LIPID NANOPARTICLES: PAST, PRESENT, AND FUTURE OPPORTUNITIES

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Introduction

Lipid nanoparticles (LNPs) have held a recognized position in the mainstream of drug delivery systems since the discovery of liposomes in the 1960s. They use nanotechnology and are well suited to stable and efficient delivery of various therapeutics. Recently, LNPs have been in the global spotlight as a vital component of COVID-mRNA vaccines, playing a key role in effectively protecting and transporting mRNA to cells. The delivery role they have played in medicine has been and continues to be extended to other fields – such as medical imaging, nutrients, cosmetics, agriculture, and other innovative areas such as nanoreactors.

In this whitepaper, we review the evolution of LNPs and analyze the CAS Content Collection™ to provide a unique landscape of LNP-related research. The growth and diversity of LNP-related publications are explored to identify emerging trends and opportunities.

The development of lipid nanoparticle technology

Liposomes, the first generation LNPs, are the earliest nanomedicine delivery platform to successfully proceed from concept to clinical application. Since their discovery in the 1960s, there have been many technological advancements to improve their functionality, ranging from procedures for liposome formation to liposome targeting (Figure 1).

The ability of LNPs to transport hydrophobic or hydrophilic molecules, including small molecules, proteins, and nucleic acids have made them an extremely versatile nanocarrier platform. Various liposomal drugs have been approved, such as Doxil (doxorubicin), an antitumor agent used to treat ovarian cancer, and Epaxal, a protein antigen used as a hepatitis vaccine. While liposomes are useful as drug carriers, they require complex production methods using organic solvents, exhibit low efficacy at entrapping drugs, and are difficult to perform on large scales. Additionally, liposomes are limited by short circulation time in the bloodstream, poor stability, and lack of selective targeting. In order to overcome these challenges, modifications and engineering of liposomal particles have led to the evolution of more advanced LNP particles (Table 1 - next page).

