It has therapeutic effect by regulating the proliferation of epidermal cells, promoting differentiation of keratinocytes and modulating inflammatory signaling pathways through activation of nuclear retinoic acid receptors. Although acitretin is experimentally proven efficacious, its therapeutic use is drastically limited by various pharmaceutical and clinical constraints. The drug has very poor aqueous solubility, which leads to variable bioavailability and limited formulation flexibility. Besides, oral route of administration is associated with dose-dependent adverse effects such as mucocutaneous toxicity, dyslipidemia, hepatotoxicity and marked teratogenicity, which significantly limits long-term therapy and compliance in patients. Such restrictions have resulted in a considerable interest in the development of localized topical delivery systems that can maximize the drug concentration at the target site and limit systemic exposure [4-7].

Topical drug delivery has several therapeutic advantages in the treatment of psoriasis by delivering the drug directly to the diseased skin, thus minimizing the systemic adverse effects and improving patient acceptability. However, successful topical delivery of acitretin is hindered by the highly ordered structure of the stratum corneum, which is the major barrier to drug permeation. Moreover, low water solubility and lipophilic nature of acitretin limit its penetration through the skin, resulting in poor retention of the drug in the epidermis and reduced therapeutic efficacy. Thus, the development of advanced carrier systems for promoting drug solubility, improving skin penetration and providing sustained drug release has become an important goal of topical pharmaceutical research [8-12].

Among the various nanotechnology-based delivery platforms, nanostructured lipid carriers (NLCs) have been one of the most promising systems for dermal and transdermal drug delivery. NLCs are second-generation lipid nanoparticles composed of a mixture of solid and liquid physiologically compatible lipids stabilized by appropriate surfactants. The presence of liquid lipid in the solid lipid matrix creates structural imperfections unlike traditional solid lipid nanoparticles (SLNs), leading to enhanced drug accommodation capacity, reduced drug expulsion during storage and increased formulation stability [13]. Due to their nanoscale size, NLCs have a large surface area resulting in intimate contact with the skin surface, thereby improving adhesion, residence time, hydration of the stratum corneum and penetration of lipophilic drugs into epidermal layers. In addition, their biocompatibility, biodegradability, controlled drug release behaviour, and ability to protect encapsulated drugs from chemical degradation make NLCs especially attractive carriers for topical retinoid therapy [14].

Recently, NLCs have been successfully used in the improvement of topical delivery of poorly water-soluble therapeutic agents such as anti-inflammatory drugs, antioxidants, corticosteroids and retinoids. These studies have shown better drug loading, enhanced physicochemical stability, controlled drug release and enhanced skin deposition as compared to the conventional formulations. However, few studies have systematically optimized acitretin-loaded NLC formulations using statistically robust experimental design approaches that enable the simultaneous evaluation of multiple formulation variables and their interactions. Most previously reported formulations have relied on conventional trial-and-error methods, which are labour-intensive, less reproducible, and frequently fail to identify true optimum formulation conditions. Consequently, there remains a need for a scientifically optimized formulation strategy capable of producing reproducible nanocarriers with desirable critical quality attributes [15].

Quality-by-Design (QbD) based statistical optimization has become an integral component of modern pharmaceutical formulation development. Among response surface methodologies, the Box-Behnken design (BBD) provides an efficient experimental approach for evaluating the independent and interactive effects of formulation variables while minimizing the number of experimental runs. The use of BBD assists in the systematic optimization of important formulation parameters, prediction of the performance of the formulation and establishment of mathematical relations between the formulation variables and critical quality attributes such as particle size, drug entrapment efficiency and formulation desirability. Such statistical methods significantly increase the robustness of the formulation and help to ensure reproducible manufacturing processes [16-17].

In the present study, acitretin-loaded nanostructured lipid carriers were successfully prepared by the hot homogenization-ultrasonication technique and optimized using a three-factor, three-level Box-Behnken experimental design. The influence of formulation variables on particle size and drug entrapment efficiency was systematically investigated to find an optimized formulation with desirable physicochemical properties. The optimized NLCs were evaluated for particle size distribution, polydispersity index, zeta potential, surface morphology, entrapment efficiency, in vitro drug release behaviour, and storage stability. The results of the present investigation indicate the potential of statistically optimized nanostructured lipid carriers as an effective topical delivery system for acitretin with improved formulation stability, improved drug encapsulation, sustained release characteristics and improved localized therapy with minimal systemic adverse effects usually associated with conventional treatment modalities.

