ISSN 1070-3632, Russian Journal of General Chemistry, 2023, Vol. 93, No. 7, pp. 1867–1899. © Pleiades Publishing, Ltd., 2023.

Supramolecular Strategy for the Design of Nanocarriers for Drugs and Natural Bioactives: Current State of the Art (A Review)

L. Ya. Zakharova[a,*], F. I. Maganova[a], K. O. Sinyashin[a], G. A. Gaynanova[a], A. B. Mirgorodskaya[a], E. A. Vasilieva[a], and O. G. Sinyashin[a]

[a] *Arbuzov Institute of Organic and Physical Chemistry, Federal Research Center "Kazan Scientific Center of the Russian Academy of Sciences", Kazan, 420088 Russia*
**e-mail: luciaz@mail.ru*

Received June 20, 2023; revised June 20, 2023; accepted July 6, 2023

Abstract—The review focuses on the lipid based nanocarriers, with special attention paid to natural bioactive payloads. First, micelles and microemulsions are considered as very attractive colloidal nanocontainers that allow for marked improving the solubility of hydrophobic bioactives. Further, liposomal vehicles are reviewed, with both advantages and limitations discussed. Literature assay covers up-to-date information of about last three to five years, although brief background is given on the pioneer works addressing the liposomes and their evolution from bench to bedside. Final part of the review is devoted to the modern modifications of vesicular nanocarriers which can be adapted to specific administration way due to improved targeting properties, permeability, muco-adhesiveness and possibility to cross biological barriers. Therein, such kinds of nanocarriers as transfersomes, niosomes, ethosomes, chitosomes are evaluated; and separate sections focus on the natural based formulations, i.e., phytosomes and invasomes.

Keywords: nanocontainer, liposome, surfactant, emulgel, natural compound, next-generation vesicles

DOI: 10.1134/S1070363223070253

1. INTRODUCTION 1867
2. AMPHIPHILE BASED NANOSYSTEMS: FROM MICELLES TO EMULGELS 1869
3. THE EVOLUTION OF VESICULAR NANOCARRIERS 1874
4. NEXT-GENERATION VESICULAR SYSTEMS 1877
5. CONCLUSIONS 1884

1. INTRODUCTION

One of the key problems of modern medicine and pharmaceutical industry is insufficient effectiveness of pharmacotherapy. This is due to a number of reasons including low drug solubility and bioavailability, side effects, premature elimination, drug self-tapering, etc. Essential part of these shortcomings can be avoided within the framework of nanomedicine approach, assuming the transition from the free drug therapy to the nanoformulated preparations [1–5]. To date, huge information block is accumulated in scientific publications involving numerous types of nanocontainers. They can roughly be classified in two groups, organic (lipid and polymeric carriers) [6, 7] and inorganic (metal oxide, gold, silica, carbon nanoparticles) [8, 9]. Moreover, obvious trend is observed to develop hybrid nanocontainers, e.g., nanoparticles decorated by polymers, silica coated liposome, etc. [10–12]. Further, special classification based on medical goals should be noted, e.g., nanoformulations for the management of cancer [13, 14], neurodegenerative diseases [15, 16], tuberculosis

[17], diabetes [18], etc. One of the key tasks that can be solved by nanomedicine tools is the overcoming the biological barriers. Therefore, nanocarriers are additionally grouped into those specialized for crossing the blood brain barrier (BBB) [16, 19–21], ocular [22] and skin [23] barriers, etc.

Despite the diversity of nanocontainers developed, it is now evident, that research activity is progressively shifted toward biomimetic systems with low toxicity and patient friendly protocols. From this viewpoint, leading positions are steadily occupied by organic nanocontainers composed of amphiphilic building blocks. Such kind of nanocontainers follows the line of biomimetic design and can be obtained within the framework of supramolecular strategy involving noncovalent self-assembly of molecular building blocks. In this context, it should be emphasized that the development of drug delivery systems (nanocontainers, nanocarriers, nanoparticles) is advanced line of researches with interdisciplinary profile, including organic synthetic chemistry, physical and colloidal chemistry, supramolecular, biological and medicinal sciences. Therefore, along with purely applied researches significant efforts are contributed to fundamental studies aimed at the elucidation of mechanisms of interaction of drug/nanocontainer and factors responsible for efficacy of formulated drugs. This can be exemplified by study [24] devoted to the comparison of physicochemical properties of Langmuir monolayers of different compositions, which may provide information on interaction of amphiphilic molecules and their packing characteristics and predict the morphological behavior of nanoparticles.

One of the intensively growing fundamental directions is devoted to the design of self-assembling systems capable of encapsulating the bioactive compounds of different natures [25–27]. Therein, much attention is paid to the supramolecular assemblies based on typical surfactants, which can be considered as simplest dynamic nanocontainers constructed through noncovalent spontaneous aggregation occurring above certain concentration, the so-called critical micelle concentration (cmc). While various benefits are known to ascribe to nonionic surfactants due to their low toxicity, high level of research activity is addressed to cationic surfactants showing high solubilization effect, antimicrobial and membrane tropic activity. Taking into account current interest in biologically derived systems much attention has been received by cationic surfactants bearing natural fragments, metallosurfactants, gemini analogs demonstrating low cmc values, especially those with biodegradable characteristics (containing cleavable ester, amide or carbamate fragments) [28–37]. It was demonstrated that these self-assembling systems are effective micellar nanocontainers and nanoreactors with high solubilization properties, complexation activity toward biopolymers, and antimicrobial effect, including that toward resistant strains. Special line of design of amphiphilic compounds focuses on the conjugates with targeting function, e.g., sugar derivatives, folic acid residues, etc. [38–42].

In the mainstream of nanomedicine strategies are naturally sourced compounds, which are actively used both as building blocks for the fabrication of nanocontainers [43–46] and as phytopharmaceuticals [47–50]. Growing interest in natural bioactives is based on the fact that they practically do not exert side effects. Furthermore, the use of naturally occurring nontoxic building blocks for the development of nanocontainers for plant derived molecules is of special importance [44]. This can be exemplified by the so-called filomicelles [51–53], in particular, those based on PLA-PEG block-copolymers modified with folic acid, which were used for the encapsulation of botulin derivatives to improve cytotoxic activity of triterpene molecules [54].

Further trend should be mentioned is that new modifications rather than principally pioneer types of nanocontainers are currently designed, which is confirmed by numerous subtypes derived from the name “liposome”, e.g., niosomes (vehicles prepared by using nonionic surfactants), transfersomes (ultra-deformable nanovesicles composed of phospholipids, surfactants, and edge activators), ethosomes (contain a high ethanol concentration up to 20–45%), invasomes (composed of phospholipids, ethanol and terpene or mixture of terpenes), vesosomes (vesicles-in-vesicles), cubosomes (liquid crystalline particles), chitosomes (decorated with chitosan), etc. [13, 24, 55–64]. This trend emphasizes the importance and benefits of noncovalent strategies over chemical conjugation techniques, which allowed for essential improving of nanocarrier efficacy, with synthetic time-consuming efforts avoided. The design of such modified nanocarriers makes it possible to solve special therapeutic tasks by tailoring them for particular way of administration or definite disease. Noteworthy, these specific nanocarriers allowed to be further modified by a variety of ligands to introduce additional targeting functions. It should be emphasized that green chemistry/

biomimetic problematics is straightly signified through the name of new generations of nanocarriers, such as phytosomes (made up of individual components from herbal extracts linked to phosphatidylcholine) [16], invasomes (composed of phospholipids, ethanol and terpene or mixture of terpenes), etc. [65].

In our work, supramolecular strategy was developed based on noncovalent modification of nanocarriers with target moiety. For this purpose, composition of lipid nanoparticles was admixed with modifying agents, with further optimization of formulations proceeded by balancing between the efficacy of therapeutic effect and cytotoxicity of preparations. Successful results were achieved in fabrication of lipid nanocontainers modified with cationic surfactants, which provide electrostatic affinity of formulations toward the negatively charged cell membranes. It was documented that positively charged nanocontainers show higher cellular uptake and therapeutic effect. Liposomes noncovalently modified with triphenylphosphonium and imidazolium amphiphilic cations demonstrated essentially improved colocalization with mitochondrion [66–68]. Authors of [64, 69, 70] developed classical liposomes and transfersomes modified with mono- and dicationic surfactants for the delivery of reactivator of acetylcholinesterase (AChE) to the brain. Liposomes, niosomes, microemultions and carbopol gel modified with cationic surfactants, including those with carbamate fragments were tested *in vitro* and *in vivo* to demonstrate increased encapsulation ability, prolonged release and improved therapy activity of anti-inflammatory drugs and natural diterpenoid abietic acid [71–74]. In work [13] chitosomes were modified with antibodies, peptides, amino acid and hyaluronic moieties to improve cytotoxicity toward tumor cells.

Taking into account the above considerations and trends this review is organized as follows. It has covered recent publications on the amphiphile based nanocontainers with special focus on those used for natural pharmaceuticals. Therefore, current state of the art rather than comprehensive analysis of publications was the purpose of this review, with the above trends and biomimetic aspect emphasized.

2. AMPHIPHILE BASED NANOSYSTEMS: FROM MICELLES TO EMULGELS

The main requirements for the development of effective delivery systems are: (1) selection of non-toxic, biocompatible components; (2) the possibility of targeted drug delivery; (3) high drug loading capacity; (4) prolonged release; (5) stimuli-responsive properties (change in pH, temperature, etc.). A significant part of the obtained nanocarriers is formed based on synthetic and natural surfactants. Such nanocontainers are self-organizing supramolecular systems formed through cooperative noncovalent interactions.

2.1. Micelles. The simplest self-organizing systems are micelles, consisting of tens to hundreds of surfactant molecules. Micelle formation is driven by such noncovalent forces as hydrophobic and electrostatic interactions, van der Waals forces, hydrogen bonding. Micellization is the only possible option for system stabilization with a gradual increase in the surfactant concentration. Micelle formation occurs through cooperative binding between surfactant molecules at concentrations above a narrow range called cmc [75, 76]. As a rule, spherical micelles are formed above the cmc, which are rearranged into ellipsoidal and cylindrical micelles as the surfactant concentration increases.

Micelles have several characteristic features:

1) a dynamic nature associated with constant intermolecular exchange between the micellar phase and the bulk solution;

2) unique characteristics of micellar pseudo-phase that has no macroscopic analogue;

3) solubilization of poorly soluble substances;

4) a sharp change in physicochemical properties from the surface to the center of the particle;

5) polymorphic transformations with increasing surfactant concentration.

Due to the presence of a nonpolar core, micelles are capable of solubilizing poorly soluble substances and acting as nanocontainers for drugs and diagnostic agents. This increases their bioavailability and penetration through biological barriers, improves biodistribution, and protects them from potential inactivation in biological environment [77–80]. By varying the hydrophilic-lipophilic balance of surfactants, introducing functional substituents into the molecular structure, adding co-surfactants and modifying additives, it is possible to control the properties of micelles, including their surface charge, size, loading efficiency, and circulation time in the bloodstream. Despite the fact that nonionic surfactants are used in a significant part of the work on micellar drug carriers [81–83], increasing attention is paid to cationic surfactants [39, 84, 85]. These surfactants are particularly

successful in systems for dermal and transdermal drug delivery. The positive charge of the micelle improves its interaction with biological surfaces, increases the solubility of anionic form of loaded drugs, facilitates their penetration through the epidermis and dermis, thereby enhancing the therapeutic effect [86–88]. The range of drugs tested for these purposes in micellar solutions is highly broad and diverse. For instance, anesthetics (lidocaine, procaine [89]), anti-inflammatory agents (meloxicam, indomethacin [90]), anxiolytics (lorazepam [91]), hormones [86, 87], anticancer drugs (methotrexate [92]), plant-derived antioxidants (ferulic acid, curcumin, ascorbic acid and its derivatives), and many others are widely explored. The main issues examined in these studies typically include the investigation of the interaction between surfactants and drugs, the evaluation of drug solubility in micellar solutions, determination of the substrate release rate and its penetration through biological barriers, assessment of the irritating and toxic effects of proposed compositions.

The ability of cationic surfactants to form complexes with DNA facilitates the delivery of genetic material into cells, which allows them to be used as effective non-viral vectors [93–95].

The high antimicrobial activity of cationic surfactants, in some cases exceeding the action of commercial antibiotics, makes them suitable for use as disinfectant solutions, preventing secondary infections during wound healing and anti-inflammatory therapy. It should be noted that cationic surfactants can show both bactericidal and fungicidal activity, including those against resistant strains [96, 97].

In recent years, mixed micelles based on cationic and nonionic surfactants are often used as drug delivery systems. This combination allows maintaining the high efficacy and reducing the toxicity. For instance, binary solutions of cationic carbamate surfactants and Tween 80 are used to improve the solubility of indomethacin and meloxicam [37, 98].

Micelles are easy to prepare and load with a drug, however, they are dynamic systems that do not have a constant composition. They are also characterized by limited solubilization capacity, which reduces the possibility of their practical application.

2.2. Micro- and nanoemulsions. Another type of practically important supramolecular systems based on surfactants are nano- and microemulsions, which are promising nanocarriers for targeted drug delivery and improvement of medicine bioavailability [99–103]. Nano- and microemulsions are emulsions with droplet sizes less than 100 nm. They typically contain three main components: aqueous and oil (hydrocarbon) phases separated by a layer of surfactants, sometimes including co-surfactants. Preparation of nanoemulsions requires energy input to the system, while microemulsions can form spontaneously with the proper selection of component ratio. These systems possess high stability and can solubilize a large amount of drug, facilitating their transport and providing prolonged release. The kinetic stability is a characteristic feature of nanoemulsions, while microemulsions are thermodynamically stable. After preparation, microemulsions maintain their properties and macrohomogeneity if the initial conditions remain unchanged. Nanoemulsions gradually break down over time, but the properties of the dispersed phase do not change upon dilution [104–106].

The features of using these systems as carriers of medicines are associated with their ability to effectively solubilize both lipophilic and hydrophilic compounds. In addition, they can deliver drugs into the body through various routes: orally, parenterally, and topically (local, transdermal delivery) [103, 107, 108]. These properties determine the advantages of nano- and microemulsions over other types of colloidal drug delivery systems.

For pharmaceutical applications, the correct selection of components for nano- and microemulsions is of fundamental importance: they should consist of biocompatible, safe, and hypoallergenic ingredients. Nonionic surfactants are commonly used as stabilizers, as they are compatible with most medicinal drugs, non-aggressive, and unlike ionic surfactants, do not cause skin irritation. Nonionic surfactants are also more resistant to changes in charge and pH of the environment compared to other classes of surfactants. The most common nonionic surfactants are polyoxyethylene sorbitans, polyoxyethylene esters of fatty acids, polyoxyethylene derivatives of castor oil (Cremophor), simple diethylene glycol ethers, and so on. Co-surfactants usually consist of short and medium chain alcohols, as well as polyglycerol derivatives. Components of the oil phase include fatty acids (most commonly oleic acid), complex esters of fatty acids and alcohols, triglycerides with medium chain length, terpenes (such as limonene, menthol, cineole). Recently, natural oils are often used, including olive, cottonseed, flaxseed, coconut, pine, eucalyptus, jojoba oil, and others [109–113].

There are numerous examples of dermal and transdermal use of nano- and microemulsions as carriers for anticancer, antimicrobial, and other drugs. The majority of publications related to such systems are focused on the delivery of nonsteroidal anti-inflammatory drugs, which are highly lipophilic and can cause various side effects [114]. The use of local or transdermal methods of administration of these drugs can reduce the side effects associated with oral administration from the gastrointestinal tract and improve drug tolerability.

A stable microemulsion based on biocompatible components for transdermal delivery of leflunomide and sodium diclofenac was obtained [115]. It was established that the combination of two anti-inflammatory agents improves anti-rheumatic activity compared to a composition containing only one drug. In [116], the properties of a nanoemulsion based on triglycerides, Span 80, and Tween 20 containing ketoprofen were studied. It was found that ketoprofen formulated in such particles penetrates the skin more easily and is better retained in the epidermis and stratum corneum.

In [117], mucoadhesive nanoemulsions containing meloxicam based on Tween 80, castor oil, and ethanol were developed. The optimal composition was characterized by a droplet size of 158.5 nm, a surface potential of –11.2 mV, high encapsulation efficiency (79.2%), prolonged retention on the mucosa, and the absence of toxicity on mouse embryonic fibroblast cell lines. The obtained nanoemulsions are recommended for intranasal administration.

Recently, cationic surfactants have been used to give a positive charge to particles in micro- and nanoemulsions with drugs, which in some cases leads to an increase in drug permeability and prolongation of pharmacological effects, particularly in transdermal delivery, as the upper layer of the skin (epidermis) is negatively charged [118, 119]. The addition of cationic carbamate-containing surfactants to biocompatible nano- and microemulsions based on oleic acid and Tween 80 loaded with indomethacin (0.5 wt %), significantly enhances their therapeutic effect: the response to carrageenan-induced inflammation in rats is approximately three times weaker than in the untreated control group. Moreover, the paw edema completely disappears in 4–5 h, while in the control group, it only decreases by half within 24 h [120].

Using positively charged micro- and nanoemulsions good results were obtained in ophthalmology [121–124]. This is due to the mucoadhesive action of the positively charged particles. For example, cationic surfactants have been used to increase the effectiveness of loading and prolonging the action of a number of anti-inflammatory drugs (diclofenac, ketorolac, flurbiprofen) in contact lenses. It has been found that the concentration of drugs increases with increasing surfactant content, and the release time of the drugs reaches 4–6 days [125].

In summary, nano- and microemulsions are an alternative tool for drug delivery, characterized by nanometer particle size, high penetration, ease of preparation, high stability, and the ability to deliver hydrophilic and lipophilic drugs. They can serve as carriers for a wide range of drugs: anticancer, anti-inflammatory, antipyretic, antifungal, and so on. The main vector of research development of these systems is aimed at increasing the bioavailability and reducing the toxicity of micro- and nanoemulsions, optimizing their composition, and reducing surfactant concentration since their excess can lead to skin problems such as contact dermatitis, erythema, and skin injuries. Ensuring the stability of systems during long-term storage and contact with biological media remains an acute problem. An important aspect is also the search for mechanisms that provide controlled drug release from the carrier. In addition, there is an increasing number of studies with *in vivo* comprehensive testing of delivery systems before clinical trials.

2.3. Emulgels. An important factor that affects the effectiveness of the use of medicinal products, especially in topical applications, is their viscosity. Viscous systems are easy to apply and remain on the surface, providing stable and prolonged release of the active ingredient. Therefore, ointment formulations containing large amount of oily bases such as vaseline, beeswax, and vegetable oils are widely used [126, 127]. However, they have a thick and greasy consistency and often excessively slow down the release of hydrophobic substrates. Another viscous medicinal composition that can maintain a shape, elasticity, and plasticity is gels [128, 139]. Gels are structured systems typically composed of high-molecular-weight and low-molecular-weight substances. They form continuous three-dimensional macromolecular network, the voids of which are filled with a low-molecular-weight solvent. Typical gel-forming agents consist of weakly crosslinked synthetic and natural polymers containing residues of polyalcohols and polysaccharides (polyvinyl alcohol, carbopol, carrageenan, chitosan, gelatin, etc.). As a low-molecular-weight dispersed phase can be used

water (hydrogels), lower mono- and oligosaccharides, and hydrocarbons (lyogels). Gels are considered to be a more promising medicinal form compared to ointments. They are easily prepared, quickly and uniformly distributed, do not clog skin pores and normalize pH. Both hydrophilic and hydrophobic medicinal substances can be incorporated into gels.

Emulgels are another viscous form for topical medication [130–133]. They composed of various forms of nanocontainers loaded with biologically active substance embedded into a gel. Niosomal solutions, nano- and microemulsions may serve as the basis for emulgel formation. Currently, these systems are actively developed for delivering a wide range of medicinal substances, expanding of their applicability and therapeutic range. This can be illustrated by a number of examples.

A niosomal gel containing febuxostat demonstrated significantly higher anti-gout activity compared to the preparation in tablet form, while also showing high stability during storage at different temperature [134]. In the study [135], the effectiveness of transdermal delivery of a niosomal gel loaded with the antihypertensive agent lacidipine was demonstrated. *In vivo* experiments testified, that the reduction of arterial pressure in rats was gradual and prolonged, unlike with the oral administration of its dispersion form. Histopathological tests did not reveal any irritant effect on the skin. A gel composition based on a microemulsion loaded with repaglinide was proposed as new alternative medicinal form for the effective treatment of type 2 diabetes [136]. The results of the glucose tolerance test allowed us to identify a significant advantage of transdermal delivery of this formulation over oral administration of suspension of repaglinide.

In [137], nanoemulsions loaded with the antimuscarinic agent oxybutynin were incorporated into gels based on carboxymethylcellulose. These formulations demonstrated high penetration effect through the skin, which can recommend them as promising drug delivery system for the treatment of hyperhidrosis, allowing to reduce systemic side effects. The antihistamine drug ebastine in the form of emulgels based on carbopol was well tolerated and safe in the treatment of urticaria [138].

