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Part I: Overview and categorization of nanocarriers

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Nanocarrier – Current state of knowledge

This report summarizes the current state of knowledge on nanocarriers. Nanocarriers are innovative materials ("advanced materials") with unique physicochemical properties that can pose particular challenges for chemical regulation and regulatory risk assessment. To this end, a literature review of existing nanocarriers or those under development and their (potential) applications was conducted. The aim of this report is to first characterize the field of nanocarriers comprehensively. Based on a working definition of nanocarriers, both the types of nanocarriers currently on the market and the technologies under development are described and classified. Additionally, this report provides an overview of (possible) fields of application of nanocarriers and their state of development.

Nanocarrier – Aktueller Stand des Wissens

Dieser Bericht fasst den aktuellen Wissensstand über Nanocarrier zusammen. Nanocarrier sind innovative Materialien (engl. "Advanced Materials") mit einzigartigen physikalisch-chemischen Eigenschaften, die besondere Herausforderungen für die Regulierung von Chemikalien und die Risikobewertung mit sich bringen können. Zu diesem Zweck wurde eine Literaturübersicht über bestehende oder in der Entwicklung befindliche Nanocarrier und ihre (potenziellen) Anwendungen erstellt. Ziel dieses Berichts ist es, zunächst den Bereich der Nanocarrier umfassend zu charakterisieren. Ausgehend von einer Arbeitsdefinition von Nanocarriern werden sowohl die derzeit auf dem Markt befindlichen Typen von Nanocarriern als auch die in der Entwicklung befindlichen, neuen Technologien beschrieben und klassifiziert. Darüber hinaus gibt dieser Bericht einen Überblick über die (möglichen) Anwendungsbereiche von Nanocarriern und ihren Entwicklungsstand.

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List of abbreviations

AC	Activated carbon
ADCs	Antibody–drug conjugates
ADME	(drug) absorption, distribution, metabolism and excretion
Ag	Silver
AOCS	Asymmetric oxygen carrier system
Au	Gold
BMV	brome mosaic virus
BPMOs	Biodegradable periodic mesoporous organosilica nanoparticles
C	Carbon
Ca	Calcium
CBNs	Carbon-based nanomaterials
CCMV	Cowpea chlorotic mottle virus
CDs	Carbon dots
Cd	Cadmium
CdSe/ZnS	Cadmium selenide quantum dots with a zinc sulfide shell
CNTs	Carbon nanotubes
COF	Covalent organic framework
CPMV	Cowpea mosaic virus
Cr	Chromium
Cu	Copper
DMAEMA	2-(dimethylamino)ethyl methacrylate
DNA	Desoxyribonucleic acid
DOX	Doxorubicin
DSPE	1,2-distearoyl-sn-glycero-3-phosphoethanolamine

dsRNA	Double-stranded RNA
DT50	Disappearance time 50
ELP-nanoparticle	Elastin-like polypeptide nanoparticle
EMA	European Medicines Agency
EU	European Union
EVs	Extracellular vesicles
FDA	U.S. Food and Drug Administration
Fe	Ferrum
Fe_2O_3	Maghemite
Fe_3O_4	Magnetite
GO	Graphene oxide
GQD	Graphene quantum dot
HAP	Hydroxyapatite
HBPs	Hyperbranched polymers
HCRSV	Hibiscus chlorotic ringspot virus
Hf	Hafnium
HNT	Halloysite nanotube
IONP	Iron oxide nanoparticle
JNPs	Janus nanoparticles
LDCs	Lipid−drug conjugates
LDH	Layered double hydroxide
LNPs	Lipid nanoparticles
mAb	Monoclonal antibody
MCN	Mesoporous carbon nanomaterial
MDDSs	Magnetic drug delivery systems
MeSNP	Metal sulfide nanomaterial
MHT	Magnetic hypothermia treatment
miRNA	MicroRNA

