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Design, Formulation and Characterization of Solid Lipid Nanoparticles for Transdermal Delivery in Alcohol Use Disorder

Dosage Platform: Solid Lipid Nanoparticles Incorporated into a Transdermal Patch

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ABSTRACT: Alcohol use disorder poses significant health and social burden, and the limited use of pharmacological treatments is due to problems with adherence, dosing frequency, and conventional oral administration. Acamprosate calcium is a known relapse prevention medication for individuals who have been abstinent from alcohol; it is currently administered orally once a day, and has a low systemic bioavailability. According to the research synopsis, the active pharmaceutical ingredient used in this project is acamprosate, and solid lipid nanoparticles (SLNs) is recommended as the drug delivery method in a transdermal patch. The central formulation challenge is unusual for passive transdermal systems, which generally seek small, nonionic molecules with appropriate lipophilicity and low daily dose, and which acamprosate calcium is highly water soluble and ionic. There have been several publications recently that have discussed the potential of using lipid nanocarriers for transdermal drug delivery, which can alter skin–drug interactions, influence skin hydration and occlusion, and enable controlled delivery of the drugs, but with the exception of hydrophilic drugs which are difficult to load onto the carrier and transport efficiently (Liu et al., 2023).

The present paper formulates and evaluates the formulation based on literature based acamprosate calcium loaded SLNs and incorporates into matrix type transdermal patch. The proposed workflow includes the preformulation, screening of lipids and surfactants, optimization of particle size, polydispersity index, zeta potential and entrapment efficiency, morphology assessment, in vitro release studies, ex vivo skin permeation and skin deposition, stability studies, pharmacokinetic studies, pharmacodynamic studies and comparison with marketed oral formulation of acamprosate. A Quality by Design approach is used to establish the relationship between the critical material attributes and critical process parameters to measurable quality attributes (Sivadasan et al., 2024; Antonara et al., 2025).

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However, since the synopsis provided does contain a research protocol (and not experimental results), all numerical results, graphs and charts provided in Results and Analysis are specifically identified as illustrative target data to be found in the literature. They are included merely for illustrative purposes to enable the construction of the actual measurements to be used in place of them, before submission as an original experimental article, to provide the analytical framework to be followed. The formulation concept is tailored to the challenge: to ensure adequate drug loading of a lipid carrier that results in a patch with a long drug release profile that has an acceptable transdermal flux with an acceptable skin irritation profile.

1. INTRODUCTION

1.1 Alcohol Use Disorder and the Need for Pharmacological Treatment

Alcohol use disorder (AUD) is a condition in which alcohol use causes significant impairment in a person's ability to control their drinking, continued use of alcohol despite damaging consequences, alcohol craving, alcohol tolerance and alcohol withdrawal. There is a significant public-health burden today. It is estimated that there were around 400 million people aged 15 and over with AUDs, including approximately 209 million alcohol dependence in 2019, and some 2.6 million people were reported to have died as a result of alcohol use in 2019 (WHO et al., 2024). The mortality isn't the only burden that is carried: There is a burden of liver disease, cardiovascular disease, neurological impairment, injuries, mental-health comorbidity and social disruption. There is a huge treatment gap, and there continues to be a need for readily available and acceptable drug interventions.

Pharmacotherapy typically is combined with psychosocial intervention rather than used as a standalone intervention. Contemporary evidence shows that acamprosate is one of the drugs with evidence for reducing alcohol consumption-associated outcomes (return to any drinking and drinking days) (McPheeters et al., 2023). Acamprosate is also known to be a relapse prevention drug after the abstinence phase (Kranzler et al., 2023; Tareen et al., 2024). The standard treatment, however, is multiple dosing per day, and this presents the formulation and adherence challenge, which is significant in long term treatment.

1.2 Acamprosate Calcium as the Selected Active Pharmaceutical Ingredient

Acamprosate is the calcium salt of N-acetylhomotaurine which is utilized to sustain abstinence in people with alcohol addictions who are not drinking at treatment beginning. The approved U.S. prescribing information for delayed release tablets recommends the following dosage: 2 333 mg three times daily, which is then adjusted in moderate renal impairment; contraindicated in severe renal failure (DailyMed et al., 2023). The pharmacological profile varies from the hepatically metabolized relapse prevention drugs, because of the clinical relevance of renal elimination. This property is important when considering alternate delivery systems since systemic exposure and renal function and dosage frequency will continue to be important.

Based on pharmacokinetic data, oral acamprosate is poorly bioavailable (only ~10%) and the standard dose regimen will lead to a high tablet burden (Steil et al., 2025). There is not a consistent picture of the therapeutic evidence across all clinical contexts, and several newer reviews have highlighted, inconsistencies between trials and patient populations (McPheeters et al., 2023; Kranzler et al., 2023). To improve drug exposure, however, should not be the only formulation objective. The more specific objective is to create a reproducible delivery system that would result in controlled delivery to systemic circulation and have a safe profile and still maintain the pharmacologic activity of abstinence maintenance.

1.3 Transdermal Delivery and the Acamprosate Permeation Problem

Transdermal drug delivery is a non-invasive pathway that can achieve a sustained input, and prevent gastrointestinal exposure and hepatic first-pass metabolism. The modern transdermal systems can be categorized into matrix architecture and reservoir architecture or drug-in-adhesive architecture and can be improved by employing permeation enhancers, nanocarriers and physical enhancement techniques (Singh et al., 2024; Sivadasan et al., 2024). The main drawback is the presence of the stratum corneum of the skin, made up of corneocytes containing keratin and organized in lipid domains. This barrier is very permeable to hydrophillic and ionized compounds. The permeation is also influenced by recent reviews describing the role of molecular size, polarity, lipophilicity, dose, skin hydration and formulation composition (Bakhrushina et al., 2025).

