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Sequential Combination Technology for Dual-Source Exosome Delivery: A Research Framework for Medical-Grade Cosmeceutical Patches and Hydrogels

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ABSTRACT

Background.Extracellular vesicles (EVs, often referred to as exosomes in the cosmetic vernacular) from human mesenchymal stem cell (hMSC) cultures can promote dermal repair, while plant-derived exosome-like nanoparticles (PELNs) provide antioxidant/photoprotective activity. Translating both into safe, high-performance skincare requires clean separation, rigorous quality controls, and delivery systems that stage effects over time. **Objective**.We outline a Sequential Combination Technologythat (1) uses membrane-based microfiltration and charge-aware fractionationto enrich EVs by size/charge, and (2) layers plant vesicles as an outer "shield"(UV/oxidation defense) with human EVs inside(deep repair), formatted into microneedle (MN) patchesor hydrogel masksfor time-release dual action. Rationale & Evidence.The platform aligns with MISEV-2023 guidance for EV isolation/characterization, leverages size- and charge-based separations, integrates literature showing UV/oxidative protection by PELNs, and builds on MN/hydrogel deliverydata for sustained EV release and skin regeneration.

1. Introduction

EVs are nanoscale (≈50–150 nm) lipid vesicles carrying proteins, lipids, and regulatory RNAs. Consensus standards (MISEV-2023) emphasize rigorous reporting of production variables, separation (size/charge/affinity), and multiparametric characterization to ensure reproducibility and safety—requirements that are directly applicable to cosmetic translation.

Scientific premise.

※Human EVs (hMSC-EVs): support fibroblast activity, collagen remodeling, angiogenesis, and anti-inflammatory balance—key for post-procedure recovery and photoaging repair.

※Plant EVs (PELNs): naturally carry polyphenols/lipids with antioxidant and anti-UVeffects that help maintain epidermal barrier homeostasis. ScienceDirect

Hypothesis.

A two-layer vesicle architecture—outer PELN shield + inner hMSC-EV core—delivered via MN patches or hydrogel maskswill (i) buffer UV/oxidative stress at the surface and (ii) provide delayed, deeper regenerative signaling, improving outcomes versus either source alone. This is enabled by membrane microfiltrationand charge-aware separationsto fine-tune vesicle populations before assembly. ScienceDirect +1

2. Technology Concept

2.1. Clean separation (size + charge)

Step A — Microfiltration & pre-clear:
0.45→0.22 µm filters remove cells/debris from hMSC-conditioned media and botanical juices.
Step B — Size/charge enrichment:

✔ Size selection:membrane-based concentration (e.g., TFF with 100–300 kDa cutoffs) or rapid membrane sieving enriches 50–150 nm vesicles.

✔ Charge-aware cleanup:emerging charge-based isolationcan remove negatively charged impurities and lipoproteins while preserving EV bioactivity, complementing size-based steps. ScienceDirect +1

Standards:Document inputs, fraction IDs, and recovery per MISEV-2023(including orthogonal sizing by NTA/TRPS and morphology by TEM).

2.2. Layered assembly: "PELNs-outside / hEVs-inside"

Using mild electrostatic/adsorptive interactions, PELNs(often carrying anionic phospholipids/polyphenols) can be adsorbed as an outer layeraround a depot containing hMSC-EVs, creating a sequential barrier: first-contact antioxidant/anti-UV effects (outer layer) followed by delayed release of regenerative hEVs. (Charge-based EV handling supports feasibility of gentle, non-denaturing assembly.) PMC

2.3. Finished forms for time-release

✔ Microneedle (MN) patches:Dissolving or hydrogel-forming MNs co-load PELNs on the surface (fast) and hEVs in deeper matrices (slow); MNs improve penetration and patient compliance in EV delivery. PMC +2 ScienceDirect +2

✔ Hydrogel masks:Shear-thinning or photo-crosslinked hydrogels protect vesicles and stage releasevia diffusion/degradation kinetics; multiple reviews document EV stability and controlled release with hydrogels. BioMed Central +2 Theranostics +2

3. Mechanistic Model (Dual-Action)

※**Outer PELN "shield"**: scavenges ROS and attenuates UV-induced signaling (e.g., AP-1), limiting photoaging cascades and barrier disruption. Evidence includes ginseng-derivedand lavender-derivednanovesicles protecting skin from UV/oxidative injury in cell/mouse models. ScienceDirect +1

※**Inner hMSC-EV core**: delivers miRNA/protein cargos that boost fibroblast migration, collagen I/III synthesis, and pro-angiogenic pathways for deeper repairafter initial stress is blunted. (Supported broadly by EV-for-skin regeneration literature and EV-MN studies.) PMC

4. Materials & Methods (Proposed)

4.1. Isolation

Human source:serum-free hMSC cultures (early passages, mycoplasma-free).