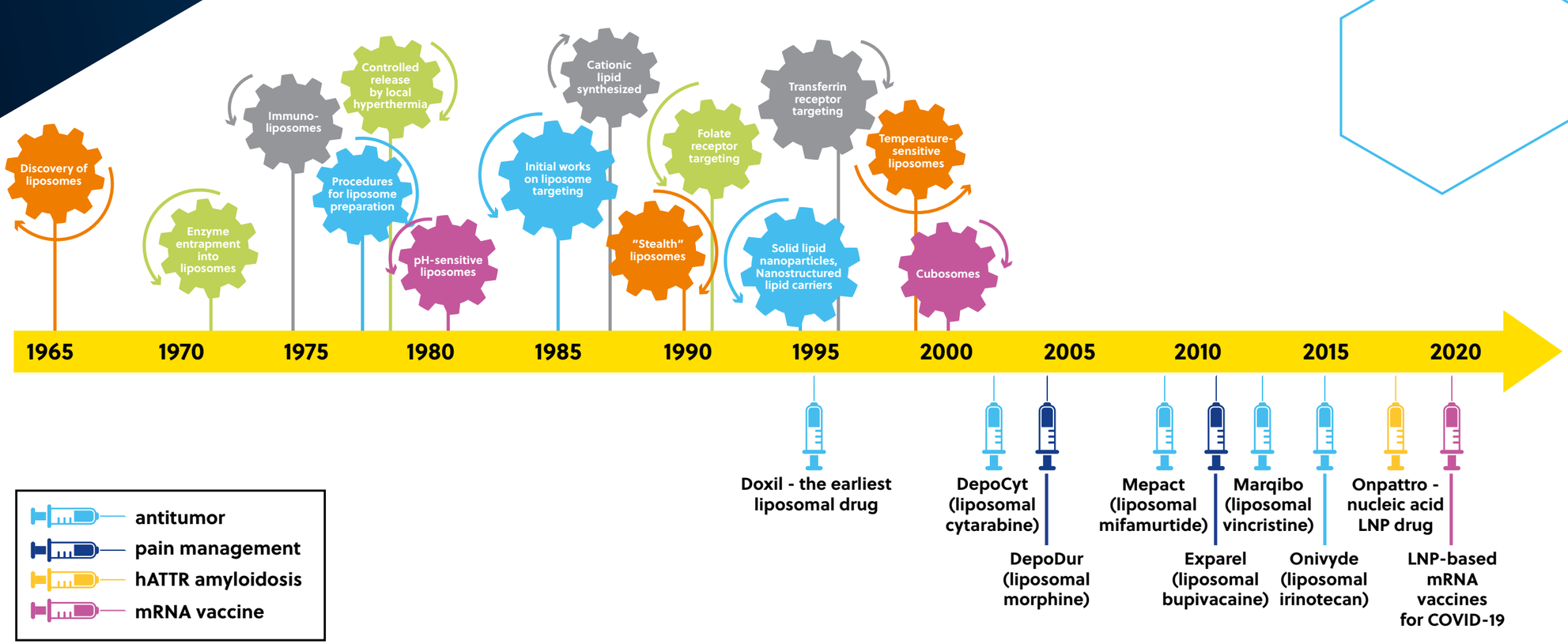


Figure 1. Timeline of LNP advancements

Types of lipid nanoparticles

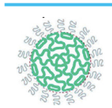
LNP	Role	Development
Liposome Liquid-crystalline lipid bilayers	• Hydrophilic drugs encapsulated in aqueous interior • Hydrophobic drugs entrapped in their hydrocarbon chain	• Earliest generation of LNP • Delivered wide variety of drugs and gene therapies in clinical trials
Solid lipid nanoparticles (SLN) Solid lipids **Nanostructured lipid carriers (NLC)** Solid and liquid-crystalline lipids	• Enhanced physical stability • Higher loading capacities and cargo bioavailabilities • Reduced mobility – greater degree of control over the drug's release	• Produced a simpler process than creating liposomes • Easier to scale-up
Cationic LNP Complex of cationic lipids and anionic nucleic acids	• Stabilizes nucleic acids • Increases their resistance to nuclease degradation	• The most widely used non-viral delivery system for nucleic acid drugs
Targeted liposome Small-molecule ligands, peptides or monoclonal antibodies (mAbs) are conjugated to the surface	• Surface-attached ligands to recognize and bind to specific receptors on cells	• The first targeted liposomes, such as immunoliposomes, can improve efficiency by 100x
Stealth liposome LNP coated with biocompatible inert polymers, typically polyethylene glycol (PEG)	• 'Invisible' to the immune system • Increase circulation half-lives • Enhance passive accumulation	• PEGylation originally developed for protein drugs, but found to be useful for enabling LNPs to evade the immune response
 **Cubosome** Formed from lipid cubic phases and stabilized by polymer-based outer coronas	• Highly stable • Tunable pore size • Can include bioactive lipids	• Used in a variety of applications, such as drug delivery systems, membrane bioreactors, and biosensors

Table 1: Types of lipid nanoparticles: structure, role and development

The landscape of LNP research, its application and future opportunities

To identify the research trends emerging in LNP, we analyzed the CAS Content Collection to build a picture of the LNP research landscape over the past two decades.

The CAS Content Collection is the largest human-curated collection of published scientific knowledge. Of the more than 216,000 LNP-related scientific publications in the CAS Content Collection, over 170,000 are from the period 2000-2020 alone. We examined the growth and diversity of LNP-related publications and their distribution among research areas and applications. LNP-related research has been dominated by pharmaceutical research, in both patents and non-patents (Figure 2), which is unsurprising, considering the utility of LNPs in drug delivery.

