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Nanocarriers

Innovative carrier systems at a glance

Summary

Nanocarriers are innovative delivery and encapsulation systems with different chemical compositions and structures and are classified as advanced materials. They are used in a variety of applications, especially in medicine, cosmetics, and agriculture, as well as in food supplements and household products. Nanocarriers can protect sensitive active ingredients, delay their release, and even enable targeted delivery to the site of action, thereby increasing effectiveness and reducing any side effects. In the scientific literature, the term "nanocarrier" covers not only nanomaterials up to a size of 100 nm according to the definition proposed by the European Commission, but also structures up to 1,000 nm. At present, there is no uniform definition or categorisation of nanocarriers. In this dossier, they are classified on the basis of their origin and chemical composition, and categorised as organic, inorganic, and hybrid systems (material combinations of organic and inorganic materials) as well as supraparticles. To date, there has been little research on how nanocarrier systems behave in the various environmental compartments (soil, water, air). Analytical challenges and the lack of standardised test protocols make comprehensive risk assessments difficult.

The review presented in this dossier is the result of a project funded by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) and commissioned by the German Federal Environment Agency (UBA).

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Introduction

More and more innovative materials, material combinations, and substances are being developed and being used in a wide range of areas, ranging from aircraft technology to medicine. There is no standard definition for these materials, commonly referred to as advanced materials in the English-speaking world. In general, they are recognised as any material that has a number of unusual properties (mechanical, electrical, optical, magnetic, etc.) or functionalities (e.g., self-repairing or shapechanging) because of the precise control of their composition and structure. This and their advanced manufacturing methods distinguish advanced materials from other, conventional materials. Advanced materials include novel composites, special polymers, alloys of metals, fibres, and also certain nanomaterials.[1;2]

Nanocarriers – innovative delivery and encapsulation systems with different chemical compositions and structures – are also considered advanced materials. They are used in various fields of application with the intention of improving the solubility and bioavailability of, for example, lipophilic active ingredients. The aim of such nanoscale carrier systems is to ensure targeted and improved dosage at the desired site of action (targeted delivery) and controlled release of active ingredients (controlled release). Nanocarriers therefore serve as "packaging" for active ingredients on the one hand, and as "transport vehicles" on the other. Active ingredients can either be enclosed inside hollow, vesicular or droplet-shaped structures or attached to the surface of such nanocarriers. In addition to spherical structures, nanocarriers can also have many other shapes, such as fibrous, triangular and hexagonal, tree-shaped branched, "flower"-shaped or prismatic. The field of nanocarriers is very heterogeneous and diverse – it ranges from single fat droplets made of double lipid membranes (Figure 1) to highly complex structures made of organic and inorganic materials. These are not always nanomaterials at the size range of up to 100 nm, as defined in the proposal of the European Commission[3], but the scientific literature also counts structures up to 1,000 nm amongst the group of nanocarriers.[4]

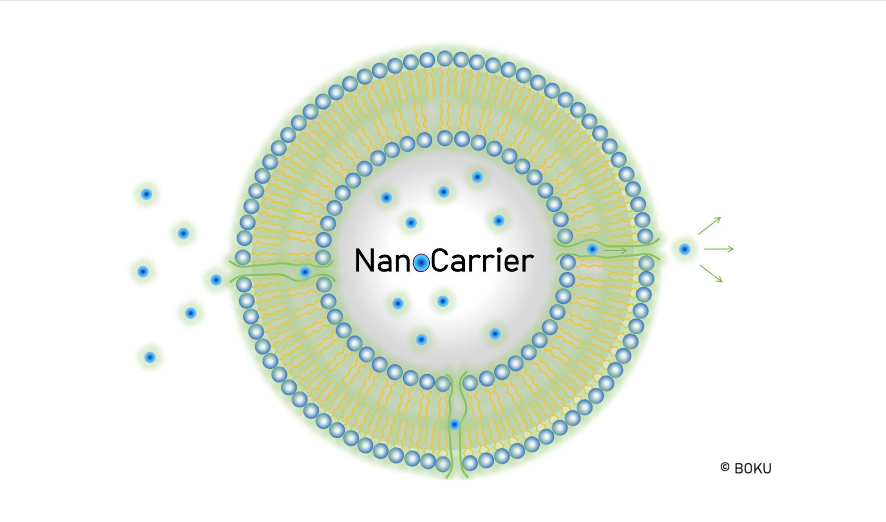

Figure 1: *Schematic representation of a nanocarrier (graphic: BOKU).*

Nanocarriers are being intensively researched, particularly in medicine, and some are already being used, for example in newly developed RNA vaccines against COVID19 or in cancer therapy. The special properties of nanocarriers are also useful in other areas of application, such as cosmetics (see [5]), agriculture, the food industry, food supplements, household products, and even vehicle batteries. The range of active ingredients that can be delivered is therefore very diverse, ranging from drugs, vitamins, antioxidants, enzymes, peptides, cosmetic active ingredients, pesticides, fragrances and flavours to nucleic acid chains for gene therapy or plant protection.

