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Review Article

Formulation and Evaluation of Isotretinoin Nano Sponges-Loaded Transdermal Patch: A Review

Indra Ramesh[1, *], Lakshmi Barath[2], Keerthi Bala[2], John Samuel[2], Younoos[2], Idhaya Jeevan[2], Yukeshwaran[2]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Karpagam Academy of Higher Education, Coimbatore, India
[2]Faculty of Pharmacy, Karpagam Academy of Higher Education, Coimbatore, India

Abstract

Isotretinoin, an oral retinoid derived from vitamin A, remains one of the most effective agents available for the management of moderate-to-severe and treatment-resistant acne vulgaris because it simultaneously addresses sebum overproduction, follicular hyper keratinization, Cuti bacterium acnes proliferation, and inflammation. However, its clinical use by the oral route is limited by teratogenicity, mucocutaneous dryness, hyperlipidemia, hepatotoxicity, and musculoskeletal and psychiatric adverse effects, while conventional topical isotretinoin formulations suffer from poor aqueous solubility, photo instability, and marked skin irritation. Nano sponge technology, comprising hyper-cross-linked polymeric or cyclodextrin-based three-dimensional networks capable of entrapping lipophilic and poorly soluble drugs within nanosized cavities, offers a promising platform to improve isotretinoin's solubility, stability, and localized skin delivery while minimizing systemic exposure. Incorporating isotretinoin-loaded nano sponges into a transdermal patch further combines the sustained- and controlled-release advantages of matrix-type transdermal drug delivery systems with the solubilization and targeting benefits of nano sponges. This review compiles and synthesizes the current literature on the pharmacology and limitations of isotretinoin, the design and preparation methods of nano sponges, transdermal patch technology, and the physic ochemical, in vitro, ex vivo, and stability evaluation parameters relevant to the formulation and evaluation of an isotretinoin nano sponge-loaded transdermal patch, and it outlines the advantages, challenges, and future prospects of this delivery approach.

Keywords

Isotretinoin, Nano Sponges, Transdermal Patch, Cyclodextrin, Acne Vulgaris, Controlled Drug Delivery, Skin Permeation

1. Introduction

Acne vulgaris is among the most common chronic inflammatory disorders of the pilosebaceous unit, and isotretinoin has long been regarded as the benchmark therapy for its severe and recalcitrant forms because it is the only agent that intervenes across the full spectrum of acne pathogenesis [38, 39] Despite this efficacy, systemic isotretinoin therapy carries a well-documented burden of adverse effects, including teratogenicity, xerosis, cheilitis, hyperlipidemia, hepatic enzyme elevation, musculoskeletal complaints, and psychiatric symptoms, all of which necessitate close clinical monitoring and

*Correspondence: Indra Ramesh (indra.ramesh@kahedu.edu.in)

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have prompted continued interest in delivery systems that can localize drug action to the skin while limiting systemic absorption [40, 43, 44].

Conventional topical isotretinoin preparations, such as creams and gels, have historically been constrained by the drug's poor water solubility, chemical instability under light and oxygen, and tendency to provoke local irritation at concentrations needed for therapeutic effect [4, 5]. These limitations have motivated a shift toward nanocarrier-based topical and transdermal systems—including solid lipid nanoparticles, self-nanoemulsifying systems, liposomes, and nano sponges—that aim to enhance drug solubilization, protect the molecule from degradation, and direct its accumulation within the epidermal and follicular compartments of the skin rather than the systemic circulation [1, 3, 4, 7-9].

Nano sponges are a distinct class of nanocarrier composed of hyper-cross-linked polymers or cyclodextrins arranged in a porous, sponge-like three-dimensional matrix capable of encapsulating both hydrophilic and lipophilic actives within their nanoscale cavities [9, 12, 13]. When such nano sponges are further incorporated into a polymeric transdermal patch, the resulting system may combine the solubility-enhancing and controlled-release characteristics of the nanocarrier with the sustained, patient-compliant, and dose-controlled delivery inherent to transdermal patch technology [6, 20, 23]. This review consolidates literature relevant to each stage of developing such a system—drug and carrier rationale, nano sponge preparation, transdermal patch fabrication, and the evaluation methodologies required to characterize the final dosage form.