A variety of studies focus on the properties and therapeutic effects of emulgel formulations loaded with nonsteroidal anti-inflammatory drugs such as indomethacin [139], naproxen [140], etoricoxib [141], ketoprofen [142], meloxicam [143], and others. Benefits and effectiveness of these compositions is supported by the wide range of commercial gels used in medical practice, such as Ketonal gel, Fastum gel, Voltaren emulgel, etc.

Literature analysis allows us to conclude that transdermal administration of the combined emulsion/gel formulations provide essential improvement of key properties, including increased composition stability and extended skin retention time, uniform and prolonged drug release, improved penetration through skin and increased drug loading efficiency. Nevertheless, there are still some limitations related to the lack of a standard for fabrication of emulgels, which requires optimizing their composition and technological parameters, e.g., the mixing speed in the homogenizer. In addition, gel-forming agents may be sensitive to fluctuations in pH and temperature, which can disrupt the gel structure and cause leaching of chemical substances. However, these limitations do not outweigh the positive characteristics of emulgels, which offer broad prospects for their therapeutic use.

2.4. Nanocontainers for biologically active substances of plant origin. In recent years, great attention has been paid to the development and use of biocompatible nanocarriers loaded with plant-derived drugs. Such drugs include essential oils, resins, plant extracts containing terpenes, polyphenols, glycosides, flavonoids, and other active substances that have primarily anticancer, antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties [144–146].

This can be exemplified by recent studies. The development of an emulgel for the treatment of skin infections caused by bacteria using anise essential oil as an active ingredient is reported [147]. The emulgel was formulated using Span 80, Tween 80, and Carbopol 940; its properties were evaluated based on various parameters such as viscosity, pH, the efficiency of anise oil encapsulation, and *in vitro* release profile. The obtained emulgel was stable, showed high encapsulation efficiency, and was active against *Escherichia coli* (*E. coli*). In addition, the emulgel was biocompatible with human keratinocytes, which is a good indicator of its safety for topical use. The emulgel exhibited much stronger antibacterial and anticancer properties, due to the small size of its particles and the large surface area, which improved the interaction between the emulgel and bacteria.

Significant antimicrobial activity against *E. coli* and *Staphylococcus aureus* has been demonstrated

for nanoemulsions formed on the basis of Tween 80, polyglycerin myristate, and carbopol, loaded with essential oils obtained from cumin [148]. In [149], nanoemulgels containing essential oils of clove and cinnamon were presented, which showed bactericidal and fungicidal activity. The high mucoadhesive action of the obtained compositions allowed them to be proposed for combating infections of the oral cavity.

Natural biologically active substances are included in the wound-healing compositions that prevent acute diseases associated with the antibiotic-resistant infections. The review [150] addresses the application of flavonoids for these purposes, which have wound-healing properties due to their anti-inflammatory and antioxidant effects, angiogenesis, and reepithelialization. Among various delivery systems designed for flavonoids, significant attention is paid to hydrogels and emulgels, which enhance the bioavailability and effectiveness of the active substance [150, 151].

The wound healing properties are also described in [74], for emulgels based on biocompatible components and modified with the addition of cationic carbamate surfactants. These formulations loaded with abietic acid, active component of pine resin, exhibit high antioxidant activity and promote the healing of a cutaneous wound on the back of rats, reducing the force required to break the wound by almost half.

It should be noted the high therapeutic potential of other nanosized formulations containing biologically active substances derived from pine trees. In [152], a stable nanoemulsion was prepared, based on nonionic surfactants and ethanol, containing 5% pine oil as the oil phase; and its AChE activity was tested. It was found that the system possesses dose-dependent properties, which reach a maximum at nanoemulsion concentration of 0.10%. In this case, the inhibitory activity toward AChE was approximately 95%, which suggests possible therapeutic value for the treatment of Alzheimer's disease.

Nanoemulsions containing essential oil obtained from cedar cones (*P. koraiensis*) were developed [153]. This oil, rich in terpenoids (primarily limonene and pinenes), exhibits various types of physiological activity, including inhibiting the proliferation of MGC-803 cells and accelerating cellular apoptosis. When tested for antitumor activity on mice with MGC-803 tumors (stomach cancer), the formulated systems were found to increase the bioavailability of cedar oil and exert a greater therapeutic effect than free oil at the same concentration.

Terpenes included in nanosized carriers not only exhibit therapeutic effects but also act as enhancers facilitating the overcoming of skin barriers. They are capable of disrupting the tightly packed stratum corneum enhancing the diffusion of the drug through the cell membrane, as well as create ion channels within the dermal layer [154]. These properties of terpenes have been realized in several studies. For example, a higher anticancer effect of doxorubicin loaded into nanoemulsions was achieved by introducing d-limonene [155]. In [156], calamus essential oil containing more than 50% 1,8-cineole was added to microemulsions to improve the transdermal delivery of the anti-inflammatory drug flurbiprofen. The terpene alcohol borneol, extracted from Siberian fir, is often used in combination with other drugs to reduce their dosage, enhance therapeutic effects, and reduce side effects [157, 158]. It has been shown that borneol loaded nanoemulsions acts as a chemotherapeutic sensitizer for antitumor therapy, exhibiting synergistic effects with the anticancer drug gefitinib, allowing for successful combined therapy in the treatment of lung cancer [159]. Terpenes are capable of enhancing the effects not only of synthetic drugs but also of natural bioactive compounds. For example, nanoemulsions containing the natural antioxidant curcumin, modified with terpene compounds such as eucalyptol and pinene, facilitate its penetration through the superficial layers of the skin and improve system stability [160].

Curcumin deserves special attention; this compound belongs to natural polyphenols and is widely used for therapeutic purposes due to its antioxidant, anti-inflammatory, and anticancer activities. Nanoemulsions, microemulsions, and emulgels are widely used to increase the solubility of curcumin in physiological environments, to enhance its bioavailability and stability. This issue is elucidated in a significant number of publications, e.g. [161–163].

Thus, the analysis of modern literature shows that the encapsulation of biologically active natural compounds into nanosized carriers and using natural components for their fabrication is one of the promising trends in the pharmacology and medicine, allowing the development of effective, low toxic systems capable of overcoming physiological barriers and exerting improved therapeutic effects.

3. THE EVOLUTION OF VESICULAR NANOCARRIERS

3.1. Liposomes: from the lab bench to clinical practice. Traditional liposomes, first described in the early 1960s by Alec D. Bangham [164], became the platform for a whole cascade (several dozen) of nanocontainers containing "some" in their name (cerasomes, porphysomes, niosomes, transfersomes, ethosomes, glycerosomes, etc.) [57, 165]. Due to the unique bilayer structure surrounding water pool, liposomes can encapsulate both hydrophobic and hydrophilic molecules, which makes them versatile nanocarriers for a wide range of pharmaceutical and diagnostic agents [5, 166, 167]. Stability, targeted delivery, toxicity, solubility, and biocompatibility of substrate can be influenced by encapsulating it within liposomes [168, 169]. The building blocks of liposomes, lipids, are biodegradable, making them safe for *in vivo* use. At the same time liposomes have certain limitations, including premature substrate release, uptake by the reticuloendothelial system, tendency to aggregate and fuse, and challenges in scaling up the production of liposomal formulations [11, 170].

In the current stage of vesicular carrier evolution, classical liposomes are primarily used as a base that can be modified using covalent or noncovalent methods [171, 172]. Early attempts to use liposomes as drug carriers were limited by their instability and rapid clearance from the bloodstream. In the 1980s, more stable liposomal formulations were developed by incorporating cholesterol into the membrane, which improved their stability and slowed down the release of encapsulated compounds [173]. Cholesterol lowers the phase transition temperature, increases membrane density, and participates in the formation of lipid fragments known as rafts or domains [174–176]. Using liposomes based on 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) and the hydrophilic dye sulforhodamine B as an example, it was shown that cholesterol slows down the release rate at a concentration of 5 mol % or higher [177]. The release kinetics of sulforhodamine B has a two-phase character: non-Fickian diffusion during the initial period (0–10 h) and Fickian diffusion between 10 and 48 h. For sphingomyelin-based liposomes, increasing the cholesterol content in the membrane led to enhanced loading efficiency and reduced release rate of ibuprofen, most likely due to hydrophobic interactions between ibuprofen and cholesterol [178].

The next step in modifying traditional liposomes was associated with their rapid clearance from the bloodstream, and it involved PEGylation of liposomes, i.e., the formation of a protective coating on the surface using PEG chains [179–181]. The modification of liposomes with PEG-conjugated lipids, which prevents their recognition by macrophages and thereby ensures prolonged circulation in the bloodstream, was successfully implemented in the development of the drug Doxil®. However, later it turned out that such modification is not a "magic bullet" and has, as a reverse side, a set of problems known as the PEG dilemma, which involves difficulty in cellular uptake and subsequent escape from endosomes [182, 183]. To address this issue, PEG lipids with cleavable fragments or having a lower molecular weight, as well as the addition of other polymers that do not elicit an immune response, have been proposed [184–186].

The number of published papers on liposomal topic is huge, but the number of products after clinical trials is orders of magnitude lower [187–189]. Doxil®, a PEGylated liposomal doxorubicin, was the first liposomal drug to receive FDA approval (Table 1). However, after 1995, there was no rapid growth in the number of approved nanoparticle-based drugs [190–191], since the way of drug formulation from the lab bench to bedside requires significant time and financial investments. The most challenging aspect is reproducing successful results of *in vivo* experiments involving laboratory animals during clinical trials. Nevertheless, the search for new formulations using nanocarriers allows for the establishment of a fundamental basis for the development of this pharmacy field.

As seen from the information gathered in Table 1, the vast majority of commercial liposomal products are aimed at the treatment of oncological diseases [192]. However, there are examples of therapy of fungal infections. Most successful liposomal drugs are administered intravenously, which is due to the aggressive environment of the gastrointestinal tract. Basically, the commercial product is available as a ready suspension or lyophilized form. Myocet and Marqibo are kits consisting of three vials containing the active pharmaceutical ingredient, liposome dispersion, and a buffer solution for pH adjustment, and the preparation of the final composition requires the use of a water bath and constant stirring [165].

3.2. From the first generations of liposomes to theranostics and hybrid carriers. Liposomes are a

Table 1. Examples of liposomal products approved by FDA [165, 187–189][a]

Product name	API	Approved year	Lipid composition	Indication
Doxil	Doxorubicin hydrochloride	1995	HSPC, Chol, DSPE–PEG2000	Ovarian cancer, Kaposi's sarcoma, myeloid melanoma, breast cancer
DaunoXome	Daunorubicin	1996	DSPC, Chol	Kaposi's sarcoma
AmBisome	Amphotericin B	1997	HSPC, DSPG, Chol	Fungal infection
Depocyte	Cytarabine	1999	DOPC, DPPG, Chol, triolein	Lymphomatous meningitis
Visudyne	Verteporfin	2000	EPG, DMPC	Ocular histoplasmosis, age-related mascular degeneration, pathologic myopia
Myocet	Doxorubicin hydrochloride	2000	EPC, Chol	Breast cancer
DepoDur	Morphine	2004	DOPC, DPPG, Chol, triolein	Postoperative pain
Marqibo	Vincristine sulfate	2012	Egg sphingomyelin, Chol	Leukemia
Vyxeos	Daunorubicin, cytarabine	2017	DSPC, DSPG, Chol	Leukemia
Onivyde	Irinotecan hydrochloride trihydrate	2015	DSPC, DSPE-PEG2000 Carboxylic Acid, Chol	Pancreatic adenocarcinoma
Shingrix	Varicella-zoster virus, glycoprotein E	2018	DOPC, Chol	Against shingles, post-herpetic neuralgia
Arikayce	Amikacin sulfate	2018	DPPC, Chol	Lung disease

[a] API—active pharmaceutical ingredient; HSPC—L-α-phosphatidylcholine, hydrogenated (soybean); EPC—egg phosphatidylcholine; EPG—egg phosphatidylglycerol; Chol—cholesterol; DSPC—1,2-distearoyl-sn-glycero-3-phosphocholine; DOPC—1,2-dioleoyl-sn-glycero-3-phosphocholine; DMPC—1,2-dimyristoyl-sn-glycero-3-phosphocholine; DPPC—1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine; DSPG—1,2-distearoyl-sn-glycero-3-phosphoglycerol; DPPG—1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol; DSPE–PEG2000 Amine—1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[amino(polyethylene glycol)-2000] (ammonium salt); DSPE-PEG2000 Carboxylic Acid—1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[carboxy(polyethylene glycol)-2000] (sodium salt).

promising platform for theranostics since they allow encapsulating a drug within a nanocarrier regardless of its nature and conjugating of diagnostic or targeting ligands to the surface [193–195]. This makes it possible to target the therapeutic agent to the affected tissue while providing real-time visualization of drug distribution and accumulation (Fig. 1). Additionally, liposomes address the issue of the lipophilic nature (low water solubility) of most photosensitizers and are suitable for photodynamic therapy [196–197].

For instance, a multifunctional porphyrin dendrimer was developed [198], which can be incorporated into a liposomal platform for nanoparticle visualization using fluorescence microscopy and magnetic resonance imaging (MRI), followed by photodynamic therapy. Porphysomes based on porphyrin from crude oil, capable of remote laser-triggered destruction at a wavelength of 405 nm and doxorubicin release, were obtained [199]. Liposomes with surface-attached antibodies for targeting were loaded with curcumin as a therapeutic agent and carbon dots as a contrast molecule [200].

Another actively developing trend is the design of hybrid nanocarriers [201, 202]. Cerasomes, a relatively new type of vesicular nanoparticles, combine the advantages of a lipid platform with the stability of inorganic silica nanoparticles [11, 203–205]. Cerasomes are formed from lipids with triethoxysilane head group capable of self-assembly into vesicular structures, followed by polymerization through hydrolysis of ethoxysilyl groups under acidic conditions. Encapsulation of substrates in cerasomes promotes their sustained release and enhances their activity. Cerasomes modified with nonionic surfactant Tween 80 were loaded with paclitaxel for the treatment of T98G glioblastoma [10]. It

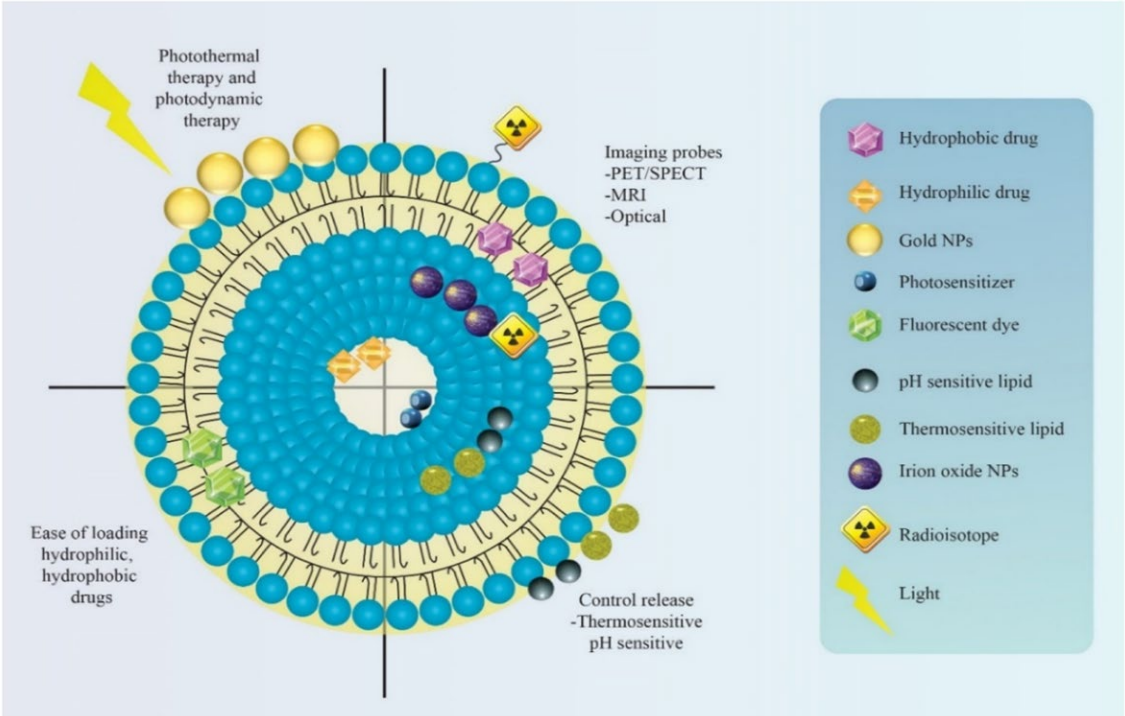

Fig. 1. Schematic representation of the advantages of the liposomal platform for theranostics [194].

was shown that encapsulation of paclitaxel in cerasomes increased its cytotoxic effect by 36 times compared with the free drug. An electrochemical biosensor for cholesterol detection was developed based on cerasomes and graphene quantum dots [206]. The soft layer-by-layer self-assembly method provided good biocompatibility to maintain the biological activity of cholesterol oxidase, while the nanocarrier facilitated more efficient electron transport between the enzyme and the electrode. A novel liposomal nanocomposite was fabricated by self-assembly of cerasomes and gold nanoparticles stabilized with ionic liquid [207]. Immobilized on a stable three-dimensional lipid bilayer membrane, the enzyme demonstrated enhanced electrocatalytic activity toward hydrogen peroxide and nitrite.

Cerasomes are also used for theranostics [208–210]. For instance, highly stable cerasomal perfluorocarbon nanodroplets modified with a targeting peptide for co-delivery of oxygen and doxorubicin have been developed [208]. High-intensity focused ultrasound was utilized to trigger the simultaneous release of doxorubicin and oxygen during chemo-hyperthermia therapy, resulting in complete tumor destruction without relapse or metastasis. Targeted cerasomes with hyaluronic acid were loaded with rosuvastatin for the treatment of atherosclerotic plaques [209], and additional encapsulation of the contrast agent gadodiamide (Omniscan) improved MRI imaging of pathological elements.

3.3. Liposomal forms of natural bioactivities. Another important direction in liposome researches is the encapsulation of natural compounds [211–215]. Experimental data have been reported on the encapsulation in liposomes of thymoquinone for the treatment of dry eye disease [216]; caffeic acid for the treatment of Alzheimer's disease [217]; basil essential oil as an antibacterial agent in nanofiber composition [218]; betulinic acid for the treatment of colorectal cancer [219]; carvacrol and thymol for the treatment of *Candida* fungal infections [220]; spirulina extract as an antioxidant [221].

Curcumin and resveratrol have become classic substrates in the field of using nanocarriers for encapsulating natural compounds and are often used as standards when comparing different delivery systems. In [222], it was shown that curcumin loaded into liposomes can act as both a photosensitizer and a therapeutic agent with enhanced selectivity toward

melanoma (MugMel2) and squamous cell carcinoma (SCC-25) compared with healthy cell lines. Cationic deformable liposomes demonstrated effective penetration of curcumin through the skin and inhibited the growth of *Staphylococcus aureus* and *Streptococcus pyogenes* [223]. A liposomal combination of curcumin and tetrandrine (a dibenzylisoquinoline alkaloid extracted from the Stephania tetrandra plant) showed increased cytotoxicity toward MDA-MB-231 breast cancer cells compared with individual natural compounds [224]. A mixture of curcumin and orientin in a cationic liposomal nanocomposition, consisting of two types of lipids (DOTAP:POPC), demonstrated a synergistic effect against glioblastoma [225]. Among the four natural compounds studied, acteoside had the highest activity in liposomes against the T98G cell line, with an IC_{50} value of 2.9 μM after 24 h of incubation.

Cationic liposomal formulation of resveratrol demonstrated improved cytotoxicity toward human hepatocellular carcinoma cells (HepG2), enhanced internalization efficiency, and favorable pharmacokinetic parameters [226]. In [227], liposomal forms of resveratrol and epicatechin were developed and integrated into chitosan-based hydrogels for the treatment of vaginal infections. These hydrogels demonstrated the ability for prolonged release of natural compounds for up to 8 h. Liposomes containing epirubicin and resveratrol showed the ability to penetrate through the blood-brain barrier and had therapeutic effects against glioma [228].

Propolis has shown anti-inflammatory, antimicrobial, and antioxidant effects. Propolis extract was loaded into liposomes based on soy phosphatidylcholine and cholesterol. The phosphatidylcholine-to-cholesterol mass ratio of 8 : 1 was found to be optimal in terms of size (275.9 nm) and encapsulation efficiency (66.9%) [229]. The antiviral potential of Egyptian propolis components was demonstrated in [230]. According to molecular docking results, propolis components demonstrated high binding affinity to the 3-CL protease of SARS-CoV. Inhibitory effects on COVID-19 viral replication were significantly enhanced by encapsulating propolis extract in liposomes and were comparable to the inhibitory effect of the antiviral drug remdesivir. An effective formulation for local application in the treatment of wounds using liposomal compositions containing propolis was developed [231]. The obtained liposomes remained stable for 3 months at 4°C. Statistically significant enhancement of propolis-mediated apoptosis was observed in head and neck squamous cell carcinoma cell lines (Hep-2) through its encapsulation in liposomes [232].