This dossier provides an overview of the broad field of nanocarriers, their chemical composition, structure and functionalities, as well as actual and potential applications. In addition, the environmental behaviour and analytical challenges are addressed. The review presented in this dossier is an extract from a project funded by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) and commissioned by the German Federal Environment Agency (UBA), the results of which have been published in a comprehensive report.[6]

Categorisation of nanocarriers

Nanocarriers can be made from a wide variety of organic or inorganic materials, as well as from combinations of materials (hybrid systems). The literature contains a large number of different terms for nanocarriers, and some of them are also used synonymously. Figure 2 represents an attempt to structure the field of research whilst giving an impression of the diversity of materials and structures used as nanocarriers, without claiming to be complete. The nanocarriers are categorised on the basis of their origin and chemical composition into organic, inorganic, and hybrid systems (material combinations of organic and inorganic materials) as well as supraparticles (Figure 2).

Organic nanocarriers

As can be seen in Figure 2, organic nanocarriers can either be of cellular origin or consist of natural pollen and spore envelopes, or they can be made from chemical compounds.

In the field of medicine, **human cells** such as red blood cells (erythrocytes), phagocytes (macrophages), immune cells (T cells), and stem cells are being researched as nanocarriers, for example for drugs to treat cancer or inflammation, and as carriers for contrast agents. They can increase the residence time of an active ingredient in the body and are characterised by high flexibility and good tolerability.[7] The **envelopes of a large number of virus species**, especially plant viruses and bacteriophages[8], can also be used as transport vehicles. These nanocarriers are known as "virus-like particles" or virosomes; they have the advantage of being biocompatible and can also be easily functionalised (e.g. by antibodies). In medicine, they are being researched as delivery systems. Virusbased nanocarriers may also offer advantages in agriculture, as they are highly mobile in the soil and can deliver pesticides to the roots. In the U.S., a nanocarrier based on the tobacco mosaic virus has already been approved to deliver a herbicide. The red clover mosaic virus is also being developed as a nanocarrier for the delivery of the pesticide abamectin.[4] Live, killed or genetically modified **bacteria**, e.g. of the genera *Clostridium* or *Salmonella*, are being researched for the delivery of anticancer drugs or DNA in gene therapy. These bacteria-based nanocarriers are characterised by high mobility; they can deliver several therapeutic agents simultaneously. Living bacteria can grow in tumour tissue and subsequently be eliminated by antibiotics.[9] **Yeast cells** are suitable nanocarriers for both fat-soluble (lipophilic) and water-soluble (hydrophilic) substances because of their cell wall of phospholipids.[10] Since yeast is also used in the food industry, and with their production being very inexpensive, yeast cells are particularly suitable for the protection, delivery, and encapsulation of food additives, such as flavours or vitamins.[11] The **envelopes of pollen or spores** are also attracting research interest in medicine and the food industry. These natural microcapsules are highly resistant to acids, bases, and high temperatures. They can be filled with active ingredients, protect them from environmental influences, and increase their bioavailability.[12]

In the case of nanocarriers based on chemical compounds, it is particularly the **polymeric nanocarriers** that have attracted great research interest in recent years because they are water-soluble, biocompatible, stable during storage, and often easily degradable.[13] A large number of different natural and synthetic polymers are being researched for their suitability as nanocarriers; these include biopolymers such as proteins (e.g., albumin) and polysaccharides (e.g., chitosan, alginate, cellulose) as well as the synthetic polymers polylactic acid, polylactidecoglycolide, polyethylene glycol or polycaprolactone. Various gels can be produced from polymers and used to deliver active ingredients, such as ultralight aerogels or polymers crosslinked to form hydrogels. Polymeric micelles are spherical struc-