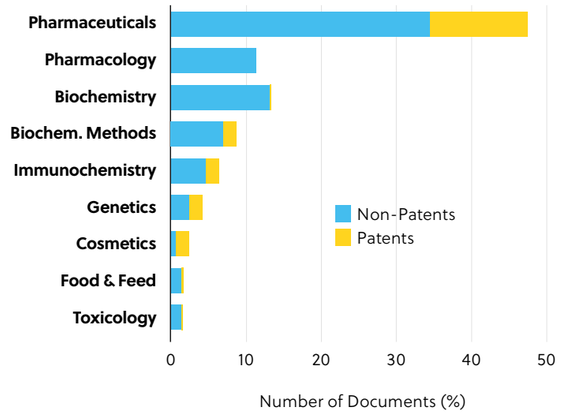


Figure 2. Distribution of LNP-related documents among top research areas in the CAS Content Collection in the years 2000–2021, presented as percentage of all LNP documents

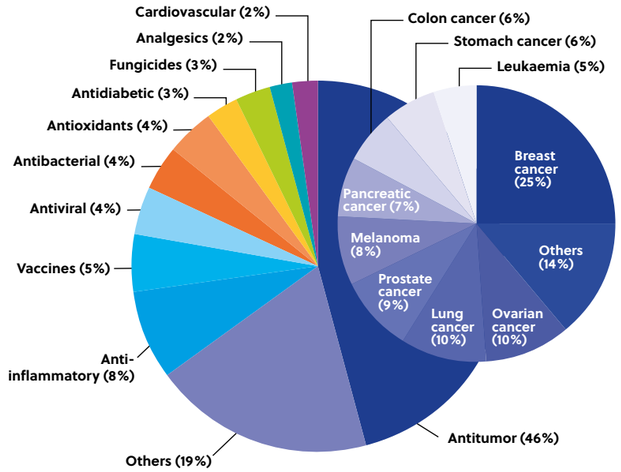


Figure 3. Distribution of documents in the CAS Content Collection related to LNP pharmaceutical formulations with respect to their target diseases

We further examined the distribution of pharmaceutical treatment areas using LNP formulations (Figure 3). Most documents related to the use of LNP were for antitumor formulations, including those used to treat breast cancer, ovarian cancer, and lung cancer (25%, 10% and 10% of publications within the antitumor space, respectively). Every other therapeutic category had a share of <10%, which includes antioxidants, vaccines, and anti-inflammatory drugs.

A number of LNP drug formulations have been approved and used in medical practice. The treatment areas with the largest application of LNP includes cancer, fungal and analgesics (Figure 4).

Figure 4. Approved LNP drugs and the diseases they target

In addition to published papers, CAS has analyzed the patent landscape from 2000–2020 and found that nearly 60% of patents containing LNP apply for pharmaceutical research (Figure 5). Figure 5 also shows the primary and secondary research areas of these patents related to LNPs.

Figure 6 shows the number of patent filings by country or patent office. The US has the largest volume of patent filings overall (almost 35%). However, patent filings in China have increased significantly, growing from 1% of total patent filings in 2000 to 33% in 2020.