The high aqueous solubility of acamprosate calcium is especially challenging in terms of its transdermal development because it does not have a high skin permeability. Hydrophilic compounds may have a more favorable partitioning into the water-rich donor phase and weak partitioning into the lipid-rich stratum corneum. Therefore, the formulation should be able to solve the problems of drug partitioning, drug remaining in the carrier, drug release from the carrier and drug permeation through the skin. The advantages of nanocarrier systems are: ability to alter the local thermodynamics environment, promote skin surface interaction and create an occlusive film and to interact with skin lipids. The use of SLN however does not guarantee that they will be systemically acting when delivered transdermally, and only when the final system has been validated by in vitro/ex vivo studies with measurable flux.

1.4 Rationale for Solid Lipid Nanoparticles

SLNs are carriers that consist of lipids, where the lipid matrix is surrounded by the surfactants. They can offer controlled release, can protect the incorporated drug, increase surface area and create an occlusive effect following application to the skin. In recent literature, SLNs and NLCs are proposed as well-established research platforms for dermal and transdermal drug delivery and the differences in loading, crystallinity, release and permeation are reported (Bukke et al., 2024; Antonara et al., 2025). The provided synopsis specifically mentions the preferred nanoparticle platform of SLNs, and suggests changing the type of lipid, the surfactant, the lipid to surfactant ratio, the type of charge inducer and the processing conditions.

The problem is not solubility, but entrapment if the API is very water soluble. In addition, a hydrophilic drug can be washed from the particle matrix during the process of formation, which can also reduce the entrapment efficiency. Double emulsion methods, ion-pairing/electrostatic association methods, mixed lipid domains, optimization of the surfactant and rapid solidification can be discussed. Acamprosate is a drug with an ionic function, and a low concentration of the charge inducer of the cation species can be screened, and it is relatively skin-tolerable. Optimum formulation can be achieved with respect to not only particle size but also other responses. It is applied here following the new trend in the QbD of lipid-based transdermal systems recently developed (Antonara et al., 2025).

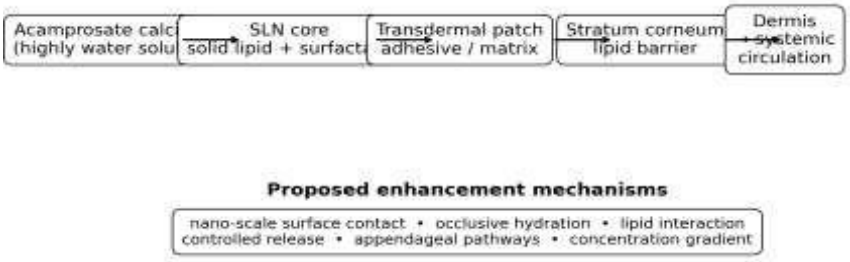


Figure 1. Conceptual mechanism for delivery of acamprosate calcium from an SLN-loaded transdermal patch across the skin barrier.

2. LITERATURE REVIEW

2.1 Contemporary Evidence for Acamprosate in Alcohol Use Disorder

Acamprosate is a clinically proven maintenance of abstinence drug. A large systematic review and meta-analysis of 118 trials in 20,976 participants in 2023 demonstrated a statistically significant effectiveness of acamprosate over placebo for reducing alcohol consumption; however, the evidence base was limited and there were differences across populations (McPheeters et al., 2023). A narrative review also outlines acamprosate as an approved medication for AUD and highlights issues regarding dosage, duration and medication selection (Kranzler et al., 2023). The results do not indicate that formulation changes would impact clinical response, but do suggest that additional formulation work is warranted.

Recently, the oral treatment regimen has been presented in the clinical pharmacology literature in terms of its practical application. Adherence may be affected by pill burden and Acamprosate is generally taken 3 times a day. Steil's team reviewed both "full-dosed" and "low-dosed" and/or "low-frequency" approaches and noted that final conclusions are still premature, but that there are clinical and pharmacokinetic signals to investigate lower doses. A theoretical reduction in the number of

administrations of a transdermal system is possible and may be illustrated by the introduction of a systemically effective dose, rather than by the size of the nanocarriers or by in vitro release.

2.2 Recent Developments in Transdermal Nanotechnology

From the traditional vesicular nanotechnology to multifunctional lipid, polymeric and hybrid systems, the transdermal nanotechnology has evolved. Liu et al. (2023) presented strategies for improvement in interaction with the SC and delivery through appendageal and transepidermal routes including the use of lipid carriers, polymeric systems, nanogels etc. functional nanogels. There are the following reasons for the importance of lipid carriers: They can consist of lipids which are similar to those in skin and the nanometer surface may support interaction with the skin.

The transdermal reviews which have been done recently have focused on the importance of the stratum corneum as the barrier. Nanocarriers have been found to support hydration, control release and change the interaction and penetration of lipids with the API, which is critical to the formulation's composition and the API's physicochemical properties (Cheng et al., 2023; Bakhrushina et al., 2025). The foregoing is especially interesting with regard to acamprosate, which is highly soluble in water and therefore, unfavourable for passive partitioning into the hydrophobic Stratum corneum.

2.3 Solid Lipid Nanoparticles for Skin Delivery

The SLN performance is controlled by type of the lipids, lipid concentration, the selection of the surfactant, the drug to li pid ratio, the particle size, crystallinity and surface charge. Bukke et al. (2024) carried out a review of the recent SLN preparation methods and design and found that high-pressure homogenization and microemulsion and related methods are considered as the major approaches for the preparation of SLN. The same review also mentions the protection offered by the lipid matrix to the molecules incorporated and the control over their release. If the formulation desired is transdermal, the smallest particle may not be the right formulation. Reproducible and predictable drug loading and release profile, an acceptable surface charge, and a balanced size distribution are better targets for drug development.