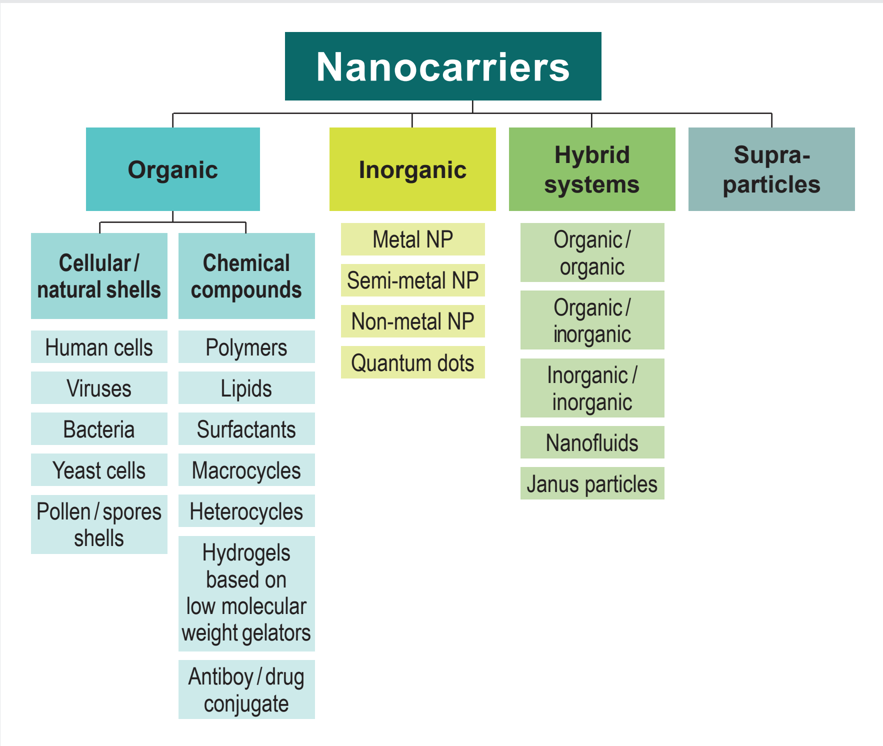

Figure 2: *Categories of nanocarrier systems based on their origin and chemical composition (graphic: according to BOKU).*

tures with hydrophobic (water-repelling) and hydrophilic (water-attracting) components. They are of interest for the delivery of active ingredients in both medicine and agriculture.[4] It should also be mentioned at this point that, in addition to polymers, surfactants or emulsifiers also form micelles spontaneously in water. This form of micellar nanocarrier is not only being researched for use in medicine, but is already being used in food supplements for active ingredients not easily soluble in water such as curcumin.[14]

So-called polymersomes are artificial vesicles that enclose an aqueous core in which drugs for cancer treatment, but also vaccines, can be enclosed. A number of other spherical polymeric nanocarriers can be found in the literature under different names, such as microcapsules or nanocapsules, “microbeads”, “nanospheres” or “unispheres”[15], which are of interest for applications in cosmetics, as well as sponge-like three-dimensional networks of polymers known as “nanosponges”[16], and so-called “nanocages”, i.e. protein structures formed by selfassembly, where drug molecules can be loaded into the interior whilst the external surfaces can be engineered to improve biocompatibility and enable targeted drug delivery.[17] Polymeric nanocarriers that have a “tree-like” structure are also known as dendrimers. Polymeric nanocarriers can be designed to release a drug in a targeted manner. Stimuli of a physical (e.g., temperature, light), chemical (e.g., pH value) or biological (e.g., certain enzymes) nature can trigger a targeted release, depending on the design of the carrier. This makes this type of nanocarrier particularly interesting for medical applications, for example for the targeted release of drugs for cancer treatment in tumour tissue.[18]

From a chemical point of view, the nucleic acids DNA and RNA are considered polymers and are also the subject of research as nanocarriers. DNA nanostructures are designed on the computer, and methods such as the “DNA origami” technique facilitate the construction of sophisticated and complex structures that can act as carrier systems for drugs and release an active ingredient after stimulation.[19]