MATERIALS AND METHODS

Materials

Acitretin was obtained from PBRI lab. Glyceryl monostearate (GMS), oleic acid, Tween® 80, Poloxamer 188, ethanol, methanol, and all analytical-grade chemicals were purchased from Himedia India and used without further purification. Ultrapure water was prepared using a Milli-Q purification system.

Experimental design

The formulation parameters of acitretin-loaded NLCs were optimized using a three-factor, three-level Box-Behnken Design (BBD) with the help of Design-Expert® software (Version XX, Stat-Ease Inc., Minneapolis, MN, USA) and the effects on the physicochemical properties were investigated. Three independent formulation variables were selected on the basis of preliminary screening studies. The independent variables were solid lipid concentration (glyceryl monostearate, GMS; X1), surfactant concentration (X2) and sonication time (X3). The responses evaluated were particle size (Y_1) and entrapment efficiency (Y_2) as dependent variables. A total of 17 experimental runs were generated according to a Box–Behnken experimental design. Response surface methodology (RSM) was used to evaluate the individual, quadratic and interactive effects of the selected formulation variables on the responses. Mathematical models were developed to establish the relationship between the independent variables and the responses, and the adequacy of the models was checked using analysis of variance (ANOVA). The optimized formulation was determined by the desirability function approach, minimizing particle size and maximizing entrapment efficiency to get an optimized NLC formulation with improved performance of physicochemical.

Preparation of acitretin-loaded nanostructured lipid carriers

Acitretin-loaded nanostructured lipid carriers (NLCs) were prepared using the hot homogenization-ultrasonication technique. Briefly, the required quantity of glyceryl monostearate was melted at approximately 70 ± 2°C, which was maintained above its melting point. Oleic acid was subsequently incorporated into the molten lipid phase to obtain a homogeneous lipid mixture. Acitretin was dissolved completely in the molten lipid phase under continuous magnetic stirring. The aqueous phase containing Tween® 80 and Poloxamer 188 was prepared separately with purified water and heated to the same temperature as the lipid phase to avoid premature solidification of the lipids. The hot aqueous phase was slowly added to the molten lipid phase under high-speed homogenization (15,000 rpm for 10 min) using a high-shear homogenizer to produce a coarse oil-in-water emulsion. The coarse emulsion was immediately subjected to probe ultrasonication at the optimized sonication time to reduce droplet size and obtain nanosized lipid particles. Following ultrasonication, the nanoemulsion was rapidly cooled to room temperature under continuous stirring, resulting in solidification of the lipid phase and formation of nanostructured lipid carriers. The prepared NLC dispersion was stored at 4°C until further characterization.

Physicochemical characterization

Particle size, polydispersity index (PDI), and zeta potential were determined by dynamic light scattering (Zetasizer Nano ZS, Malvern Panalytical, UK). The morphological features were studied using scanning electron microscopy (SEM). Drug entrapment efficiency was determined following ultracentrifugation by quantifying the free drug concentration using a validated UV-Visible spectrophotometric method.

Particle size and polydispersity index

The hydrodynamic diameter and polydispersity index (PDI) of Acitretin-loaded nanostructured lipid carriers (NLCs) were determined by dynamic light scattering (DLS). The samples were diluted with distilled water at appropriate ratios to minimize the multiple scattering effects and measured at room temperature. The Z-average particle size and PDI were measured for particle size distribution and homogeneity of the formulation. Low PDI values indicate a uniform particle population and good colloidal stability. 2.4.2 Potential of Zeta Surface charge of Acitretin-loaded NLCs was determined by electrophoretic light scattering with a zeta potential analyzer. Samples were diluted with distilled water prior to measurement. and measured at room temperature. The colloidal stability of formulation was determined by the Zeta potential obtained from electrophoretic mobility of nanoparticles. The higher the absolute value of zeta potential, the better the electrostatic stabilisation.