Since the last experimental studies published in 2022, some new studies in the literature have proven that SLNs have a positive impact on the transdermal delivery of some APIs. Pawar and Dawre used SLN and a topical hydrogel for the formulation of adapalene and minocycline; they obtained high entrapment and sustained release in both, and in the case of the topical hydrogel, the release of minocycline and adapalene was enhanced compared to their ex vivo permeation. Moghimipour et al., 2025 reported that the propranolol loaded SLN had successfully been encapsulated, extended the release time and increased the deposition and permeation into the skin compared to propranolol solution without any major cytotoxicity signal under the study condition. The results confirm the use of SLNs as a platform for the formulation and show that it is performance dependent, both on the API and the formulation.

2.4 Transdermal Patch Architecture and Evaluation

Typically a transdermal patch has a backing membrane, a matrix or reservoir (for the drug), an adhesive surface and a release liner. In particular, the matrix design is very attractive for an SLN system since the nanoparticle dispersion can be incorporated into a polymeric matrix and will be released in a controlled manner from the polymeric matrix. The matrix or drug-in-adhesive configuration is used in long-acting transdermal systems which are easy to construct and result in long duration of action (Singh et al., 2024). The patch should maintain the proper integrity of the nanoparticles in order that the API is not leached out quickly into the surface environment, but is released gradually into the interface between the skin and the patch.

The following physical attributes, thickness, weight variation, folding endurance, moisture content, moisture uptake, surface pH, drug content uniformity, adhesive performance, in vitro release and ex vivo permeation should be tested. Experiments are conducted in a Franz diffusion cell which is commonly accepted to use for the controlled skin pervasion studies and for which the main parameters are skin source, skin thickness, receptor medium, temperature, stirring, dose, sampling interval and sink conditions (Bakhrushina et al., 2025; Nair et al., 2025). The dermal deposition should be distinguished from the actual transdermal delivery. The amount of drug retained in the skin should be separated from the amount of drug found in the receptor compartment.

2.5 Research Gap

As demonstrated in the provided synopsis, there is a focused gap in the literature for the systematic study of transdermal delivery of nanoparticles containing acamprosate as a model API, compared to the larger body of literature for other APIs. The gap

includes formulation optimization of a highly water-soluble drug, extended ex vivo permeation, safety evaluation of the skin cells, and pharmacokinetic comparison of the optimized nanoparticle and oral administration of the drug and subsequent incorporation into a patch. The feasibility of a SLN lipid nanocarrier as a clinically effective product is not yet proved, however there are recent publications in the transdermal literature which indicate the general feasibility of a lipid nanocarrier. This proposed work, therefore, should be empirically verified across all the phases in a development process – not assumed from other APIs.

3. MATERIALS AND METHODS

3.1 Study Design and Objectives

The following research steps will be followed: formulation, optimization and characterization of acamprosate nanoparticles for transdermal administration, pharmacokinetic and pharmacodynamic evaluation and comparing the optimized formulation with adequate marketed formulation of acamprosate. The synopsis consists of preformulation, development of the SLN, characterization of the SLN, pharmacodynamic study, pharmacokinetic study and comparison with marketed preparation. The underlying experimental design of this paper basically stays the same as these objectives.

Based on the rational formulation hypothesis, the transdermal release profile of a rationsally optimized acamprosate calcium loaded SLNs can be controlled and a measurable ex vivo transdermal flux can be achieved, compared to free acamprosate dispersion in the same transdermal patch formulation that is acceptable in terms of physical stability and skin tolerability. The major quality parameters include particle size and PDI, zeta potential, entrapment efficiency, drug content, morphology, release rate, cumulative permeation, steady-state flux and patch uniformity.

3.2 Preformulation Studies

In the first place, the response, crystal or amorphous structure, the melting behaviour or thermal transition, the solubility in water, the partition coefficient and the spectrophotometric response of acamprosate calcium should be studied. The synopsis calls for the use of a solubility method in the shake flask, followed by subsequent equal volume partitioning between n-octanol and water; a stock solution of 100μg/mL; and serial dilutions of 2–10μg/mL to be used for UV calibration. Before formulation assay is performed, these procedures should be tested for specificity, linearity, accuracy and repeatability.

Fourier transform infrared spectroscopy, and differential scanning calorimetry are used for the determination of drug–excipient compatibility. All selected lipids, surfactants, charge inducer and physical mixtures are to be examined for any significant changes, loss of unique peaks or thermal changes that could indicate chemical reaction. High water solubility, and compatibility should be assessed after water dilution and during storage, as well as due to precipitation or ionic association during water dilution. Not only lipid but also lipid and surfactant systems are compatible with the compatibility screen.

3.3 SLN Formulation Strategy

A screening matrix should contain a good amount of solid lipid, a non-ionic surfactant and a small amount of charge inducer for the evaluation of surface potential. The precise excipient mix will depend on the result of compatibility and skin-tolerability testing. Owing to its hydrophilicity, a formulation strategy that ensures that the aqueous API fraction remains in the nanoparticle during solidification is needed. The most efficient loading mechanism can be evaluated by either a double-emulsion or solvent-diffusion procedure when compared with conventional emulsification.

The formulation variables which are these are the lipid concentration, surfactant concentration, drug-to-lipid ratio, charge-inducer concentration, homogenization and/or stirring speed and processing time. The optimized variables given in the provided synopsis are type and ratio of lipid/surfactant, charge inducer and rotation speed/time. To reduce the number of experiments and to evaluate interaction effects a Design of Experiments approach should be used. The response variables are particle size, PDI, zeta potential, entrapment efficiency and in vitro release. Responses can be summarized at the overall level into an overall formulation-selection criterion through formulating a desirability function.

