**HEALTH AND MEDICINE**

Treatment of psoriasis with NFKBIZ siRNA using topical ionic liquid formulations

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Systemic antibodies targeting tumor necrosis factor–α (TNF-α) and interleukin-17A (IL-17A) are effective in plaque psoriasis. Despite their popularity, safety concerns pose a challenge for systemic biologics. While anti–TNF-α and anti–IL-17A antibodies effectively inhibit respective proteins, we hypothesize that an approach based on local silencing of an upstream target such as NFKBIZ can be advantageous for treating psoriasis. However, effective delivery of small interfering RNA (siRNA) into the skin is a substantial hurdle due to skin’s barrier function and poor stability of siRNA. Using ionic liquids as an enabling technology, we report on the effective delivery of NFKBIZ siRNA into the skin and its therapeutic efficacy in a psoriasis model. Treatment with IL-siRNA suppressed aberrant gene expression and resulted in down-regulation of psoriasis-related signals including TNF-α and IL-17A. These results provide a framework for a topical delivery platform for siRNA.

**INTRODUCTION**

Psoriasis is one of the most debilitating chronic skin diseases affecting more than 125 million people worldwide with an estimated economic burden of $135 billion/year in the United States (1). Its pathogenesis and the underlying mechanisms are still not fully understood. Nuclear factorκB (NF-κB), a ubiquitously expressed transcription factor, is considered as the master regulator of immune responses and is implicated in several autoimmune inflammatory diseases including psoriasis (2). Several therapeutics targeting NF-κB signaling pathways are available in the clinic; however, concerns regarding the lack of specificity and side effects pose a challenge (3). This is particularly challenging since systemic inhibition of poteptropic proteins like NF-κB might lead to serious side effects as they provide essential basal activity as survival factors. Network-centric approaches involving pathway-specific inhibitors have gained considerable therapeutic interests (4). In this regard, infliximab and adalimumab [both anti-tumor necrosis factor–α (TNF-α) monoclonal antibodies] as well as secukinumab [an anti-interleukin-17A (IL-17A) antibody] have been approved by the U.S. Food and Drug Administration and are claimed to mediate their therapeutic effects through the modulation of NF-κB activity (5).

NFKBIZ, a gene encoding atypical inhibitor of nuclear factor κB (IκB) protein IκBζ, has gained interests for therapeutic intervention due to its crucial role in the regulation of NF-κB complexes (6, 7). It is reported to be a direct transcription activator of TNF-α-, IL-17A-, and IL-36–inducible psoriasis-related gene products that are involved in inflammatory signaling, neutrophil chemotaxis, and leukocyte activation (8–11). In addition, strong expression of NFKBIZ in patients with psoriasis could be correlated to elevated IL-36– and IL-17A–type responses (12). Local silencing of NFKBIZ can be advantageous since it can potentially broaden the population of patients that can benefit from the treatment compared with that by a single antibody.

Silencing of NFKBIZ through topical applications of small interfering RNA (siRNA) offers a noninvasive and self-administered treatment option with minimal side effects (13). However, the greatest challenge of this route is that only a limited number of drugs with low molecular weights (up to few hundred daltons) and high octanol-water partition coefficients are usable for successful topical delivery (14). Transdermal and topical delivery of hydrophilic molecules, particularly macromolecules such as antibodies and nucleic acids, remains challenging, owing to their high molecular weights (15). Several reports have showcased topical siRNA delivery using techniques such as spherical nucleic acids (16) and self-assembling framework nucleic acids (17). Microneedles have also been explored for topical delivery of siRNA (18). Methods such as electroporation (19) and peptide carriers have also been explored (20–22). Strategies have also been developed to deliver siRNA to treat cutaneous wounds (23, 24). Recently, ionic liquids (ILs) have emerged as a class of versatile materials for topical and transdermal delivery (25). ILs provide a number of potential benefits including tunability, broad applicability, and excellent safety profile (26). ILs have shown potential for delivering siRNA, but their ability to induce a therapeutic effect by silencing a target in vivo has not been demonstrated.

Here, we report a modular IL-based siRNA delivery approach for silencing various genes of interest. Specifically, we have identified a combination of ILs that simultaneously stabilizes siRNA and enhances siRNA penetration into the skin following topical application. We demonstrate the efficacy of the formulation in silencing NFKBIZ in vivo in an imiquimod-induced psoriasis mouse model.