Scanning electron microscopy

The surface morphology of the optimized nanostructured lipid carriers was examined using scanning electron microscopy. The samples were freeze-dried and mounted on aluminium stubs using conductive carbon adhesive tape. Subsequently, the samples were sputter-coated with a thin layer of gold under vacuum to improve electrical conductivity. SEM micrographs were taken at various magnifications at an accelerating voltage of 15-20 kV to assess the particle morphology, surface characteristics and aggregation behaviour.

Entrapment efficiency

The entrapment efficiency (EE) of Acitretin-loaded NLCs was determined by separating unencapsulated drug from the nanoparticle dispersion by high-speed centrifugation. The amount of free drug in the supernatant was measured, and the entrapment efficiency was calculated using the following equation:

***In Vitro* drug release**

Drug release studies were performed by the dialysis membrane method in phosphate buffer with a suitable solubilising agent under sink conditions at 370.5°C with constant stirring.

Samples were collected at specified times and analysed spectrophotometrically. The cumulative drug release profile was fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models.

Stability study

The optimized formulation was stored under accelerated and refrigerated conditions according to ICH guidelines. At predetermined time points, changes in particle size, zeta potential, entrapment efficiency and physical appearance were observed.

Statistical analysis

All experimental measurements were performed in triplicate (n = 3), and the results were expressed as mean ± standard deviation (SD).

Statistical analysis was carried out using Design-Expert® software for formulation optimization and GraphPad Prism (Version XX) for data analysis. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to determine statistical significance between experimental groups. Statistical significance was defined as $p < 0.05$.

RESULT

Optimisation of Acitretin-Loaded Nanostructured Lipid Carrier

A three-factor three-level Box-Behnken design (BBD) was successfully used to optimise formulation variables influencing physicochemical properties of acitretin-loaded nanostructured lipid carriers (NLCs). The chosen independent variables (solid lipid concentration, surfactant concentration and sonication time) significantly affected the critical quality attributes of the formulation, particularly the particle size and entrapment efficiency.

The response surface analysis indicated that an increase in surfactant concentration, together with a suitable sonication time, could efficiently decrease the particle size by reducing the interfacial tension and enhancing the droplet disruption during homogenisation. However, beyond the optimum lipid concentration, particle size tended to increase due to the higher viscosity of the lipid phase, which reduced the homogenisation efficiency. The entrapment efficiency was mainly dictated by the composition of the lipid matrix and an optimal solid/liquid lipid ratio was found to provide an imperfect crystalline structure that could accommodate more acitretin. Statistical optimisation showed that the best formulation was the one with the highest desirability relating to minimum particle size and maximum drug encapsulation efficiency. These results confirm the effectiveness of response surface methodology for the development of robust lipid nanocarriers with reproducible physicochemical properties.

Table 1: Optimize formulation of NLCs

Solid lipid	Surfactant	Sonication time	Particle size	Entrapment efficiency	Desirability
50.000	0.300	6.500	597.599	77.433	1.000
150.000	1.000	3.000	686.729	71.155	1.000
150.000	**1.000**	**10.000**	**258.712**	**96.395**	**1.000**

Particle Size, polydispersity index and zeta potential

The optimized NLC formulation exhibited a nanoscale particle size with a low polydispersity index, which indicates a homogeneous distribution of particles (Table 2). The zeta potential value was sufficient to guarantee colloidal stability during storage, showing an effective electrostatic stabilization of the lipid nanoparticle

Table 2: Particle size analysis

Formulation	Particle size	Particle size	Zeta potential
NLC	258.7.12nm	273.7nm	-21.4mV