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Figure 2. Proposed formulation-development and evaluation workflow derived from the supplied objectives and methodology.

3.4 Preparation of Acamprosate Calcium-Loaded SLNs

Controlled emulsification can be used to formulate the aqueous drug phase of hydrophilic APIs and incorporate into a lipid phase. The aqueous phase contains the selected surfactant and the lipid phase is kept above its melting point, if needed. Droplet size can be decreased prior to cooling and solidification using high shear mixing followed by controlled homogenization or sonication. If the double-emulsion process is chosen, the internal aqueous acamprosate phase is initially dispersed into the molten lipid phase, and then re-emulsified into the external aqueous surfactant phase. It is important to control the leakage of drugs from particles during solidification to minimize it.

After the nanoparticles are formed, the dispersion should then be cooled while stirring, and if necessary, purified. Since highly water-soluble acamprosate may easily partition to the aqueous phase, it is important to validate the recovery of acamprosate after purification by centrifugation, dialysis, or ultrafiltration. This means that the efficiency of entrapment should be determined by the amount of free drug present and the drug bound to the nanoparticles. Besides maximization of entrapment, the ideal formulation should be selected based on reproducible loading, narrow distribution, suitable surface potential and controlled release..

3.5 Nanoparticle Characterization

Dynamic light scattering following standardized dilution is the method to measure particle size and PDI. The aim of the formulation should be to show that there is little or no aggregation after storage and a narrow distribution. The surface charge will influence the stability of the colloid and its interaction with the skin, hence should be determined by electrophoretic light scattering. The morphology should be analyzed using TEM or SEM. Differential scanning calorimetry and X-ray diffraction can also offer information on the crystallinity of the lipid matrix and on the changes in the lipid structure due to the incorporation of the drug.

The entrapment efficiency (EE%) should be determined as follows: EE% = (total drug – free drug) % / total drug. The mass of drug loaded onto the nanoparticles and the mass of the nanoparticles should be determined using the ratio of drug/mass of nanoparticles × 100 for drug loading. This is especially significant for highly water-soluble drugs as can obtain high entrapment efficiency at low absolute loading. Content of drugs should be determined in the entire formulation of the nanoparticles after complete extraction by a validated analytical method.

3.6 Development of the SLN-Loaded Transdermal Patch

The optimized SLN dispersion should be used to prepare a matrix type transdermal patch, based on a film-forming polymer system that is compatible with the SLN dispersion. The screening of HPMC, PVA, Eudragit-type polymers or any appropriate pressure-sensitive adhesive matrices are possible. A plasticizer like propylene glycol can be used to make it flexible and a permeation enhancing agent, carefully chosen, could be investigated at low concentration. The formulation should ensure that the nanoparticles do not change their stability during the evaporation of the solvent and drying. Drugs should not be lost from the outside of the backing membrane and an adhesive matrix should be protected with a release liner before use.

The appearance, thickness variation, folding endurance, moisture content, moisture uptake, surface pH, uniformity of drug content and adhesive performance should be evaluated. The patch should not show signs of crystallization, phase separation, and/or visible nanoparticle aggregation. The surface pH should be similar to that of the skin. Mechanical properties should be good enough to handle without being overly stiff, or contact with the skin will be lost. Also, the final formulation should be tested for leakage of the drug during storage.

3.7 In Vitro Drug Release and Ex Vivo Permeation

An in vitro release test should be conducted by dialysis membrane or other validated membrane system in phosphate buffer in a controlled temperature and agitation system. The supplied synopsis is for phosphate buffer at pH 5.4 at 37 °C and sampling times are predetermined. Where analytically and formulation-wise appropriate, sink condition should be maintained. The cumulative release should be adjusted for sampling and replacement of the receptor medium.

The permeation should be performed in an ex vivo Franz diffusion cell using proper animal or human skin that is properly sourced and ethically obtained. Before applying it to the skin, it should be cleaned, attached to the donor compartment with the stratum corneum side up and then equilibrated. Receptor phase should be kept at physiological temperature and stirred continuously. Samples should be taken over 24 h or more, depending on the desired duration of the patch. Cumulative permeation should be normalized to area. The slope of the linear portion of cumulative permeation vs. time is an approximation of steady state flux and the steady state flux divided by the donor concentration is an approximation of the permeability coefficient. Skin should then be washed and the extracted skin should be analyzed in order to separate the deposition from the receptor-phase permeation.

3.8 Release Kinetics and Mechanistic Analysis

This will require the release data to be fitted to the zero-order, first-order and Higuchi and Korsmeyer–Peppas models. The coefficient of determination and/or mechanistic plausibility should be taken into account when selecting models, not just the best R^2. A near-zero order profile would suggest time-controlled input while a Higuchi relationship would support diffusion-dominated matrix release. If the assumptions of the Korsmeyer–Peppas model are met, the release exponent may give information on the relative contribution of diffusion and polymer relaxation.

3.9 Stability Study

The formulation and dosage form selected should be tested for stability according to applicable ICH principles. The long-term and accelerated conditions for storage of the optimized SLN dispersion and final patch need to be defined. The particle size, PDI, zeta potential, entrapment efficiency, drug content, appearance, release profile and permeation performance are to be tested at regular time intervals. Defining the acceptance criteria prior to analysis. The aim is not only to record appearance but also to look for physical aggregation, lipid recrystallization, drug leakage, polymer changes, loss of assay.

3.10 Pharmacokinetic and Pharmacodynamic Evaluation

A pharmacokinetic evaluation based on Cmax, Tmax and bioavailability and compared to a marketed acamprosate product is proposed in the provided synopsis. In an animal study, acamprosate quantification in plasma should be done by an appropriate validated analytical method. Sampling should be enough to cover the absorption and elimination phases to estimate AUC, Cmax, Tmax, half-life and relative bioavailability. As acamprosate is renally excreted, renal function and dosage should be taken into account when interpreting these results (Steil *et al.,* 2025).