Lipid-based nanocarriers are the longest established, best researched, and most versatile of the various nanocarrier types. Their advantages are their simple production, ability to self-assemble, and high level of biocompatibility. In addition, they can be loaded with relatively large quantities of active ingredients.[12] The lipid-based nanocarriers that have been used the longest are the so-called liposomes – vesicles made of phospholipids that are well suited for use in medicine because of their biocompatibility and their easy-to-modify surfaces. Because of their doublelayered structure, both hydrophobic and hydrophilic active ingredients, drugs or contrast agents can be enclosed. Liposomes can be stabilised, for example, by attaching polyethylene glycol (PEG) to the surface, a process known as PEGylation. Liposomal delivery systems can significantly improve the efficacy of drugs by stabilising the enclosed active ingredients and by improving targeted uptake in the tissue.[20] The first liposomal nanocarrier used in medicine for the active ingredient doxorubicin – an anticancer drug – was approved in the USA as early as 1995. By controlling the lipid composition and the length of the fatty acid chains, liposomal nanocarriers can be manufactured to respond to a specific temperature or pH value. This enables a controlled release of the active ingredients under physiological conditions specific to the site of the disease.[4] Liposomes have been used in cosmetic products since the 1980s (see [5]). Improved liposomes, such as transfersomes (phospholipids and surfactants), ethanol-containing ethosomes or niosomes made of non-ionic surface-active substances (especially alkylglycerols in combination with cholesterol) can penetrate the intercellular spaces of the upper skin layer (*stratum corneum*), which is difficult for active ingredients to penetrate, and deliver agents into deeper skin layers.[21] In addition, there are a number of enhanced or advanced liposomes with a variety of names, only some of which can be listed here. These include yeast-based liposomes, bilosomes modified with bile salts, and vesosomes (liposomes that encapsulate smaller liposomes).[22]

Other lipid-based nanocarriers are lipid nanoparticles, which, unlike liposomes, have a micellar structure inside and can also be solid, or so-called nanostructured lipid carriers, which are engineered from solid and liquid lipids as well as emulsifiers.[23] Lipid-based emulsions, oil/water mixtures stabilised with emulsifiers and referred to as microemulsions or nanoemulsions, or “pickering emulsions” in which solid particles are used for stabilisation instead of emulsifiers, are also promising nanocarriers.[24] Lipid nanoparticles are already being used in medicine (e.g. in RNA vaccines against COVID19) and in cosmetics. Similar to nanoemulsions, they hold promise for applications in the food sector and in agriculture. Lipid-based organogels based on oils, organic solvents, and a gelling agent such as lecithin are also being researched for use as nanocarriers in medicine.[25] Lipid-based nanocarriers also include extracellular vesicles such as exosomes or endosomes, which are formed naturally by cells but are not cells themselves. They are involved in numerous natural physiological processes in the body. Extracellular vesicles can be compared with liposomes since they are also based on phospholipids. As nanocarriers, they are the subject of medical research because they can delivery active ingredients to specific cells or tissues in a targeted manner.[26]

Cyclodextrins, which belong to **macrocyclic compounds**[28], are ring-shaped oligosaccharides obtained from starch. Their amphiphilic character with a hydrophobic core and hydrophilic outer shell makes them interesting for various active ingredients and applications. Cyclodextrins are therefore relevant not only in the medical field and in agriculture, but also in the food industry, cosmetics, textiles, and household products, such as air and textile fresheners, where they are already being used.[29]

Heterocyclic compounds[30] such as spiropyrans – organic molecules that can switch between an open and closed form in response to stimuli (e.g. light, pH value, temperature) – and porphyrins, which consist of four pyrrole units in a circular array[31], have also been researched as potential nanocarriers in recent years, particularly in the field of medicine.[32;33]

Hydrogels based on low-molecular-weight gelators (e.g., sugar-functionalised naphthalimide) are being considered as nanocarriers for the delivery of drugs through the skin as well as for the controlled release of anti-inflammatory agents at a given pH value.[34]

Organic nanocarriers also include **compounds (conjugates) of antibodies and drugs**, which represent an innovative combination of chemotherapy and immunotherapy in medicine. During this process, a monoclonal antibody is combined with an anticancer drug. The antibody matches a corresponding antigen on the surface of a cancer cell, enabling targeted drug delivery.[35]

Inorganic nanocarriers

Inorganic “nanocarriers” include metallic, semimetallic, and nonmetallic particles as well as quantum dots.

