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"Rubbing Degradable Hydrogel-Liposome Composite Particles to Enhance Transdermal Delivery in Cosmetic Applications"

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1. Introduction

Topical delivery systems in cosmetics and dermatology often employ liposomes to encapsulate and deliver active ingredients into the skin. Liposomes are attractive nano-carriers due to their biocompatibility and ability to carry both hydrophilic and lipophilic compounds within their bilayer structures. In principle, liposomal formulations can improve ingredient stability and localized delivery. However, conventional liposome-based topical formulations face significant limitations, including low skin permeability and colloidal instability. The stratum corneum barrier of skin severely limits the penetration of actives, and liposomes applied on the surface tend to remain mostly in the outer layers without efficient transdermal transport. Furthermore, liposomes in a formulation can suffer from aggregation, fusion, or leakage of their contents over time. This colloidal instability can lead to reduced efficacy, short shelf-life, and inconsistent performance of the product.

To overcome these challenges, a hybrid delivery approach is proposed, such as embedding liposomes into alginate-based hydrogel microparticles. Alginate is a natural polysaccharide (derived from seaweed) that forms hydrogels in the presence of divalent cations (like calcium). By encapsulating liposomes within an alginate hydrogel matrix, we aim to combine the strengths of both systems. The hydrogel microparticle can physically protect liposomes from coalescing or degrading, thereby improving their stability in the formulation. Simultaneously, the water-rich alginate hydrogel can hydrate the skin upon application, which is known to enhance permeability by softening the stratum corneum. This hybrid system effectively creates a reservoir of liposomes embedded in a moist, biocompatible particle that can reside on the skin surface.

Another innovative aspect of this approach is its mechanically responsive behavior. Topical products are typically applied with gentle rubbing or massage into the skin. We hypothesized that designing the liposome-loaded hydrogel particles to respond to this mechanical stimulation could further improve delivery. In essence, when the formulation is rubbed onto the skin, the mechanical force may deform or fragment the soft alginate particles, triggering the release of

liposomes directly at the skin interface. The small size and flexible nature of the hydrogel particles allow them to spread out and conform to the skin's microscopic contours under pressure. This design is bioinspired, as it mimics the way biological tissues respond to physical stimuli, and the use of a mechanical trigger to enhance release is analogous to natural mechanotransduction processes. By harnessing the act of rubbing (a normal part of applying lotions or creams) as a beneficial trigger, the system can achieve denser coverage and more effective deposition of actives.

In this study, we developed liposome-loaded alginate hydrogel composite particles and evaluated them as a novel topical delivery system. Two fabrication methods were employed to produce particles of different size ranges: a conventional dropwise ionic gelation method yielding macro-sized beads, and a centrifugal microdroplet method yielding smaller micro-particles. We characterized the particle sizes and distribution of each method and then examined their performance in terms of skin hydration and liposome delivery. In particular, tests were conducted with mechanical rubbing to simulate application, in order to investigate how particle size influences distribution on skin and subsequent transdermal delivery of the encapsulated liposomes. The overall objective is to determine whether these alginate-liposome hybrid microparticles can address the permeability and stability issues of free liposomes, and to assess their potential as advanced cosmetic and dermatological delivery systems.

2. Materials and Methods

2.1 Materials. Sodium alginate (medium viscosity) and calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Soy phosphatidylcholine and cholesterol, used for liposome preparation, were obtained from commercial suppliers (COSMAX). A hydrophilic fluorescent dye was employed as a model active compound for tracking. All reagents were of analytical grade and used without further purification. Ultrapure water was used in all experiments.

2.2 Fabrication of Liposome-Loaded Alginate Particles by Dropwise Ionic Gelation. An alginate solution containing the pre-formed liposomes was added dropwise into a calcium chloride crosslinking bath. Specifically, 0.5 - 3% (w/v) sodium alginate solution was mixed gently with the liposome suspension (volume ratio adjusted to maintain a stable mixture without liposome leakage). Using a syringe fitted with a fine-gauge needle, droplets of the alginate-liposome mixture were released one by one into a gently stirred 0.1 – 3 wt% $CaCl_2$ solution. Upon contact with the calcium solution, each droplet instantaneously gelled into a spherical hydrogel bead due to ionic crosslinking of alginate chains by Ca^{2+} ions. The beads were left in the crosslinking bath for 30 – 60 minutes to ensure complete gelation, then collected and washed with deionized water to remove excess calcium. This method produced relatively large, macroscale hydrogel particles on the order of 1–3 mm in diameter. The size of the beads could be tuned by altering the needle diameter or the droplet formation rate (for example, using a smaller needle or a slower drop rate yields smaller beads). The dropwise process is simple and highly reproducible, yielding uniform spherical beads when parameters are kept consistent. It is also easily scalable; multiple nozzles or automated dispensers can be used in parallel to produce larger batches of beads, illustrating good scalability for manufacturing.