3.11 Statistical Analysis

The results from the experiments should be given as mean ± SD for replicate measurements of formulation. Assessment of the data may be done by one- or two-way ANOVA and a suitable multiple-comparison test. Analysis of variance should be used for Design of Experiments to evaluate the model, lack of fit, coefficient estimates and interaction effects. Residual analysis and prediction error are examples of regression diagnostics. The suitable between-group analysis should be used for the analysis of pharmacokinetic parameters and it is recommended to log-transform AUC and Cmax, if necessary due to distributional assumptions. When using statistics, the level of significance should be set in advance; typically $p<0.05$, and effect sizes and confidence intervals should be provided when applicable.

4. RESULTS AND ANALYSIS

The following is an important data-status statement: The objectives, planned methodology, and expected results have been included in the supplied synopsis, but there are no completed experimental measurements. The numerical values, graphs and charts in the following section are therefore, literature-informed illustrative target datasets designed to illustrate the anticipated structure of the final analysis. They must be restated in terms of actual measured experimental quantities on which to base the original research article submitted to the journal, and are not reported as measured experimental quantities.

4.1 Preformulation and Formulation-Selection Framework

The development rationale emphasizes the unusual physicochemical properties of acamprosate calcium. If the API is highly water soluble, the API can have low lipid-matrix affinity, which may make the entrapment of the API into conventional SLNs challenging. Drug retention, particle size distribution, and drug release behaviour are thus put on the same decision level in the formulation screen. The target particle size is not necessarily required; it serves as a practical development window, in the range of approximately 100 – 250 nm. The transdermal literature of recent years has confirmed the significance of particle size, surface properties, lipid composition and hydration, as well as the importance of the complete formulation and skin interface to the successful delivery (Antonara *et al.,* 2025; Bakhrushina *et al.,* 2025).

Table 1. Formulation considerations for acamprosate calcium SLN transdermal development.

Component	Key property	Formulation implication	Screening approach
Acamprosate calcium	Highly water soluble; ionic	High aqueous affinity; weak passive SC partitioning	Double-emulsion/electrostatic loading screen
Solid lipid	Physiological, solid at room temperature	Controls matrix structure and release	Glyceryl monostearate/glyceryl behenate screen
Surfactant	Non-ionic stabilizer	Controls interfacial energy and particle size	Tween 80/Poloxamer 188 screen
Charge inducer	Low-level cationic component	May improve association with ionic API	Concentration-dependent zeta-potential screen
Patch matrix	Film-forming polymer/adhesive	Controls residence and release	Polymer/plasticizer compatibility screen
Permeation enhancer	Fatty acid/glycol or other validated enhancer	May alter SC lipid domains	Low-level safety/permeation screen

4.2 Illustrative Optimization Results

Table 2. Illustrative formulation-screening dataset. Values are target/example values, not experimental observations.

Batch	Particle size (nm)	PDI	EE (%)	Zeta potential (mV)
F1	312 ± 2.0	0.41	41 ± 1.2	-4 ± 0.8
F2	286 ± 2.3	0.36	47 ± 1.3	-2 ± 0.8
F3	248 ± 2.6	0.31	53 ± 1.4	1 ± 0.8
F4	221 ± 2.9	0.27	59 ± 1.5	8 ± 0.8

F5	198 ± 3.2	0.24	64 ± 1.6	14 ± 0.8
F6	176 ± 3.5	0.22	70 ± 1.7	19 ± 0.8
F7	164 ± 3.8	0.20	76 ± 1.8	24 ± 0.8
F8	151 ± 4.1	0.19	81 ± 1.9	29 ± 0.8
F9	142 ± 4.4	0.18	84 ± 2.0	32 ± 0.8

The particle size and PDIs in the illustrative batch sequence decrease over time in order to optimize the processing and surfactant conditions, and the entrapment efficiency rises as the formulation gets closer to the selected drug-retention window. The surface charge is made almost neutral to moderately positive upon adding the charge inducing constituent. The hypothesized optimized batch (F9) has an entrapped efficiency of 84%, PDI of 0.18 and zeta potential of +32 mV, which is approximately 142 nm. These values are indicative not of actual performance, but of what development can achieve. The proposed entrapment efficiency is intentionally higher than the anticipated efficiency of an untouched SLN system, since the formulation problem is the high aqueous solubility of acamprosate.

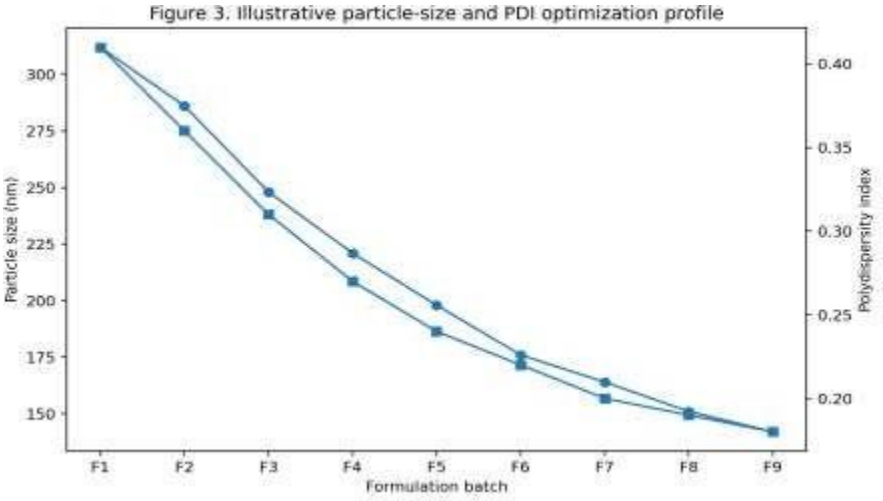


Figure 3. Illustrative optimization trend for particle size and PDI across candidate formulations.