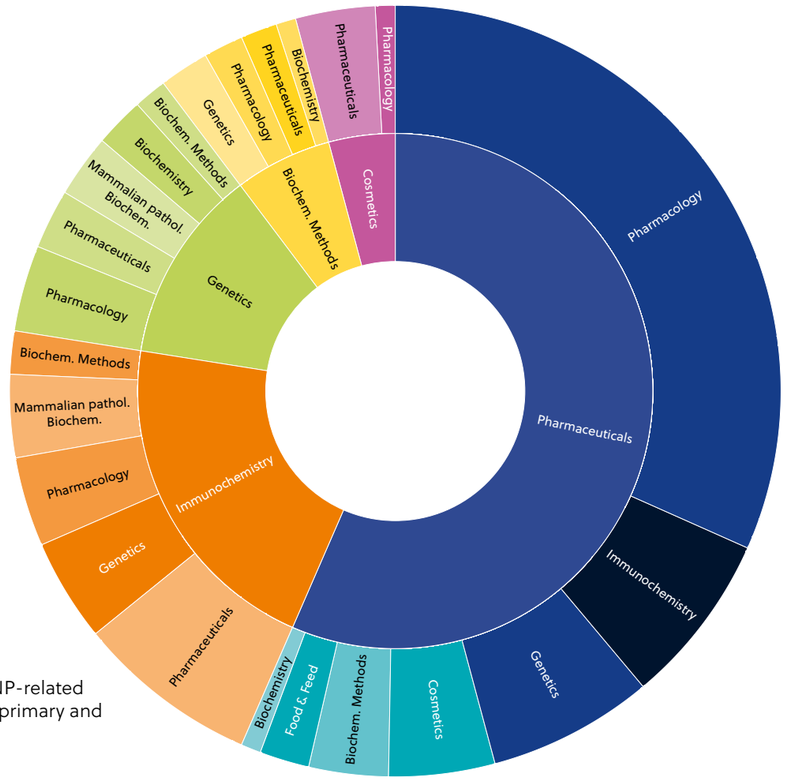


Figure 5. Distribution of LNP-related patents according to their primary and secondary scientific area

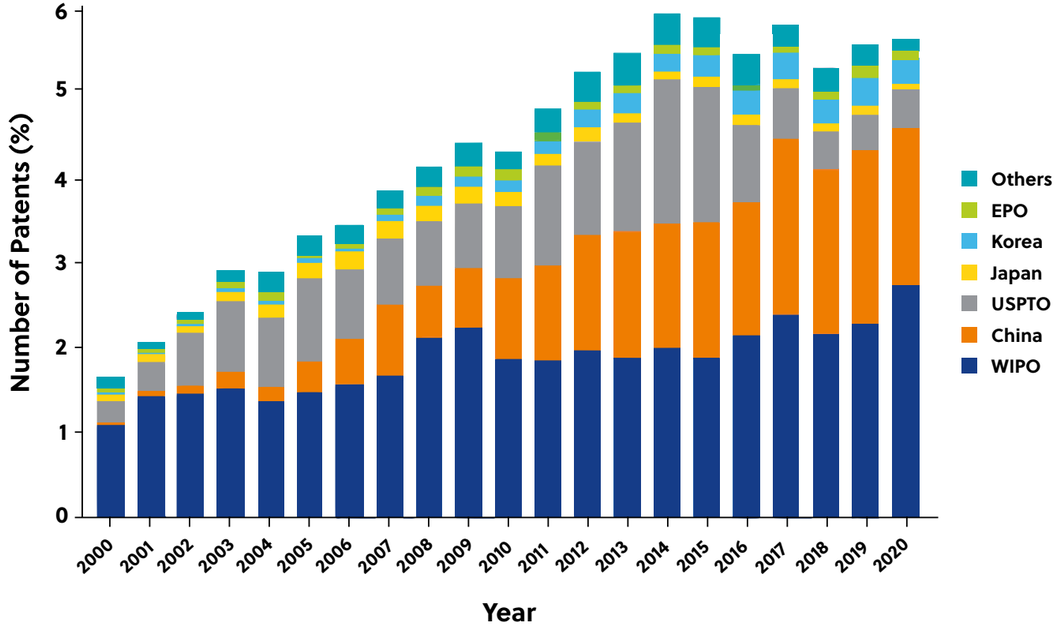


Figure 6. LNP-related patents per year for the top patent offices presented as percent of the total number of LNP-related patents in the years 2000–2020. EPO, European Patent Office; USPTO, US Patent and Trademark Office; WIPO, World Intellectual Property Organization

Application of different LNP types

Each of the different LNP types has different advantages and disadvantages, which determine their value for use in a variety of therapies. To better understand this, we correlated the various LNP formulations with the therapies that they may be applied to (Figure 7). As the heatmap shows, immunoliposomes and stealth liposomes are the most ubiquitous LNP types for antitumor therapy, while cationic liposomes are most commonly used for gene therapy.