Polyphenols from *Abies sibirica L.* purified extract, known for their antioxidant, anti-inflammatory, and hepatoprotective properties, were incorporated into multilamellar liposomes with an average size in the micrometer range [233]. The influence of chemical structure, octanol/water partition coefficient, and Henry's law constant on the encapsulation and release of monoterpenes (eucalyptol, pulegone, α-terpineol, and thymol) and phenylpropenes (estragole and isoeugenol) was studied for nanocarriers such as "drug-in-cyclodextrin-in-liposome" [234]. It is interesting to note the successful attempts by the authors [235] to obtain complexes of organometallic compounds with natural medicinal agents extracted from ginger root (6-gingerol and 6-gingerdione). The uptake of the synthesized complex encapsulated in liposomes by cancer cells increased by 20 times.

Thus, liposomes are nanocarriers that address the issues of low bioavailability of natural compounds and can reveal their potential for the treatment of a range of diseases, including oncological, neurodegenerative, viral, and fungal. Researchers' efforts in this stage are focused on exploring new types of nanocarriers through diverse modifications of the liposomal platform.

4. NEXT-GENERATION VESICULAR SYSTEMS

This chapter focuses on next-generation vesicular systems, their characteristics, advantages, and ability to encapsulate various classes of therapeutic components. The number of publications on new nanocarriers is rapidly increasing due to the significant advantages of nanoformulations compared with traditional drug forms. As mentioned above, lipid-based drug delivery systems, primarily liposomes, have numerous attractive properties such as biocompatibility, ease of preparation, tissue/cellular specificity, scalability, low toxicity, targeted delivery, prevention of macrophage uptake, and sustained release of loaded substances. Although essential disadvantages typical for classical liposomal formulation were eliminated, some limitations still remain that need to be avoided: (1) phospholipid oxidation followed by loss of stability; (2) rapid systemic clearance; (3) aggregation; (4) limited penetration through biological barriers.

Modification of liposomes with various amphiphilic and polymeric compounds allows minimizing the

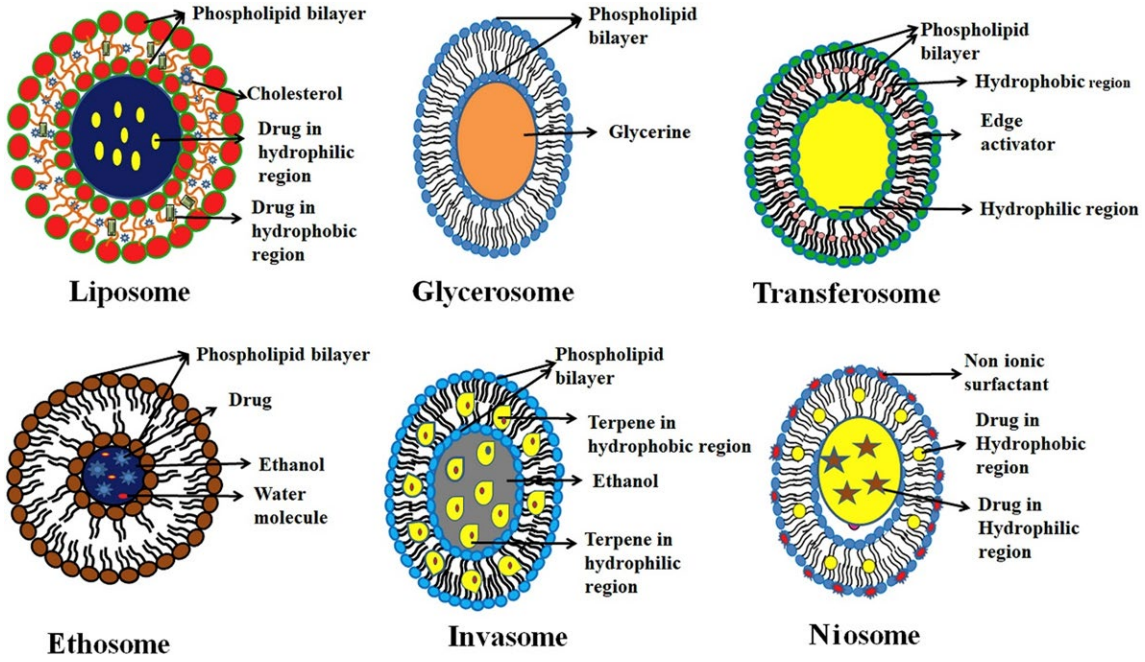

Fig. 2. Some representatives of next-generation lipid vesicles [58] (reproduced with permission, Elsevier, Copyright 2011).

listed disadvantages of liposomes and facilitates the construction of new generations of lipid delivery systems. Over the past five years, the number of publications on the development, characterization, and practical application of next-generation vesicular carriers (niosomes, invasomes, transfersomes, chitosomes, ethosomes, phytosomes, etc.) has increased significantly [236]. However, with the development of science and medicine, the requirements for therapeutic carrier systems become stricter, focusing on improving stability, penetration ability, storage time [237], principles of patient convenience, and low toxicity. These criteria define the modern design lines of lipid carriers, among which the following should be noted:

1) Delivery of pharmaceutical agents across biological barriers such as the skin, mucous membranes, and the BBB. Overcoming the BBB is one of the key challenges in the development of lipid nanocarriers and is actively discussed in the literature [237]. Drug delivery to the brain is a separate major area of research as the BBB blocks access to the brain for over 95% of existing drugs;

2) Enhancing the biocompatibility of therapeutic molecules. Most existing drugs or bioactive substances are poorly water-soluble compounds. Poor solubility, and consequently low bioavailability of promising active pharmaceutical ingredients is a serious obstacle to promote commercialization of nanoindustry developments;

3) Optimization of liposomal nanocarriers for non-invasive routes of administration such as transdermal and intranasal, since the traditional administration of drugs (oral and intravenous) is often limited by a large number of side effects;

4) Protection of drugs from the immune system and rapid clearance from the body;

5) Focus on therapy using natural based drugs, which have low toxicity, fewer side effects, and good therapeutic potential. This trend is clearly apparent in the case of serious diseases such as cancer, neurodegenerative and cardiovascular diseases.

New modifications of vesicular systems allow minimizing disadvantages, imparting desired properties, targeting, and thus increasing the therapeutic efficacy [236, 238]. Some representatives of the next-generation lipid vesicles are shown in Fig. 2.

4.1. Niosomes. Niosomes are vesicular nanocarriers, synthetic analogues of liposomes, composed of cholesterol and nonionic surfactants [237]. Nonionic surfactants such as Tween, Span, Brij and their combinations are commonly used. The first mention of niosomes were

associated with well-known cosmetic companies L'Oreal (1975) and Lancome (1987) [239, 240]. The enormous potential of niosomes for dermal/transdermal applications [237, 241, 242] and in biomedicine are highlighted in recent studies. Nonionic surfactants with a larger radius of curvature act as edge activators, imparting flexibility/deformability to the carrier [243, 244]. The acquired deformability gives niosomes the ability to overcome biological barriers and enhances their penetration capability in transdermal therapy [245]. The authors suggest that a possible mechanism is related to the reduction of water loss and, consequently, hydration of the stratum corneum and disruption of the cellular structure. An alternative mechanism may be achieved through an increase in the activity gradient of the drug. Additional advantages of niosomal drug formulations can be obtained through subsequent functionalization with polymers and targeting agents, including PEGylation, antibody decoration [246], and modification with cationic surfactants [73]. The application of niosomes for diabetes, tumor, hypertension, skin disorder, and inflammatory process treatment, as well as for anesthesia is described [237, 247–249]. Niosomes are being actively developed for dermal/transdermal, parenteral and oral drug administration [250]. It is reported that a Tween 80/cholesterol niosomes were developed for encapsulating the antidiabetic drugs glipizide and metformin [251]. Niosomes based on Span 40 and Span 60, containing insulin, were vaginally administered to Wistar rats with alloxan-induced diabetes. A decrease in blood glucose levels and an increased bioavailability of insulin compared with subcutaneous administration have been shown [252]. Oral administration of niosomes based on nonionic surfactants Span/Tween and cholesterol, containing carvedilol, was described. Component concentrations had a significant effect on the size and stability of nanovesicles [247]. Niosomes based on Span 60 and cholesterol with the addition of surfactants Cremophor and Solutol were developed using thin film hydration and microfluidic techniques to enhance the bioavailability of the antihistamine drug cinnarizine [253]. An increase in the monodispersity of samples, the efficiency of encapsulation, and a decrease in the rate of drug release were achieved using microfluidic technology. Span 80/cholesterol niosomes were used for transdermal delivery of anesthesia drug propofol [254]. Improved *in vivo* bioavailability of the niosomal propofol was demonstrated compared with a control gel formulation of propofol. Modification with nonionic surfactants allows overcoming the limitations of liposomes associated with large-scale production, sterilization, and chemical stability [255].

Scaling up of liposomal and niosomal formulations of caffeine and spironolactone was performed [256]. Using a membrane contactor, the volume of liposomal and niosomal formulations were increased by 25 and 50 times, respectively, with the encapsulation efficiency and size remained the same as in the case of a syringe device. It is possible to impart a positive charge to niosomes by introducing a small amount of charged molecules into the composition [257, 258]. This can improve their ability to pass through biological barriers (skin, mucous membranes), increase stability, and enhance cellular uptake [73, 259]. For example, modification of Tween 80/cholesterol niosomes with cationic carbamate-containing surfactants and cetyltrimethylammonium bromide increased their ζ-potential up to 60 mV and enhanced the water solubility of the anti-inflammatory drug indomethacin by 20 times [73]. Abtahi et al. reported that a novel composition of cationic niosomes Tween 60/Tween 80/cholesterol/lysine containing curcumin was effective *in vitro* and *in vivo* [257]. The transfection efficiency of retinal pigment epithelia 19 cells and rat primary embryonic cerebral cortex cells was increased by modification with cationic lipids [260].

It should be noted that cholesterol cannot form a bilayer structure but can act as a lipid additive that regulates the structure, flexibility, fluidity, and phase state of the membrane. The amphiphilic nature of the components makes niosomes efficient carriers for encapsulating both lipophilic and hydrophilic molecules. The properties of niosomes depend on the structure and quantity of surfactants, the concentration of cholesterol/drug, temperature, etc. Therefore, the main advantages of niosomes are biodegradability, low immunogenicity/toxicity, and high stability. Niosomes are less light-sensitive and more stable at room temperature compared with liposomes. Controlled composition and size allow us to optimize them for different drug delivery routes [255, 261]. Additionally, niosomes are more cost-effective than liposomes.

4.2. Chitosomes. Chitosan is a natural polysaccharide widely used for the development of drug delivery systems due to its low toxicity, high biodegradability, and biocompatibility [262–264]. Chitosan is often applied in order to give mucoadhesive properties to nanocarriers. In case of liposomes, the formed systems

are commonly called chitosomes. An increase in the stability, a sustained release of drugs and their increased penetration through biological barriers, especially mucous membranes, is achieved by coating liposomes with chitosan or its derivatives. The interaction between liposomes and chitosan mainly occurs by an electrostatic mechanism due to the negatively charged head groups of phospholipids and the quaternized amino groups of chitosan [265]. The characteristics of chitosan (molecular weight, structure, concentration, modification) and lipids (structure, concentration), as well as external conditions (temperature, pH, ionic strength), play a crucial role in the formation of chitosomes [266]. The potential application of chitosomes as nanocarriers for drugs and bioactive natural compounds for transdermal and intranasal delivery has been investigated [263, 267, 268]. A key aspect of these investigations was the comparison of chitosomes with conventional liposomes.

Despite significant advantages provided by chitosomes, the low solubility of unmodified chitosan and the uncontrolled release of encapsulated substrates should be noted as disadvantages. Thereby the development of chitosan derivatives by introducing carboxylate, thiol, and arginine groups, as well as the preparation of quaternized amphiphilic derivatives, is of great importance [63, 264, 269]. The three-dimensional network through electrostatic cross-linking of quaternized amino groups of chitosan with polyanions (alginates, tripolyphosphates, citrates, etc.) is a solution to the problem of drug release control [264]. The main challenges that limit the widespread use of chitosomes in medicine, cosmetics, and the food industry are associated with requirements to strictly comply with regulatory standard and to create green technological lines [264]. In this regard, the use of 3D technologies and 4D printing open up vast opportunities for scaling up production. This will make it possible the transition from traditional scaled reproduction of composite materials to the creation of smart systems with specified properties.

4.3. Transfersomes. Transfersomes are lipid vesicular systems that were proposed by Gregor Cevc in 1991 [270]. Phosphatidylcholine, a major component of cell membranes, is widely used in transfersomes due to its high skin tolerability and compatibility. The second main component of transfersomes is nonionic surfactants such as sodium cholate/deoxycholate, Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80, oleic acid, and potassium glycyrrhizinate. These surfactants integrate into the vesicular bilayer and disorder them, thereby providing variable morphology of nanoparticles [271]. It is necessary to strictly maintain the ratio between phospholipids and edge activators to impart elasticity to the systems [272]. Typically, the concentration of nonionic surfactants in the formulation is from 4 to 20%. The destruction of vesicles and the formation of mixed micelles can occur at higher concentrations of nonionic surfactant [273]. The surfactant structure affects the penetration ability of transfersomes, and an increase in the content of nonionic surfactants reduces the encapsulation efficiency [273]. Deformability allows transfersomes to reduce their diameter by several times and penetrate through the pores of the epidermis. This is their main advantage in dermal/transdermal drug administration compared with traditional liposomes (Fig. 3) [271]. The modified transfersomes based on soy phosphatidylcholine, Tween 20, and cationic pyrrolidinium surfactants were developed for transdermal delivery of acetylcholinesterase reactivator, pralidoxime chloride (2-PAM) [64]. It was shown that transfersomes can increase the level of reactivated AChE *in vivo* up to 23% compared to free 2-PAM, and improve the rat survival from 55 to 90%. The same group of authors demonstrated that encapsulation of the fungicide carboxin in transfersomes protects it from light-induced degradation, increases its water solubility up to 7 times, and enhances penetration through the potato peel [274]. In [275], a dry transfersomal gel was developed, which increased the bioavailability of felodipine by 1.7 times in rabbits compared with commercial tablets (Plendil). Omar et al. developed an optimal composition of nanotransfersomes containing the migraine drug sumatriptan. An increased bioavailability of the formulated sumatriptan by 4.09 times compared with the oral solution was shown in pharmacokinetic studies [276].

Currently, the use of transfersomes in combination with physical methods such as iontophoresis, electroporation, and microneedles to enhance drug delivery through the skin is also under investigation [277–279]. For example, improved penetration *ex vivo* of the antipsychotic drug risperidone from optimized transfersomal gel using iontophoresis was demonstrated on pig ear skin [280]. Yang et al. showed that microneedles can effectively penetrate into the rat skin and release doxorubicin from transfersomes into the dermis through self-dissolution. The accumulation of the drug in the lymph nodes and the

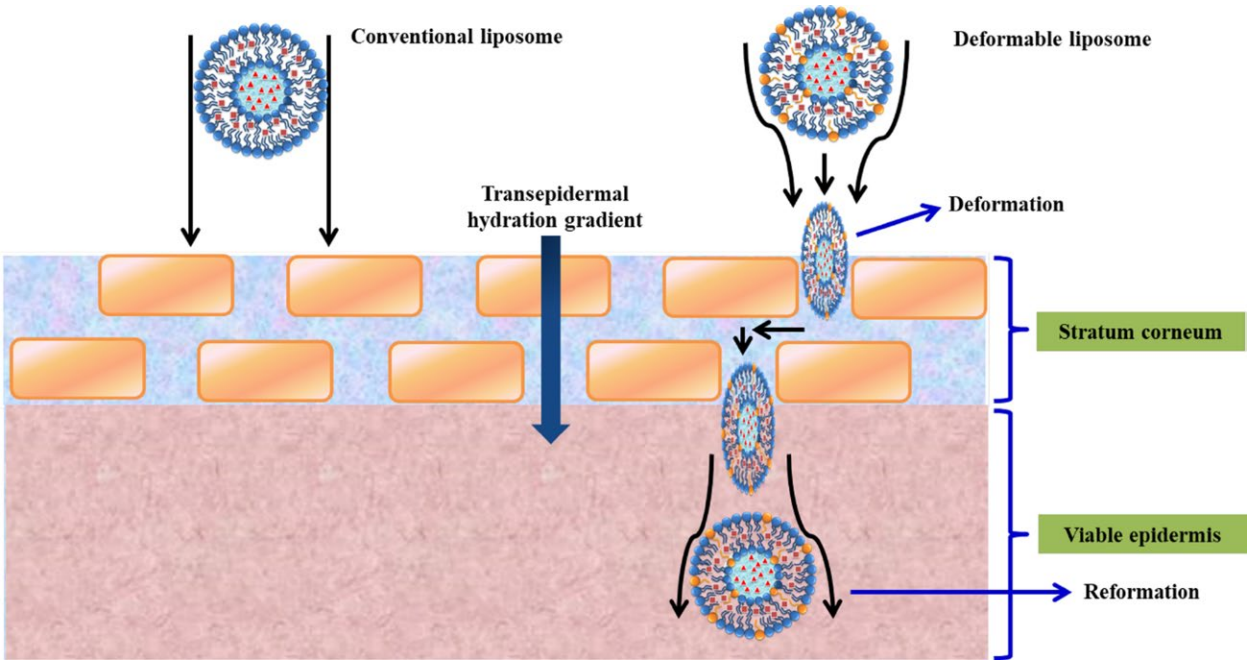

Fig. 3. Penetration mechanisms of traditional and deformable liposomes through the skin [271].

increase of its bioavailability in plasma can occur due to the combined protocol [279].

4.4. Ethosomes. Ethosomes are one of the varieties of deformable liposomes, which consist of phospholipids and ethanol in high concentration (20–45%). The term was first introduced by E. Touitou et al. in 2000 as a new type of transdermal drug delivery system [281]. The addition of ethanol imparts deformability, flexibility, and fluidity to the vesicles, changes the lipid bilayer, which provides efficient drug delivery to deeper skin layers. Ethosomes, like other lipid vesicles, can encapsulate hydrophilic, lipophilic, and amphiphilic drugs, and are characterized by high encapsulation efficiency. As reported in [282] ethosomal curcumin promotes the burn healing in rats due to antibacterial activity.

The ethosomal form of ketoconazole, which is more effectively retained on the skin compared with the ketoconazole suspension, has a significantly improved penetration through the skin (almost two times higher) [283]. In [284], it was demonstrated that berberine loaded into the ethosomes penetrates to the basal layers of the skin and enhances inhibitory effect on melanoma cells. Current trends in the design of nanocarriers for transdermal drug delivery, including various types of alcohol-containing lipid systems were analyzed in reviews [3, 285]. Along with ethosomes, vesicular systems containing ethylene glycol or glycerin can be considered as new subclasses of such particles. In the case of glycerosomes, the increased permeability of the epidermis may be associated with the moisturizing effect of glycerin, which leads to the disruption of biomembrane. The authors note that significant efforts are aimed at establishing the factors and mechanism that determine the high penetrating ability of ethosomes. It has been shown that at a sufficiently high concentration (~40%) of ethanol promotes the formation of pores and significantly increases substance transport. The increase in skin permeability upon ethanol exposure is attributed to two factors. Firstly, there is an evaporation-induced "push effect" that can enhance the concentration gradient during transdermal absorption. Secondly, a "pool effect" is observed, wherein the permeability of drug molecules is increased due to the reduction of barrier functions in the stratum corneum. This is attributed to ethanol interacting with the lipid components of the stratum corneum, disrupting their highly ordered structure and inducing pseudo-liquidity, thereby reducing barrier functions [3].

4.5. Natural compounds as building blocks for next-generation vesicular systems. The focus of nanomedicine on the use of natural substances, even for the treatment

of serious diseases such as cancer, is obvious from the publication survey [286]. An increase of drug anticancer activity with the addition of curcumin has been reported [287]. It has been shown that niosomal formulations can achieve greater synergistic effects compared with free drugs. *In vitro* study of curcumin-loaded niosomes have been conducted [288]. Optimized formulations were stable for two months and demonstrated prolonged drug release. Unlike non-toxic empty niosomes, encapsulated curcumin (encapsulation efficiency >99%) demonstrated dose-dependent cytotoxicity toward cancer cells. Currently, a niosomes with doxorubicin and curcumin are in clinical trials for anticancer activity [289]. In [290] flavonoid morusin loaded niosomes with antibacterial, anti-inflammatory, and antitumor effect were formed. Niosomes containing propolis have been developed for tuberculosis therapy [291]. The binding of PEGylated propolis-loaded niosomes to mycobacterium tuberculosis was demonstrated by confocal microscopy. The application potential of niosomal lavender oil in regenerative medicine was highlighted [292].