MLV	Multilamellar vesicle
MM	Mixed micelle
mm	Millimeter
MNPs	Metal nanoparticles
MOF	Metal-organic frameworks
MRI	Magnetic resonance imaging
$mSiO_2$	Mesoporous silica
MWCNTs	Multi-walled carbon nano tubes
NB	Nanobubble
NIR	Near infra-red
NLC	Nanostructured lipid carriers
nm	Nanometer
NP	Nanoparticle
O	Oxygen
OECD	Organization for Economic Co-operation and Development
P	Phosphor
PAA	Polyacrylic acid
PACA	Poly(alkyl cyanoacrylate)
PAMAM	Polyamidoamine
PCL	Poly(ε-caprolactone)
PDMAEMA	Poly(2-(dimethylamino)ethyl methacrylate
pDNA	Plasmid DNA
Pd	Palladium
PEG	Polyethylene glycol
PEI	Polyethyleneimine
PGA	Polyglycolic acid
pH	Potentia hydrogenii

PHA	Polyhydroxyalkanoate
PIC	Polyion complex
PICM	Polyion Complex Micelle
PLA	Polylactic acid
PLGA	Polylactic-co-glycolide
PLL	Poly-L-lysine
PNIPAM	Poly(N-isopropylacrylamide)
PMO	Periodic mesoporous organosilica
PSA	Polysebacic acid anhydride
PS	Polystyrene
Pt	Platinum
PVP	Poly(vinyl alcohol) polymer
QD	Quantum dot
RCNMV	Red clover necrotic mosaic virus
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RNA	Ribonucleic acid
RNAi	RNA interference
ROS	Reactive oxygen species
S	Sulfur
Se	Selene
SLNs	Solid lipid nanoparticles
SMEDDS	Self-microemulsifying drug delivery system
SNEDDS	Self-nanoemulsifying drug delivery system
Si	Silicium
siRNA	Small interfering RNA
SOD	State of development
SPs	Spiropyrans

SPc	Star polycation
SQDs	Semiconductor quantum dots
SPION	Superparamagnetic iron oxide nanoparticle
SWCNT	Single-walled carbon nano tube
t½	Half-life
TiO_2	Titanium dioxide
TMV9	Tobacco mosaic virus
TPGS	Tocopheryl polyethylene glycol succinate
TRL	Technology readiness level
TYMV	Turnip yellow mosaic virus
UCNPs	Upconversion nanoparticles
US	United States of America
UV	Ultraviolet
VLPs	Virus-like particles
Zn	Zinc
%	Percent
µm	Micrometer
3D	Three dimensional

Summary

This report provides an overview of the latest development in the field of nanocarriers. For this purpose, nanocarriers have been characterized based on systematic research in scientific literature and patents. The literature review shows that many of the nanocarriers are still under development, but it is a fast-growing, diverse field. This study aimed to categorize the wide range of nanocarriers, with a focus on the state of development and the actual purpose of application.

Depending on the area of application and the requirements associated with the properties of the active ingredient, nanocarriers can perform different tasks, ranging from the simple carrier function, protection of the active ingredient against degradation or improvement of its solubility, to its targeted transport and controlled release. The diverse applications of nanocarriers are also reflected in the materials and the intricate composition used for their design. Even complex biological structures up to living cells are developed or used as carriers of active substances. Certain nanocarriers are also designed to actively perform functions in a specific context, such as a structural change that releases the drug without the carrier degrading. Based on this capability, nanocarriers can also be subclassified into active and passive types.

The prefix "nano" in "nanocarrier" suggests a particle size of 1-100 nm, following e.g., the EU definition of nanomaterials. However, such a delimitation would neglect many developments, as the term “nanocarrier” in the field of medical research often also includes structures in the micrometer range. Chariou et al. (2020) therefore propose to include carriers under the designation “nanocarrier” as long as at least one dimension of their outer structure is less than or equal to 1 µm. Based on this proposal, nanocarriers in the size range of 1-1000 nm have been considered in this report.