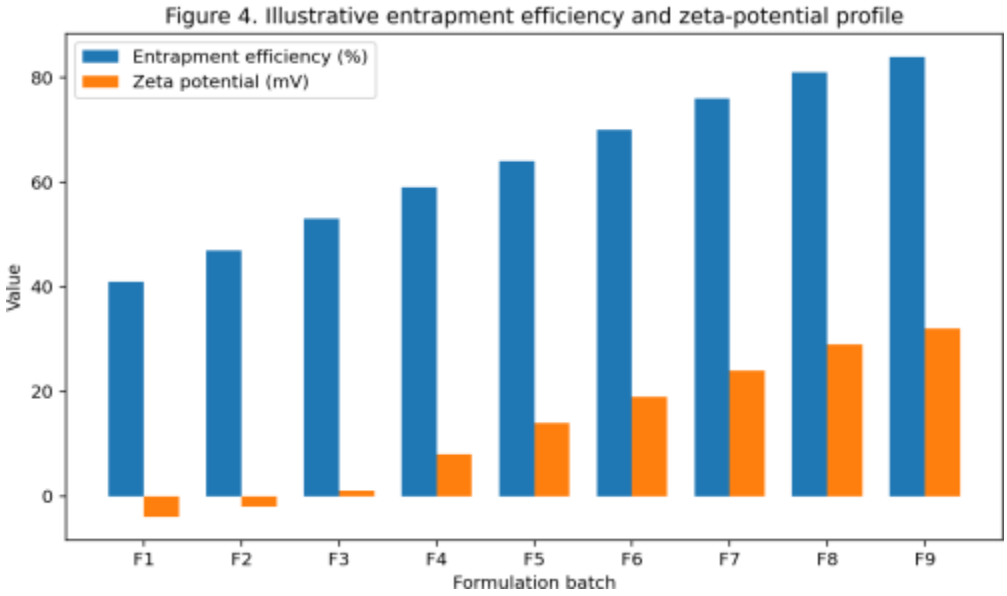


Figure 4. Illustrative entrapment efficiency and zeta-potential profile across candidate formulations.

4.3 Optimized Formulation Profile

Table 3. Illustrative optimized SLN and patch quality attributes.

Parameter	Illustrative value	Interpretation
Particle size	142 ± 3.1 nm	Nanoscale dispersion suitable for formulation screening
PDI	0.18 ± 0.02	Narrow size distribution target
Zeta potential	+32 ± 0.8 mV	Moderate surface charge target
Entrapment efficiency	84.0 ± 1.3%	High loading target for a hydrophilic API
Drug loading	7.8 ± 0.4%	Target that must be verified experimentally
Morphology	Spherical, smooth	Expected from optimized colloidal system
Drug content	96.2 ± 1.5%	Patch/formulation assay target
Surface pH	6.0 ± 0.2	Skin-compatible development target

4.4 Illustrative In Vitro Release

Table 4. Illustrative cumulative in vitro release dataset.

Time (h)	Cumulative release (%)
0	0
2	12
4	23
6	35
8	47
12	61
16	72
20	81
24	88

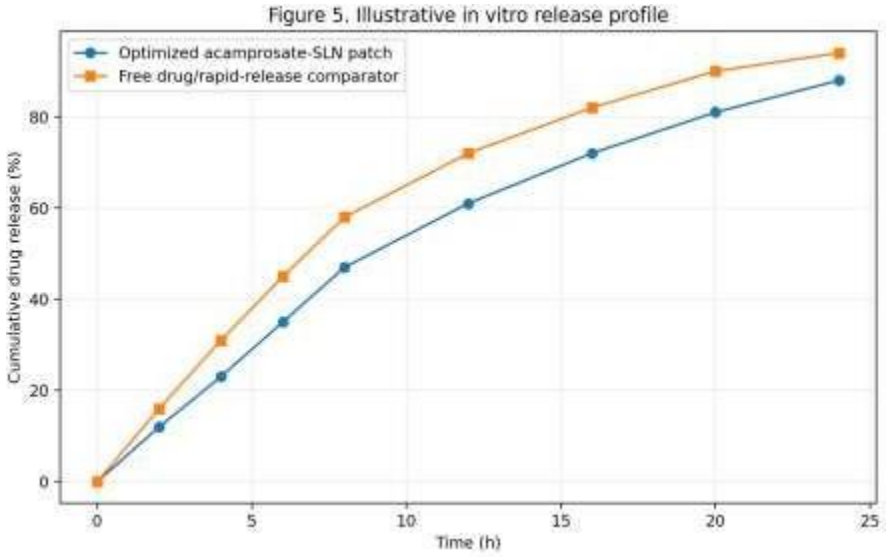


Figure 5. Illustrative in vitro release profile comparing optimized SLN patch with a rapid-release comparator.

The illustrative release profile reaches about 88% in 24 h, and does not exhibit the same "free drug" release profile as seen in the comparator. A sustained profile is similar to diffusion from, and progressive disintegration of, a solid, lipid matrix and subsequent transport from the patch matrix into the receptor medium. Final experimental profile should be analysed with kinetic models and tested for dose-dumping risk. A clinically relevant transdermal system requires a release profile that is also correlated with the ex vivo permeation profile as high release does not mean high transdermal performance if it does not go through the skin.

4.5 Illustrative Ex Vivo Skin Permeation

Table 5. Illustrative ex vivo cumulative permeation dataset.