Glucosamine loaded transfersomes were tested *in vivo* using a papain-induced arthritis model [293]. Radiological studies on rabbits using a gel form of transfersomes confirmed the effectiveness of transdermal therapy of knee osteoarthritis. Examples of successful development of transfersomes and ethosomes loaded with quercetin, which demonstrated improved penetration and retention in topical therapy of dermatological diseases, are reviewed [294]. The application of new types of vesicular carriers (niosomes, ethosomes, cubosomes, transfersomes) with natural compounds to burn treatment is discussed in a review [295]. Enhanced penetration of encapsulated drugs, prolonged drug release, reduced side effects, and improved healing of damaged tissues are demonstrated.

The most commonly used phytochemicals for encapsulation in chitosomes are essential oils, antioxidants, and vitamins [265]. Liposomes were decorated with chitosan or hyaluronic acid to enhance the protection and bioavailability of the curcumin. The polymer coating increased the ability of curcumin of protecting human adenocarcinoma A549 cells from hydrogen peroxide-induced oxidative stress [296]. In [297], chitosomes with acteoside, which have antibacterial, anti-inflammatory, and neuroprotective effects, were obtained. Increased stability and oral bioavailability of acteoside *in vivo* were demonstrated using Sprague–Dawley rats.

Park et al. emphasized the potential of chitosomes as a transdermal delivery system for resveratrol. Chitosan-coated vesicles demonstrated more effective penetration of resveratrol through the skin of ICR albino mice compared to unmodified samples [298]. The encapsulation efficiency of vitamin D in tripolyphosphate (TPP) chitosomes was reached 97%, and stability increased up to 49 days compared to the unencapsulated form [299]. It is important to note that TPP-chitosomes are attractive for controlled release of substances due to the three-dimensional network of chitosan, which has higher stability in a low pH compared to conventional liposomes or chitosomes. The encapsulation of various natural substances in chitosomes and comparison with conventional liposomes were reviewed [268].

The incorporation into transfersomes of natural components, such as resveratrol, grape extracts, rose extracts, curcumin, and sinomenine, which are recommended for the treatment of skin diseases, have been conducted [277, 300–302]. Tocopherol acetate was loaded into transfersomes with different polysorbates (Tween 20, 40, 60, and 80). Biocompatibility toward skin cells (keratinocytes and fibroblasts), protective effect against oxidative damage, and enhanced wound healing has been shown for these vesicles. At the same time, the modification with surfactants little affected the observed properties [302]. Another widely used antioxidant, resveratrol, was encapsulated in transfersomes to enhance stability, *in vitro* skin penetration, and reduce cytotoxicity [303]. In [301], a combined approach that includes the use of transfersomes and transpapillary iontophoresis was proposed for the treatment of breast cancer. Enhanced penetration of transfersomes containing resveratrol across the mammary papilla was demonstrated. This improved method resulted in a significant reduction in the tumor volume in a chemically induced breast cancer rat model. Transferosomes loaded with sinomenine hydrochloride [300], which is commonly used for the treatment of rheumatism and arthritis, has been developed and optimized. It was shown the transdermal penetration of the phytochemical in transfersomes increased by 1.7 times compared to liposomes *ex vivo*.

The review [48] focuses on phytotherapy for skin cancer using nanomedicine approaches and presents a comparative analysis of various vesicular carriers (liposomes, ethosomes, and transfersomes). A wide range of natural bioactive substances such as quercetin, resveratrol, curcumin, ursolic acid, among others, as

well as their combinations are considered as therapeutic components. It is noted that along with enhanced penetrating ability, phytochemicals in nanocontainers significantly reduce side effects.

Thus, a review of the current literature on nanomedicine indicates a significant interest in the use of natural compounds within new generations of lipid carriers. The following sections confirm this trend: currently, two subtypes of vesicles, invasomes and phytosomes, were formed as specifically for this purpose.

Invasomes. One of promising directions in drug delivery is the development of nanocarriers with skin penetration enhancers. Among these carriers are invasomes, new flexible nanovesicles consisting of phospholipids, terpenes and ethanol [58,304]. Terpenes and ethanol are permeation enhancers. Terpenes are mainly extracted from medicinal plants (generally essential oils). They are attractive for the formulation of cosmetic and pharmaceutical products due to their non-irritating effect on the skin and safety compared to synthetic enhancers (such as surfactants) [305]. For example, successful development of an invasomal cream based on the *Ocimum basilicum* against acne has been described [305]. The most commonly used terpenes are 1,8-cineole, menthol, limonene, menthone, and nerolidol [306]. The addition of terpenes and ethanol is assumed to create deformable vesicles that can increase the fluidity of the skin lipid bilayers. The disruption of the bilayer in the stratum corneum is the basis for the invasome action [65]. The effectiveness of invasomes has been demonstrated in transdermal delivery of isradipine [307], nimesulide [308], azelaic acid [309], temoporfin [310], and avanafil [311], compared to ethanol and liposomal forms. It is important that the permeation ability of invasomes is dependent on the concentration of terpenes, but only in combination with the lipid and ethanol. The structure of the terpene significantly influences the size of the invasomes, as demonstrated with three different terpenes: citral, limonene, and eucalyptus essential oil. It has been observed that invasomes containing limonene demonstrate the highest drug penetration through cell membranes [308].

Phytosomes. Many synthetic pharmaceutical drugs cause side effects, lead to addiction, require increased doses, and can be toxic [255]. Therefore, a promising area is the use of natural-based drugs [312, 313]. Phytosomes are a type of liposomes specifically developed for the delivery of natural compounds [314]. They are obtained by complexation a plant extract with phospholipids, typically phosphatidylcholine [315]. This process creates a unique structure that can easily penetrate through cell membranes and deliver the plant extract to target tissues. The development of phytosomal formulations for the delivery of apigenin, silybin, rutin, quercetin, grape seed extracts, tobacco, and Centella asiatica has been reported [316–319].

The improved *in vitro/in vivo* bioavailability, increased antioxidant and anti-inflammatory activity, and enhanced stability of medicines in the phytosomes were demonstrated. In [320], a high bioavailability of silybin phytosome and the absence of the liver influence on their destruction were reported. A transdermal form of phytosomes containing rutin exhibited superior skin absorption (*ex vivo*) and could be recommended for the treatment of arthritis and rheumatism [321]. Phytosomes based on quercetin, vitamin C, lecithin, and cholesterol, which had a negative charge, nanometer-size (~60 nm), and good stability, were developed [322]. Antiparasitic activity of quercetin in phytosomes at a concentration of 400 μg/mL was shown [323]. Preclinical pharmacokinetic and clinical trials were conducted to assess the effectiveness of phytosomal curcumin [18]. The study involving 38 patients with diabetes showed improvement in microangiopathy and retinopathy after 4 weeks of treatment with phytosomal curcumin (Meriva®). In [324], human research demonstrated 29 times better absorption of Meriva® compared to a free curcuminoids. Thus, the use of phytosomes is a promising method for enhancing the absorption and bioavailability of natural compounds.

A wide variety of plants and herbs are used as medicinal substrates for phytosomes. Nature is a rich source of potential medicines, and many anticancer drugs based on natural compounds have been developed [314]. Phytochemistry, which focuses on the extraction of biologically active substances such as phenols, terpenoids, and alkaloids, is one of the fields involved in the production of bioactive compounds [325]. Among the most studied compounds are antioxidants: curcumin, resveratrol, quercetin, catechins, vitamins (retinol, tocopherol, ascorbic acid), and essential oils [326]. Antioxidants are found in anti-aging and sunscreens [327]. In [328], data are given that many natural substances have immune-stimulating properties and potential activity against COVID-19. Unfortunately, low water solubility, poor stability in the gastrointestinal tract,

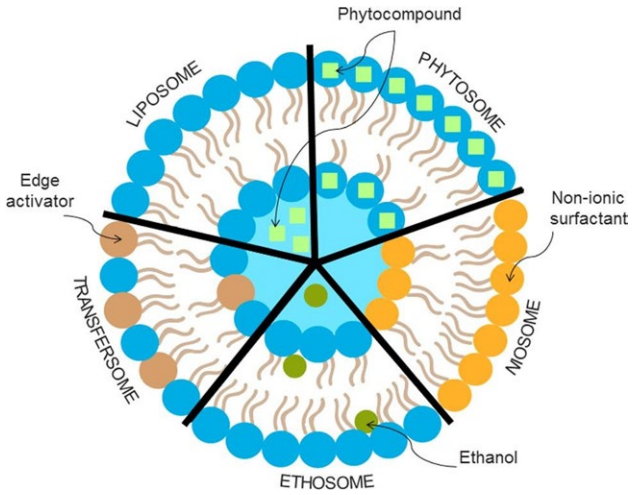

Fig. 4. Schematic representation of vesicle derivatives used for encapsulation of natural compounds [330] (reproduced with permission, Elsevier, Copyright 2019).

and rapid elimination are the most common challenges associated with the poor oral bioavailability of many natural drugs [325]. Additionally, biologically active substances should be protected from the destructive influence of environmental factors such as pH, light, oxygen, temperature, and enzyme effects. Therefore, the development of delivery systems is a key approach to address these challenges [329].

New lipid-based nanocarriers containing natural components have numerous advantages in terms of therapeutic effect compared to the pure form of compounds. These advantages include enhanced permeability across biological barriers (such as skin and mucous membranes), increased stability, solubility, bioavailability, and reduced side effects. Additionally, nanocarriers can provide controlled particle size, shape, multifunctionality, and prolonged release. Alkaloids, terpenoids, sulfur-containing compounds, and polyphenols (such as epigallocatechin-3-gallate, luteolin, quercetin, and resveratrol) are the most commonly used compounds for encapsulation in lipid nanocarriers. Schematic representation of the most widespread vesicular systems for the encapsulation of natural components are shown in Fig. 4.

The examples of the next-generation vesicular carriers for natural substances are summarized in Table 2. Based on this table, it can be concluded:

1) Improved mucosal and stratum corneum penetration efficiency has been demonstrated for novel lipid carriers with herbal drugs. These vesicles have a deformable morphology, flexibility, and improved ability to penetrate biological barriers, which provides delivery of drugs to deeper tissues due to the presence of an edge activator (transfersomes, niosomes), ethanol (ethosomes), terpenes (invasomes), and combination of chitosan and an edge activator (chitosomes).

2) The novel vesicular systems containing plant components have proven effective in the prevention and treatment of neurodegenerative diseases, tumors, cardiovascular, skin disorders, diabetes, etc.

3) Increased solubility, bioavailability, and enhanced therapeutic effect, can be achieved by encapsulating natural compounds in nanocarriers.

5. CONCLUSIONS

To sum up, survey of recent publications demonstrates that intensive progress in design and practical applications of lipid nanocarriers occurred, with several trends highlighted:

(1) simple micellar nanocontainers, microemulsions and nanoemulsions are of practical importance for development of drug delivery systems by means of rational choice of constituents and optimization of the composition. Importantly, they can be used as precursors for the fabrication of emulgels, for which carbopol, chitosan, cellulose and other polymers are used as gel bases;

(2) liposomal formulations attract much attention as the most answered to criteria of clinic trials in terms of biocompatibility, bioavailability and adjustability to different drugs and administration ways;

(3) noncovalent modification technique provides a powerful tool for improving various functional parameters of liposomes, including stability, prolonged circulation, targeting and crossing the biological barriers;

(4) design of nanocarriers for combination delivery is one of hallmarks of current researches in nanomedicine; in some cases, the combination of drugs is aimed, in others the combination of therapeutic and diagnostic tasks is sought;

(5) natural components tend to be actively used even for the treatment of serious diseases; they are processed

Table 2. Examples of natural compounds loaded into the new vesicular systems[a]

Active substances	System, composition	Effects	Administration route	Trial phase	References
Paclitaxel	Transfersomes Span/Carbopol 940	Improved penetration through the skin	Transdermal	*in vitro*	[331]
Sinomenine hydrochloride (SH)	Transfersomes Epc/cholesterol/ vitamin E/sodium deoxycholate	Improved transdermal permeation of transfersomal SH	Transdermal	*in vivo/ ex vivo*	[300]
Rose bengal (RB)	Transfersome Lipoids 100/ cholesterol/span 80	Maximize intradermal delivery of RB by transfersomes and microneedles in the treatment of melanoma	Intradermal	*in vitro/ ex vivo*	[277]
Insulin	Chitosomes Pc/tween 80/ chitosan	Improved learning and memory in rats; increased mucosal uptake	Intranasal	*in vivo*	[332]
Resveratrol	Transfersomes Spc/tween 20; Lecithin/tween 80/ tween 20/ethanol	Significant reduction in the tumor volume	Transpapillary; transdermal	*in vivo/ in vitro*	[301, 303]
Tocopherol acetate	Transfersomes SPC/Tween 20; Tween 40; Tween 60; Tween 80	A higher accumulation of tocopherol acetate in the dermis	Topical	*in vitro*	[302]
Asiatic acid (AA)	Transfersomes Spc/tween 80/span 80/sodium deoxycholate	Significantly increased the percentage of aa penetration and flux into the strat-m® membrane	Transdermal	*in vitro*	[333]
Tempranillo grape extract (TE)	Transfersomes Phospholipon 90 g/ tween 80/20	Increased antioxidant activity of the TE	Dermal	*in vitro*	[334]
Cannabidiol (CBD)	Transfersomes Sl/polysorbate 80/ cholesterol	Considerably improved the diffusivity and permeation of CBD across excised Colorectal membrane	Rectal	*in vitro/ ex vivo*	[335]
Glucosamine	Transfersomes Phospholipid 90G/ Tween 80 or Span 80	Effectiveness of glucosamine loaded transfersomes in healing the osteoarthritis	Transdermal	*in vivo*	[293]
Indocyanine green	Chitosomes Dmpc/cholesterol/chitosan (50–190 kda)	Enhanced skin permeation	Skin	*in vitro*	[336]
Curcumin	Chitosomes Chitosan (50–190 kda)/ lipoid s75	Improved the curcumin ability to protect a549 cells from the oxidative stress	Pulmonary	*in vitro*	[296]
Acteoside	Chitosomes Spc/chitosan (50–190 kda)	Improved stability and bioavailability	Oral	*in vivo*	[297]
Quercetin	Chitosomes Epc/chitosan (50–190 kda)/tween 20	Better antioxidant activity and stability	Skin	*in vitro*	[264]
Spirulina	Chitosomes Spc/chitosan/ Soybean lecithin	Increased the antioxidant activity	Gastrointestinal	*in vitro*	[337]
Resveratrol	Chitosomes EPC/chitosan (50–190 kda)	Increased skin-permeation efficiency with the coating	Transdermal	*in vivo*	[298]

Table 2. (Contd.)

Active substances	System, composition	Effects	Administration route	Trial phase	References
Curcumin	Niosomes Cholesterol/span 20/ tween 20	Increased antinociceptive and anti-inflammatory activities of curcumin in skin layers and the receptor chamber	Dermal	*in vivo*	[338]
Curcumin	Invasome Spc/ethanol/eucalyptol	Invasomal curcumin permeation across the pig ear skin was 2.5 times higher than curcumin solution	Transdermal	*ex vivo*	[339]
Curcumin	Invasome Pc/ethanol /limonene, fenchone or nerolidol	Improved intradermal penetration of curcumin	Transdermal	*ex vivo*	[340]

[a] DMPC—1,2-Dimyristoyl-sn-glycero-3-phosphocholine; SPC—soybean phosphatidylcholine; EPC—egg phosphatidylcholine; SL—soybean lecithin.

both as cargoes (supplemented bioactives or basic drugs) and building blocks for engineering the nanocarriers.

AUTHOR INFORMATION

L.Ya. Zakharova, ORCID: https://orcid.org/0000-0002-2981-445X

F.I. Maganova, ORCID: https://orcid.org/0000-0002-1095-3126

G.A. Gaynanova, ORCID: https://orcid.org/0000-0002-0406-4066

A.B. Mirgorodskaya, ORCID: https://orcid.org/0000-0002-5594-0679

E.A. Vasilieva, ORCID: https:// orcid.org/0000-0002-1825-7803

O.G. Sinyashin, ORCID: https://orcid.org/0000-0002-2241-9764

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Pacheco, C., Baião, A., Ding, T., Cui, W., and Sarmento, B., *Adv. Drug Deliv. Rev.,* 2023, vol. 194, p. 114724. https://doi.org/10.1016/j.addr.2023.114724
2. Kaur, N., Popli, P., Tiwary, N., and Swami, R., *J. Control. Rel.,* 2023, vol. 355, p. 417. https://doi.org/10.1016/j.jconrel.2023.01.032
3. Guillot, A.J., Martínez-Navarrete, M., Garrigues, T.M., and Melero, A., *J. Control. Rel.,* 2023, vol. 355, p. 624. https://doi.org/10.1016/j.jconrel.2023.02.006
4. Sun, T., and Jiang, C., *Adv. Drug Deliv. Rev.,* 2023, vol. 196, p. 114773. https://doi.org/10.1016/j.addr.2023.114773
5. Gaynanova, G., Vasileva, L., Kashapov, R., Kuznetsova, D., Kushnazarova, R., Tyryshkina, A., Vasilieva, E., Petrov, K., Zakharova, L., and Sinyashin, O., *Molecules,* 2021, vol. 26, p. 6786. https://doi.org/10.3390/molecules26226786
6. German-Cortés, J., Vilar-Hernández, M., Rafael, D., Abasolo, I., and Andrade, F., *Pharmaceutics,* 2023, vol. 15, p. 831. https://doi.org/10.3390/pharmaceutics15030831
7. Akkewar, A., Mahajan, N., Kharwade, R., and Gangane, P., *Curr. Drug Deliv.,* 2023, vol. 20, p. 350. https://doi.org/10.2174/1567201819666220421113127
8. Długosz, O., Matyjasik, W., Hodacka, G., Szostak, K., Matysik, J., Krawczyk, P., Piasek, A., Pulit-Prociak, J., and Banach, M., *Nanomaterials,* 2023, vol. 13, p. 1130. https://doi.org/10.3390/nano13061130
9. Patel, R.J., Pandey, P., Patel, A.A., Prajapati, B.G., Alexander, A., Pandya, V., Trivedi, N., Shah, S., and Patel, V., *J. Drug Deliv. Sci. Technol.,* 2023, vol. 82, p. 104306, https://doi.org/10.1016/j.jddst.2023.104306