Although nanocarriers have been used since the 1980s, the term "nanocarrier" did not appear in the scientific literature until the beginning of the 21st century. Since the first approvals of nanocarriers in the field of agriculture, the range of applications and thus the spectrum of types of nanocarriers has expanded significantly. In view of the increasing number of scientific publications (more than 9600 articles between 2000 and 2022) and the number of diverse types of carriers still under development, one can speak of a very dynamic and heterogeneous field, which is considered as key enabling technology (European Commission, 2012). Nanocarriers are primarily used in medicine and agriculture, but also for cosmetics, food and nutritional supplements, household products, textiles, and electronic and electric devices.

The most common and most developed area of application for nanocarriers is medicine or pharmacy. In this field, nanocarriers are mainly developed and applied for the treatment of cancer, but also for vaccines or antibiotics. In addition, nanocarriers can also be used for a combination of diagnostic and therapy. This special application is also known as “theranostics”. The cosmetics industry also frequently uses innovative types of nanocarriers, for example to encapsulate water-insoluble substances or transport active ingredients into deeper layers of the skin. In the field of functional foods or food supplements, nanocarriers enable the encapsulation of volatile or poorly water-soluble active substances as well as the masking of bad-tasting bioactive ingredients. The concept for the use of nanocarrier systems in agriculture is in principle similar to that of medicine. So-called nanoagrochemicals are designed to achieve a targeted transport of active ingredients such as pesticides or fertilizers to the desired site of action. In addition to medicine, cosmetics, agriculture and food, further areas of applications have also been identified such as household products (e.g., air and textile fresheners) and electrochemistry (e.g., lithium-ion batteries).

In summary, the range of applications for nanocarriers is now very broad. However, an examination of the state of development of the identified types of nanocarriers revealed that many of these types are close to market penetration but not yet commercialized and are therefore not yet used on a large scale. Most of the nanocarrier types are organic ones consisting of lipids and polymers. Other nanocarrier types, such as supra-particles, inorganic or hybrid systems, were mostly assigned to the lower development stage on a laboratory scale or prototype testing. The present study shows that a comparatively large number of types of new nanocarriers, consisting of very different materials and complex structures, will come into use in the next few years. It is necessary to accompany this rapid development in order to assess possible risks at an early stage, to be able to take necessary regulatory measures, and to establish an orientation towards the principle of "safe and sustainable by design".

Zusammenfassung

Dieser Bericht gibt einen Überblick über die neuesten Entwicklungen auf dem Gebiet der Nanocarrier. Zu diesem Zweck wurde eine systematische Auswertung von wissenschaftlicher Literatur und Patenten vorgenommen. Diese Recherche zeigt, dass sich viele Nanocarrier noch in der Entwicklung befinden und es sich bei ihnen um ein schnell wachsendes und vielfältiges Gebiet handelt. Mit dieser Studie sollte das breite Spektrum von Nanocarriern kategorisiert werden, wobei ihr Entwicklungsstadium und Anwendungszweck im Vordergrund standen.

Je nach Anwendungsbereich und den Anforderungen an die Eigenschaften des Wirkstoffs können Nanocarrier unterschiedliche Aufgaben erfüllen, die von der einfachen Trägerfunktion, dem Schutz des Wirkstoffs vor Abbau oder der Verbesserung seiner Löslichkeit bis hin zu seinem gezielten Transport und der kontrollierten Freisetzung reichen. Die vielfältigen Einsatzmöglichkeiten von Nanocarriern spiegeln sich auch in den Materialien und ihrem teilweise recht komplizierten Aufbau wider. Selbst komplexe biologische Strukturen – bis hin zu lebenden Zellen – werden als Wirkstoffträger in Betracht gezogen oder bereits eingesetzt. Bestimmte Nanocarrier sind auch so konzipiert, dass sie in einem bestimmten Kontext aktiv Funktionen erfüllen, z. B. eine Strukturveränderung, die den Wirkstoff freisetzt, ohne dass sich die Trägerstruktur abbaut. Angesichts dieser Fähigkeit können Nanocarrier auch in aktive und passive Typen unterschieden werden.