2. Acne Vulgaris and the Pharmacology of Isotretinoin

Isotretinoin (13-cis-retinoic acid) was approved for the treatment of severe acne in 1982 and continues to be considered the gold-standard therapy for nodulocystic and scarring disease because of its multimodal action on sebaceous gland activity, corneocyte adhesion, follicular keratinization, and local immune regulation [39, 40]. Oral dosing regimens have been studied extensively, and systematic reviews comparing low-dose and standard-dose protocols report broadly comparable efficacy with differing adverse-effect and relapse profiles, underscoring that dose optimization alone does not eliminate the drug's systemic liabilities [41].

The adverse-effect profile of oral isotretinoin extends across multiple organ systems: mucocutaneous dryness and cheilitis are near-universal, while hepatic, lipid, musculoskeletal, ocular, and neuropsychiatric effects occur with variable frequency and have been the subject of dedicated retrospective and cross-sectional analyses [40, 43-46]. Ocular surface dryness associated with oral therapy, for instance, has been managed with adjunctive hyaluronic acid–based eye drops in clinical studies, illustrating the extent of extracutaneous impact that a purely systemic dosing strategy can produce [41]. These findings collectively support the rationale for localized, skin-restricted delivery approaches that could, in principle, preserve efficacy while reducing systemic drug exposure.

3. Limitations of Conventional Isotretinoin Delivery

Isotretinoin is a Biopharmaceutics Classification System class II-type lipophilic molecule with very low aqueous solubility, and its topical formulations must overcome poor partitioning into the hydrophilic layers of the skin as well as susceptibility to photo- and oxidative degradation [4, 5].

Marketed topical gels have been reported to retain some degree of systemic absorption and to cause local irritation, particularly at the higher concentrations required for clinical benefit, which limits patient tolerability and adherence [4, 5].

Nanoparticulate strategies such as solid lipid nanoparticles and self-nanoemulsifying drug delivery systems have been explored specifically to improve isotretinoin's skin-targeting behavior; solid lipid nanoparticle formulations, for example, have demonstrated a marked increase in cutaneous drug accumulation relative to conventional tincture controls while limiting permeation into deeper tissue compartments [4]. Similarly, self-nanoemulsifying and combination antioxidant-loaded systems have been optimized to improve ex vivo permeation flux and to counter isotretinoin-associated hepatotoxicity when co-formulated with hepatoprotective agents such as resveratrol or quercetin [1, 7-9]. These approaches validate the broader premise that nanocarrier engineering can materially change isotretinoin's delivery behavior, providing the conceptual foundation for a nano sponge-based approach.

4. Skin Barrier Considerations Relevant to Formulation Design

Rational design of any topical or transdermal isotretinoin system must begin from the physiology of the barrier it is intended to cross. The stratum corneum, the outermost layer of the epidermis, is composed of terminally differentiated corneocytes embedded in a highly ordered lamellar lipid matrix of ceramides, cholesterol, and free fatty acids, and this brick-and-mortar arrangement is what confers the skin's exceptional resistance to the passage of both hydrophilic and many lipophilic molecules [60,61]. Because the stratum corneum also restricts the permeation of molecules above approximately 500 Da and imposes gender-, site-, and health-dependent variability in permeability, formulation scientists have developed a range of ex vivo and in vitro barrier models—including excised human and porcine skin, reconstructed human epidermis, and synthetic membranes such as Strat-M—to predict permeation behavior before in vivo testing is undertaken [62,63].

Reviews of the percutaneous absorption literature emphasize that the macroscopic alternation of lipoidal and hydro-

philic domains within the stratum corneum governs the partitioning and diffusion of a permeant, and that overcoming this barrier generally requires either modifying the physicochemical state of the drug (for example, through nanocarrier entrapment or complexation) or transiently altering the barrier itself via chemical or physical enhancement strategies. These principles directly inform the layered design rationale of an isotretinoin nano sponge-loaded patch, in which the nano sponge addresses drug-side solubility and stability limitations while the patch matrix and any incorporated enhancer address barrier-side resistance.