10. Pavlov, R., Romanova, E., Kuznetsov, D., Lyubina, A., Amerhanova, S., Voloshina, A., Buzyurova, D., Babaev, V., Zueva, I., Petrov, K., Lukashenko, S., Gaynanova, G., Zakharova, L., *Int. J. Mol. Sci.,* 2023, vol. 24, p. 3632. https://doi.org/10.3390/ijms24043632
11. Kashapov, R., Ibragimova, A., Pavlov, R., Gabdrakhmanov, D., Kashapova, N., Burilova, E., Zakharova, L., and Sinyashin, O., *Int. J. Mol. Sci.,* 2021, vol. 22, p. 7055, https://doi.org/10.3390/ijms22137055
12. Spiridonov, V.V., Sybachin, A.V., Pigareva, V.A., Afanasov, M.I., Musoev, S.A., Knotko, A.V., and Zezin, S.B., *Polymers*, 2023, vol. 15, p. 1437. https://doi.org/10.3390/polym15061437
13. Alhodieb, F.S., Barkat, Md.A., Barkat, H.A., Hadi, H.A., Khan, M.I., Ashfaq, F., Rahman, M.A., Hassan, Mohd.Z., and Alanezi, A.A., *Int. J. Biol. Macromol.,* 2022, vol. 217, p. 457. https://doi.org/10.1016/j.ijbiomac.2022.06.201
14. Das, C.G.A., Kumar, V.G., Dhas, T.S., Karthick, V., and Kumar, C.M.V., *Nanomedicine Nanotechnol. Biol. Med.,* 2023, vol. 47, p. 102613. https://doi.org/10.1016/j.nano.2022.102613
15. Bhosale, A., Paul, G., Mazahir, F., and Yadav, A.K., *OpenNano,* 2023, vol. 9, p. 100111. https://doi.org/10.1016/j.onano.2022.100111
16. Rajput, A., Pingale, P., and Dhapte-Pawar, V., *Front. Pharmacol.,* 2022, vol. 13, p. 979682. https://doi.org/10.3389/fphar.2022.979682
17. Verma, N., Arora, V., Awasthi, R., Chan, Y., Jha, N.K., Thapa, K., Jawaid, T., Kamal, M., Gupta, G., Liu, G., Paudel, K.R., Hansbro, P.M., George Oliver, B.G., Singh, S.K., Chellappan, D.K., Dureja, H., Dua, K.J., *Drug Deliv. Sci. Technol.,* 2022, vol. 75, p. 103690. https://doi.org/10.1016/j.jddst.2022.103690
18. Bahloul, B., Castillo-Henríquez, L., Jenhani, L., Aroua, N., Ftouh, M., Kalboussi, N., Vega-Baudrit, J., and Mignet, N., *J. Drug Deliv. Sci. Technol.,* 2023, vol. 82, p. 104377. https://doi.org/10.1016/j.jddst.2023.10437
19. Maher, R., Moreno-Borrallo, A., Jindal, D., Mai, B.T., Ruiz-Hernandez, E., and Harkin, A., *Pharmaceutics,* 2023, vol. 15, p. 746. https://doi.org/10.3390/pharmaceutics15030746
20. Sánchez-Dengra, B., González-Álvarez, I., Bermejo, M., and González-Álvarez, M., *Int. J. Pharm.*, 2023, vol. 636, p. 122759. https://doi.org/10.1016/j.ijpharm.2023.12275
21. Gonzales-Aloy, E., Ahmed-Cox, A., Tsoli, M., Ziegler, D.S., and Kavallaris, M., *Adv. Drug Deliv. Rev.*, 2023, vol. 196, p. 114777. https://doi.org/10.1016/j.addr.2023.114777
22. Wang, C., and Pang, Y., *Adv. Drug Deliv. Rev.,* 2023, vol. 194, p. 114721. https://doi.org/10.1016/j.addr.2023.114721
23. Phatale, V., Vaiphei, K.K., Jha, S., Patil, D., Agrawal, M., and Alexander, A., *J. Control. Rel.,* 2022, vol. 351, p. 361. https://doi.org/10.1016/j.jconrel.2022.09.025
24. Arslanov, V.V., Ermakova, E.V., Krylov, D.I., and Popova, O.O., *J. Colloid Interface Sci.,* 2023, vol. 640, p. 281. https://doi.org/10.1016/j.jcis.2023.02.110
25. Kashapov, R., Gaynanova, G., Gabdrakhmanov, D., Kuznetsov, D., Pavlov, R., Petrov, K., Zakharova, L., and Sinyashin, O., *Int. J. Mol. Sci.,* 2020, vol. 21, p. 6961. https://doi.org/10.3390/ijms21186961
26. Antipin, I.S., Alfimov, M.V., Arslanov, V.V., Burilov, V.A., Vatsadze, S.Z., Voloshin, Y.Z., Volcho, K.P., Gorbatchuk, V.V., Gorbunova, Y.G., Gromov, S.P., Dudkin, S.V., Zaitsev, S.Yu., Zakharova, L.Ya., Ziganshin, M.A., Zolotukhina, A.V., Kalinina, M.A., Karakhanov, E.A., Kashapov, R.R., Koifman, O.I., Konovalov, A.I., Korenev, V.S., Maksimov, A.L., Mamardashvili, N.Zh., Mamardashvili, G.M., Martynov, A.G., Mustafina, A.R., Nugmanov, R.I., Ovsyannikov, A.S., Padnya, P.L., Potapov, A.S., Selektor, S.L., Sokolov, M.N., Solovieva, S.E., Stoikov, I.I., Stuzhin, P.A., Suslov, E.V., Ushakov, E.N., Fedin, V.P., Fedorenko, S.V., Fedorova, O.A., Fedorov, Y.V., Chvalun, S.N., Tsivadze, A.Yu., Shtykov, S.N., Shurpik, D.N., Shcherbina, M.A., and Yakimova, L.S., *Russ. Chem. Rev.*, 2021, vol. 90, p. 895. https://doi.org/10.1070/RCR5011
27. Kashapov, R.R., Mirgorodskaya, A.B., Kuznetsov, D.M., Razuvaeva, Yu.S., and Zakharova, L.Ya., *Colloid J.,* 2022, vol. 84, p. 502. https://doi.org/10.1134/S1061933X22700016
28. Samarkina, D.A., Gabdrakhmanov, D.R., Lukashenko, S.S., Nizameev, I.R., Kadirov, M.K., and Zakharova, L.Ya., *J. Mol. Liq.,* 2019, vol. 275, p. 232. https://doi.org/10.1016/j.molliq.2018.11.082
29. Kuznetsova, D.A., Gabdrakhmanov, D.R., Lukashenko, S.S., Voloshina, A.D., Sapunova, A.S., Kashapov, R.R., and Zakharova, L.Ya., *Chem. Phys. Lipids,* 2019, vol. 223, p. 104791. https://doi.org/10.1016/j.chemphyslip.2019.104791

30. Zakharova, L.Ya., Kaupova, G.I., Gabdrakhmanov, D.R., Gaynanova, G.A., Ermakova, E.A., Mukhitov, A.R., Galkina, I.V., Cheresiz, S.V., Pokrovsky, A.G., Skvortsova, P.V., Gogolev, Y.V., and Zuev, Y.F., *Phys. Chem. Chem. Phys.,* 2019, vol. 21, p. 16706. https://doi.org/10.1039/C9CP02384D
31. Kushnazarova, R.A., Mirgorodskaya, A.B., Mikhailov, V.A., Belousova, I.A., Zubareva, T.M., Prokop'eva, T.M., Voloshina, A.D., Amerhanova, S.K., and Zakharova, L.Ya., *Russ. J. Gen. Chem.*, 2022, vol. 92, p. 659. https://doi.org/10.1134/S1070363222040077
32. Zhil'tsova, E.P., Ibatullina, M.R., Safina, N.Kh., and Zakharova, L.Ya., *Russ. J. Gen. Chem.,* 2022, vol. 92, p. 668. https://doi.org/10.1134/S1070363222040089
33. Kuznetsova, D.A., Kuznetsov, D.M., Amerhanova, S.K., Buzmakova, E.V., Lyubina, A.P., Syakaev, V.V., Nizameev, I.R., Kadirov, M.K., Voloshina, A.D., and Zakharova, L.Ya. *Langmuir,* 2022, vol. 38, p. 4921. https://doi.org/10.1021/acs.langmuir.2c00299
34. Zakharova, L.Ya., Voloshina, A.D., Ibatullina, M.R., Zhiltsova, E.P., Lukashenko, S.S., Kuznetsova, D.A., Kutyreva, M.P., Sapunova, A.S., Kufelkina, A.A., Kulik, N.V., Kataeva, O., Ivshin, K.A., Gubaidullin, A.T., Salnikov, V.V., Nizameev, I.R., Kadirov, M.K., and Sinyashin O.G., *ACS Omega,* 2022, vol. 7, p. 3073. https://doi.org/10.1021/acsomega.1c06465
35. Kuznetsova, D.A., Vasilieva, E.A., Kuznetsov, D.M., Lenina, O.A., Filippov, S.K., Petrov, K.A., Zakharova, L.Ya., Sinyashin, O.G., *ACS Omega*, 2022, vol. 7, p. 25741. https://doi.org/10.1021/acsomega.2c03039
36. Kuznetsova, D.A., Kuznetsov, D.M., Vasileva, L.A., Toropchina, A.V., Belova, D.K., Amerhanova, S.K., Lyubina, A.P., Voloshina, A.D., and Zakharova, L.Ya., *J. Mol. Liq.*, 2021, vol. 340, p. 117229. https://doi.org/10.1016/j.molliq.2021.117229
37. Kushnazarova, R.A., Mirgorodskaya, A.B., Kuznetsov, D.M., Tyryshkina, A.A., Voloshina, A.D., Gumerova, S.K., Lenina, O.A., Nikitin, E.N., and Zakharova, L.Ya., *J. Mol. Liq.*, 2021, vol. 336, p. 116318. https://doi.org/10.1016/j.molliq.2021.116318
38. Jackson, M.A., Evans, K.O., Price, N.P.J., Blackburn, J.A., Ward, C.J., Ray, K.J., and Vermillion, K.E., *ACS Sustain. Chem. Eng.*, 2021, vol. 9, p. 13842. https://doi.org/10.1021/acssuschemeng.1c04703
39. Gonçalves, R.A., Holmberg, K., and Lindman, B., *J. Mol. Liq.*, 2023, vol. 375, p. 121335, https://doi.org/10.1016/j.molliq.2023.121335
40. Kawamura, H., Yoshino, N., Murakami, K., Kawamura, H., Sugiyama, I., Sasaki, Y., Odagiri, T., Sadzuka, Y., and Muraki, Y., *Eur. J. Pharm. Biopharm.*, 2023, vol. 182, p. 1. https://doi.org/10.1016/j.ejpb.2022.11.023
41. Jesus, C.F., Alves, A.A.S., Fiuza, S.M., Murtinho, D., and Antunes, F.E., *J. Mol. Liq.*, 2021, vol. 342, p. 117389. https://doi.org/10.1016/j.molliq.2021.117389
42. Colombo, E., Coppini, D.A., Maculan, S., Seneci, P., Santini, B., Testa, F., Salvioni, L., Vanacore, G.M., Colombo, M., and Passarella, D., *RSC Adv.*, 2022, vol. 12, p. 35484. https://doi.org/10.1039/D2RA06306A
43. Kumar, S., Dhiman, R., Prudencio, C.R., da Costa, A.C., Vibhuti, A., Leal, E., Chang, C.-M., Raj, V.S., and Pandey, R.P., *Mini-Rev. Med. Chem.*, 2023, vol. 23, p. 187. https://doi.org/10.2174/1389557522666220609102010
44. Rosales, T.K.O. and Fabi, J.P., *Int. J. Biol. Macromol.*, 2023, vol. 229, p. 11. https://doi.org/10.1016/j.ijbiomac.2022.12.292
45. Xu, H., Nie, W., Dai, L., Luo, R., Lin, D., Zhang, M., Zhang, J., and Gao, F., *Carbohydr. Polym.*, 2023, vol. 301, p. 120311. https://doi.org/10.1016/j.carbpol.2022.120311
46. Al-Hetty, H.R.A.K., Kadhim, M.S., Al-Tamimi, J.H.Z., Ahmed, N.M., Jalil, A.T., Saleh, M.M., Kandeel, M., and Abbas, R.H., *Emergent Mater.*, 2023, vol. 6, p. 1. https://doi.org/10.1007/s42247-023-00453-8
47. Alexander, A., Ajazuddin, Patel, R.J., Saraf, S., and Saraf, S., *J. Control. Rel.,* 2016, vol. 241, p. 110. https://doi.org/10.1016/j.jconrel.2016.09.017
48. Yasmeen, Iqubal, M.K., Khan, M.A., Agarwal, N.B., Ali, J., and Baboota, S. *J. Drug Deliv. Sci. Technol.,* 2021, vol. 66, p. 102912. https://doi.org/10.1016/j.jddst.2021.102912
49. Gupta, M.K., Sansare, V., Shrivastava, B., Jadhav, S., and Gurav, P., *J. Liposome Res.*, 2022, vol. 32, p. 211. https://doi.org/10.1080/08982104.2021.1968430
50. Mahomoodally, M.F., Sadeer, N., Edoo, M., and Venugopala, K.N., *Mini-Rev. Med. Chem.*, 2021, vol. 21, p. 2731. https://doi.org/10.2174/1389557520666200730160911
51. Bobbala, S., Vincent, M.P., and Scott, E.A., *Nanoscale*, 2021, vol. 13, p. 11349. https://doi.org/10.1039/D1NR02188E
52. Raith, M., Kauffman, S.J., Asoudeh, M., Buczek, J.A., Kang, N.-G., Mays, J.W., and Dalhaimer, P., *J. Control. Rel.*, 2021, vol. 337, p. 448. https://doi.org/10.1016/j.jconrel.2021.07.045

53. Mougin, J., Bourgaux, C., and Couvreur, P., *Adv. Drug Deliv. Rev.*, 2021, vol. 172, p. 127. https://doi.org/10.1016/j.addr.2021.02.018
54. Jelonek, K., Kaczmarczyk, B., Orchel, A., Chodurek, E., Jaworska-Kik, M., Paduszyński, P., Bębenek, E., Chrobak, E., Musiał-Kulik, M., Foryś, A., Boryczka, S., Li, S., and Kasperczyk, J., *J. Drug Deliv. Sci. Technol.*, 2021, vol. 65, p. 102717. https://doi.org/10.1016/j.jddst.2021.102717
55. Gautam, L., Shrivastava, P., Yadav, B., Jain, A., Sharma, R., Vyas, S., and Vyas, S.P., *Drug Discov. Today*, 2022, vol. 27, p. 1184–1195. https://doi.org/10.1016/j.drudis.2021.12.007
56. Chacko, I.A., Ghate, V.M., Dsouza, L., and Lewis, S.A., *Colloids Surf. B Biointerfaces* 2020, vol. 195, p. 111262. https://doi.org/10.1016/j.colsurfb.2020.111262
57. Kusuma Priya, M.D., Vinod, K., Damini, V.K., Eswar, K., Kadiri, R.R., Brito Raj, S., and Sucharitha, P., *Int. J. Appl. Pharm.*, 2020, vol. 12, p. 7. https://doi.org/10.22159/ijap.2020v12i6.38996
58. Jain, S., Tripathi, S., and Tripathi, P.K., *J. Drug Deliv. Sci. Technol.*, 2021, vol. 61, p. 102166. https://doi.org/10.1016/j.jddst.2020.102166
59. Emad, N.A., Ahmed, B., Alhalmi, A., Alzobaidi, N., and Al-Kubati, S.S., *J. Drug Deliv. Sci. Technol.,* 2021, vol. 64, p. 102642. https://doi.org/10.1016/j.jddst.2021.102642
60. Yasamineh, S., Yasamineh, P., Ghafouri Kalajahi, H., Gholizadeh, O., Yekanipour, Z., Afkhami, H., Eslami, M., Hossein Kheirkhah, A., Taghizadeh, M., Yazdani, Y., and Dadashpour, M., *Int. J. Pharm.*, 2022, vol. 624, p. 121878. https://doi.org/10.1016/j.ijpharm.2022.121878
61. Stefanov, S.R. and Andonova, V.Y., *Pharmaceuticals*, 2021, vol. 14, p. 1083. https://doi.org/10.3390/ph14111083
62. Kumar, B., Sahoo, P.K., and Manchanda, S., *OpenNano*, 2022, vol. 7, p. 100058. https://doi.org/10.1016/j.onano.2022.100058
63. Vasilieva, E.A., Kuznetsova, D.A., Valeeva, F.G., Kuznetsov, D.M., Zakharov, A.V., Amerhanova, S.K., Voloshina, A.D., Zueva, I.V., Petrov, K.A., and Zakharova, L.Ya., *Pharmaceutics*, 2022, vol. 14, p. 2846. https://doi.org/10.3390/pharmaceutics14122846
64. Vasileva, L., Gaynanova, G., Zueva, I., Lyubina, A., Amerhanova, S., Buzyurova, D., Babaev, V., Voloshina, A., Petrov, K., and Zakharova, L., *Int. J. Mol. Sci.*, 2022, vol. 23, p. 14992. https://doi.org/10.3390/ijms232314992
65. Babaie, S., Bakhshayesh, A.R.D., Ha, J.W., Hamishehkar, H., and Kim, K.H., *Nanomaterials*, 2020, vol. 10, p. 341. https://doi.org/10.3390/nano10020341
66. Kuznetsova, D.A., Gaynanova, G.A., Vasileva, L.A., Sibgatullina, G.V., Samigullin, D.V., Sapunova, A.S., Voloshina, A.D., Galkina, I.V., Petrov, K.A., and Zakharova, L.Ya., *J. Mater. Chem. B,* 2019, vol. 7, p. 7351. https://doi.org/10.1039/C9TB01853K
67. Kuznetsova, D.A., Vasileva, L.A., Gaynanova, G.A., Pavlov, R.V., Sapunova, A.S., Voloshina, A.D., Sibgatullina, G.V., Samigullin, D.V., Petrov, K.A., Zakharova, L.Ya., and Sinyashin, O.G., *J. Mol. Liq.*, 2021, vol. 330, p. 115703. https://doi.org/10.1016/j.molliq.2021.115703
68. Kuznetsova, D.A., Gabdrakhmanov, D.R., Gaynanova, G.A., Vasileva, L.A., Kuznetsov, D.M., Lukashenko, S.S., Voloshina, A.D., Sapunova, A.S., Nizameev, I.R., Sibgatullina, G.V., Samigullin, D.V., Kadirov, M.K., Petrov, K.A., and Zakharova, L.Ya., *Colloids Surf. Physicochem. Eng. Asp.*, 2021, vol. 610, p. 125673. https://doi.org/10.1016/j.colsurfa.2020.125673
69. Pavlov, R.V., Gaynanova, G.A., Kuznetsova, D.A., Vasileva, L.A., Zueva, I.V., Sapunova, A.S., Buzyurova, D.N., Babaev, V.M., Voloshina, A.D., Lukashenko, S.S., Rizvanov, I.Kh., Petrov, K.A., Zakharova, L.Ya., and Sinyashin, O.G., *Int. J. Pharm.*, 2020, vol. 587, p. 119640. https://doi.org/10.1016/j.ijpharm.2020.119640
70. Kuznetsova, D.A., Gaynanova, G.A., Vasilieva, E.A., Pavlov, R.V., Zueva, I.V., Babaev, V.M., Kuznetsov, D.M., Voloshina, A.D., Petrov, K.A., Zakharova, L.Y., and Sinyashin, O.G., *Pharmaceutics*, 2022, vol. 14, p. 1950. https://doi.org/10.3390/pharmaceutics14091950
71. Kuznetsova, D.A., Vasileva, L.A., Gaynanova, G.A., Vasilieva, E.A., Lenina, O.A., Nizameev, I.R., Kadirov, M.K., Petrov, K.A., Zakharova, L.Ya., and Sinyashin, O.G., *Int. J. Pharm.*, 2021, vol. 605, p. 120803. https://doi.org/10.1016/j.ijpharm.2021.120803
72. Mirgorodskaya, A.B., Koroleva, M.Y., Kushnazarova, R.A., Mishchenko, E.V., Petrov, K.A., Lenina, O.A., Vyshtakalyuk, A.B., Voloshina, A.D., and Zakharova, L.Y., *Nanotechnology*, 2022, vol. 33, p. 155103. https://doi.org/10.1088/1361-6528/ac467d
73. Kushnazarova, R.A., Mirgorodskaya, A.B., and Zakharova, L.Ya., *Russ. Chem. Bull.* 2021, vol. 70, p. 585. https://doi.org/10.1007/s11172-021-3129-z