**RESULTS**

**IL selection**

A library of ILs was designed and synthesized to assess siRNA delivery into skin. Cholinium was used as the cation in all ILs due to its known biocompatibility and prior use in humans (27). Several different anions were used to synthesize ILs (fig. S1). Geranic acid was used...
as the reference anion in the IL library [that is, choline and geranic acid (CAGE) as a reference IL] due to its prior use for transdermal delivery of macromolecules (28–30). Other anions were chosen for several reasons. First, anions containing shorter linear carbon chains were chosen in contrast to geranic acid to assess the impact of the chain length on siRNA stability and delivery. Anions with aromatic groups were chosen since they might interact with the stacked RNA base pairs via electrostatic, hydrophobic, and polar interactions. All ILs were prepared at a stoichiometric ratio of 1:2 (cation:anion) and were assessed for stability and siRNA delivery. Of the ILs synthesized, CAGE, choline and dimethylacrylic acid (CADA), choline and isovaleric acid (CAVA), and choline and phenylpropanoic acid (CAPA) remained as a viscous liquid at room temperature (RT), whereas choline and 4-phenolsulfonic acid (CASA), choline and phenylphosphonic acid (CAPP), and choline and biphenyl-3-carboxylic acid (CABA) solidified or formed a gel (fig. S1). Representative 1H nuclear magnetic resonance (NMR) spectra can be found in fig. S1, confirming the successful synthesis and purity of the ILs. In addition, since both interleukin and ILs have been denoted as “IL,” for the purpose of clarity, all interleukins are referred by a numerical value throughout the manuscript.

**Effect of ILs on siRNA stability**

We first assessed the effect of ILs on siRNA stability. Circular dichroism (CD) spectroscopy of siRNA incubated with aqueous solutions of individual ILs at 50% (v/v) concentration revealed notable alteration in the α helix backbone (confirmed from the negative band at 210 nm) in the presence of CAGE, CADA, and CABA. On the other hand, CAVA and CAPA retained the secondary structure of siRNA (Fig. 1A). Bands obtained from the native gel electrophoresis complemented with the CD results (Fig. 1B). The improved stability of siRNA in the presence of CAPA suggested the possibility of synergistic effects between the ILs prepared from two structurally different anions. Consequently, we assessed the effect of IL mixtures on siRNA stability to determine whether the compatibility of CAPA with siRNA might offer additional protection against the adverse effects of CAGE and CABA on the siRNA structure. The combination of CAGE (25% v/v) and CAPA (25% v/v) led to a prominent band indicative of retention of siRNA structure (fig. S1).

**Screening of optimal IL combinations for siRNA delivery**

The individual ILs and their combinations were then evaluated by epidermal permeation of Cy5-labeled siRNA into porcine skin in Franz diffusion cells (FDCs) (Fig. 1C). Some epidermal uptake for naked siRNA was seen in controls. CAGE exhibited the highest delivery among all tested ILs (Fig. 1D). About 0.20 nmol/cm² of siRNA was delivered into the epidermis in the presence of CAGE (50% v/v) compared with 0.07 nmol/cm² in case of naked siRNA. Since 50% CAGE had a potential effect on the siRNA structure, we also measured the ability of IL combinations to deliver siRNA into skin. A combination of CAPA and CAGE (25% v/v each) led to ~0.4 nmol/cm² siRNA getting delivered into the skin (Fig. 1E). Because the CAGE + CAPA combination yielded the highest epidermal delivery as well as high stability, it was selected as the lead formulation for further studies (fig. S2).

**IL-mediated lipid membrane dynamics modulation**

To assess the insertion and translocation of the IL into the lipid bilayers, simulations of the lipid bilayer in the presence of IL were conducted (Fig. 3, A to C). In addition to improving the stability and solvation of the RNA, the compact packing of the ionic species leading to the formation of aggregates seems to augment the IL–lipid membrane interactions. The aggregates formed by the individual ionic moieties appear to enable a continuity between the IL system and the molecules, making up the lipid bilayer. It is possible that the collective mass of the ionic aggregates plays a crucial role in facilitating membrane permeation in addition to ILs, particularly geranic acid’s ability to extract or fluidize lipids as previously reported (26).