Würde die Definition der Europäischen Kommission (2022) zu Nanomaterialien auch für die Größenabgrenzung von Nanocarriern zugrunde gelegt, dann bezöge sich der Begriff "Nanocarrier" nur auf eine Partikelgröße von 1-100 nm. Eine solche Abgrenzung würde jedoch viele Entwicklungen vernachlässigen, da z. B. der Begriff „Nanocarrier“ in der medizinischen Forschung häufig Strukturen im Mikrometerbereich umfasst. Chariou et al. (2020) schlagen daher vor, Wirkstoffträger unter der Bezeichnung „Nanocarrier“ zu erfassen, sofern mindestens eine Dimension ihrer äußeren Struktur kleiner oder gleich 1 µm ist. Auf der Grundlage dieses Vorschlags wurden in diesem Bericht Nanocarrier im Größenbereich von 1-1000 nm betrachtet.

Obwohl Nanocarrier bereits seit den 1980er Jahren verwendet werden, tauchte der Begriff "Nanocarrier" in der wissenschaftlichen Literatur erst zu Beginn des 21. Jahrhunderts auf. Seit den ersten Zulassungen von Nanocarriern im Bereich der Landwirtschaft hat sich der Anwendungsbereich und damit das Spektrum der Arten von Nanocarriern deutlich erweitert. Angesichts der steigenden Zahl wissenschaftlicher Publikationen (mehr als 9600 Artikel zwischen 2000 und 2023) und der Menge an unterschiedlichen Trägertypen, die sich noch in der Entwicklung befinden, kann man von einem sehr dynamischen und heterogenen Technologiefeld sprechen. Von der Europäischen Kommission werden Nanocarrier als Schlüsseltechnologie angesehen (European Commission, 2012). Nanocarrier werden vor allem in der Medizin und der Landwirtschaft eingesetzt, aber auch für Kosmetika, Lebensmittel und Nahrungsergänzungsmittel, Haushaltsprodukte, Textilien sowie elektronische und elektrische Produkte.

Der häufigste Anwendungsbereich für Nanocarrier ist die Medizin bzw. Pharmazie. In diesem Bereich werden Nanocarrier hauptsächlich für die Behandlung von Krebs, aber auch für Impfstoffe oder Antibiotika entwickelt und eingesetzt. Darüber hinaus können Nanocarrier auch für eine Kombination aus Bildgebung und Therapie eingesetzt werden. Diese spezielle Anwendung wird als "Theranostik" bezeichnet. Auch die Kosmetikindustrie nutzt häufig neuartige Nanocarrier, um beispielsweise wasserunlösliche Substanzen zu verkapseln oder Wirkstoffe in tiefere Hautschichten zu transportieren. Im Bereich der funktionellen Lebensmittel oder Nahrungsergänzungsmittel ermöglichen Nanocarrier die Verkapselung von flüchtigen oder schwer wasserlöslichen Wirkstoffen sowie zur Maskierung von schlecht schmeckenden

bioaktiven Inhaltsstoffen. Das Konzept für den Einsatz von Nanocarrier-Systemen in der Landwirtschaft ähnelt im Prinzip dem der Medizin. Sogenannte Nanoagrochemikalien sollen einen gezielten Transport von Wirkstoffen wie Pestiziden oder Düngemitteln an den gewünschten Wirkort ermöglichen. Neben der Medizin, der Kosmetik, der Landwirtschaft und Lebensmitteln konnten zwei weitere Anwendungsbereiche identifiziert werden: Haushaltsprodukte (z. B. bei Luft- und Textilerfrischern) sowie die Elektrochemie (z. B. bei Lithium-Ionen-Akkumulatoren).