We examined the number of documents by LNP formulations to gain an insight into the growth pattern of the different LNP types (Figure 8). Documents related to NLC and cubosomes have seen the fastest growth in recent years, while those related to SLN and cationic liposomes have reduced– although they still make up the highest proportion of documents in total. This reflects the fact that NLC are becoming the preferred formulation for many applications.

	antitumor	gene therapy	anti-inflammatory	antiviral	anti-bacterial	anti-infective	vaccines	anti-diabetic	fungicides	cardio-vascular	analgesics	immuno-therapy
immunoliposomes / ligands	11289	1987	1729	896	499	386	975	382	398	329	341	1861
stealth / sterically stabilized	5253	273	645	331	171	108	235	169	212	144	158	311
nanostructured lipid carriers (NLC)	181	13	92	14	35	10	3	15	29	2	13	2
solid lipid nanoparticles (SLN)	508	76	171	54	78	24	9	56	68	2	34	11
cationic liposomes/ lipoplexes	1208	1916	105	116	53	22	214	11	13	11	15	145

Figure 7. Correlation of the number of documents for the various LNP types and therapies they have been applied to

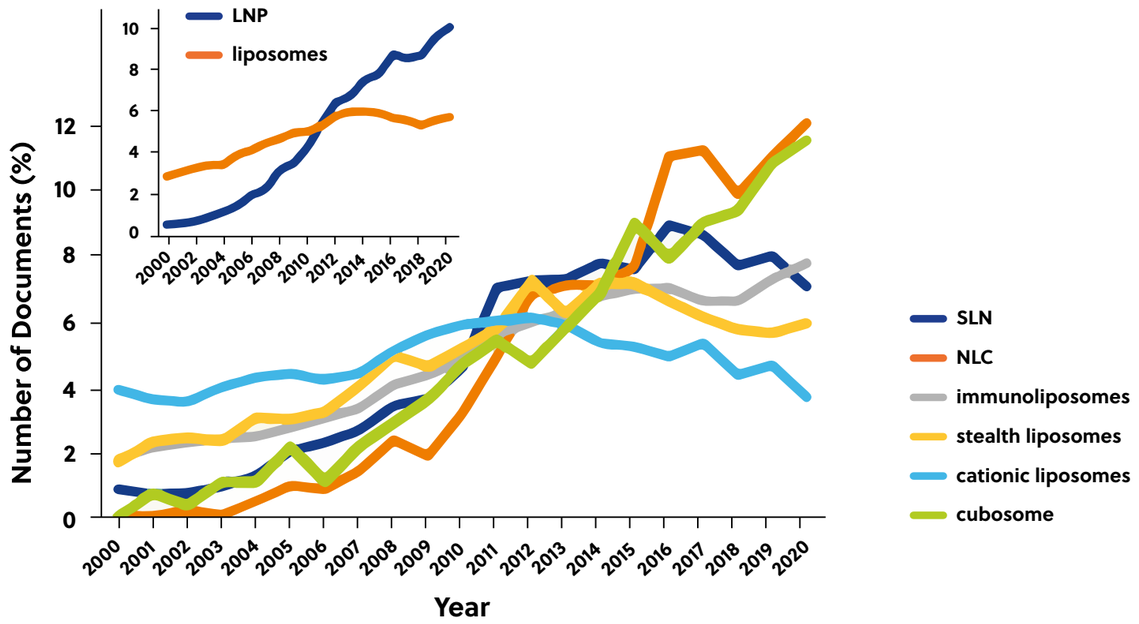


Figure 8. Number of LNP-related documents per year (%) in the CAS Content Collection in the years 2000–2020, with respect to different types of LNPs. The percentages are calculated within the given type. The inset shows the LNP vs liposome documents (%) per year

An emerging new class of drugs is nucleic acid therapeutics, which is showing potential for treating various diseases. The first of these to receive approval is Patisiran (ONPATTRO), a small interfering RNA (siRNA) formulated in LNPs to reduce transthyretin protein formation in the liver for the treatment of hereditary transthyretin-mediated amyloidosis.

Perhaps the most well-known for and recent applications of LNPs is as a delivery vehicle in two approved COVID-19 messenger RNA (mRNA) vaccines developed by Pfizer/BioNTech and Moderna. These vaccines deliver the mRNA encoding the SARS-CoV-2 spike protein into the cytoplasm of host cells, which is then translated and acts as an antigen for the development of an immune response against the virus.