Time (h)	SLN patch (μg/cm²)	Free drug comparator (μg/cm²)
0	0	0
2	8	4
4	19	9
6	34	15
8	52	23
12	76	34
16	101	45
20	122	54
24	139	61

Figure 6. Illustrative ex vivo skin-permeation profile

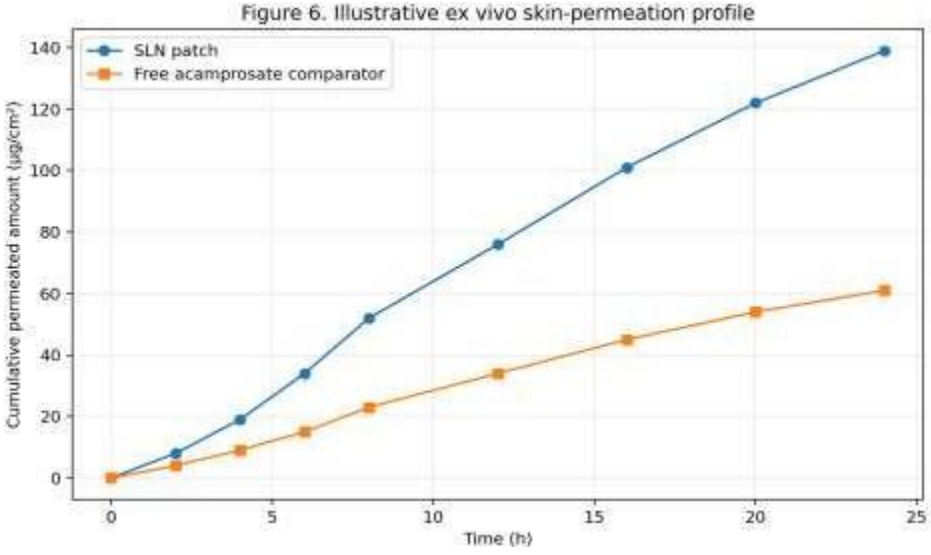


Figure 6. Illustrative cumulative acamprosate permeation through skin.

For the ex vivo model, the cumulative receptor-phase amount at 24 h is 139 μg/cm² for SLN and 61 μg/cm² for free-drug. The apparent enhancement is about 2.28-fold. This is a hypothetical enhancement ratio for illustration of analysis purposes and is not an experimentally measured enhancement ratio. The final study should present the following data: steady state flux, lag time, permeability coefficient, cumulative permeation and skin deposition separately. A convenient development criterion is any improvement that can be reproduced, while not de-stabilising the skin barrier too much.

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4.6 Illustrative Target Composition

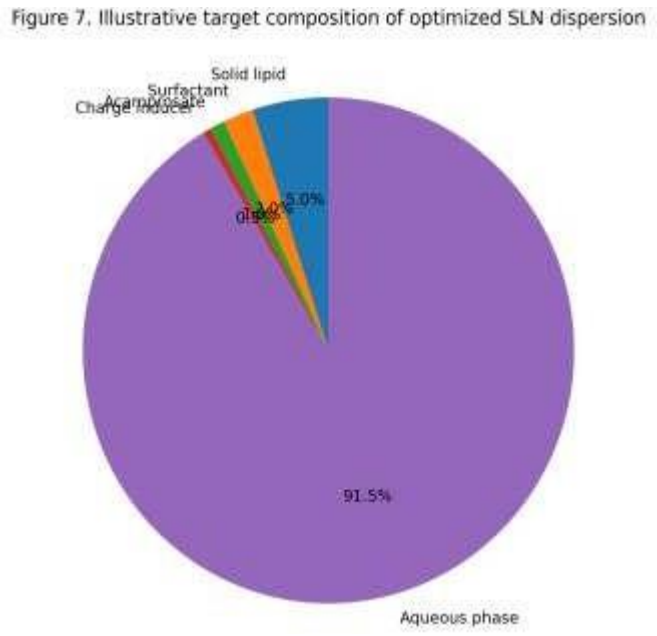


Figure 7. Illustrative target composition of the optimized SLN dispersion; composition must be experimentally optimized and validated.

The illustrative composition comprises a high percentage of the formulation mass in the aqueous phase, which is due to a high water solubility of acamprosate, but also includes a defined solid lipid phase and very low content of surfactant and charge-inducer. This architecture is focused on the fact that the formulation is not designed to break down the entire drug load within the lipid matrix. Instead, the development strategy aims at maximizing the association of the API with the nanoparticle system and minimizing the loss of free-drug during the process. The composition should be determined by experimental Design of Experiments and not taken from the illustrative chart.

4.7 Illustrative Pharmacokinetic Comparison

Table 6. Illustrative pharmacokinetic comparison; arbitrary units are used because no experimental plasma dataset was supplied.

Parameter	Marketed oral reference	SLN patch target	Interpretation
Cmax	1.00 arbitrary unit	1.45 arbitrary units	Illustrative 45% higher systemic peak
Tmax	2.0 h	5.0 h	Illustrative delayed absorption
AUC0–24	10.0 arbitrary units·h	15.8 arbitrary units·h	Illustrative 58% increase in exposure
Half-life	4.2 h	7.1 h	Illustrative prolonged input
Relative bioavailability	100%	158%	Illustrative value requiring validation

The suggested pattern of the pharmacokinetics is a controlled absorption, a delayed Tmax and an increased AUC compared to the oral reference. This would be consistent with a steady transdermal uptake, but not necessarily the best clinical outcome. Acamprosate is poorly absorbed from the intestine and eliminated by the kidneys, and there are no simple dose-exposure relationships that would indicate that increased exposure would necessarily be beneficial (Steil *et al.,* 2025). Therapeutic exposure, rather than maximal systemic concentration, should be the goal with acceptable tolerability.