74. Mirgorodskaya, A., Kushnazarova, R., Pavlov, R., Valeeva, F., Lenina, O., Bushmeleva, K., Kuryashov, D., Vyshtakalyuk, A., Gaynanova, G., Petrov, K., Zakharova, L. Ya., *Molecules*, 2022, vol. 27, p. 6447. https://doi.org/10.3390/molecules27196447
75. Rusanov, A.I., *Micelle Formation in Surfactant Solutions*, St. Petersburg: Khimiya, 1992.
76. Perinelli, D.R., Cespi, M., Lorusso, N., Palmieri, G.F., Bonacucina, G., and Blasi, P., *Langmuir*, 2020, vol. 36, no. 21, p. 5745. https://doi.org/10.1021/acs.langmuir.0c00420
77. Vinarov, Z., Katev, V., Radeva, D., Tcholakova, S., and Denkov, N.D., *Drug Dev. Ind. Pharm.*, 2018, vol. 44, p. 677. https://doi.org/10.1080/03639045.2017.1408642
78. Lu, Y., Zhang, E., Yang, J., and Cao, Z., *Nano Res.*, 2018, vol. 11, no. 10, p. 4985. https://doi.org/10.1007/s12274-018-2152-3
79. Zeng, X., Zhang, Y., Xu, X., Chen, Z., Ma, L., Wang, Y., Guo, X., Li, J., and Wang, X., *Drug Deliv.*, 2022, vol. 29, p. 792. https://doi.org/10.1080/10717544.2022.2048132
80. Wang, Q., Atluri, K., Tiwari, A.K., and Babu, R.J., *Pharmaceuticals*, 2023, vol. 16, p. 433. https://doi.org/10.3390/ph16030433
81. Das, B., Kumar, B., Begum, W., Bhattarai, A., Mondal, M.H., and Saha, B., *Chemistry Africa*, 2022, vol. 5, no. 3, p. 459. https://doi.org /10.1007/s42250-022-00345-0
82. Naharros-Molinero, A., Caballo-González, M.Á., De La Mata, F.J., and García-Gallego, S.*, Pharmaceutics*, 2022, vol. 14, no. 12, p. 2628. https://doi.org/10.3390/pharmaceutics14122628
83. Volkova, T., Simonova, O., and Perlovich, G., *Pharmaceutics*, 2023, vol. 15, no. 2, p. 422. https://doi.org/10.3390/pharmaceutics15020422
84. Talat, R., Fayyaz, S., Ali, S., Khalid, N., Haider, A., Shah, A., and Ullah, F., *J. Dispers. Sci. Technol.*, 2019, vol. 40, p. 958. https://doi.org/10.1080/01932691.2018.1489279
85. Ahmady, A. R., Hosseinzadeh, P., Solouk, A., Akbari, S., Szulc, A.M., and Brycki, B.E., *Adv. Colloid Interface Sci.,* 2022, vol. 299, p. 102581. https://doi.org/10.1016/j.cis.2021.102581
86. Zhang, D., Wang, H.-J., Cui, X.-M., and Wang, C.-X., *Pharm. Dev. Technol.,* 2017, vol. 22, no. 4, p. 511. https://doi.org/10.3109/10837450.2015.1131718
87. Hmingthansanga, V., Singh, N., Banerjee, S., Manickam, S., Velayutham, R., and Natesan, S., *Pharmaceutics*, 2022, vol.14, no. 12, p. 2818. https://doi.org/10.3390/pharmaceutics14122818
88. Sugumar, V., Hayyan, M., Madhavan, P., Wong, W.F., and Looi, C.Y., *Biomedicines*, 2023, vol. 11, no. 3, p. 664. https://doi.org/10.3390/biomedicines11030664
89. Pal, A., and Yadav, A., *J. Mol. Liq.*, 2018, vol. 251, p. 167. https://doi.org/10.1016/j.molliq.2017.12.058
90. Vasileva, L.A., Kuznetsova, D.A., Valeeva, F.G., Vasilieva, E.A., Lukashenko, S.S., Gaynanova, G.A., and Zakharova, L.Ya., *Russ. Chem. Bull.*, 2021, vol. 70, p. 1341. https://doi.org/10.1007/s11172-021-3221-4
91. Nokhodchi, A., Shokri, J., Dashbolaghi, A., Hassan-Zadeh, D., Ghafourian, T., and Barzegar-Jalali, M., *Int. J. Pharm.*, 2003, vol. 250, no. 2, p. 359. https://doi.org/10.1016/s0378-5173(02)00554-9
92. Zhao, Y., Zheng, H., Wang, X., Zheng, X., Chen, Y., Fei, W., Zheng, Y., Wang, W., and Zheng, C. *Int. J. Nanomedicine*, 2020, vol. 15, p. 3539. https://doi.org/10.2147/IJN.S251431
93. Sharma, D., Arora, S., Singh, J., and Layek, B., *Int. J. Biol. Macromol.*, 2021, vol. 183, p. 2055. https://doi.org/10.1016/j.ijbiomac.2021.05.192
94. Lu, Z., Zongjie, G., Qianyu, Z., Xueyan, L., Kexin, W., Baoyan, C., Ran, T., Fang, R., Hui, H., and Huali, C., *Eur. J. Pharm. Biopharm.*, 2023, vol. 182, p. 92. https://doi.org/10.1016/j.ejpb.2022.12.002
95. Gabdrakhmanov, D.R., Vasilieva, E.A., Voronin, M.A., Kuznetsova, D.A., Valeeva, F.G., Mirgorodskaya, A.B., Lukashenko, S.S., Zakharov, V.M., Mukhitov, A.R., Faizullin, D.A., Salnikov, V.V., Syakaev, V.V., Latypov, S.K., Zuev, Y.F., and Zakharova, L.Ya., *J. Phys. Chem. C,* 2020, vol. 124, p. 2178. https://doi.org/10.1021/acs.jpcc.9b10079
96. Fait, M.E., Bakas, L., Garrote, G.L., Morcelle, S.R., and Saparrat, M.C.N., *Appl. Microbiol. Biotechnol.*, 2019, vol. 103, p. 97. https://doi.org/10.1007/s00253-018-9467-6
97. Amerkhanova, S.K., Voloshina, A.D., Mirgorodskaya, A.B., Lyubina, A.P., Kuznetsova, D.A., Kushnazarova, R.A., Mikhailov, V. A., and Zakharova, L.Ya., *Int. J. Mol. Sci.*, 2021, vol. 22, no. 23, p. 13148. https://doi.org/10.3390/ijms222313148
98. Mirgorodskaya, A.B., Kushnazarova, R.A., Lukashenko, S.S., and Zakharova, L.Ya. *J. Mol. Liq.*, 2019, vol. 292, p. 111407. https://doi.org/10.1016/j.molliq.2019.111407
99. Pires, P.C., Paiva-Santos, A.C., and Veiga, F., *Pharmaceutics,* 2022, vol. 14, p. 2825. https://doi.org/10.3390/pharmaceutics14122825

100. Shukla, T., Upmanyu, N., Agrawal, M., Saraf, S., Saraf, S., and Alexander, A., *Biomed. Pharmacother.*, 2018, vol. 108, p. 1477. https://doi.org/ 10.1016/j.biopha.2018.10.021
101. Wilson, R.J., Li, Y., Yang, G., and Zhao, Ch.-X., *Particuology*, 2022, vol. 64, p. 85. https://doi.org/10.1016/j.partic.2021.05.009
102. Suhail, N., Alzahrani, A.K., Basha, W.J., Kizilbash, N., Zaidi, A., Ambreen, J., and Khachfe, H.M., *Front. Nanotechnol*., 2021, vol. 3, p. 754889. https://doi.org/10.3389/fnano.2021.754889
103. Souto, E.B., Cano, A., Martins-Gomes, C., Coutinho, T.E., Zielińska, A., and Silva, A.M., *Bioengineering,* 2022, vol. 9, p. 158. https://doi.org/10.3390/bioengineering9040158
104. McClements, D.J., *Soft Metter.*, 2012, vol. 8, p. 1719. https://doi.org/10.1039/C2SM06903B
105. Pavoni, L., Perinelli, D.R., Ciacciarelli, A., Quassinti, L., Bramucci, M., Miano, A., Casettari, L., Cespi, M., Bonacucina, G., and Palmieri, G.F., *J. Drug Delivery Sci. Technol*., 2020, vol. 58, p. 101772. https://doi.org/10.1016/j.jddst.2020.101772
106. Tartaro, G., Mateos, H., Schirone, D., Angelico, R., and Palazzo, G., *Nanomaterials*, 2020, vol. 10, p. 1657. https://doi.org/ 10.3390/nano10091657
107. Gibaud, S., and Attivi, D., *Expert Opin. Drug Deliv*., 2012, vol. 9, no. 8, p. 937. https://doi.org/10.15 17/17425247.2012.694865
108. Sabjan, K.B., Munawar, S.M., Rajendiran, D., Vinoji, S.K., and Kasinathan, K., *Curr. Drug. Res. Rev*., 2020, vol. 12, no. 1, p. 4. https://doi.org/10.2174/2589977511666191024173508
109. Ande, S.N., Sonone, K.B. Bakal, R.L., Ajmire, P.V., and Sawarkar, H.S., *Res. J. Pharm. Technol*., 2022, vol. 15, no. 10, p. 4829. https://doi.org/10.52711/0974-360X.2022.00811
110. Malode, G.P., Chavhan, S.A., Bartare, Sh.A., Malode, L.L., Manwar, J.V., and Bakal, R.L., *J. Pharm. Sci. Res*., 2022, vol. 4, no. 3, p. 6. https://doi.org/10.31069/japsr.v4i3.2
111. Fernández-Peña, L., Mojahid, B.Z.E., Guzmán, E., Ortega, F., and Rubio, R.G., *Colloids Interfaces*, 2021, vol. 5, p. 50. https://doi.org/10.3390/colloids5040050
112. Thakur, D., Kaur, G., Puri, A., and Nanda, R., *Curr. Drug Delivery*, 2021, vol. 18, no.9, p. 1218. https://doi.org/10.2174/1567201818666210217161240
113. Muhammed, S.A., and Al-Kinani, K.K., *F1000 Res.*, 2023, vol. 2, p. 315 https://doi.org/10.12688/f1000research.130749.1
114. Benbow, T. and Campbell, J. *Drug. Dev. Ind. Pharm*., 2019, vol. 45, no. 12, p. 1849. https://doi.org/10.1080/03639045.2019.1680996
115. Shewaiter, M.A., Hammady, T.M., El-Gindy, A., Hammadi, S.H., and Gad, Sh., *Drug Delivery Sci. Technol*., 2021, vol. 61, p. 102110. https://doi.org/10.1016/j.jddst.2020.102110
116. Lucca, L.G., Porto de Matos, S., Weimer, P., Teixeira, H.F., and Koester, L.S., *Arab. J. Chem.,* 2020, vol. 13, no. 2, p. 4505. https://doi.org/10.1016/j.arabjc.2019.09.005
117. Sipos, B., Csóka, I., Szivacski, N., Budai-Szűcs, M., Schelcz, Z., Zupkó, I., Szabó-Révész, P., Volk, B., and Katona, G., *Eur. J. Pharm. Sci*., 2022, vol. 175, p. 106229. https://doi.org/10.1016/j.ejps.2022.106229
118. Schirone, D., Tartaro, G., Gentile, L., and Palazzo, G., *JCIS Open*, 2021, vol. 4, p. 100033. https://doi.org/10.1016/j.jciso.2021.100033.
119. Altamimi, M.A., Hussain, A., Alshehri, S., Imam, S.S., and Alnemer, U.A., *Pharmaceutic*s, 2021, vol. 13, p. 1218. https://doi.org/10.3390/pharmaceutics13081218
120. Mirgorodskaya, A.B., Kushnazarova, R.A., Lenina, O.A., Petrov, K.A., and Zakharova, L.Ya., *Russ. J. Gen. Chem*., 2023, vol. 93. no. 3, p. 593. https://doi.org/10.1134/S1070363223030167
121. Bazán Henostroza, M.A., Curo Melo, K.J., Nishitani Yukuyama, M., Löbenberg, R., and Araci Bou-Chacra, N. *Colloids. Surf. A. Physicochem. Eng. Asp.,* 2020, vol. 597, p. 124755. https://doi.org/10.1016/j.colsurfa.2020.124755
122. Dukovski, J.B., Juretic, M., Bracko, D., Randjelovic, D., Savic, S., Crespo Moral, M., Diebold, Y., Filipović-Grčić, J., Pepić, I., and Lovrić, J., *Int. J. Pharm*. 2020, vol. 576, p. 118979. https://doi.org/10.1016/j.ijpharm.2019.118979
123. Koutsoviti, M., Siamidi, A., Pavlou, P., and Vlachou, M., *Materials*, 2021, vol. 14, no.15, p. 4290. https://doi.org/10.3390/ma14154290
124. Choradiya, B.R., and Patil, S.B., *J. Mol. Liq.,* 2021, vol. 339, p. 116751. https://doi.org/10.1016/j.molliq.2021.116751
125. Torres-Luna, C., Hu, N., Tammareddy, T., Domszy, R., Yang, J., Wang, N.S., and Yang. A., *Cont. Lens. Anterior. Eye,* 2019, vol. 42, no. 5, p. 546. https://doi.org/10.1016/j.clae.2019.04.011
126. Garg, T., Rath, G., and Goyal, A.K., *Drug Delivery*, 2015, vol. 22, no. 8, p. 969. https://doi.org/10.3109/10717544.2013.879355
127. Molokhova, E.I., Sorokina, Yu.V., and Lipin, D.E., *Drug Develop. Registrat.*, 2021, vol. 10, no. 4, p. 89. https://doi.org/10.33380/2305-2066-2021-10-4-89-95

128. Patil, P., Datir, S., and Saudagar, R., *J. Drug Delivery Therap.*, 2019, vol. 9, p. 989. https://jddtonline.info/index.php/jddt/article/view/2930
129. Bohidar, H.B, Dubin, P., and Osada, Y., *Polymer Gels, Fundamentals and Applications*, Washington, DC, USA: American Chemical Society, 2003, 1st ed.
130. Donthi, M.R., Munnangi, S.R., Krishna, K.V., Saha, R.N., Singhvi, G., and Dubey, S.K., *Pharmaceutics*, 2023, vol. 15, p. 164. https://doi.org/10.3390/pharmaceutics15010164
131. Ahmad, M.Z., Ahmad, J., Alasmary, M.Y., Akhter, S., Aslam, M., Pathak, K., Jamil, P., and Abdullah, M.M., *J. Drug Deliv. Sci. Technol*., 2022, vol. 72, p. 103420. https://doi.org/10.1016/j.jddst.2022.103420
132. Pandey, P., Minocha, N., Vashist, N., Shah, R., Saini, S., Makhija, M., Purohit, D., and Kaushik, D., *Drug Deliv. Lett.,* 2022, vol. 12, no. 4, p. 227. https://doi.org/10.2174/2210303112666220818115231
133. Lal, D.K., Kumar, B., Saeedan, A.S., and Ansari, M.N., *Pharmaceutics,* 2023, vol. 15, p. 1187. https://doi.org/10.3390/pharmaceutics15041187
134. Singh, S., Parashar, P., Kanoujia, J., Singh, I., Saha, S., and Saraf, S.A., J. *Drug Delivery Sci. Technol*., 2017, vol. 39, p. 348. https://doi.org/10.1016/j.jddst.2017.04.020
135. Qumbar, M., Ameeduzzafar, Imam, S.S., Ali, J., Ahmad, J., and Ali, A., *Biomed. Pharmacother*., 2017, vol. 93, p. 255. https://doi.org/10.1016/j.biopha.2017.06.043
136. Shinde, U.A., Modani, S.H., and Singh, K.H., *AAPS Pharm. Sci. Tech*. 2018, vol. 19, p. 315. https://doi.org/10.1208/s12249-017-0811-4
137. Mohammadi-Samani, M. Masoumzadeh, P., Ghasemiyeh, P., and Alipour, S., *Front. Mater*., 2022, vol. 9, p. 848629. https://doi.org/10.3389/fmats.2022.848629
138. Khan, B.A., Ali, A., Hosny, K.M., Halwani, A.A., Almehmady, A.M., Iqbal, M., Alharbi, W.S., Abualsunun, W.A., Bakhaidar, R.B., Murshid, S.S.A., and Khan, M.K., *Drug Delivery*, 2022, vol. 29, no. 1, p. 52. https://doi.org/10.1080/10717544.2021.2015483
139. Castro, M.A., Reis, P.H., Fernandes, C., Sousa, R.G., Inoue, T.T., Fialho, S.L., and Silva-Cunha, A. *Int. J. Pharm.,* 2023, vol. 631, p. 122468. https://doi.org/10.1016/j.ijpharm.2022.122468
140. Khan, B.A., Ahmad, S., Khan, M.K., Hosny, K.M., Bukhary, D.M., Iqbal, H., Murshid, S.S., Halwani, A.A., Alissa, M., and Menaa, F., *Gels*, 2022, vol. 8, p. 608. https://doi.org/10.3390/gels8100608
141. Adegbenro, O.O., Opeyemi, O.T., *Univers. J. Pharm. Res*. 2019, vol. 4, p. 23. https://doi.org/10.22270/ujpr.v4i3.265
142. Chandur, V. K., Thrishna, T.K., and Shabaraya, A.R., *Int. J. Health. Sci. Res*., 2023, vol. 13, no.1, p. 44. https://doi.org/10.52403/ijhsr.20230108
143. Mwangi, A.N., Njogu, P.M., Maru, S.M., Njuguna, N.M., Njaria, P.M., Kiriiri, G.K., and Mathenge, A.W., *Saudi Pharm. J.*, 2021, vol. 29, no. 4, p. 351. https://doi.org/10.1016/j.jsps.2021.03.005
144. Albahri, G., Badran, A., Hijazi, A., Daou, A., Baydoun, E., Nasser, M., and Merah, O., *Life*, 2023, vol. 13, p. 317. https://doi.org/10.3390/life13020317
145. McClements, D.J., Das, A.K., Dhar, P., Nanda, P.K., and Chatterjee, N., *Front. Sustain. Food Syst*., 2021, vol. 5, p. 643208. https://doi.org/10.3389/fsufs.2021.643208
146. Kataev, V.E., Strobykina, I.Yu., and Zakharova, L.Ya., *Russ. Chem. Bull.*, 2014, vol. 63, p. 1884. https://doi.org/10.1007/s11172-014-0680-x
147. Azam, F., Alqarni, M.H., Alnasser, S.M., Alam, P., Jawaid, T., Kamal, M., Khan, S., and Alam, A., *Gels*, 2023, vol. 9, no. 2, p.111. https://doi.org/10.3390/gels9020111
148. Alqarni, M.H., Foudah, A.I., Aodah, A.H., Alkholifi, F.K., Salkini, M.A., and Alam, A., *Gels,* 2023, vol. 9, no. 3, p. 193. https://doi.org/10.3390/gels9030193
149. Ullah, N., Amin, A., Farid, A., Selim, S., Rashid, S.A., Aziz, M.I., Kamran, S.H., Khan, M.A., Rahim Khan, N., Mashal, S., and Mohtasheemul Hasan, M., *Gels*, 2023, vol. 9, no. 3, p. 252. https://doi.org/10.3390/gels9030252
150. Zulkefli, N., Che Zahari, C.N.M., Sayuti, N.H., Kamarudin, A.A., Saad, N., Hamezah, H.S., Bunawan, H., Baharum, S.N., Mediani, A., Ahmed, Q.U., Ismail, A.F.H., and Sarian, M.N., *Int. J. Mol. Sci.,* 2023, vol. 24, p. 4607. https://doi.org/10.3390/ijms24054607
151. Sychrová, A., Škovranová, G., Čulenová, M., and Bittner Fialová, S., *Molecules*, 2022, vol. 27, no. 14, p. 4491. https://doi.org/10.3390/molecules27144491
152. Handa, M., Ujjwal, R.R., Vasdev, N., Flora, S.J.S., and Shukla, R., *ACS Omega*, 2020, vol. 6, no. 1, p. 559. https://doi.org/10.1021/acsomega.0c05033
153. Zhang, Y., Xin, C., Cheng, C., and Wang, Z., *Arab. J. Chem*., 2020, vol. 13, no. 11, p. 8226. https://doi.org/10.1016/j.arabjc.2020.09.058
154. Kumar, B., Pandey, M., Aggarwal, R., and Sahoo, P.K., *Futur. J. Pharm. Sci.,* 2022, vol. 8, p. 50. https://doi.org/10.1186/s43094-022-00440-6

155. Assali, M., Jaradat, N., and Maqboul, L., *ACS Omega,* 2022, vol. 7, no. 46, p. 42096. https://doi.org/10.1021/acsomega.2c04238
156. Dong, J., Zhu, X.M., Wu, F.Y.,Yang, B.Q., Feng, H., Dong, Y.F,. Gu, W., and Chen, J., *Drug. Dev. Ind. Pharm*., 2020, vol. 46, no. 1, p. 91. https://doi.org/10.1080/03639045.2019.1706548
157. Li, J., Xie, Q., Ma, R., Li, Y., Yuan, J., Ren, M., Li, H., Wang, J., Lu, D., Xu, Z., and Wang, J., *Front. Med*., 2021, vol. 8, 750170. https://www.frontiersin.org/articles/10.3389/fmed.2021.750170
158. Liu, S., Long, Y., Yu, S., Zhang, D.,Yang, Q., Ci, Z., Cui, M., Zhang, Y., Wan, J., Li, D., Shi, A., Li, N., Yang, M., Lin, J., *Pharm. Res*., 2021, vol. 169, p. 105627. https://doi.org/10.1016/j.phrs.2021.105627
159. Yuan, R., Huang, Y., Chan, L., He, D., and Chen, T., *ACS Appl. Mater. Interfaces*, 2020, vol. 12, no. 41, p. 45714. https://doi.org/10.1021/acsami.0c08069
160. Nikolic, I., Mitsou, E., Pantelic, I., Randjelovic, D., Markovic, B., Papadimitriou, V., Xenakis, A., Lunter, D.J., Zugic, A., and Savic, S., *Eur. J. Pharm. Sci*., 2020, vol. 142, p. 105135. https://doi.org/10.1016/j.ejps.2019.105135
161. Lu, K.H., Lu, P.W., Lu, E.W., Lin, C.W., and Yang, S.F., *Int. J. Biol. Sci*., 2023, vol. 19(4), p. 1241. https://doi.org/10.7150/ijbs.80590
162. Laurindo, L.F., de Carvalho, G.M., de Oliveira Zanuso, B, Figueira, M.E., Direito, R., de Alvares Goulart, R., Buglio, D.S., Barbalho, S.M., *Pharmaceutics*. 2023, vol. 15, no. 1, p. 229. https://doi.org/10.3390/pharmaceutics15010229
163. Wendorff-Tobolla, L.M., Wolgin, M., Wagner, G., Klerings, I., Dvornyk, A., Kielbassa, A.M., *Biomedicines*, 2023, vol. 11, p. 481. https://doi.org/10.3390/biomedicines11020481
164. Bangham, A.D., *Hosp. Pract.*, 1992, vol. 27, p. 51. https://doi.org/10.1080/21548331.1992.11705537
165. Apolinário, A.C., Hauschke, L., Nunes, J.R., and Lopes, L.B., *Prog. Lipid Res*., 2021, vol. 82, p. 101096. https://doi.org/10.1016/j.plipres.2021.101096
166. Eloy, J.O., Claro De Souza, M., Petrilli, R., Barcellos, J.P.A., Lee, R.J., and Marchetti, J.M., *Colloids Surf., B*, 2014, vol. 123, p. 345. https://doi.org/10.1016/j.colsurfb.2014.09.029
167. Hwang, J.Y., Li, Z., and Loh, X.J., *RSC Adv.*, 2016, vol. 6, p. 70592. https://doi.org/10.1039/C6RA09854A
168. Jebastin, K. and Narayanasamy, D., *J. Liposome Res.*, 2023, vol. 33, p. 1. https://doi.org/10.1080/08982104.2022.2069809
169. Bhatia, R., Sharma, A., Narang, R.K., and Rawal, R.K., *Curr. Mol. Pharmacol.*, 2021, vol. 14, p. 350. https://doi.org/10.2174/1874467213666200730114943
170. Pedziwiatr-Werbicka, E., Horodecka, K., Shcharbin, D., and Bryszewska, M., *Curr. Med. Chem.*, 2020, vol. 28, p. 346. https://doi.org/10.2174/0929867327666200130101605
171. Dymek, M. and Sikora, E., *Adv. Colloid Interface Sci.* 2022, vol. 309, p. 102757. https://doi.org/10.1016/j.cis.2022.102757
172. Shah, S., Famta, P., Raghuvanshi, R.S., Singh, S.B., and Srivastava, S., *Colloid Interface Sci. Commun.*, 2022, vol. 46, p. 100570. https://doi.org/10.1016/j.colcom.2021.100570
173. Briuglia, M.-L., Rotella, C., McFarlane, A., and Lamprou, D.A., *Drug Deliv. Transl. Res.*, 2015, vol. 5, p. 231. https://doi.org/10.1007/s13346-015-0220-8
174. Feigenson, G.W., *Biochim. Biophys. Acta BBA – Biomembr.*, 2009, vol. 1788, p. 47. https://doi.org/10.1016/j.bbamem.2008.08.014
175. McMullen, T.P.W., Lewis, R.N.A.H., and McElhaney, R.N., *Curr. Opin. Colloid Interface Sci.*, 2004, vol. 8, p. 459. https://doi.org/10.1016/j.cocis.2004.01.007
176. Binder, W.H., Barragan, V., and Menger, F.M., *Angew. Chem. Int. Ed.*, 2003, vol. 42, p. 5802. https://doi.org/10.1002/anie.200300586
177. Kaddah, S., Khreich, N., Kaddah, F., Charcosset, C., and Greige-Gerges, H., *Food Chem. Toxicol.*, 2018, vol. 113, p. 40. https://doi.org/10.1016/j.fct.2018.01.017
178. Lim, E.-B., Haam, S., and Lee, S.-W., *Colloids Surf., A*, 2021, vol. 618, p. 126447. https://doi.org/10.1016/j.colsurfa.2021.126447
179. Milla, P., Dosio, F., and Cattel, L., *Curr. Drug Metab.*, 2012, vol. 13, p. 105. https://doi.org/10.2174/138920012798356934
180. Steffes, V.M., Zhang, Z., MacDonald, S., Crowe, J., Ewert, K.K., Carragher, B., Potter, C.S., and Safinya, C.R., *ACS Appl. Mater. Interfaces*, 2020, vol. 12, p. 151. https://doi.org/10.1021/acsami.9b16150
181. Klein, M.E., Mauch, S., Rieckmann, M., Martínez, D.G., Hause, G., Noutsias, M., Hofmann, U., Lucas, H., Meister, A., Ramos, G., Loppnow, H., and Mäder, K., *Nanomedicine Nanotechnol. Biol. Med.*, 2020, vol. 23, p. 102096. https://doi.org/10.1016/j.nano. 2019.102096
182. Zalba, S., ten Hagen, T.L.M., Burgui, C., and Garrido, M.J., *J. Control. Rel.*, 2022, vol. 351, p. 22. https://doi.org/10.1016/j.jconrel.2022.09.002