5. Nano Sponges as Carriers for Poorly Soluble Drugs

5.1. Structure and Classification

Nanosponges are typically described as spherical, porous colloidal particles, generally under 1 micron and often below 500 nanometers in diameter, formed by cross-linking polymers such as ethyl cellulose or cyclodextrins with agents like diphenyl carbonate or carbonyldiimidazole to generate a rigid, mesh-like nanostructure with internal cavities [13, 19, 32]. Cyclodextrin-based nanosponges in particular combine the molecular inclusion-complexation capacity of the cyclodextrin torus with the three-dimensional cross-linked scaffold, allowing them to accommodate drug molecules both within individual cyclodextrin cavities and within the interstitial nanochannels of the polymer network [9-11].

This dual encapsulation mechanism underlies several pharmaceutically desirable properties: enhanced aqueous solubility and dissolution of poorly water-soluble drugs, protection of labile molecules from light- or oxygen-mediated degradation, high drug loading and entrapment efficiency, and the possibility of sustained or triggered release [11, 12, 14, 18]. Nanosponge platforms have accordingly been investigated across a wide range of therapeutic applications, including oncology, anti-infective, and topical delivery, with cyclodextrin nanosponges specifically reported to increase the oral bioavailability of poorly soluble actives by more than two-fold relative to plain drug suspensions in some studies [16, 58, 59].

5.2. Methods of Preparation

The emulsion solvent diffusion method is among the most widely used techniques for nanosponge fabrication: the drug and a polymer such as ethyl cellulose are dissolved in a water-immiscible organic solvent such as dichloromethane to form the dispersed phase, which is then added dropwise into an aqueous continuous phase containing a stabilizer such as polyvinyl alcohol under continuous stirring; solvent diffusion into the aqueous phase precipitates porous nanosponge particles that are subsequently filtered, washed, and dried [30, 31, 33, 35]. This method is favored for its operational simplicity, use of pharmaceutically acceptable solvents, and reasonably high formulation yield [31].

Alternative preparation routes described in the literature include the ultrasound-assisted (solvent-free) method, in which a cyclodextrin polymer is reacted directly with a cross-linking agent under sonication at elevated temperature to yield uniformly sized spherical nanosponges, and the melting method, in which the polymer and cross-linker are co-melted, homogenized, and subsequently washed to remove unreacted excipients [32, 33, 37]. Drug loading is typically achieved either during synthesis or by subsequently suspending the blank nanosponges in a saturated drug solution under stirring or sonication, followed by centrifugation or freeze-drying to isolate the drug-loaded particles [33, 37]. The choice among these methods is generally guided by the physicochemical properties of the drug and polymer, desired particle size range, and acceptable residual solvent limits [36].

5.3. Characterization of Nanosponges

Nanosponge characterization commonly includes particle size and polydispersity analysis by dynamic light scattering, surface morphology evaluation by scanning or transmission electron microscopy, and confirmation of drug–polymer compatibility and complexation by (FTIR), differential scanning calorimetry, and powder X-radiation diffraction [9, 10]. Practical formulation studies on structurally similar retinoid and topical actives, such as isoniazid- and tretinoin-loaded nanosponges, have additionally reported drug entrapment efficiencies in the range of roughly 47–75% and 90–97% respectively, with spherical, spongy particle morphology confirmed by electron microscopy, illustrating the parameter ranges typically targeted during optimization [2, 6].

