released after 2h was (24.32 ± 0.13%) and after 24h was (81.175 ± 0.325%). The Safety of the Proniosomes for topical application was confirmed by the histopathological examination. The CLZ-loaded proniosomes showed promising results with high potential to deliver it across the skin.[56] Clozapine (CLZ) loaded proniosomal gel (PN) gel was prepared by the coacervation phase separation method utilizing span-60, cholesterol and lecithin. The optimized formulation had the highest entrapment efficiency of 90% and the average particle size of approximately 325 nm. polydispersity index (PDI) reflected homogeneity in the formulation. zeta potential (ZP) was -59.76 mV, high enough to indicate a stable formulation. The in vitro release studies manifested a sustained release behavior of clozapine from the proniosomal gel. The ex vivo permeation showed noteworthy permeation of the drug through stratum corneum with a steady state flux of 18.26 ug/cm2/hr.[57] Galantamine hydrobromide is used for the treatment of Alzheimer's disease. Galantamine hydrobromide is formulated as proniosome gel by Coacervation phase separation method to overcome the side effects of oral delivery. Microscopical observations of the gels showed vesicles of optimum size from 3.030 mm - 3.735 mm. The gel also showed optimum rate of spontaneity in the range 9.60 mm3x1000 to 11.80 mm3x1000 and entrapment efficiency of vesicles in the range 66.15% to 86.92%. The gels had pH in suitable range of skin (5.92-6.9). The in vitro drug diffusion studies revealed that the proniosomal gel containing Tween 80 showed maximum drug diffusion (99.24%) and the gel containing Span 20 showed minimum drug diffusion (71.74%).[58]

Intranasal routes

The nasal drug delivery method has some limitations like mucociliary clearance, degradation of drugs by the enzyme. Vesicular drug delivery systems can circumvent these limitations. Duloxetine (DX) is a new norepinephrine (NE) reuptake inhibitor (SNRI) used in the treatment of depression. But it has high first-pass metabolism, and low bioavailability (< 50%) following oral administration eventually leading to low cerebrospinal fluid (CSF) concentrations. khatoon et al.[59] designed mucoadhesive thiolated chitosan (TCS) gel containing proniosomes of Duloxetine (DX) for the intranasal drug delivery to enhance the drug's contact time with nasal mucosa, bypass the first-pass effect and target the brain possibly using the olfactory pathway. Here soya lecithin, cholesterol, Tween 80 were used in the preparation of the gel. The pH of the Duloxetine-loaded proniosomal gel (D-MPNG) was 5.67 ± 0.145, indicating the compatibility of formulations within the nasal cavity without producing irritation. Notably, the D-MPNG showed better control, releasing only 24% DX at pH 7.4 over 24 h compared to 78% release at pH 5.5. The presence of thiol groups of TCS significantly controls the water uptake, resulting in moderate swelling and higher viscosity; thus, providing a sustained effect for a longer period.[59]

Cosmeceuticals application of Proniosomes

Cosmeceutical is generally used to refer to skincare products that contain active ingredients that are beneficial to improving skin's appearance and promoting healthy skin.[60] Anti-aging cosmeceuticals are most frequently recommended by physicians who use them as an integral part of a comprehensive skin rejuvenation program. Moisturizers and serums containing ingredients like vitamin C, niacinamide, retinol, peptides, growth factors, and botanicals can all be used in this regard. In addition, patients undergoing cosmetic procedures such as laser resurfacing and chemical peels may be given cosmeceuticals to "prime" the skin for procedures, encourage healing, and reduce complications after. Cosmeceuticals are also recommended for patients with acne, rosacea, eczema, and other skin conditions where they are commonly used in combination with prescription medications. For example, moisturizers containing anti-inflammatory botanical ingredients may be used in conjunction with prescription medications for treating rosacea.

Cosmeceuticals containing soy can be used to provide added skin lightening benefits when paired with hydroquinone.