Metallic nanoparticles made of silver, gold, palladium, titanium, zinc or copper are being intensively researched in medicine as nanocarriers for various active ingredients (chemotherapeutics, antibodies, nucleic acids, peptides, etc.) that can be bound to the surface of the particles.[36] Magnetic nanoparticles such as iron oxide nanoparticles are particularly interesting for targeted drug delivery. By applying an external magnetic field, these nanocarriers can be guided to the desired site of action where the active ingredient is released in a targeted manner.[37]

Nanoparticles made of the **semimetal** silicon dioxide (SiO_2; silica), particularly mesoporous[38] silicon dioxide, are well suited as nanocarriers because of their high loading capacity and the possibility of surface modification. As a result, they are being intensively researched in medicine. For example, a drug for cancer treatment can either passively enter the tumour tissue and accumulate there in a non-specific way or be applied in a targeted manner by binding certain molecules to the surface of the nanocarrier, which then bind to corresponding receptors of the cancer cells. Silica nanocarriers can also be engineered in such a way that, after binding to a cancer cell, they release the active ingredient in a targeted manner in response to a specific stimulus (pH value, light, etc.).[39]

In the case of **non-metallic** nanocarriers, it is mainly clay minerals or layered silicates (phyllosilicates), such as montmorillonite, kaolin or halloysite, that are of medical and other interest where the delivery of various active ingredients is concerned; this is because of their good biocompatibility and large specific surface area. In medicine, for example, they are being researched as nanocarriers for antibiotics and cancer drugs. A slow and targeted release of the drugs and an improvement in solubility is possible with these nanocarriers.[40] Halloysite can also be used to encapsulate materials for lithium ion batteries, extending the life of the batteries through their slow release.[41] Layered double hydroxides[42] can not only deliver and slowly release drugs inside their layered structure, they are also being researched as nanocarriers for novel spray and RNA-based pesticides.[43] Studies have also shown that the mineral hydroxyapatite is suitable as a nanocarrier in the medical field because of its resistance and good loading capacity with active ingredients. Material combinations with hydroxyapatite are also being researched for the slow release of fertilisers in agriculture.[44]

Nanocarriers based on carbon, such as carbon nanotubes, carbon dots, graphene, nanodiamonds, activated carbon or fullerenes ("buckyballs") are also being researched for medical applications, especially for cancer treatments. Because of the nanocarriers' small size, hopes are also being pinned on their ability to cross the bloodbrain barrier and deliver drugs into the brain. However, possible negative effects of these carbon-based delivery systems, such as oxidative stress on cells and the resulting inflammatory reactions, hinder their potential use in medicine and necessitate further research into their safety profiles.[19] Activated carbon with pore sizes of 0.5 to 2 nm is also being researched as a carrier for pesticides for use in agriculture, since this material has a good absorption capacity for active ingredients because of its high specific surface area, and because it is classified as nontoxic or environmentally compatible.[27]

Quantum dots are nanocrystals made of semiconductor materials that either consist of only one material (e.g., cadmium sulphide or zinc sulphide) or consist of a core and a shell made of two different semiconductor materials. Quantum dots are interesting as nanocarriers because they have a high specific surface area to which active substances can be bound. In addition, they have optical properties, which makes them suitable for procedures involving diagnostic imaging .[45] To improve their biocompatibility and water solubility, various heavy metal-free compositions and different surface modifications are being researched.[38]

Hybrid nanocarrier systems

The organic and inorganic materials presented in this dossier are promising variants for use as nanocarriers. However, many of them also have limitations. Combinations of different materials are therefore being researched to develop optimal nanocarriers that combine the advantages of the different materials. For such hybrid nanocarriers, different oils, metals, minerals, polymers, and lipids are combined into complex core/shell structures and investigated for their suitability. For example, an outer layer of gold can impart better physical and chemical resistance to a polymer core that encloses the active ingredient. Or a liposome carrying a drug can be magnetised with the use of a shell made of iron oxide, thus enabling targeted release of the active ingredient.[46]

Hybrid systems also include nanosuspensions (nanofluids). They consist of nanoparticles that are finely dispersed in liquids. Suspensions of magnetic nanoparticles can be used, for example, in cancer therapy and, beyond drug delivery, also for procedures involving diagnostic imaging.[47]

A special form of hybrid nanocarriers are the so-called "Janus" nanoparticles, which are currently the subject of intensive research. These are particles that have two sides made of different materials with very different properties. With these nanoparticles, it is possible, for example, to deliver two different active ingredients with different solubilities (hydrophilic and hydrophobic) at the same time. A combination of treatment and diagnostic procedures as well as a controlled release through specific stimuli is also possible. Various combinations of materials, such as different polymers, gold, silica, and other materials, are currently being researched.[48]