5.4. Cyclodextrin Inclusion Complexation Chemistry

Because cyclodextrin-based nanosponges derive part of their drug-loading capacity from classical host–guest inclusion complexation, the underlying chemistry of cyclodextrin complexation is directly relevant to formulation design. Beta-cyclodextrin and its hydrophilic derivatives, such as hydroxypropyl-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin, form inclusion complexes in which a lipophilic guest molecule is partially or fully accommodated within the truncated-cone hydrophobic cavity, thereby improving the apparent aqueous solubility and dissolution rate of poorly soluble drugs [15, 64]. Phase-solubility analysis, Job's plot titration, and stability-constant determination are standard tools used to establish complex stoichiometry and binding strength, and have been applied across a wide range of poorly soluble actives including rivaroxaban, carbamazepine, aripiprazole, mefenamic acid, and norfloxacin, consistently demonstrating solubility gains of several-fold over the free drug [17].

Preparation techniques for binary and ternary drug–cyclodextrin systems—kneading, solvent (co-) evaporation, freeze-drying, microwave irradiation, and hot-liquid extrusion—have each been shown to influence complexation efficiency and resulting dissolution performance, with freeze-drying and solvent evaporation methods frequently outperforming simple physical mixing [52,55]. Comparative work with structurally diverse guests such as beta-lapachone and pomalidomide further indicates that hydrophilic cyclodextrin derivatives generally achieve higher solubilization than native beta-cyclodextrin, a consideration relevant to selecting the specific cyclodextrin grade used in fabricating isotretinoin-loaded nanosponges [56, 57].

6. Transdermal Drug Delivery Systems

6.1. Rationale and Types of Transdermal Patches

Transdermal drug delivery avoids first-pass hepatic metabolism, provides sustained and controlled plasma or local tissue drug levels, and generally improves patient compliance relative to oral dosing, which has made it an attractive route for both systemic and localized dermatological therapy [23, 28]. Transdermal patches are broadly classified into reservoir-type systems, in which the drug is contained in a separate compartment behind a rate-controlling membrane, and matrix-type systems, in which the drug is dispersed directly within an adhesive or non-adhesive polymer matrix; bilayered matrix designs have also been reported to combine the mechanical and release advantages of both approaches [25, 28].

A nanosponge-loaded matrix-type patch is a logical configuration for isotretinoin because it allows the drug-loaded nanocarrier to be homogeneously dispersed within the polymer film, from which the nanosponges—and the isotretinoin they contain—can be released gradually as the polymer hydrates or erodes upon contact with the skin surface, similar in principle to nanosponge-loaded gel systems already reported for structurally related retinoids such as tretinoin [6].

6.2. Components and Methods of Preparation

A typical transdermal patch formulation comprises the drug (or drug-loaded carrier), a film-forming polymer such as hy (HPMC), (EC), (PVP), or carboxymethyl cellulose sodium, a plasticizer such as propylene glycol or dibutyl phthalate to impart flexibility, a penetration enhancer, and backing and release-liner materials [21, 22, 26, 27]. The solvent casting method is the most widely reported laboratory-scale preparation technique, in which the polymer(s) and drug (or drug-loaded nanosponges) are dissolved or dispersed in a common solvent system, cast onto a mold or backing membrane, and dried under controlled conditions to form a uniform film; hot-melt extrusion has also been used at larger scale [23, 24].

Polymer selection and ratio substantially influence patch performance: increasing the proportion of hydrophilic polymers such as HPMC or sodium carboxymethyl cellulose in matrix patches has been repeatedly shown to increase swelling index, drug release rate, and ex vivo permeation and skin retention relative to more hydrophobic polymer-dominant formulations [20, 26, 27]. These structure–function relationships, established for other small-molecule actives, provide a template for polymer optimization when designing an isotretinoin nanosponge-loaded patch (EC), the hydrophobic polymer most frequently used both to fabricate the nanosponge scaffold itself and as a film-forming excipient in matrix-type transdermal patches, is widely regarded as nontoxic, nonallergenic, and chemically stable, and produces tough, coherent films, although its inherently low water permeability means it is usually blended with hydrophilic polymers such as (HPMC) to tune drug release and film flexibility. Studies on ethyl cellulose-based transdermal films of other small molecules confirm that varying the ethyl cellulose-to-hydrophilic-polymer ratio, along with the choice of plasticizer and penetration enhancer, materially changes steady-state permeation flux and cumulative drug release, findings that are directly transferable to the design of the outer patch matrix surrounding isotretinoin-loaded nanosponges.