Applying therapeutic and cosmetic agents onto or through skin requires a non-toxic, dermatologically acceptable carrier, which not only controls the release of the agent for prolonging action but also enhances the penetration to the skin layer.[61] Proniosome gel meets such criteria which are useful for delivery of cosmetics and Cosmeceuticals. The therapeutic agents which can be utilized for incorporation into proniosomal carrier systems include, moisturizing, nutritional, anti-wrinkle, anti-aging, cleansing, sunscreen particles, etc. Proniosomes are a potentially scalable method for producing niosomes for the delivery of hydrophobic or amphiphilic drugs.[62] Anti-aging cream containing the methanolic purple glutinous rice extract loaded in niosomes was formulated by Manosroi et. al.[63] Anthocyanin present in purple glutinous rice extract is responsible for the anti-aging activity. After 6 cycles of heating and cooling test, the formulation with 1%w/v of the purple glutinous rice extract contains 52.28% anthocyanin of the initial. For *in vivo* antiaging activities, a cream containing niosomes loaded with the extract gave significantly decreased melanin index and skin roughness reduction of 14.05 and 9.95% of the initial, respectively. The % changes of the increased skin hydration, skin elastic extension, and skin elastic recovery when applied on human volunteers' skin with this formulation were +48.73, 24.51, and +35.98%, respectively

Tretinoin (TRT) is a widely used retinoid for the topical treatment of acne, photo-aged skin, psoriasis, and skin cancer. TRT-loaded Proniosomes were prepared by slurry method with the help of Span 60 and D-Sorbitol, Span 40, Cholesterol 95% stabilized, and Tween 20.[64] Prepared hydrated proniosome was characterized by evaluation particle size, the effect of drug concentration, entrapment efficiency, etc. The entrapment efficiency of all hydrated proniosomal dispersions ranged from 76.6% ± 0.001 prepared using Span 40 to 94.15% ± 0.041 prepared using Span 60. *In-Vitro* drug release was increased till the 5th hour.

Diferuloylmethane or curcumin is obtained from turmeric, which possesses inflammatory properties blocking the formation of reactive oxygen species.[65] Proniosomes of curcumin were prepared using nonionic surfactants (tween 80, span 60) either solely or in combinations with cholesterol. The highest encapsulation efficiency of curcumin in niosomal formulations was 99.74%. Kinetically, niosomes fitted to the Korsmeyer-Peppas model with non-Fickian transport. The anti-inflammatory activity of curcumin in various formulations was evaluated using a rat hind paw edema method and the % of swelling was 17.5% following 24h in the group treated with curcumin niosomal emulgel.[66]

Coenzyme Q10 (CoQ10) also known as ubiquinone, an essential compound is found in every cell of the human body. Coenzyme Q10 (CoQ10), an essential compound of cellular bioenergetics also acts as a strong antioxidant and protects the body against aging.[67] Coenzyme Q10 proniosomes were prepared by using the standard method with the help of Q10, Span 85, soya lecithin, and Cholesterol. *In-vitro* drug release of CoQ10 followed a special cubic model, as the statistics of the chosen model were found significant (p= 0.0006). Change in the levels of soy lecithin had a great impact and showed a synergistic effect on the release characteristics. Skin permeation study showed the cumulative amount of CoQ10 permeated in 12 h was found to be 515.85, 463.25, and 507.49 mg/cm2, respectively for selected Proniosomal gel (PN) formulations. Animal skin was treated with UV radiations followed by treatment of PN gel CoQ10 and conventional CoQ10 present in a gel base. The effectiveness of the treatment was evaluated based on biochemical estimation and histopathological studies. By using CoQ10 PN gel formulation, levels of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and