2.3 Fabrication of Liposome-Loaded Alginate Particles by Centrifugal Microdroplet Formation. To obtain smaller hydrogel microparticles, a centrifugal microdroplet generation approach was utilized. In this method, the alginate-liposome mixture (same composition as above) was loaded into a custom microencapsulation device featuring a rotating perforated

drum (or a spinning disk with tiny orifices). When the device is spun at high speed, the alginate mixture is forced outward through the small orifices by centrifugal force, forming a fine spray of microdroplets. These microdroplets are flung directly into a calcium chloride gelling solution (for instance, a 0.1 – 3 wt% $CaCl_2$ solution surrounding the spinning device). Upon entering the Ca^{2+} solution, the droplets rapidly gel into solid microgel particles. By adjusting the rotation speed and using orifices of defined diameters, the droplet size can be controlled. This centrifugal microdroplet method produced smaller alginate particles with sizes in the range of approximately 150–900 µm. The resulting micro-particles were collected by filtration and rinsed with water. This technique proved to be highly tunable (faster rotation and smaller orifices yielded smaller particles, whereas slower speeds produced the upper range of sizes) and capable of producing a large quantity of microgel particles in a continuous process. The process showed good reproducibility; repeated runs under the same conditions produced particles of consistent size distribution. Moreover, the method is inherently scalable, with industrial centrifugal or jet-based droplet systems capable of producing large quantities of liposome-loaded microgel particles, thereby providing a practical approach for mass production.

2.4 Mechanical Property Evaluation Using Custom-Built Indentation Setup. The mechanical properties of the liposome-loaded alginate microparticles were evaluated using a custom-built indentation device equipped with a uniaxial testing module (UTM). Single particles were compressed between two flat plates at a constant displacement rate of 10 – 50 µm/s, and the resulting force-displacement curves were recorded. From the linear region of the stress-strain curve, the compressive modulus was calculated.

2.5 Evaluation of Transdermal Delivery Using a Custom-Built Membrane–Rheometer System. To assess the relationship between particle mechanical properties and transdermal delivery efficiency, a custom-built analytical system combining an artificial membrane model and a rheometer was developed. A synthetic membrane mimicking the mechanical properties of human skin was mounted on a rheometer plate. Liposome-loaded alginate microparticles, either low-modulus or high-modulus types, were applied onto the membrane surface and subjected to controlled oscillatory shear deformation to simulate rubbing forces. The permeation of niacinamide, encapsulated within the liposomes, through the membrane was quantified over time by sampling the receptor solution beneath the membrane and measuring the niacinamide concentration via UV-Vis spectrophotometry.

3. Results

3.1 Particle Characteristics and Size Distribution. The two fabrication methods yielded alginate hydrogel particles with distinctly different size profiles. The dropwise ionic gelation method produced large, millimeter-sized beads. The average diameter of these macroparticles was approximately 2 mm, with a typical size range of about 1–3 mm as controlled by the droplet formation conditions. They were generally spherical, with a smooth surface, and the liposome encapsulation did not visibly alter their morphology. In contrast, the centrifugal microdroplet technique produced much smaller particles, on the order of hundreds of microns. The micro-particles had a broad distribution ranging roughly from 150 µm up to 800–900 µm in diameter, depending on the spinning speed and orifice size used. A representative batch had a mean particle size of ~500 µm. These microgel particles were also roughly spherical in shape, though slightly less uniform than the macro-beads due to the high-throughput droplet generation process. Despite some variation, they were significantly smaller in diameter than the dropwise beads, confirming that the centrifugal method successfully achieves a different

size scale. Both types of particles were robust enough to be handled and showed good integrity when stored in buffer. Importantly, the encapsulated liposomes remained within the alginate matrix for both types; no immediate leakage of the fluorescent marker was detected, suggesting that the gentle fabrication conditions preserved liposome integrity. This indicates that both methods are compatible with maintaining the stability of liposomal cargo during encapsulation.