The relative effect of the ILs including CAGE, CAPA, and CAGE + CAPA on membrane dynamics was assessed by measuring the average thickness of the lipid bilayer in the presence of ILs over a simulation time of 350 ns. The highest thickness was observed in the presence of CAGE (50% v/v), indicating greater IL intercalation within the lipid bilayer. Similar thickness was noted for the water and CAPA (50% v/v) groups, while CAGE (25% v/v) with CAPA (25% v/v) led to a higher thickness (Fig. 3D). The MD simulation snapshots highlight the dynamics of interactions of the individual ionic species in the IL with phospholipid membrane. Conclusive intercalation of the ionic species of the IL combination with the bilayer was detected (Fig. 3B). Furthermore, upon visualizing the trajectories of the individual ionic species within the CAGE + CAPA simulation, we were able to observe reduced mobility of geranic acid relative to phenylpropanoic acid (fig. S3). When focusing on an IL aggregate that consists of all three IL species (choline, geranic acid, and phenylpropanoic acid), we observed that each geranic acid molecule tends to remain in contact with the aggregate over the course of the simulation, while choline and phenylpropanoic acid are able to move between both the aggregate of heterogeneous species and the bulk.
Biocompatibility of ILs in mice

The optimized CAGE + CAPA IL formulation was evaluated for toxicity in vivo in mice. IL–glyceroldehyde-3-phosphate dehydrogenase (GAPDH) siRNA formulation (25 μl) was applied topically for four consecutive days to the dorsal skin of SKH-1 elite (SKH-1E) hairless mice (Fig. 4A). No signs of inflammation, redness, and/or irritation were observed for the IL-treated animals (Fig. S4). Skin tissue was further harvested, and sections were cut and stained for histopathology and toxicology markers. Groups treated with the IL formulation exhibited no signs of epidermal thickening and keratinocyte hyperproliferation and were equivalent to the untreated and/or naked siRNA-treated animals (Fig. 4B and fig. S4). We also tested TNF-α gene expression levels in healthy mice. Animals treated with naked siRNA were statistically equivalent to the untreated animals. Mice treated with IL-GAPDH siRNA and IL–siCon (control siRNA used for subsequent experiments) demonstrated slightly lower TNF-α mRNA transcripts compared with the untreated group (fig. S4). Such inhibition of TNF-α expression might potentially arise from the inherent properties of the individual components of the ILs and need to be studied in future studies.

IL-siRNA penetration and GAPDH silencing in healthy mice

Cy5 fluorescence within the epidermis was measured in healthy mice following transdermal application for four consecutive days. Confocal images revealed a marked increase in Cy5 fluorescence in the epidermis for the IL-treated group compared with the naked siRNA in mice (Fig. 4C). Upon determining the GAPDH gene silencing efficiency using quantitative polymerase chain reaction (qPCR), the expression levels of GAPDH were found to be reduced 4.5- and 8.6-fold for the IL-siRNA–treated group in contrast to the naked siRNA and untreated mice, respectively (Fig. 4D). A slight decrease in the GAPDH mRNA expression was also observed for the naked siRNA–treated group. Consecutively, it was necessary to ascertain if the change in GAPDH mRNA expression translated into protein reduction. Consistent with the gene knockdown
results, the IL-siRNA–treated group demonstrated a statistically significant decay (~2-fold) in the GAPDH protein expression compared with all the other treatment groups (Fig. 4E). The reduced GAPDH mRNA expression for the naked siRNA–treated group did not down-regulate GAPDH protein expression.