total proteins were restored by 81.3%, 72.1%, 74.8, and 77.1% respectively to that of a control group. Histopathological studies revealed better protection of skin treated with CoQ10 PN gel compared to free CoQ10. Prepared PN gel did not interact with the normal histology hence, tolerated by animal skin compare to conventional gel. Assessments of the formulations for various Enzymatic and non-enzymatic estimation in animal skin after UV irradiations proved the efficacy of the developed formulation.
Proniosomal formulations containing the natural antioxidant Resveratrol (RSV) were prepared by M. Schlich et. al.[68] Resveratrol (trans-3,5,4′-trihydroxystilbene, RSV) is a polyphenol compound having anti-inflammatory [69], neuro-protective[70], anti-aging[71], and anti-cancer effects.[72] Proniosomal powders were prepared by the slurry method and characterized. the hydration and sonication of proniosomes resulted in the formation of lipid nanoparticles with a mean diameter in the range 180-300 nm and a highly negative surface charge. The RSV release from proniosome-derived niosomes was investigated in simulated gastric and intestinal fluid. biocompatibility assay carried out on intestinal cells (Caco2) demonstrated that proniosomes prepared with an HLB of 13.5 showed to be significantly less toxic than their HLB16.7 counterpart. All the tested formulations could be employed safely at the doses commonly administrated by oral route.
Canthaxanthin (CTX) is a xanthophyll (a subclass of carotenoids) with widespread applications in the pharmaceutical, cosmetic. It is a superior antioxidant and scavenger of free radicals as compared with carotenoids such as β-carotene.[73] canthaxanthin (CTX) was encapsulated in proniosome powders. Proniosome powders were prepared with an equimolar ratio of span 60/cholesterol and four different carriers, namely maltodextrin, mannitol, lactose, and pullulan.[74] The study showed that the niosomes produced by hydration and sonication of the proniosomes were small in size (≤ 200 nm) and quite homogeneously dispersed (PDI ≤ 0.3). The encapsulation efficiency of CTX in formulations varied between 55.3±1.8% and 74.1±2.7% after hydration and sonication. Although light and high temperatures affected the stability of CTX drastically, encapsulation in proniosomes retarded its degradation. This formulation can provide convenient, nontoxic, and inexpensive vehicles for dissolving and stabilizing CTX in functional food products.
O-Padimate is a UV-B Filter widely used as a sunscreen agent. This study aimed to investigate the combined influence of 3 independent variables in the preparation of O-Padimate Proniosomes were prepared by the slurry method with Span: Brij, surfactant. The formulated gels were characterized for Vesicle size, morphology & Encapsulation efficiency, Skin permeation studies, Rheological properties, and Sun Protection Factor (SPF). Results reveal that optimized O-Padimate Proniosomal formulations showing high SPF and low TWEL (Transepidermal water loss).[75]
Rutin (Rut) is a natural flavonol that has a wide range of therapeutic properties including antioxidant and antitumor activities. Rutin proniosomal gel for cutaneous applications was designed to improve the poor aqueous solubility of rutin. The gel was prepared by coacervation phase-separation method and complies with the standard requirements in terms of particle size (140.5 ± 2.56 nm), zeta potential (-27.33 ± 0.09 mV), encapsulation capacity (> 50%), pH (7.002 ± 0.18), and rheological properties. The results showed high biocompatibility of the gel on the 3D reconstructed human epidermis model characterized by increased viability of the cells and a lack of irritant and phototoxic potential. The evaluations on 2D cells confirm the preferential cytotoxic effect of Rut on melanoma cells (IC_{50} value = 8.601 μM, nuclear fragmentation)

compared to normal keratinocytes. Our data suggest that the proniosomal gel is a promising drug carrier for Rut in the management and prevention of skin disorders.[76]