183. Klein, M.E., Rieckmann, M., Sedding, D., Hause, G., Meister, A., Mäder, K., Lucas, H., *Pharmaceutics*, 2021, vol. 13, p. 282. https://doi.org/10.3390/pharmaceutics13020282
184. Fang, Y., Xue, J., Gao, S., Lu, A., Yang, D., Jiang, H., He, Y., and Shi, K., *Drug Deliv.*, 2017, vol. 24, p. 22. https://doi.org/10.1080/10717544.2017.1388451
185. Zhang, D., Atochina-Vasserman, E.N., Maurya, D.S., Huang, N., Xiao, Q., Ona, N., Liu, M., Shahnawaz, H., Ni, H., Kim, K., Billingsley, M.M., Pochan, D.J., Mitchell, M.J., Weissman, D., and Percec, V., *J. Am. Chem. Soc.*, 2021, vol. 143, p. 12315. https://doi.org/10.1021/jacs.1c05813
186. Yao, X., Qi, C., Sun, C., Huo, F., and Jiang, X., *Nano Today*, 2023, vol. 48, p. 101738. https://doi.org/10.1016/j.nantod.2022.101738
187. Liu, P., Chen, G., and Zhang, J., *Molecules*, 2022, vol. 27, p. 1372. https://doi.org/10.3390/molecules27041372
188. Thapa Magar, K., Boafo, G.F., Li, X., Chen, Z., and He, W., *Chin. Chem. Lett.*, 2022, vol. 33, p. 587. https://doi.org/10.1016/j.cclet.2021.08.020
189. Zhang, L., Gu, F., Chan, J., Wang, A., Langer, R., and Farokhzad, O., *Clin. Pharmacol. Ther.*, 2008, vol. 83, p. 761. https://doi.org/10.1038/sj.clpt.6100400
190. Park, K., *ACS Nano*, 2013, vol. 7, p. 7442. https://doi.org/10.1021/nn404501g
191. Farjadian, F., Ghasemi, A., Gohari, O., Roointan, A., Karimi, M., and Hamblin, M.R., *Nanomed.*, 2019, vol. 14, p. 93. https://doi.org/10.2217/nnm-2018-0120
192. Deshantri, A.K., Varela Moreira, A., Ecker, V., Mandhane, S.N., Schiffelers, R.M., Buchner, M., and Fens, M.H.A.M., *J. Control. Rel.*, 2018, vol. 287, p. 194. https://doi.org/10.1016/j.jconrel.2018.08.034
193. Mehta, S., Kulkarni, S., Nikam, A.N., Padya, B.S., Pandey, A., and Mutalik, S., *Curr. Pharm. Des.*, 2021, vol. 27, p. 1977. https://doi.org/10.2174/1381612827666210311142100
194. Bukhari, S.I., Imam, S.S., Ahmad, M.Z., Vuddanda, P.R., Alshehri, S., Mahdi, W.A., Ahmad, J., *Pharmaceutics*, 2021, vol. 13, p. 840. https://doi.org/10.3390/pharmaceutics13060840
195. Llop, J. and Lammers, T., *ACS Nano*, 2021, vol. 15, p. 16974. https://doi.org/10.1021/acsnano.1c09139
196. Cheng, X., Gao, J., Ding, Y., Lu, Y., Wei, Q., Cui, D., Fan, J., Li, X., Zhu, E., Lu, Y., Wu, Q., Li, L., and Huang, W., *Adv. Sci.,* 2021, vol. 8, p. 2100876. https://doi.org/10.1002/advs.202100876
197. Rabiee, N., Yaraki, M.T., Garakani, S.M., Garakani, S.M., Ahmadi, S., Lajevardi, A., Bagherzadeh, M., Rabiee, M., Tayebi, L., Tahriri, M., and Hamblin, M.R., *Biomaterials*, 2020, vol. 232, p. 119707. https://doi.org/10.1016/j.biomaterials.2019.119707
198. Zhang, H., Bo, S., Zeng, K., Wang, J., Li, Y., Yang, Z., Zhou, X., Chen, S., and Jiang, Z.-X., *J. Mater. Chem. B*, 2020, vol. 8, p. 4469. https://doi.org/10.1039/D0TB00083C
199. Pavlov, R.V., Mironov, N.A., Gaynanova, G.A., Lyubina, A.P., Voloshina, A.D., Yakubov, M.R., and Zakharova, L.Ya., *Russ. Chem. Bull.*, 2022, vol. 71, p. 1992. https://doi.org/10.1007/s11172-022-3619-7
200. Demir, B., Moulahoum, H., Ghorbanizamani, F., Barlas, F.B., Yesiltepe, O., Gumus, Z.P., Meral, K., Odaci Demirkol, D., and Timur, S., *J. Drug Deliv. Sci. Technol.*, 2021, vol. 62, p. 102363. https://doi.org/10.1016/j.jddst.2021.102363
201. Musumeci, T., Bonaccorso, A., De Gaetano, F., Larsen, K.L., Pignatello, R., Mazzaglia, A., Puglisi, G., and Ventura, C.A., *J. Liposome Res.*, 2020, vol. 30, p. 407. https://doi.org/10.1080/08982104.2019.1682603
202. Ghorbanizamani, F., Moulahoum, H., Zihnioglu, F., Timur, S., *Biomater. Sci.*, 2020, vol. 8, p. 3237. https://doi.org/10.1039/D0BM00401D.
203. Katagiri, K., Hashizume, M., Ariga, K., Terashima, T., and Kikuchi, J., *Chem.-Eur. J.,* 2007, vol. 13, p. 5272. https://doi.org/10.1002/chem.200700175
204. Yue, X., and Dai, Z., *Adv. Colloid. Interface Sci.*, 2014, vol. 207, p. 32. https://doi.org/10.1016/j.cis.2013.11.014
205. Denieva, Z.G., Budanova, U.A., and Sebyakin, Yu.L., *Biol. Membr.*, 2021, vol. 38, p. 44. https://doi.org/10.31857/S0233475520060043
206. Wu, S., Jiang, M., Mao, H., Zhao, N., He, D., Chen, Q., Liu, D., Zhang, W., and Song, X.-M., *Anal. Bioanal. Chem.*, 2022, vol. 414, p. 3593. https://doi.org/10.1007/s00216-022-03986-9
207. Liu, D., Wu, Q., Zou, S., Bao, F., Kikuchi, J., and Song, X.-M., *Bioelectrochemistry*, 2020, vol. 132, p. 107411. https://doi.org/10.1016/j.bioelechem.2019.107411
208. Ma, X., Yao, M., Shi, J., Li, X., Gao, Y., Luo, Q., Hou, R., Liang, X., and Wang, F., *ACS Nano*, 2020, vol. 14, p. 15904. https://doi.org/10.1021/acsnano. 0c07287
209. Ma, Q., Wu, S., Yang, L., Wei, Y., He, C., Wang, W., Zhao, Y., Wang, Z., Yang, S., Shi, D., Liu, Y., Zhou, Z., Sun, J., and Zhou, Y., *Adv. Sci.*, 2023, vol. 10, p. 2202416. https://doi.org/10.1002/advs.202202416

210. Shen, P., Ge, Q., Zhao, Y., Zhu, M., Huang, T., and Sun, Q., *ACS Appl. Nano Mater.*, 2023, vol. 6, p. 772. https://doi.org/10.1021/acsanm.2c05172
211. Saka, R. and Chella, N., *Environ. Chem. Lett.*, 2021, vol. 19, p. 1097. https://doi.org/10.1007/s10311-020-01103-9
212. Chaudhari, V.S., Murty, U.S., and Banerjee, S., *Environ. Chem. Lett.*, 2020, vol. 18, p. 1803. https://doi.org/10.1007/s10311-020-01042-5
213. Gao, Q., Feng, J., Liu, W., Wen, C., Wu, Y., Liao, Q., Zou, L., Sui, X., Xie, T., Zhang, J., and Hu, Y., *Adv. Drug Deliv. Rev.*, 2022, vol. 188, p. 114445. https://doi.org/10.1016/j.addr.2022.114445
214. Halevas, E.G., Avgoulas, D.I., Katsipis, G., and Pantazaki, A.A., *Eur. J. Med. Chem. Rep.*, 2022, vol. 5, p. 100059. https://doi.org/10.1016/j.ejmcr.2022.100059
215. Turuvekere Vittala Murthy, N., Agrahari, V., and Chauhan, H., *Eur. J. Pharm. Biopharm.*, 2021, vol. 161, p. 66. https://doi.org/10.1016/j.ejpb.2021.02.003
216. Landucci, E., Mazzantini, C., Calvani, M., Pellegrini-Giampietro, D.E., and Bergonzi, M.C., *Pharmaceutics*, 2023, vol. 15, p. 578. https://doi.org/10.3390/pharmaceutics15020578
217. Andrade, S., Pereira, M.C., and Loureiro, J.A., *Colloids Surf. B: Biointerfaces,* 2023, vol. 225, p. 113270. https://doi.org/10.1016/j.colsurfb.2023.113270
218. Li, C., Bai, M., Chen, X., Hu, W., Cui, H., and Lin, L., *Food Biosci.*, 2022, vol. 46, p. 101578. https://doi.org/10.1016/j.fbio.2022.101578
219. Wang, G., Yang, Y., Yi, D., Yuan, L., Yin, P.-H., Ke, X., Jun-Jie, W., and Tao, M.-F., *J. Liposome Res.*, 2022, vol. 32, p. 250. https://doi.org/10.1080/08982104.2021.1999974
220. Miranda-Cadena, K., Dias, M., Costa-Barbosa, A., Collins, T., Marcos-Arias, C., Eraso, E., Pais, C., Quindós, G., and Sampaio, P., *Antimicrob. Agents Chemother.*, 2021, vol. 65, p. e01628-20. https://doi.org/10.1128/AAC.01628-20
221. Rigi, M., Ojagh, S.M., Alishahi, A., and Hasani, S., *J. Aquat. Food Prod. Technol.*, 2022, vol. 31, p. 591. https://doi.org/10.1080/10498850.2022.2081951
222. Woźniak, M., Nowak, M., Lazebna, A., Więcek, K., Jabłońska, I., Szpadel, K., Grzeszczak, A., Gubernator, J., and Ziółkowski, P., *Pharmaceuticals*, 2021, vol. 14, p. 374. https://doi.org/10.3390/ph14040374
223. Ternullo, S., Gagnat, E., Julin, K., Johannessen, M., Basnet, P., Vanić, Ž., and Škalko-Basnet, N., *Eur. J. Pharm. Biopharm.*, 2019, vol. 144, p. 154. https://doi.org/10.1016/j.ejpb.2019.09.016
224. Song, J.-W., Liu, Y.-S., Guo, Y.-R., Zhong, W.-X., Guo, Y.-P., and Guo, L., *Int. J. Mol. Sci.*, 2022, vol. 23, p. 6858. https://doi.org/10.3390/ijms23126858
225. Piwowarczyk, L., Mlynarczyk, D.T., Krajka-Kuźniak, V., Majchrzak-Celińska, A., Budzianowska, A., Tomczak, S., Budzianowski, J., Woźniak-Braszak, A., Pietrzyk, R., Baranowski, M., Goslinski, T., and Jelinska, A., *Cancers*, 2022, vol. 14, p. 6222. https://doi.org/10.3390/cancers14246222
226. Jagwani, S., Jalalpure, S., Dhamecha, D., Jadhav, K., and Bohara, R., *ACS Biomater. Sci. Eng.*, 2020, vol. 6, p. 4969. https://doi.org/10.1021/acsbiomaterials.0c00429
227. Jøraholmen, M., Basnet, P., Tostrup, M., Moueffaq, S., and Škalko-Basnet, N., *Pharmaceutics*, 2019, vol. 11, p. 53. https://doi.org/10.3390/pharmaceutics11020053
228. Kong, D., Hong, W., Yu, M., Li, Y., Zheng, Y., and Ying, X., *Int. J. Nanomedicine*, 2022, vol. 17, p. 1087. https://doi.org/10.2147/IJN.S346948
229. Ramli, N.A., Ali, N., Hamzah, S., and Yatim, N.I., *Heliyon*, 2021, vol. 7, p. e06649. https://doi.org/10.1016/j.heliyon.2021.e06649
230. Refaat, H., Mady, F.M., Sarhan, H.A., Rateb, H.S., and Alaaeldin, E., *Int. J. Pharm.*, 2021, vol. 592, p. 120028. https://doi.org/10.1016/j.ijpharm.2020.120028
231. Aytekin, A.A., Tuncay Tanrıverdi, S., Aydın Köse, F., Kart, D., Eroğlu, İ., and Özer, Ö., *J. Liposome Res.*, 2020, vol. 30, p. 107. https://doi.org/10.1080/08982104.2019.1599012
232. El-aziz, E.A.E.A., Elgayar, S.F., Mady, F.M., Abourehab, M.A.S., Hasan, O.A., Reda, L.M., and Alaaeldin, E., *Pharmaceutics*, 2021, vol. 13, p. 2184. https://doi.org/10.3390/pharmaceutics13122184
233. Vanaga, I., Gubernator, J., Nakurte, I., Kletnieks, U., Muceniece, R., and Jansone, B., *Molecules*, 2020, vol. 25, p. 1801. https://doi.org/10.3390/molecules25081801
234. Hammoud, Z., Gharib, R., Fourmentin, S., Elaissari, A., and Greige-Gerges, H., *Int. J. Pharm.*, 2020, vol. 579, p. 119151. https://doi.org/10.1016/j.ijpharm.2020.119151
235. Sumithaa, C., Manjunathan, T., Mazuryk, O., Peters, S., Pillai, R.S., Brindell, M., Gopinath, P., and Ganeshpandian, M., *ACS Appl. Bio Mater.*, 2022, vol. 5, p. 3241. https://doi.org/10.1021/acsabm.2c00231
236. Verma, S. and Utreja, P., *Micro Nanosyst.,* 2022, vol. 14, p. 3. https://doi.org/10.2174/1876402913666210406163452

237. Maddiboyina, B., Ramaiah, Nakkala, R.K., and Roy, H., *Chem. Biol. Drug Des.*, 2023, p. 1. https://doi.org/10.1111/cbdd.14230
238. Nayak, A.K., Hasnain, M.S., Aminabhavi, T.M., and Torchilin, V.P., *Systems of Nanovesicular Drug Delivery*, Amsterdam: Elsevier, 2022, p. 1. https://doi.org/10.1016/B978-0-323-91864-0.00026-7
239. Zhu, H., Yang, C., and Ma, K., *Applications of Nanovesicular Drug Delivery*, Amsterdam: Elsevier, 2022, p. 103. https://doi.org/10.1016/B978-0-323-91865-7.00012-2
240. Abdelkader, H., Alani, A.W.G., and Alany, R.G., *Drug Deliv.,* 2014, vol. 21, p. 87. https://doi.org/10.3109/10717544.2013.838077
241. Ge, X., Wei, M., He, S., and Yuan, W.-E., *Pharmaceutics,* 2019, vol. 11, p. 55. https://doi.org/10.3390/pharmaceutics11020055
242. Izhar, M.P., Hafeez, A., Kushwaha, P., and Simrah, *J. Clust. Sci.,* 2023, https://doi.org/10.1007/s10876-023-02423-w
243. Basha, M., Abd El-Alim, S.H., Shamma, R.N., and Awad, G.E.A., *J. Liposome Res.,* 2013, vol. 23, p. 203. https://doi.org/10.3109/08982104.2013.788025
244. Wagdi, M.A., Salama, A., El-Liethy, M.A., and Shalaby, E.S., *J. Drug Deliv. Sci. Technol.,* 2023, vol. 84, p. 104456. https://doi.org/10.1016/j.jddst.2023.104456
245. Saeidi, Z., Giti, R., Rostami, M., and Mohammadi, F., *Adv. Pharm. Bull.,* 2023, vol. 1, p. 1. https://doi.org/10.34172/apb.2023.070
246. Momekova, D.B., Gugleva, V.E., and Petrov, P.D., *ACS Omega,* 2021, vol. 6, p. 33265. https://doi.org/10.1021/acsomega.1c05083
247. Taymouri, S., and Varshosaz, J., *Adv. Biomed. Res.,* 2016, vol. 5, p. 48. https://doi.org/10.4103/2277-9175.178781
248. Alam, M., Rizwanullah, Md., Mir, S.R., and Amin, S., *OpenNano,* 2023, vol. 10, p. 100123. https://doi.org/10.1016/j.onano. 2023.100123
249. Al-Zuhairy, S.A.S., S. El-Sawy, H., El-Nabarawi, M.A., and Teaima, M.H., *Int. J. Appl. Pharm.,* 2023, p. 36. https://doi.org/10.22159/ijap.2023v15i1.46280
250. Marianecci, C., Di Marzio, L., Rinaldi, F., Celia, C., Paolino, D., Alhaique, F., Esposito, S., and Carafa, M., *Adv. Colloid Interface Sci.,* 2014, vol. 205, p. 187. https://doi.org/10.1016/j.cis.2013.11.018
251. Samed, N., Sharma, V., and Sundaramurthy, A., *Appl. Surf. Sci.* 2018, vol. 449, p. 567. https://doi.org/10.1016/j.apsusc.2017.11.055
252. Ning, M., Guo, Y., Pan, H., Yu, H., and Gu, Z., *Drug Deliv.,* 2005, vol. 12, p. 399. https://doi.org/10.1080/10717540590968891
253. Yeo, L., Olusanya, T., Chaw, C., and Elkordy, A., *Pharmaceutics,* 2018, vol. 10, p. 185. https://doi.org/10.3390/pharmaceutics10040185
254. Zhang, W., Zhao, X., Yu, G., and Suo, M., *J. Biomater. Sci. Polym. Ed.,* 2021, vol. 32, p. 858. https://doi.org/10.1080/09205063.2021.1877064
255. Ferreira, M.D., Duarte, J., Veiga, F., Paiva-Santos, A.C., and Pires, P.C., *Pharmaceutics,* 2023, vol. 15, p. 678. https://doi.org/10.3390/pharmaceutics15020678
256. Pham, T.T., Jaafar-Maalej, C., Charcosset, C., and Fessi, H., *Colloids Surf. B,* 2012, vol. 94, p. 15. https://doi.org/10.1016/j.colsurfb.2011.12.036
257. Abtahi, N.A., Naghib, S.M., Haghiralsadat, F., Reza, J.Z., Hakimian, F., Yazdian, F., and Tofighi, D., *Nanotechnol. Rev.,* 2021, vol. 10, p. 1895. https://doi.org/10.1515/ntrev-2021-0119
258. Al Qtaish, N., Gallego, I., Villate-Beitia, I., Sainz-Ramos, M., López-Méndez, T.B., Grijalvo, S., Eritja, R., Soto-Sánchez, C., Martínez-Navarrete, G., Fernández, E., Puras, G., and Pedras, J.L., *Pharmaceutics,* 2020, vol. 12, p. 198. https://doi.org/10.3390/pharmaceutics12030198
259. Roque, L., Fernández, M., Benito, J.M., and Escudero, I., *Colloids Surf., A,* 2020, vol. 601, p. 124999, https://doi.org/10.1016/j.colsurfa.2020.124999
260. Ojeda, E., Puras, G., Agirre, M., Zarate, J., Grijalvo, S., Eritja, R., Martinez-Navarrete, G., Soto-Sánchez, C., Diaz-Tahoces, A., Aviles-Trigueros, M., Fernandez, E., and Pedraz, J.L., *Biomaterials* 2016, vol. 77, p. 267. https://doi.org/10.1016/j.biomaterials.2015.11.017
261. Kaushal, U., Kaur, M., Nagpal, M., Bhuyan, M., and Gounder, K.P., *Curr. Drug Res. Rev.,* 2023, vol. 15, p. 15. https://doi.org/10.2174/2589977514666220913120718
262. Elkomy, M.H., Ali, A.A., and Eid, H.M., *J. Control. Rel.,* 2022, vol. 351, p. 923. https://doi.org/10.1016/j.jconrel.2022.10.005
263. Colino, C.I., Velez Gomez, D., Alonso Horcajo, E., and Gutierrez-Millan, C., *J. Drug Deliv. Sci. Technol.*, 2022, vol. 68, p. 103094, https://doi.org/10.1016/j.jddst.2022.103094
264. Maleki, G., Woltering, E.J., and Mozafari, M.R., *Trends Food Sci. Technol.,* 2022, vol. 120, p. 88. https://doi.org/10.1016/j.tifs.2022.01.001
265. Yaroslavov, A.A., Efimova, A.A., Krasnikov, E.A., Trosheva, K.S., Popov, A.S., Melik-Nubarov, N.S., Krivtsov, G.G., *Int. J. Biol. Macromol.,* 2021, vol. 177, p. 455. https://doi.org/10.1016/j.ijbiomac.2021.02.169