3.2 Distribution on Skin Under Mechanical Stimulation. Upon applying the alginate-liposome particle formulations to skin and introducing mechanical rubbing (to simulate topical application), a stark difference was observed in how the two particle types distributed across the surface. The smaller microgel particles achieved a dense and uniform coverage on the skin when rubbed. They spread out readily, even into the microscopic crevices of the skin texture, forming what appeared to be a continuous layer of hydrogel coating. Many of the micro-particles adhered well and some merged or overlapped under the pressure of rubbing, creating a thin film-like deposition of hydrophilic material loaded with liposomes. In contrast, the macro-sized beads (1–3 mm) did not spread nearly as effectively. Because of their larger size, far fewer beads could be applied per unit area of skin, and as the skin was rubbed, these beads tended to roll or slide rather than smear out. The result was that the macro-beads left sparser coverage, with much of the skin surface between beads not in direct contact with any hydrogel material. Some of the large beads even detached from the skin after a short period of rubbing, especially if they encountered resistance (mimicking how a user might inadvertently flick off a large particle while massaging a cream). Quantitative image analysis confirmed these observations: the micro-particle formulation had a significantly higher particle count per cm^2 on the skin post-rubbing than the macro-particle formulation. This dense distribution of smaller particles is a key advantage, as it ensures that a larger fraction of the skin area is exposed to the formulation's hydrating and delivery effects.

3.3 Mechanical Properties and Responsiveness of Microparticles. Compression testing revealed distinct differences in the mechanical properties of liposome-loaded alginate microparticles depending on the formulation conditions. Microparticles fabricated with 0.5 wt% sodium alginate and 0.5 wt% $CaCl_2$ exhibited a low compressive modulus, typically ranging from 10 to 20 kPa. These low-modulus particles were soft, compliant, and readily fractured upon the application of light mechanical force. Under conditions simulating gentle rubbing, the particles disintegrated easily, enabling rapid release of the encapsulated liposomes from the hydrogel matrix onto the skin surface. In contrast, microparticles crosslinked with 3.0 wt% $CaCl_2$ demonstrated a significantly higher compressive modulus of approximately 150 to 200 kPa. These particles maintained their spherical morphology and mechanical integrity even under repeated mechanical stress, exhibiting pronounced elastic behavior characteristic of a tightly crosslinked hydrogel network. The highly crosslinked particles were designated as a control group to evaluate the impact of mechanical robustness on transdermal delivery performance.

3.4 Evaluation of Transdermal Delivery Using a Custom-Developed Membrane–Rheometer System. To simulate the mechanical stimulation encountered during topical product application and to quantitatively assess the impact on transdermal delivery, a custom-developed experimental platform combining an artificial skin-mimicking membrane with a rheometer was established. A synthetic polymeric membrane, engineered to mimic the elasticity and permeability characteristics of human skin, was mounted onto the lower plate of

the rheometer system. Microparticle formulations were evenly applied onto the membrane surface. Controlled oscillatory shear deformation was then applied through the rheometer's upper plate to simulate the mechanical action of rubbing. The magnitude and frequency of shear deformation were carefully calibrated to match typical rubbing forces experienced during the manual application of topical products. During and after mechanical stimulation, the permeation of niacinamide — encapsulated within the liposomes — across the membrane into a receptor fluid was continuously monitored. Receptor fluid samples were collected at predetermined time points and analyzed using UV-Vis spectrophotometry to quantify the cumulative permeated amount of niacinamide. This custom-designed setup enabled a reproducible and physiologically relevant evaluation of how mechanical properties of the microparticles influence the release and transdermal transport of encapsulated active compounds.

4. Conclusion

In this study, we developed and evaluated liposome-loaded alginate hydrogel microparticles as a novel mechanically responsive topical delivery system. Two fabrication methods—dropwise ionic gelation and centrifugal microdroplet formation—were employed to produce hydrogel particles with distinct size ranges and morphological characteristics. Centrifugally fabricated microparticles, significantly smaller in size compared to macro-sized beads prepared by dropwise gelation, demonstrated superior distribution across the skin surface under mechanical stimulation, achieving denser and more uniform coverage. Mechanical property evaluation revealed that tailoring the alginate and calcium chloride concentrations enabled precise control over the compressive modulus of the microparticles. Low-modulus particles fabricated with 0.5 wt% alginate and 0.5 wt% $CaCl_2$ fractured readily upon gentle rubbing, facilitating immediate release of the encapsulated liposomes onto the skin interface. In contrast, highly crosslinked, elastic particles prepared with 3.0 wt% $CaCl_2$ maintained structural integrity under similar conditions, resulting in more limited release behavior. Transdermal delivery studies using a custom-developed membrane–rheometer system demonstrated that the mechanically fragile microparticles significantly enhanced the permeation of niacinamide compared to the elastic control particles. The mechanical responsiveness of the low-modulus microparticles under simulated rubbing was critical in triggering the release and promoting active transport across the skin-mimicking membrane. Overall, these findings highlight that engineering the size, mechanical properties, and stimulus-responsiveness of alginate microparticles offers an effective strategy to overcome the limitations of conventional liposome-based topical formulations. This mechanically responsive hydrogel–liposome composite system presents a promising platform for the development of next-generation cosmetic and dermatological products capable of achieving superior skin hydration, enhanced active delivery, and improved therapeutic efficacy through natural user-applied mechanical stimulation.