Clinical trials with Proniosomes

Selected proniosomal formulation of vinpocetine was tested *in-vivo* to compare the pharmacokinetics of vinpocetine from a proniosomal patch containing vinpocetine (treatment A) to an oral commercial tablet containing the same dose of vinpocetine (treatment B) using a non-blind, two treatment, two-period, randomized, crossover design.[77] Twelve healthy non-smoking male volunteers (26–37 years, 78–96 kg) participated in the study and were randomly assigned to one of the two treatment groups of equal size. The study result showed significant differences in the shape of the concentration-time courses between the two treatments. For Vinpocetine oral tablet a rapid sharp peak was found at 1.5 hours followed by a fast decline in plasma drug levels. On the other hand, for the vinpocetine proniosomal patch, the absorption was much slower and extended over a longer period. Moreover, the patch exhibited higher drug levels in the plasma from 6 to 12 h compared to the tablet. The average C_{max} was significantly lower ($p < 0.05$) for the patch (12.44 ± 1.87 ng/ml) compared with the oral tablet (63.69 ± 8.32 ng/ml) while t_{max} was significantly higher ($p < 0.05$) in the case of the transdermal patch (12 h) compared with the oral tablet (1.5 h). The extent of absorption of vinpocetine from the patch expressed by $AUC_{0–t}$ was determined to be about 101% larger and statistically significantly different when compared to the oral tablet. The relative bioavailability of vinpocetine proniosomal patch to the oral tablet was estimated to be on average 206%. The elimination half-lives of vinpocetine after oral and transdermal administration were 1.36 ± 0.27 h and 13.94 ± 1.2 h, respectively, and were statistically significant ($p < 0.01$).[77]

Tretinoin (TRT) loaded Proniosomes was prepared by slurry method with the help of Span 60 and D-Sorbitol, Span 40, Cholesterol 95% stabilized, and Tween 20. The formulated proniosomal gel was studied clinically on 12 Egyptian patients aged >18 years (2 males and 10 females; with an average of 20 (± 4 years) with acne (papules, closed comedones, and open comedones) on their face.[64] The result showed only very slight erythema (score = 0.143 ± 0.377) for TRT proniosomal gel in comparison to 0.025 % TRT gel (score = 1.70 ± 0.755). The similarly marketed product showed an erythema score of 1.50 ±0.534 and was not able to diminish the irritation caused by topical application of TRT. Overall improvement of the individual lesions was also better than the marketed product during the 4 weeks study period.

Niosomal (Hydrated form of proniosome) Benzoyl Peroxide (BPO) and Clindamycin (CL) Lotion were prepared and compared with Niosomal Clindamycin in acne vulgaris. In both cases, the concentration of the drug was 1%. A double-blind clinical trial study on 100 patients with acne vulgaris was conducted in Afzalipour hospital in Kerman.[72] The efficacy of treatment protocols was evaluated in the 2nd, 4th, 8th, and 12th weeks of treatment by counting lesions (severity and grading acne lesions) and quality of life (QoL). Furthermore, the side effect was evaluated at each treatment visits. The reduction in mean percentage of acne lesions in the case group (treated with BPO 1% and CL1%) (64.21%) was higher than the control group (treated with niosomal CL 1%) (59.04%), but the statistical difference was not significant. A sum of excellent and good results was found in 80% and 76.1% of the case and control groups, respectively (P=0.377). Also adding BPO to the treatment formulation in the case group did not increase adverse effects, as the statistical difference between the 2 groups was not significant.[78]

Patents on Proniosomes
Brief description of Patents on Proniosomes

Patent application ID	**Inventors**	**Title**	**Patent description in brief**	**References**
CN103340823A	Liu Qiang, Zhang Bin, Liu Li, Zhu Hongxia, Li Shasha, Jiang Xiao	Formulation of paeonol proniosomes and preparing method thereof	Paeonol proniosomes are an effective method for solving the problems of easy aggregation and easy fusion of niosomes and leakage of drugs in a solution state and a storage process of the non-ionic surfactant noisomes. The paeonol proniosomes can be directly applied to skins, and also can be prepared into a gel agent, an ointment, a patch and other transdermal drug delivery formulations.	79
1288/DEL/2012	Kiran Yadav Deepak Yadav Sanju Nanda Kamal Saroha	Curcumin proniosomal/niosomal formulation, method for its preparation and use thereof	Niosomal/proniosomal vesicular system can improve the dispersibility of curcumin and thus providing advantage to make curcumin in administrable or applicable form for its cosmetic/therapeutic/medical purposes.	80
3228/DEL/2012	Munish Garg Monika Joon	Novel Proniosomal Gel of *Withania Somnifera*	This invention relates to preparation of proniosomal gel of standardised *Withania somnifera* leaves extract, for better bioavailability, anti-inflammatory activity, to be used as transdermal application.	81
3231/DEL/2012	Munish Garg Parul Garg	Novel Ursolic Acid Loaded Proniosomal Gel and Method of Preparation Thereof	Ursolic acid is a well-known anti-inflammatory bioactive compound. This invention relates to the preparation of Ursolic	82