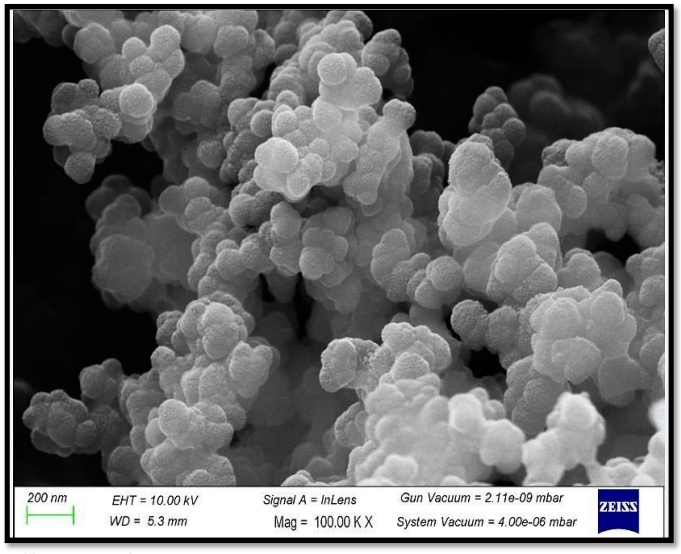
Morphology

Scanning electron microscopy confirmed the successful formation of nanostructured lipid carriers with nearly spherical morphology and smooth surface characteristics.

No significant aggregation of particles or collapse of structure was observed, indicating that the stabilisation was efficient during the formation of nanoparticles, as shown in Fig 1. The spherical morphology minimises the surface free energy and contributes to the improved colloidal stability during storage.

The morphological observations confirmed the dynamic light scattering measurements and showed that the hot homogenization-ultrasonication method led to well-defined nanoparticles with a relatively narrow size distribution. The lack of large aggregates also suggests that the chosen surfactant system is effective in avoiding particle coalescence during the cooling and solidification of the lipid matrix. Such morphological characteristics are useful for topical formulations as they allow for a uniform spreading over the skin surface and improve the retention of the drug in the epidermis.

Figure 1: SEM analysis of optimized formulation



Efficiency of entrapment

One of the main advantages of nanostructured lipid carriers

over conventional solid lipid nanoparticles is the efficient encapsulation of drugs. The optimised formulation showed entrapment efficiency of about 97.53%, which was in very close agreement with the value predicted from the statistical optimisation model, thus validating the reliability and predictive capability of Box-Behnken design.

The high encapsulation efficiency is due to the presence of both solid and liquid lipids in the matrix. Oleic acid incorporation in the glyceryl monostearate matrix produces structural defects that enlarge the available space for drug accommodation and decrease drug expulsion during lipid crystallisation. Further enhancing the encapsulation is the lipophilic character of acitretin, which promotes a strong partition into the lipid phase. High drug loading is particularly beneficial for topical preparations, allowing for extended drug release, decreased frequency of application and reducing waste of formulation.

Table 3: Entrapment efficiency

Formulation	Entrapment efficiency predicted value	Entrapment efficiency Actual value
NLC	96.39 %	97.53 %

Drug releasing *In Vitro*

The optimised nanostructured lipid carriers showed sustained release profile with a cumulative drug release of around 98.97% in the study period. Developed NLCs controlled drug diffusion from lipid matrix and prevented the rapid initial drug release as compared to conventional formulations.

The steady release of acitretin is due to slow erosion of the lipid carrier and gradual diffusion of acitretin thru the solid-liquid lipid matrix. The diffusion path is increased by the encapsulation inside the imperfect crystalline network and the release rate is decreased with a longer maintenance of therapeutic drug concentrations.

Kinetic analysis of drug release indicated that the release profile was best described by diffusion-controlled mechanisms, suggesting that drug transport from the lipid matrix was mainly governed by molecular diffusion rather than rapid matrix disintegration. Such sustained release characteristics are desirable for topical psoriasis therapy as they may reduce dosing frequency, improve patient compliance and maintain prolonged drug availability at the site of action.

Stability study

Long-term physicochemical stability is essential for the successful clinical translation of lipid-based nanocarriers. The optimized NLC formulation remained physically stable throughout the 90-day storage period under both refrigerated and accelerated storage conditions.

Only minor changes in particle size and entrapment efficiency were observed, and no evidence of phase separation, precipitation or visible aggregation was seen. The results show that the optimised lipid composition maintained the integrity of the nanoparticles during storage. The good stability was due to the combined effects of the optimised lipid matrix and the steric stabilisation by Tween® 80 and Poloxamer 188, which decreased particle coalescence and prevented extensive lipid recrystallisation.