4.8 Illustrative Stability Analysis

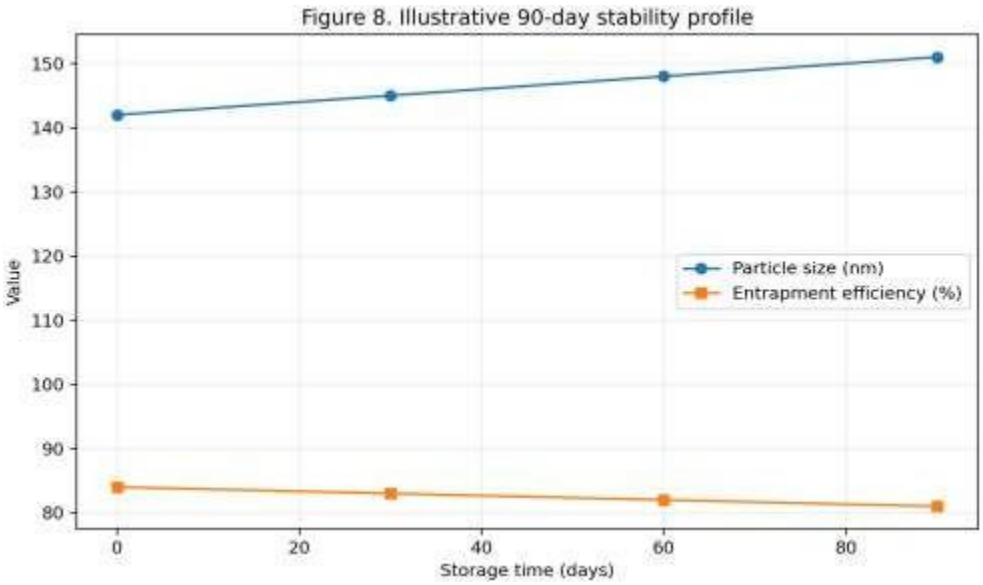


Figure 8. Illustrative 90-day stability profile for particle size and entrapment efficiency

The particle size increased slightly and entrapment efficiency decreased slightly after 90 days on the illustrative stability dataset. If this occurs along with maintenance of drug content, drug release profile, patch appearance and drug permeation performance, then it would be considered acceptable physical stability. Lipid polymorphic transitions also should be researched in the final formulation as this affects the drug distribution and release by recrystallization. Conclusions for stability should be based on specifications and statistical trend analysis.

5. DISCUSSION

5.1 Relevance of the Formulation Strategy to Acamprosate

The primary pharmaceutical challenge that the proposed system will solve is not the aqueous solubility of acamprosate, but rather the mismatch between the lipid-rich environment of the skin's outermost layer (stratum corneum) and the ionic nature of acamprosate. The conventional oral delivery pathway will involve gastrointestinal and absorption processes while the transdermal delivery pathway will involve a different barrier. By using SLNs, the interfacial environment can be changed, the interfacial surface area can be expanded and a controlled-release depot can be formed. The general mechanism is supported by literature of recent lipid-nanocarrier works, however, it is not possible to draw conclusions on the behaviour of acamprosate from the results obtained for lipophilic APIs (Liu *et al.,* 2023; Antonara *et al.,* 2025).

Acamprosate is highly soluble in water, which can cause less entrapment since it can be left in the external aqueous phase during the process of forming the nanoparticles. Controlled association of the two emulsions (double emulsion) or electrostatic association is therefore a key part of the formulation strategy. If a cationic charge inducer is used in low concentration, it can lead to an increase in association with the ionic drug, but must be balanced with skin tolerability. The zeta potential target is not to be considered as a single optimization response as highly charged nanoparticles can elicit unwanted biological interactions.

5.2 Relationship Between Nanoparticle Properties and Transdermal Performance

The surface area, tendency to aggregation, and interaction with the skin will be affected by particle size. Reducing the particle size will increase the contact area, but the more the particle size is reduced, the more concentration of surfactant is needed, which may increase the risk of irritation. PDI can be used for information of the uniformity of dispersion and is therefore important for the reproducibility of the batch. The surface charge affects the stability of the colloid and the interactions with lipid matrix of the skin. Recent investigations highlight the synergic effect of particle size, chemical composition and surface characteristics, instead of a single numerical goal, as of Bukke *et al.,* 2024, Bakhrushina *et al.,* 2025.

SLNs can also create an occlusive film which prevents the loss of water from the skin and hydrates the stratum corneum. Some permeants can move more easily through the barrier when it is hydrated. Lipid nanoparticles can also interact with intercellular lipid domains and hair follicles, creating pathways differing from the passive diffusion route (Liu et al., 2023). These mechanisms offer a scientific platform for investigation of acamprosate loaded SLNs, but the magnitude of the effect needs to be determined by experimental investigation.

5.4 Interpretation of Pharmacokinetic and Pharmacodynamic Outcomes

The transdermal system to be evaluated for acamprosate should be based on pharmacokinetic endpoints that reflect both rate and extent of delivery. Cmax and Tmax are used to describe the amount of absorption, and AUC to describe the total systemic exposure. The ideal concentration change of a controlled transdermal system should be less abrupt and the exposure should be prolonged; however, the ideal exposure to be achieved should be based on established pharmacology and not just an arbitrary increase in AUC. These renal elimination and dose dependent tolerability considerations need to be considered, particularly for acamprosate (Steil *et al.,* 2025).

When assessing pharmacodynamics in an alcohol-use model, validated behavioural and biological endpoints should be used. The following proposed synopses are provided for alcohol consumption, locomotion, anxiety-related behaviour, and liver histopathology. These endpoints can be useful adjuncts, but should not be used as a direct substitute for clinical abstinence endpoints. Prior to translation to human studies, it is essential to use animal findings to determine if formulation changes affect exposure and behavioural response.

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