**Local NFKBIZ silencing in the skin inhibits imiquimod-induced psoriasis**

The ability of NFKBIZ siRNA to treat psoriasis was tested using CAGE + CAPA as a topical formulation. Following induction of psoriasis and topical application of IL-NFKBIZ siRNA formulation (Fig. 5A), skin tissue was harvested and analyzed. Macroscopically, local knockdown of NFKBIZ in the dorsal skin markedly reduced imiquimod-induced inflammation, showing reduced erythema and scaling in the area where IL-NFKBIZ siRNA was applied compared with the untreated, IL-treated, and IL-siCon–treated groups (Fig. 5B and fig. S5). Hematoxylin and eosin (H&E) staining of skin sections from the mice revealed that the knockdown of NFKBIZ by IL-siRNA reduced epidermal thickening, acanthosis, hyperkeratosis, and club-shaped rete ridges (Fig. 5C and fig. S5). Likewise, immunohistochemistry (IHC) analysis revealed hyperproliferation of keratinocytes in the untreated, IL-treated, and IL-siCon–treated groups, whereas the group treated with IL-NFKBIZ siRNA exhibited lack of keratinocyte proliferation (Ki67 staining) (Fig. 5D and fig. S5). The common characteristic features of imiquimod-induced skin inflammation (erythema and scaling) were scored daily throughout the induction/application period. Individual scores for erythema and scaling demonstrated fair reduction starting from day 3 with topical IL-siRNA application (Fig. 5, E and F). Maximum cumulative scores were obtained for the untreated and IL-treated groups and were markedly lowered in the IL-siRNA–treated group (fig. S6). Double skin-fold thickness (DSFT) for measuring skin thickness did not yield major differences between the groups (fig. S6).

**DISCUSSION**

Limited understanding of key inflammatory signaling pathway regulators and the chronological order of the underlying mechanisms presents a challenge in the treatment of psoriasis. Signaling pathways including NF-κB, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), and p38 mitogen-activated protein kinase have recently been found to play a major role in the pathogenesis of this complex disease (31). NFKBIZ, a gene encoding IκBζ, is a crucial transcriptional coactivator mediating downstream effects of an array of specific inflammatory cytokines and is particularly...
imperative in the light of recent findings by Johansen et al. (6) and Müller et al. (12), which indicated IκBζ to be a key modulator of IL-17A, IL-23, and IL-36 (32). Thus, targeting NFKBIZ/IκBζ to inhibit proinflammatory signaling pathways and production of psoriasis-related gene products is a viable strategy for psoriasis treatment. Clinically, antibodies targeting TNF-α and IL-17A have shown promise in meeting the primary endpoints and improving the disease condition (33). However, as biologics, these antibodies have challenges of potential systemic toxicity, generation of anti-antibodies, and high cost.

Here, we present an IL combination capable of improving epidermal accumulation and delivery of RNA through skin. We hypothesized that a combination of ILs would stabilize the siRNA and, at the same time, would improve its penetration. We validated this hypothesis in an imiquimod-induced psoriasis-like skin inflammation model that resembles plaque-type psoriasis in humans. Topical application of IL-siRNA for four consecutive days generated substantial reduction in the levels of inflammatory cytokines and an array of psoriasis-related gene products.

CAGE + CAPA IL formulation offers several advantages over other transdermal drug delivery systems. The components of the IL formulation, choline bicarbonate, geranic acid, and phenylpropanoic acid, have been proven safe or GRAS (generally recognized as safe) chemicals and provide a strong foundation for the safety of ILs. In addition, simple synthesis and scale-up processes, high solvating power, and tunability offer additional advantages over other volatile organic solvents. This system is particularly suitable for transdermal delivery of nucleic acids due to both its complex intercalation between the stacked RNA base pairs and aromatic rings of the IL, and enhanced interaction with the lipid bilayer.

Our results demonstrate that ILs can complex with nucleic acids without compromising the bioactivity, thus making them ideal for transdermal drug delivery. The salt metathesis or anion exchange reaction for IL synthesis is particularly advantageous because it does not require integration of harsh organic solvents for siRNA delivery. The individual IL components could be modulated to interact with nearly any nucleic acid based on the binding characteristics and molecular mechanism of interactions.

Tunable ion stoichiometry and physicochemical properties are other key features of IL-based systems. Previous work in our group has indicated the role of interionic interactions in solvation and partitioning of the active ingredient into the skin (34). In addition, Chandran et al. (35) have demonstrated the importance of electrostatic interactions and groove binding associations of ILs in DNA.
stability. Hitherto, the role of ILs in improving the stability and solvation of siRNA has not been comprehensively explored. We systematically varied the anionic component of the IL with structural similarity to geranic acid and/or containing an aromatic ring at a stoichiometry ratio of 1:2 and developed an in-house cholinium-based IL library. We observed that the anions of the ILs that contained aromatic rings generally solidified or formed a gel at RT except phenylpropanoic acid. Excellent siRNA stability was observed in the presence of CAVA, CAPA, and CAGE + CAPA in comparison to other ILs and combinations, possibly due to superior interactions with the siRNA. The IL combination CAGE + CAPA generated the highest epidermal accumulation of siRNA, notably higher than any individual ILs and/or combination.