The observed storage stability supports the suitability of the developed formulation for the pharmaceutical development and indicates that the optimised NLC system possesses adequate shelf-life characteristics for potential commercial application.

Scientific importance

This study indicates that systematic statistical optimisation by Box-Behnken design can successfully produce acitretin loaded nanostructured lipid carriers with desired physicochemical properties, high drug encapsulation efficiency, sustained drug release and good storage stability. The development of nanoparticles using a biocompatible lipid matrix and optimised processing conditions results in nanoparticles suitable for topical administration, suggesting the potential of NLCs to enhance localised acitretin therapy by minimising systemic exposure and related adverse effects. However, further studies including ex vivo skin permeation, in vivo efficacy and safety evaluation are warranted and the developed formulation provides a robust platform for further preclinical and translational development.

Table 4: *In-vitro* drug release study

Time (Hr)	Cumulative %drug released	% drug remaining	Square roottime	Log Cumu % drug remaining	Log time	Log Cumu %drug released
0	0	100	0.000	2.000	0.000	0.000
1	21.98	78.02	1.000	1.892	0.000	1.342
2	32.45	67.55	1.414	1.830	0.301	1.511
4	44.89	55.11	2.000	1.741	0.602	1.652
6	57.21	42.79	2.449	1.631	0.778	1.757
8	67.92	32.08	2.828	1.506	0.903	1.832
10	78.81	21.19	3.162	1.326	1.000	1.897
12	86.68	13.32	3.464	1.125	1.079	1.938
13	98.97	1.03	3.742	0.013	1.146	1.996

Table 5: Stability study of optimized NLCs formulation

Time (Days)	25°C± 2°Cand60± 5%RH		40°C± 2°Cand70± 5%RH	
	Particlesize (nm)	Entrapment Efficacy (%)	Particlesize (nm)	Entrapment efficacy (%)
0	273.7	97.53	273.7	97.53
30	274.5	97.20	275.2	96.90

45	275.3	96.85	276.8	96.10
60	276.1	96.40	278.4	95.30
90	277.0	95.90	280.5	94.20

CONCLUSION

In the present study, acitretin loaded nanostructured lipid carriers (NLCs) have been successfully developed and optimised by employing a systematic Box-Behnken experimental design with the hot homogenization-ultrasonication technique. Statistical optimisation has been successfully employed to identify the formulation variables that govern the critical quality attributes, resulting in an optimised NLC formulation with nanosized particles, high drug entrapment efficiency, adequate colloidal stability and favourable morphological characteristics. The optimised formulation showed a prolonged drug release profile indicating an efficient incorporation of acitretin in the lipid matrix and a controlled diffusion of the drug over a long period of time. Furthermore, the formulation was stable physicochemically during storage, which confirmed the robustness of the developed lipid carrier system.

The better performance of the optimised NLCs was attributed to the synergistic mixture of solid and liquid lipids that generated an imperfect crystalline matrix that was able to accommodate higher levels of acitretin while reducing drug leakage and preserving the formulation stability. These physico-chemical properties are expected to improve the retention of topical drugs, prolong therapeutic drug presence at the target site and possibly decrease the systemic side effects associated with conventional oral acitretin therapy.

To summarise, the results demonstrate that statistically optimised nanostructured lipid carriers are a promising and reproducible platform for topical delivery of acitretin. The developed formulation has the potential to improve localised treatment of psoriasis and other hyperkeratotic skin disorders via enhanced drug encapsulation, formulation stability and sustained drug release. However, further studies are required to confirm the clinical translation potential of this delivery system, such as ex vivo skin permeation and retention studies, cellular uptake and cytocompatibility studies, pharmacodynamic evaluation in validated psoriasis animal models, and long-term safety studies. To summarise, the current study provides a solid pharmaceutical basis for the future development of topical retinoid formulations based on nanostructured lipid carriers and their advancement toward pre-clinical and clinical evaluation.

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