266. Mertins, O. and Dimova, R., *Langmuir*, 2013, vol. 29, p. 14545. https://doi.org/10.1021/la403218c
267. Sebaaly, C., Trifan, A., Sieniawska, E., and Greige-Gerges, H. *Processes*, 2021, vol. 9, p. 445. https://doi.org/10.3390/pr9030445
268. Esposto, B.S., Jauregi, P., Tapia-Blácido, D.R., Martelli-Tosi, M., *Trends Food Sci. Technol.,* 2021, vol. 108, p. 40. https://doi.org/10.1016/j.tifs.2020.12.003
269. Garcia, B.B.M., Mertins, O., da Silva, E.R., Mathews, P.D., and Han, S.W., *Colloids Surf. B,* 2020, vol. 193, p. 111131. https://doi.org/10.1016/j.colsurfb.2020.111131
270. Cevc, G., and Blume, G. *Biochim. Biophys. Acta BBA – Biomembr.,* 1992, vol. 1104, p. 226. https://doi.org/10.1016/0005-2736(92)90154-E
271. Zeb, A., Arif, S.T., Malik, M., Shah, F.A., Din, F.U., Qureshi, O.S., Lee, E.-S., Lee, G.-Y., and Kim, J.-K., *J. Pharm. Investig*., 2019, vol. 49. https://doi.org/10.1007/s40005-018-00418-8
272. Dudhipala, N., Phasha Mohammed, R., Adel Ali Youssef, A., and Banala, N., *Drug Dev. Ind. Pharm.,* 2020, vol. 46, p. 1334. https://doi.org/10.1080/03639045.2020.1788069
273. Fernández-García, R., Lalatsa, A., Statts, L., Bolás-Fernández, F., Ballesteros, M.P., and Serrano, D.R., *Int. J. Pharm.,* 2020, vol. 573, p. 118817. https://doi.org/10.1016/j.ijpharm.2019.118817
274. Vasileva, L.A., Gaynanova, G.A., Nizameev, I.R., Petrova, A.A., Kadirov, M.K., Gorshkova, T.A., and Zakharova, L.Ya., *Food Biosci.* 2022, vol. 50, p. 102003. https://doi.org/10.1016/j.fbio.2022.102003
275. Kassem, M.A., Aboul-Einien, M.H., and El Taweel, M.M., *AAPS PharmSciTech,* 2018, vol. 19, p. 2155. https://doi.org/10.1208/s12249-018-1020-5
276. Omar, M.M., Eleraky, N.E., El Sisi, A.M., and Ali Hasan, O., *Drug Des. Devel. Ther.,* 2019, vol. 13, p. 4413. https://doi.org/10.2147/DDDT.S235004
277. Demartis, S., Anjani, Q.K., Volpe-Zanutto, F., Paredes, A.J., Jahan, S.A., Vora, L.K., Donnelly, R.F., and Gavini, E., *Int. J. Pharm.,* 2022, vol. 627, p. 122217. https://doi.org/10.1016/j.ijpharm.2022.122217
278. Wu, X., Li, Y., Chen, X., Zhou, Z., Pang, J., Luo, X., and Kong, M., *J. Mater. Chem. B,* 2019, vol. 7, p. 4854. https://doi.org/10.1039/C9TB00448C
279. Yang, H., Wu, X., Zhou, Z., Chen, X., and Kong, M., *Int. J. Biol. Macromol.* 2019, vol. 125, p. 9 https://doi.org/10.1016/j.ijbiomac.2018.11.230
280. Das, B., Sen, S.O., Maji, R., Nayak, A.K., and Sen, K.K., *J. Drug Deliv. Sci. Technol.,* 2017, vol. 38, p. 59. https://doi.org/10.1016/j.jddst.2017.01.006
281. Touitou, E., Dayan, N., Bergelson, L., Godin, B., and Eliaz, M., *J. Control. Rel.*, 2000, vol. 65, p. 403. https://doi.org/10.1016/S0168-3659(99)00222-9
282. Partoazar, A., Kianvash, N., Darvishi, M., Nasoohi, S., Rezayat, S., and Bahador, A., *Drug Res.,* 2016, vol. 66, p. 660. https://doi.org/10.1055/s-0042-114034
283. Aljohani, A.A., Alanazi, M.A., Munahhi, L.A., Hamroon, J.D., Mortagi, Y., Qushawy, M., and Soliman, G.M., *OpenNano,* 2023, vol. 11, p. 100145. https://doi.org/10.1016/j.onano. 2023.100145
284. Lin, H., Lin, L., Choi, Y., and Michniak-Kohn, B., *Int. J. Pharm.*, 2020, vol. 581, p. 119278. https://doi.org/10.1016/j.ijpharm.2020.119278
285. Zoabi, A., Touitou, E., and Margulis, K., *Colloids Interfaces,* 2021, vol. 5, p. 18. https://doi.org/10.3390/colloids5010018
286. Chavda, V.P., Patel, A.B., Mistry, K.J., Suthar, S.F., Wu, Z.-X., Chen, Z.-S., and Hou, K., *Front. Oncol.,* 2022, vol. 12, p. 867655. https://doi.org/10.3389/fonc.2022.867655
287. Mousazadeh, N., Gharbavi, M., Rashidzadeh, H., Nosrati, H., Danafar, H., and Johari, B., *Nanomed.,* 2022, vol. 17, p. 201. https://doi.org/10.2217/nnm-2021-0334
288. Esmaeili Rad, M., Egil, A.C., Ozaydin Ince, G., Yuce, M., and Zarrabi, A., *Colloids Surf., A,* 2022, vol. 654, p. 129921. https://doi.org/10.1016/j.colsurfa.2022.129921
289. ClinicalTrials.gov, Identifier: NCT04996004290
290. Rahman, H.S., Othman, H.H., Hammadi, N.I., Yeap, S.K., Amin, K.M., Abdul Samad, N., and Alitheen, N.B., *Int. J. Nanomedicine,* 2020, vol. 15, p. 2439. https://doi.org/10.2147/IJN.S227805
291. Sangboonruang, S., Semakul, N., Suriyaprom, S., Kitidee, K., Khantipongse, J., Intorasoot, S., Tharinjaroen, C.S., Wattananandkul, U., Butr-Indr, B., Phunpae, P., and Tragoolpua, K., *Nanomaterials*, 2023, vol. 13, p. 269. https://doi.org/10.3390/nano13020269
292. Vilela, J.D.M.V., Moghassemi, S., Dadashzadeh, A., Dolmans, M.-M., Azevedo, R.B., and Amorim, C.A., *Nanomaterials,* 2022, vol. 12, p. 1999. https://doi.org/10.3390/nano12121999
293. Rasheed, M.S., Ansari, S.F., and Shahzadi, I., *Sci. Rep.*, 2022, vol. 12, p. 19813. https://doi.org/10.1038/s41598-022-23103-1

294. Nasr, M. and Al-Karaki, R., *Curr. Drug Deliv.,* 2020, vol. 17, p. 270. https://doi.org/10.2174/1567201817666200317123224
295. Abdul Rasool, B.K., Al Mahri, N., Alburaimi, N., Abdallah, F. and Shamma, A.S.B., *Sci. Pharm.,* 2022, vol. 90, p. 39. https://doi.org/10.3390/scipharm90030039
296. Manconi, M., Manca, M.L., Valenti, D., Escribano, E., Hillaireau, H., Fadda, A.M., and Fattal, E., *Int. J. Pharm.*, 2017, vol. 525, p. 203. https://doi.org/10.1016/j.ijpharm.2017.04.044
297. Zhou, F., Xu, T., Zhao, Y., Song, H., Zhang, L., Wu, X., and Lu, B., *Food Hydrocoll.*, 2018, vol. 83, p. 17. https://doi.org/10.1016/j.foodhyd.2018.04.040
298. Park, S.N., Jo, N.R., and Jeon, S.H., *J. Ind. Eng. Chem.*, 2014, vol. 20, p. 1481. https://doi.org/10.1016/j.jiec.2013.07.035
299. Iida, A.S.L., Luz, K.N., Barros-Alexandrino, T.T., Fávaro-Trindade, C.S., de Pinho, S.C., Assis, O.B.G., and Martelli-Tosi, M., *Polímeros,* 2019, vol. 29, p. e2019049. https://doi.org/10.1590/0104-1428.04119
300. Fan, Y., Lu, Y., Cheng, B., Wei, Y., Wei, Y., Piao, J., Li, F., and Zheng, H., *Int. J. Pharm.*, 2022, vol. 621, p. 121789, https://doi.org/10.1016/j.ijpharm.2022.121789
301. Gadag, S., Narayan, R., Sabhahit, J.N., Hari, G., Nayak, Y., Pai, K.S.R., Garg, S., and Nayak, U.Y., *Biomater. Adv.*, 2022, vol. 140, p. 213085. https://doi.org/10.1016/j.bioadv.2022.213085
302. Caddeo, C., Manca, M.L., Peris, J.E., Usach, I., Diez-Sales, O., Matos, M., Fernàndez-Busquets, X., Fadda, A.M., and Manconi, M., *Int. J. Pharm.*, 2018, vol. 551, p. 34. https://doi.org/10.1016/j.ijpharm.2018.09.009
303. Wu, P.-S., Li, Y.-S., Kuo, Y.-C., Tsai, S.-J., and Lin, C.-C., *Molecules*, 2019, vol. 24, p. 600. https://doi.org/10.3390/molecules24030600
304. Shankar, R., Upadhyay, P.K., and Kumar, M., *Pharm. Nanotechnol.,* 2021, vol. 9, p. 317. https://doi.org/10.2174/2211738510666211220142126
305. Han, H.J., *J. Cosmet. Med.,* 2018, vol. 2, p. 69. https://doi.org/10.25056/JCM.2018.2.2.69
306. Chen, J., Jiang, Q.-D., Chai, Y.-P., Zhang, H., Peng, P., and Yang, X.-X., *Molecules,* 2016, vol. 21, p. 1709. https://doi.org/10.3390/molecules21121709
307. Qadri, G.R., Ahad, A., Aqil, Mohd., Imam, S.S., and Ali, A., *Artif. Cells Nanomedicine Biotechnol.,* 2017, vol. 45, p. 139. https://doi.org/10.3109/21691401.2016.1138486
308. Badran, M., *Afr. J. Pharm. Pharmacol.,* 2012, vol. 6, p. 3018. https://doi.org/10.5897/AJPP12.552
309. Shah, S.M., Ashtikar, M., Jain, A.S., Makhija, D.T., Nikam, Y., Gude, R.P., Steiniger, F., Jagtap, A.A., Nagarsenker, M.S., and Fahr, A., *Int. J. Pharm.*, 2015, vol. 490, p. 391. https://doi.org/10.1016/j.ijpharm.2015.05.042
310. Dragicevic-Curic, N., Gräfe, S., Albrecht, V., and Fahr, A., *J. Photochem. Photobiol. B,* 2008, vol. 91, p. 41. https://doi.org/10.1016/j.jphotobiol.2008.01.009
311. Ahmed, O.A.A. and Badr-Eldin, S.M., *Int. J. Pharm.*, 2019, vol. 570, p. 118657. https://doi.org/10.1016/j.ijpharm.2019.118657
312. Chougle, S., Kumar, D., Khan, A., Zehra, S., and Ali, A., *J. Exp. Clin. Med.*, 2021, vol. 38, p. 634. https://doi.org/10.52142/omujecm.38.4.42
313. Raju, M., Kunde, S.S., Auti, S.T., Kulkarni, Y.A., and Wairkar, S., *Life Sci.*, 2021, vol. 285, p. 119990. https://doi.org/10.1016/j.lfs.2021.119990
314. Hashemzadeh, H., Hanafi-Bojd, M.Y., Iranshahy, M., Zarban, A., and Raissi, H., *Sci. Rep.*, 2023, vol. 13, p. 2501. https://doi.org/10.1038/s41598-023-29237-0
315. Rudrapal, M., Mishra, A.K., Rani, L., Sarwa, K.K., Zothantluanga, J.H., Khan, J., Kamal, M., Palai, S., Bendale, A.R., Talele, S.G., Pathan, V.T., Borse, L.B., Neharkar, V.S., and Sahoo, P.K, *Molecules*, 2022, vol. 27, p. 8706. https://doi.org/10.3390/molecules27248706
316. Chittasupho, C., Chaobankrang, K., Sarawungkad, A., Samee, W., Singh, S., Hemsuwimon, K., Okonogi, S., Kheawfu, K., Kiattisin, K., and Chaiyana, W., *Gels*, 2023, vol. 9, p. 78. https://doi.org/10.3390/gels9020078
317. Telange, D.R., Patil, A.T., Pethe, A.M., Fegade, H., Anand, S., and Dave, V.S., *Eur. J. Pharm. Sci.*, 2017, vol. 108, p. 36. https://doi.org/10.1016/j.ejps.2016.12.009
318. Ju Ho, P., Jun Sung, J., Ki Cheon, K., and Jin Tae, H., *Phytomedicine*, 2018, vol. 43, p. 110. https://doi.org/10.1016/j.phymed.2018.04.013
319. Vu, H.T.H., Hook, S.M., Siqueira, S.D., Müllertz, A., Rades, T., and McDowell, A., *Int. J. Pharm.,* 2018, vol. 548, p. 82. https://doi.org/10.1016/j.ijpharm.2018.06.042
320. Loguercio, C., *World J. Gastroenterol.,* 2011, vol. 17, p. 2288. https://doi.org/10.3748/wjg.v17.i18.2288
321. Sarkar, P., Bhagavatula, S., and Suneetha, V., *J. Appl. Pharm. Sci.*, 2014, vol. 4, p. 61. https://doi.org/10.7324/JAPS.2014.40110
322. Nandayasa, W.W., Febriyenti, and Lucida, H., *Int. J. Appl. Pharm.*, 2023, vol. 15, p. 51. https://doi.org/10.22159/ijap.2023.v15s1.47507

323. Hanif, H., Abdollahi, V., Javani Jouni, F., Nikoukar, M., Rahimi Esboei, B., Shams, E., and Vazini, H., *J. Parasit. Dis.*, 2023. https://doi.org/10.1007/s12639-022-01561-8
324. Cuomo, J., Appendino, G., Dern, A.S., Schneider, E., McKinnon, T.P., Brown, M.J., Togni, S., and Dixon, B.M., *J. Nat. Prod.*, 2011, vol. 74, p. 664. https://doi.org/10.1021/np1007262
325. Sayed, N., Khurana, A., and Godugu, C., *J. Drug Deliv. Sci. Technol.*, 2019, vol. 53, p. 101201. https://doi.org/10.1016/j.jddst.2019.101201
326. Shree, D., Patra, C.N., Acharjya, S.K., and Sahoo, B.M., *Curr. Nanomedicine*, 2022, vol. 12, p. 2. https://doi.org/10.2174/1871520622666220425093718
327. Arora, R., Aggarwal, G., Dhingra, G., and Nagpal, M., *Asian J. Pharm. Clin. Res.*, 2019, vol. 12, p. 7. https://doi.org/10.22159/ajpcr.2019.v12i9.33620
328. Chime, S.A. and Madumere, C.P., *Curr. Tradit. Med.*, 2023, vol. 9. https://doi.org/10.2174/2215083808666220329122149
329. Murti, Y., Agrawal, K.K., Semwal, B.C., Gupta, J., and Gupta, R., *Curr. Tradit. Med.*, 2023, vol. 9, p. 43. https://doi.org/10.2174/2215083808666220428092638
330. Santos, A.C., Rodrigues, D., Sequeira, J.A.D., Pereira, I., Simões, A., Costa, D., Peixoto, D., Costa, G., and Veiga, F., *Int. J. Pharm.*, 2019, vol. 572, p. 118787. https://doi.org/10.1016/j.ijpharm.2019.118787
331. Raahulan, S., Sanapalli, B.K.R., and Karri, V.V.S.R., *Int. J. Res. Pharm. Sci.*, 2019, vol. 10, p. 2891. https://doi.org/10.26452/ijrps.v10i4.1569
332. Nojoki, F., Ebrahimi-Hosseinzadeh, B., Hatamian-Zarmi, A., Khodagholi, F., and Khezri, K., *Biomed. Pharmacother.*, 2022, vol. 153, p. 113450. https://doi.org/10.1016/j.biopha.2022.113450.
333. Opatha, S.A.T., Titapiwatanakun, V., Boonpisutiinant, K., and Chutoprapat, R., *Molecules*, 2022, vol. 27, p. 4865. https://doi.org/10.3390/molecules27154865
334. Asensio-Regalado, C., Alonso-Salces, R.M., Gallo, B., Berrueta, L.A., Era, B., Pintus, F., and Caddeo, C., *Nanomaterials*, 2022, vol. 12, p. 746. https://doi.org/10.3390/nano12050746
335. Moqejwa, T., Marimuthu, T., Kondiah, P.P.D., and Choonara, Y.E., *Pharmaceutics*, 2022, vol. 14, p. 703. https://doi.org/10.3390/pharmaceutics14040703
336. Lee, E.-H., Lim, S.-J., and Lee, M.-K., *Carbohydr. Polym.*, 2019, vol. 224, p. 115143. https://doi.org/10.1016/j.carbpol.2019.115143
337. Mohammadi, M., Hamishehkar, H., McClements, D.J., Shahvalizadeh, R., and Barri, A., *Food Chem.*, 2023, vol. 400, p. 133973. https://doi.org/10.1016/j.foodchem.2022.133973
338. Akbari, J., Saeedi, M., Enayatifard, R., Morteza-Semnani, K., Hassan Hashemi, S.M., Babaei, A., Rahimnia, S.M., Rostamkalaei, S.S., and Nokhodchi, A., *J. Drug Deliv. Sci. Technol.,* 2020, vol. 60, p. 102035. https://doi.org/10.1016/j.jddst.2020.102035
339. Kumar, B., Sahoo, P., and Manchanda, S., *Nanomedicine J.*, 2022, vol. 9, p. 223. https://doi.org/10.22038/nmj.2022.65785.1689
340. Lakshmi, P., Mounica, V., Manoj Kumar, Y., and Domaraju, P., *Int. J. Drug Deliv.*, 2014, vol. 6, p. 113.