The best performing IL combination that we identified in this study, CAGE + CAPA, demonstrated consistent distribution of the three ionic species through MD simulations, indicating improved molecular mobility and lower viscosity contributing to enhanced solvation effects. Furthermore, MD simulation snapshots revealed close association of phenylpropanoic acid with the RNA molecules, which could be possibly attributed to a combination of hydrophobic and polar interactions, \( \pi-\pi \) stacking, and/or intercalation between stacked RNA base pairs, leading to enhanced RNA stability. RGYR and RMSD measurements obtained from simulations over the course of 500 ns further confirmed improved IL-RNA interactions.

It is also important to understand the magnitude of IL-mediated lipid bilayer modulation. MD simulations revealed the crucial role of aggregation of ionic species in improving membrane permeation with the highest bilayer thickness obtained for CAGE (50% v/v) followed by CAGE + CAPA. Such observations from the simulations further establish geranic acid as the main driver in the translocation of the IL combination through the lipid bilayers, which is consistent with experimental results. While it seems that phenylpropanoic acid has a minor role in improving bilayer permeation by lowering the local viscosity of the overall IL system, we believe that it is also responsible for fluidizing the membrane with the formation of dynamic pores. It was earlier reported that deprotonated aromatic carboxylic acids, such as phenylpropanoic acid, permeate bilayers several orders of magnitude faster than that expected from the pH partition hypothesis, and their permeation is fully controlled by the anions at the physiological pH (36). On the basis of these results, we speculate that these ILs assist in crossing the cellular barriers to deliver siRNA into the cytosolic compartments.

To assess biocompatibility of CAGE + CAPA, we conducted a histological evaluation of skin on the fifth day, which coincided with the total duration of topical application. We did not observe any macroscopic changes in the skin structure, epidermal thickening, and keratinocyte proliferation in the IL-treated groups. Further investigation of inflammatory cytokine levels did not reveal any statistically significant increment in TNF-\( \alpha \) mRNA compared with the untreated groups. Some of the IL-treated groups demonstrated a decrease in the TNF-\( \alpha \) mRNA levels, which might be possibly due to the presence of IL and need to be further investigated. Marked inhibition of
GAPDH mRNA and protein expression was observed in the IL-GAPDH siRNA–treated groups.

NFKBIZ has been previously demonstrated to play a crucial role in the gene transcription of several proinflammatory cytokines and antimicrobial peptides responsible for the pathogenesis of psoriasis (6, 12). Using an imiquimod-induced psoriasis model, we further demonstrated that local silencing of NFKBIZ following topical application of IL-NFKBIZ siRNA formulation impaired expression of psoriasis-related gene products under in vivo conditions. IL-siRNA–treated mice exhibited substantially reduced skin pathology including reduced erythema and scaling, less epidermal thickening, and keratinocyte proliferation. The local increase in mRNA levels of some of the inflammatory cytokines and related gene products for the IL-siCon– and IL-treated groups in comparison with the untreated group could be attributed to imiquimod. Local silencing of NFKBIZ resulted in a strong inhibition of crucial proinflammatory cytokine mRNA levels including IL-17A, IL-23, and IL-36. The downstream effects of local NFKBIZ silencing were also validated and are consistent with the previously reported effects of intradermal injection of IκBζ siRNA (6). Because mouse skin is generally much more permeable than human skin, detailed studies of quantification of skin penetration were not performed in vivo.

In summary, we have developed a transdermal IL platform capable of delivering RNA to the epidermis and have combined this framework with an array of gene screening to support NFKBIZ as a key signaling target gene in psoriasis treatment. The IL formulation retained the bioactivity of the siRNA and generated notable target gene abrogation upon topical application in an imiquimod–induced psoriasis-like skin inflammation model. The optimized IL formulation did not show toxicity and is acceptable for repeated applications. This platform is amenable to broad applications to nucleic acids and can be easily manufactured and scaled up. This platform could empower transdermal drug delivery for the treatment of dermatological conditions and help augmenting long-term therapeutic efficacy by targeting such common mediators. Upon further studies focused on assessment in large animals and comparison with clinical standard of care, the method described here opens a potential option for psoriasis treatment.