While the use of LNPs is established in the delivery of pharmaceutical drugs, there are many areas where this method is relatively new. The publications discovered in the CAS Content Collection may hint at the future of research and innovation in LNP. We analyzed the applications of LNPs in different industries to uncover insight into emerging trends and summarized the use of LNPs in industries beyond pharmaceutical.

Medical Imaging

Medical imaging plays an essential role in modern precision- and individualized-medicines. LNP provide several opportunities to enhance target resolution and specificity and even act as contrast imaging agents. Various positron emission tomography (PET) and single photo emission computed tomography (SPECT) isotopes have been conjugated to liposomes for use as imaging agents.

Cosmetic Industry

Liposomes have been used in the cosmetic industry since 1986, when C. Dior released a product containing hyaluronic acid in soya lecithin liposomes. Many other cosmetic products have been developed utilizing LNP, including long-lasting perfumes, hair conditioners, and anti-aging skin creams. Nanoemulsions, SLN and NLC are used to carry various active ingredients for the prevention, delay, and treatment of skin aging, including antioxidants, biological growth factors, and retinoids. In sunscreens, NLCs are preferred due to their ability to allow sustained release of photolabile UV absorbers over time.

Nutrition

Nutrition is another area where LNPs are increasingly prominent, where food scientists are using LNPs for the controlled delivery of functional components such as proteins and enzymes, vitamins, and flavors. Recently, the use of SLNs and NLCs in food and dietary supplements has increased, due to advantages of high loading capacities, increased bioavailability, and easier large-scale production. NLC is being used to encapsulate ingredients such as vitamin C, vitamin A, and green tea extract. Bioactive compounds including essential oils, vitamins, and acids have been incorporated into SLN.

Principles for LNP development

Based on the landscape analysis of the LNP-related documents in the CAS Content Collection, we identified several key principles that should be considered when selecting lipid compositions for LNP formulations:

Structure

- Biocompatability of LNP
- Fluidity of the LNP
- Phase state and phase transition temperature of LNP
- Electric charge (zeta potential)
- Size
- Encapsulation efficiency and stability

Application

- Toxicity
- Circulation time
- Phagocytic uptake
- Cargo release

The future for LNPs

Nanotechnology has revealed a new horizon in science, particularly in medicine. Drug formulations, such as LNPs, have been used to therapeutic benefit, bringing impressive progress in modern drug therapy against many diseases. Since the discovery of the first generation liposomes in the 1960s, huge advances in LPNs have improved the effectiveness, selectivity, and biodistribution of drugs, while reducing toxicities and the limitations of conventional drug carrier systems.

As research continues to unlock the potential of personalized medicine, more sophisticated and multifunctional nanocarrier designs are being developed. Adapting nanocarrier designs that are catered to an individual patient's profile can markedly improve the delivery and response to precision therapies, and overcome biological barriers related to age, disease status, and comorbidities.

The development of nanostructured lipid carriers and the ionizable cationic nanoparticles brings further advantages to LNP formulations and enlarges the prospects of their applications. In particular, LNPs hold great promise in genetic medicine where gene editing, vaccine development and immuno-oncology rely on the ability to efficiently deliver nucleic acids into cells.

LNPs are easier to manufacture, less immunogenic, and can carry larger payloads, making them successful and efficient carriers for nucleic acid therapeutics. The use of LNPs as a delivery vector for the COVID-19 mRNA vaccines will likely expand the scope for further research. The success of LNPs in medicine is a significant motivator for further applied research in materials science. The use of LNPs in the controlled synthesis of metal nanoparticles could lead to expanded use in display technologies.

Numerous cosmetics products are already on the market and in areas such as nutrition, nutraceuticals, agrochemistry, and nanoreactors are already exploring their benefits. Furthermore, LNPs may have applications in environmental remediation such as metal detoxification. With a vast application landscape and continued development, LNPs can certainly be recognized as one of the most advantageous and promising areas in modern nanotechnology.

The complete analysis is available in a review article published in *ACS Nano*.

Learn more at cas.org

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