Pre-clear → membrane concentration → charge-cleanup; optional SEC for polish if needed.

Plant source:HACCP/GACP-managed botanicals (e.g., green tea, ginseng, lavender); cold-press/juice → pre-clear → membrane size selection.

4.2. Characterization & Release

✔ Identity/size:NTA/TRPS (mode 50–150 nm), TEM; markers: CD9/CD63/CD81 for hEVs; plant vesicle signatures per PELN literature.

✔ Purity:particle:protein ratio; ApoB/lipoprotein reduction indices; residual small-molecule screens.

✔✔ Potency (in-vitro):keratinocyte/fibroblast migration; UV-ROS suppression; COL1A1/COL3A1 and elastin mRNA; cytokine balance (IL-1α/IL-8).

✔ Safety:endotoxin (LAL with low-endotoxin-recovery controls)for hEVs; pesticide LC-MS/MS panelsfor PELNs; sterility/bioburden; HRIPT on finished forms. (Hydrogel matrices can further mitigate irritation and moderate release.) isevjournals.onlinelibrary.wiley.com +1

4.3. Formulation for time-release

※MN patches:two compartment casting/printing to localize PELNs near needle tips (fast release on insertion) and hEVs in the base (slow hydration-triggered release). EV-MN reviews and 2025 original studies support feasibility and skin-repair benefits. PMC +2 ScienceDirect +2

※Hydrogel masks:dual-layer films (PELNs outer coat; hEVs inner reservoir) or gradient-crosslinked gels to control diffusion; numerous reviews show EV–hydrogel systems enhance wound repair and sustain delivery. BioMed Central +1

5. Preclinical/Clinical Evaluation Plan

※In-vitro (3–6 months):

- Sequential release: Franz cells & MN insertion rigs quantify stage-wise particle counts and bioactivity.

- Function: UV-A/B keratinocyte model (ROS, AP-1), fibroblast scratch, collagen ELISA, OCT on 3D skin equivalents.

※In-vivo (non-clinical):

- Photoaging model (mouse):compare PELN-only vs hEV-only vs layered system on erythema, TEWL, histology (collagen, MMP-1).

- Wound/tape-stripping model: re-epithelialization, dermal density by HF ultrasound.

- Early clinical (cosmetic endpoints):Split-face study after fractional laser: downtime, profilometry (Ra/Rz), ultrasound dermal echogenicity, blinded scoring; safety via HRIPT and diary-reported irritation.

Rationale: EV-MN and EV-hydrogel literature report improved skin-repair metrics and user compatibility; PELN studies show UV/ROS attenuation—together supporting the dual-actionendpoint suite proposed here. PMC +2 BioMed Central +2

6. Quality, Safety & Compliance

✔ Standards: adopt MISEV-2023for reporting (batch metadata, orthogonal sizing, negative controls).

✔ Endotoxin control (hEVs):validated LAL with low-endotoxin-recoverychecks; document spike-and-recovery and include TLR-4 antagonism in bioassays when needed.

✔ Pesticide control (PELNs):supplier COAs + targeted LC-MS/MS on final vesicle lots.

✔ Device/cosmetic pathway: MN patches /hydrogel masks marketed with cosmetic claims(appearance, comfort, recovery) unless device/drug pathways pursued.

7. Discussion

This platform advances cosmetic EV use by (i) orthogonally enrichingvesicles via size and charge to reduce confounders, (ii) engineering sequence-of-action(PELNs first, hEVs second), and (iii) embedding in delivery matrices(MNs/hydrogels) that solve the twin challenges of skin penetrationand controlled release. The concept is consistent with field standards and leverages recent peer-reviewed evidence for PELNs' UV/ROS protectionand MN/hydrogel-mediated EV delivery. Remaining challenges include manufacturing scale-up, inter-batch variability in plant vesicles, and long-term stability—addressable via tight specifications, release testing, and real-time/accelerated stability programs. ScienceDirect +2 PMC +2

8. Conclusion

Sequential Combination Technology—size/charge-aware membrane separations + layered PELN/hEV architecture + MN/hydrogel time-release—offers a credible, standards-aligned route to medical-grade cosmeceuticalprototypes that combine surface protectionwith deep repair. Early feasibility should focus on sequential-release analytics, photoprotection biomarkers, and split-face clinical signals to de-risk scale-up and regulatory planning.

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