MATERIALS AND METHODS

Skin-penetrating IL-RNA complexes

The cholinium-based IL library was synthesized as described previously (26). Briefly, the cation, choline bicarbonate, and various anions...
were mixed at a 1:2 ratio to prepare ILs following salt metathesis reaction. The anions were dissolved in a minimum volume of ultrapure water or ethanol/methanol based on the solubility and were reacted with choline bicarbonate at 40°C for 24 hours. The resulting IL solution was dried using a rotary evaporator at 20 mbar at 60°C for 2 hours. The residual water was removed in a vacuum oven at 60°C for 48 hours. The ILs that were viscous at RT were characterized via NMR with dimethyl sulfoxide (DMSO)–d6 on an Agilent DD2 600-MHz spectrometer (Supplementary Materials and Methods). ILs were mixed with RNA (100 μM) at a volumetric ratio of 1:1 and incubated for 30 min at RT. The RNA–IL solutions (1 ml) were dialyzed against 10 mM sodium phosphate buffer for 72 hours using Dialysis Cassettes (10,000 molecular weight cutoff, Invitrogen). The concentration of RNA was confirmed and normalized using a NanoDrop instrument (Thermo Fisher Scientific). The stability of the RNA in the IL solution was determined using CD and gel electrophoresis (Supplementary Materials and Methods).

### MD simulation studies

MD simulations were performed using OpenMM MD package and the AMBER force fields ff14SB and GAFF. Three-dimensional SD files for each of the IL species were downloaded from PubChem and parameterized with Antechamber before preparing simulation input topologies with LEaP. To generate starting coordinates for the lipid membrane simulations, PACKMOL was used to build a bilayer consisting of 100 phosphatidylcholine (POPC) molecules for each of the leaflets. The remaining contents of a 60-Å cube consisted of ~1:1 water and IL, charge balanced with Na+ and Cl−. A 500-ns simulation was performed for each of the systems under periodic boundary conditions. For the simulations of siRNA, a helical starting structure for the nucleic acid was generated with Avogadro (37) before being placed in a simulation box consisting of ~1:1 water and IL for simulation under periodic boundary conditions for 350 ns. Analysis of MD trajectories was performed using the python library MDAnalysis for RGYR and RMSD of siRNA. Visual molecular dynamics (38) plugin MEMBPLUGIN (39) was used to perform analysis of membrane trajectories.

### Skin penetration studies

Skin penetration studies were performed using porcine skin in FDCs, as described previously (40). A total volume of 20 μl of Cy5-labeled RNA (50 μM) in IL solutions was applied to the porcine skin surface and was incubated at 40°C for 24 hours under occlusive conditions with moderate stirring. The permeability of RNA was visualized and quantified using confocal microscopy and tape-stripping.

### Quantification of mRNA transcripts

Flash-frozen skin tissues were pulverized to form a powder and homogenized in QIAzol Lysis Reagent to prepare the tissue lysates for qPCR. The mRNA levels were quantified and normalized following the manufacturer’s protocol. The relative abundance of mRNA transcripts and silencing in treated groups was normalized to the housekeeper gene (B-actin). The mean normalized siRNA treatment values were then plotted with their SEM (Supplementary Materials and Methods).

### Statistical analysis

One-way analysis of variance (ANOVA) and statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc.). Results are depicted as average ± SEM. Two-tailed Student’s t test was used for comparison between two groups. Parametric data were analyzed by one-way ANOVA followed by Tukey’s honestly significant difference (HSD) post hoc tests. Kruskal–Wallis tests were performed for nonparametric data. Statistical tests are indicated in the figures. P < 0.05 was considered statistically significant.

### SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/30/eabb6049/DC1

**View/request a protocol for this paper from Bio-protocol.**

### REFERENCES AND NOTES


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Treatment of psoriasis with NFkBIZ siRNA using topical ionic liquid formulations
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