Because the stratum corneum represents the principal barrier to transdermal absorption, chemical penetration enhancers are frequently incorporated to reversibly disrupt intercellular lipid packing, interact with corneocyte proteins, or increase the drug's partition coefficient into the skin [46, 48]. Reported enhancer classes include fatty acids and their esters, terpenes and essential-oil constituents, sulfoxides such as dimethyl sulfoxide, glycols, and surfactants, with essential-oil-derived terpenes shown to alter stratum corneum lipid organization without the more severe irritation sometimes associated with synthetic enhancers [47, 49]. Comparative studies on other transdermal actives have found natural enhancers such as eugenol to produce permeation enhancement comparable to that of dimethyl sulfoxide, suggesting that natural penetration enhancers may offer a favorable balance of efficacy and tolerability for an isotretinoin-loaded patch, given that skin irritation is already a recognized concern with topical retinoids [26, 46].

Physical enhancement techniques—including iontophoresis, sonophoresis, microneedle arrays, and electroporation—represent an alternative or complementary strategy to chemical enhancers and have been reviewed extensively for their capacity to transiently increase stratum corneum permeability with a generally favorable safety profile in preclinical testing [50, 51, 54]. Nanocarrier-based transdermal systems more broadly have also been shown to enhance skin penetration through mechanisms such as skin hydration, particle deformability, and tunable surface charge and size, mechanisms that are directly relevant to how nanosponge-entrapped isotretinoin might traverse the epidermis once released from the patch matrix [53].

7. Evaluation of the Nanosponge-Loaded Transdermal Patch

7.1. Physicochemical and Mechanical Evaluation

Formulated patches are conventionally evaluated for physical appearance, weight and thickness uniformity, folding endurance, tensile strength and elastic modulus, percentage moisture content and moisture uptake, water-vapor transmission rate, drug content uniformity, and surface pH, since these parameters collectively determine the mechanical robustness, handling characteristics, and dose reliability of the finished patch [20-22, 27, 28]. (FTIR) and differential scanning calorimetry are additionally used to rule out incompatibility or unwanted interaction between the drug, the nanosponge polymer, and the patch-forming excipients [22, 25, 28].

7.2. In Vitro Drug Release and Kinetic Modeling

In vitro drug release is typically assessed using Franz diffusion cells with a synthetic or biological membrane separating donor and receptor compartments, and the resulting cumulative release profiles are fitted to mathematical models—zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell—to characterize the dominant release mechanism and quantify diffusional exponents [29, 34, 36]. The Korsmeyer–Peppas model in particular is widely used to distinguish Fickian diffusion from non-Fickian (anomalous) transport in matrix and nanocarrier-based systems, information that is important for predicting whether an isotretinoin nanosponge-loaded patch will exhibit diffusion-controlled or combined diffusion/erosion-controlled release [34, 36].

7.3. Ex Vivo Permeation and Skin Compatibility Studies

Ex vivo permeation studies, generally performed using excised rat or porcine abdominal skin mounted on Franz diffusion cells, provide flux, permeability coefficient, and cumulative permeated-drug values that are used to compare candidate formulations and penetration enhancer strategies [26, 27, 29]. Skin drug retention studies, which quantify the amount of drug remaining within the skin layers after permeation testing, are particularly relevant for a topically targeted agent such as isotretinoin, since therapeutic benefit depends on adequate follicular and epidermal drug accumulation rather than systemic transfer [20, 27]. Skin irritation and hypersensitivity testing, typically conducted on rodent models, is also a standard requirement before a topical or transdermal retinoid formulation can be considered for further development, given the known irritant potential of retinoids [21, 22, 28].