			acid loaded proniosomal gel by coacervation phase separation method.	
U.S. Patent US 6051250A	Alain Ribier Jean-Thierry Simonnet	Process for the stabilization of vesicles of amphiphilic lipid(s) and composition for topical application containing the said stabilized vesicles	This invention relates to a process for stabilization of vesicles formed from a lipid-phase membrane containing at least one ionic and/or nonionic amphiphilic lipid encapsulating an aqueous phase, in the form of a dispersion in an aqueous phase, by addition of at least one stabilizing agent to the aqueous dispersion phase	83
U.S. Patent US 4830857A, 1989.	Rose M. Handjani Alain Ribier Guy Vanlerberghe Arlette Zabotto Jacqueline Griat	Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions	This invention relates to a composition consisting of a dispersion in an aqueous medium of niosome and/or liposome spherules, within which an aqueous phase is encapsulated, at least one portion of the spherules being niosomes. The formulation is usable in cosmetics or pharmaceuticals.	84
CN105311638A	Feng Jianfang, Hu Kaili, Liu Helong, Liu Mei; Wang Luting	Drug-carrying precursor vesicle, preparation method and application thereof	In this invention drug-carrying precursor vesicle can form homogeneous and mono-dispersed vesicles after hydration, has excellent stability, can significantly promote oral absorption and improve the bioavailability of poorly soluble drugs, and also has significant slow-releasing effect and is suitable for large-scale production.	85
WO2000042987	Amarjit Singh	Targeted vesicular constructs for	A novel composition for targeted vesicular	86

A8	Rajesh Jain	cytoprotection and treatment of *H. pylori* infections	constructs for treatment of H. pylori infections and for protection of the cell is disclosed.	
KR20040058196 A	CHO, Young, W. Lee, Keith, Kwang-Ho	Pro-micelle pharmaceutical compositions	The present invention provides a composition containing a pharmaceutically active drug encapsulated with an esterified C_1-C_{18} fatty acid membrane. The result of the conversion of the micelles (pro-micelle) - are pharmaceutically that effectively deliver the active drug in systemic circulation procedure.	87
EG24388A	Hanan Hosny Ellaithy Ahmed Abd Elbary Ebd Elrahman Mina Ibrahim Tadros	A method for the preparation of nebulizable micronized niosomes of cromolyn sodium using nonionic surfactants	This invention involves the controlling the rate of drug release after inhalation so that biological half-life could be increased, consequently number of doses (4 - 6 daily) should be reduced.	88

Conclusion

Proniosomes can be a promising vesicular drug delivery method for the future. They are one of the drug carriers in vesicular drug delivery methods which is a better alternative to liposomal drug delivery due to its controlled and sustained action and provide better physical, chemical stability and potentially scalable for commercial viability. They offer excellent potential for improved drug delivery, through versatile routes such as oral, parenteral, dermal, transdermal, ocular, vaginal, pulmonary, and nasal by overcoming the permeation barriers faced by several drugs. Different types of unit dosages form like tablets, capsules, and beads can be prepared with the dry form of proniosomes. Due to the versatility of proniosomes, they are widely investigated as drug carriers. There are a lot of scopes to investigate new carrier material for the preparation of proniosomes and their potential remains to be investigated to the full extent.

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