Supraparticles

To date, no standardised definition of the term "supraparticle" exists. The term is generally understood to mean defined and complex structures of nanoparticles. Supraparticles can be formed either from only one type of nanoparticle or from two or more different building blocks. The design is flexible and the size, shape, and morphology of supraparticles can be controlled. By combining individual nanoparticles into highly complex supraparticles, the properties and functionalities of the complex change, i.e. a supraparticle is more than just the sum of its parts. The new properties also make supraparticles interesting for use as nanocarriers, for example in medicine, but also in agriculture, where supraparticles made of silica nanoparticles and cellulose nanofibrils are already being researched for the delivery of agrochemicals.[49]

Environmental behaviour

Whether nanocarrier systems are released into the environment depends on the type of application. In the fields of medicine, cosmetics or foodstuffs, release is primarily unintentional, e.g. via wastewater or waste. This is not the case, however, when nanocarriers are used in agriculture. Here, the aim of the use is the release into the environment in order to deliver agrochemicals such as pesticides or fertilisers to the leaves and roots of the crops with the help of the nanocarrier. As a result, careful safety reviews and risk assessments are particularly necessary in this area.

To date, there has been little research into how nanocarrier systems behave in different environmental compartments, such as soils, sediments, water or in the air. However, their behaviour and fate generally depend very much on the prevailing environmental conditions (pH value, temperature, interaction with organic substances, etc.) as well as on the surface properties of the carrier.[50] Making generalised statements is therefore hardly possible, and the individual nanocarrier systems must be investigated on a case-by-case basis. It is not only interesting how the nanocarrier material itself behaves, whether it degrades quickly and has no negative effects on the environment. Rather, the entire system – including the delivered active ingredient – must be considered, because the nanocarrier itself can change the properties and behaviour of the active ingredient in the environment. Safety concerns about nanoformulations such as nanocarrier systems, e.g. for agrochemicals, are therefore justified, especially for those systems that, compared to conventional formulations, may show a modified behaviour of the active ingredient in terms of its mobility and degradability or stability in the environment as well as its uptake, distribution, and toxicity to organisms.[51]

Challenges for analytics

The general assumption that the carrier does not influence the fate of the active ingredient in the environment is not true for every case, as studies have shown.[52] However, there is currently no standard protocol for a comprehensive investigation into the behaviour and fate of a nanocarrier/active ingredient complex in the environment. To date, studies in the laboratory have often been conducted with unrealistically high concentrations of active ingredients, and these analyses have therefore not been representative of actual environmental conditions.

It is well known that quantitative characterisation of nanomaterials (1-100 nm) to determine their size and composition is generally a difficult task. For example, it is challenging to detect tiny particles below 10 nm in complex environmental samples using many established detection methods. It can be assumed that similar problems exist in relation to nanocarrier systems. One essential aspect of the nanocarrier quantification process is also appropriate sample preparation, which must be tailored not only to the requirements of the characterisation methods used, but also to the properties of the product to be analysed, and to the relevant environmental matrix (e.g., agricultural soil).[53] The goal of any sample preparation is to ensure that the nanocarriers are not altered during the preparation process, for example because of agglomeration, dissolution, or chemical changes. If only the size distribution is of interest, chemical changes may be acceptable as long as the size distribution is not altered. In addition, most measurement techniques for inorganic nanocarriers cannot be applied to organic material, and organic particles may lack the necessary contrast when examined under electron microscope processes. As a result, specific strategies for analysis have yet to be developed, e.g. on the basis of tip-enhanced Raman spectroscopy, Fourier transform infrared spectroscopy or nuclear magnetic resonance spectroscopy.

Conclusion

The use of nanocarriers to encapsulate and deliver active ingredients is advantageous for many areas of application. Especially in the field of medicine, they are the subject of intensive research in order to develop more effective therapies with fewer side effects, and to improve diagnostic methods and vaccines. Inspired by medical research, nanocarriers are also attracting great interest in other areas of research and fields of application and are already being used in some cases. However, little research has been done on how nanocarrier systems behave in the environment, and their toxic effects on non-target organisms. Especially for applications with intended release into the environment, such as in agriculture, extensive research is therefore necessary to ensure the safety of nanocarrier systems, and to be able to assess risks. In many cases, however, suitable analytical methods are still lacking; this means existing procedures and protocols must be refined, adapted, and standardised. Nonetheless, experience with chemicals and nanomaterials has shown that gaps in knowledge will always remain. As a result, it is particularly important to apply design principles that reduce risks to the environment and human health already during the development of new materials such as nanocarriers. The European Commission's strategy for inherently safe and sustainable chemicals and materials[54] (Safe and Sustainable by Design, SSbD) pursues this goal.

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