7.4. Stability Studies

Stability testing under accelerated and long-term storage conditions evaluates changes in drug content, physical appearance, and mechanical parameters over time, and has been used in comparable transdermal patch studies to support predicted shelf-life estimates of around two years for optimized matrix-type systems [22, 28]. For an isotretinoin-loaded product, stability assessment additionally warrants specific attention to photostability and oxidative degradation, given the well-documented light and oxygen sensitivity of retinoid compounds [4, 5].

8. Rationale for an Isotretinoin Nanosponge-Loaded Transdermal Patch

Integrating isotretinoin-loaded nanosponges into a transdermal patch is intended to address the two central limitations identified in the preceding sections simultaneously: the poor solubility, photoinstability, and irritant potential of isotretinoin, and the need for sustained, localized, and patient-compliant skin delivery. The nanosponge component is expected to improve isotretinoin's apparent solubility and protect it from degradation within the porous polymer matrix, consistent with observations reported for other retinoid- and poorly soluble drug-loaded nanosponge systems [6, 9, 14], while the surrounding patch matrix would provide a sustained, rate-controlled reservoir from which the drug-loaded nanosponges are released gradually onto the skin surface, analogous to sustained-release behavior documented for other matrix-type transdermal systems [20, 25, 27].

This dual-carrier design is further supported by reports that nanosponge-based topical gels of related retinoids, such as tretinoin, achieve consistent drug content and viscosity while enabling controlled in vitro release, and by the broader literature demonstrating that nanocarrier incorporation into transdermal films does not compromise, and can enhance, mechanical and permeation performance relative to conventional matrix patches [6, 20, 25].

9. Advantages, Challenges, and Future Perspectives

The principal anticipated advantages of an isotretinoin nanosponge-loaded transdermal patch include improved aqueous solubilization and photochemical protection of the drug, sustained and controlled release that could reduce dosing frequency, avoidance of first-pass hepatic metabolism and reduced systemic exposure relative to oral therapy, and the potential for improved patient acceptability compared with daily topical gel application [1, 9, 23, 53]. Reduced systemic ab-

sorption is of particular relevance given the extensive extracutaneous adverse-effect profile associated with oral isotretinoin, including hepatic, lipid, musculoskeletal, and neuropsychiatric effects [43-46].

Notable challenges remain, including the need to confirm adequate follicular and epidermal drug accumulation without excessive systemic permeation, to manage the intrinsic irritant potential of retinoids at the patch–skin interface, to ensure long-term photostability of the entrapped drug, and to establish scale-up-compatible, reproducible nanosponge and patch manufacturing processes [4, 5, 21, 28]. Future work is therefore likely to focus on systematic optimization of nanosponge polymer-to-drug ratios and patch polymer composition, in vivo pharmacokinetic and pharmacodynamic evaluation in animal models, comparative bioavailability studies against marketed oral and topical isotretinoin products, and long-term clinical tolerability assessment [24, 25, 42].

10. Conclusion

The convergence of nanosponge technology and transdermal patch engineering offers a rational strategy to overcome the principal solubility, stability, and tolerability limitations that have constrained conventional isotretinoin therapy. The literature reviewed here—spanning isotretinoin pharmacology, nanosponge design and preparation, transdermal patch technology, and the physicochemical, release, permeation, and stability evaluation methods applicable to such systems—provides a coherent methodological framework for the formulation and evaluation of an isotretinoin nanosponge-loaded transdermal patch. Continued preclinical and, eventually, clinical investigation will be required to translate this formulation concept into a viable localized therapy for moderate-to-severe acne vulgaris.

Abbreviations

FTIR	Fourier Transform Infrared Spectroscopy
EC	Ethyl Cellulose
HPMC	Hydroxy Propyl Methylcellulose
PVP	Polyvinylpyrrolidone

Author Contributions

Indra Ramesh: Conceptualization, Investigation, Project administration, Visualization, Writing – review & editing

Lakshmi Barath: Conceptualization, Writing – original draft

Keerthi Bala: Methodology

John Samuel: Data curation

Conflicts of Interest

The authors declare no conflicts of interest.

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