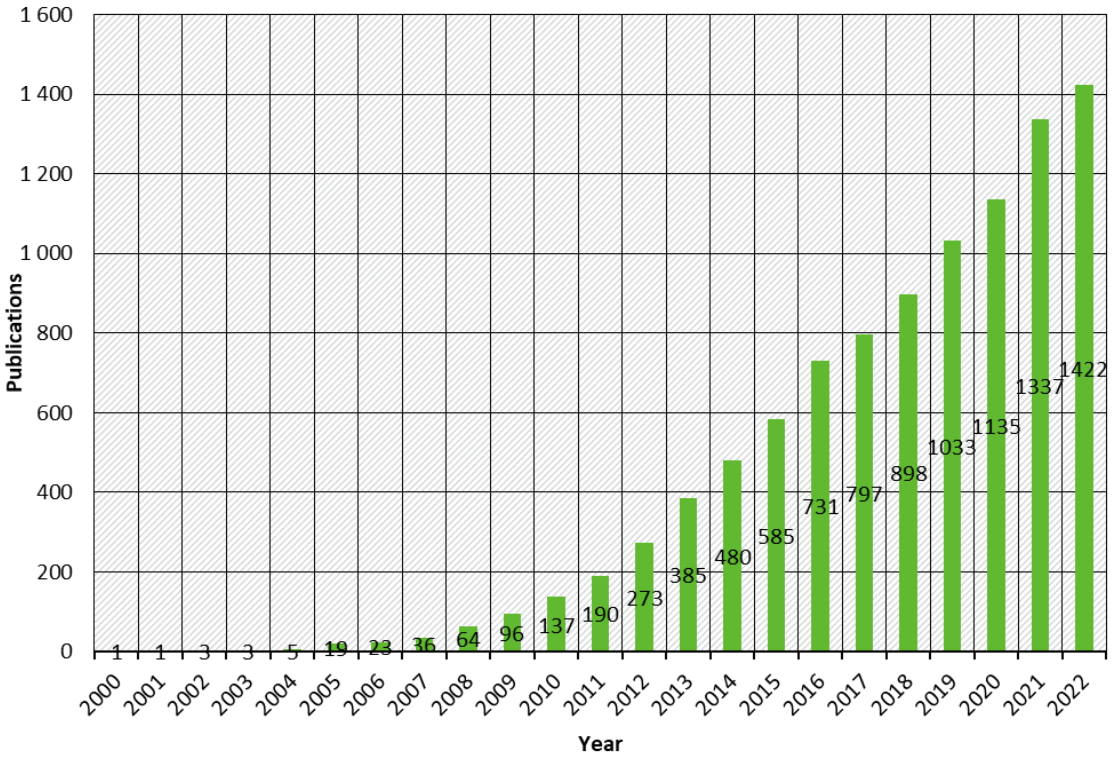
Zusammenfassend lässt sich sagen, dass die Anwendungsmöglichkeiten für Nanocarrier inzwischen sehr breit gefächert sind. Eine Untersuchung des Entwicklungsstandes der identifizierten Typen von Nanocarriern ergab jedoch, dass viele dieser Typen noch nicht anwendungsreif sind und daher noch nicht in großem Umfang genutzt werden. Die meisten der Nanocarrier, die entweder kurz vor der Marktdurchdringung stehen oder bereits verwendet werden, gehören zur Kategorie organischer Carrier und basieren auf Lipiden oder Polymeren. Für diese Materialien konnten in dieser Studie gleichzeitig die mit Abstand meisten Typen von Nanocarriern aller Kategorien identifiziert werden. Andere Nanocarrier-Typen, wie z. B. Suprapartikel, anorganische oder Hybrid-Systeme, wurden meist dem unteren Entwicklungsstadium der experimentellen Analyse im Labormaßstab bzw. der Prototypenerprobung zugeordnet. Die vorliegende Studie zeigt, dass in den nächsten Jahren eine vergleichsweise große Anzahl neuer Typen von Nanocarriern, die aus sehr unterschiedlichen Materialien und Strukturen bestehen, zur Anwendungsreife gelangen wird. Es ist notwendig, diese rasche Entwicklung zu begleiten, um mögliche Risiken früh abzuschätzen, notwendige regulatorische Maßnahmen ergreifen zu können, sowie auf die Orientierung am Prinzip des „safe and sustainable by design“ hinzuwirken.

1 Introduction

Nanocarriers can to a large extent be assigned to the field of advanced materials (Giese et al., 2020). Advanced materials are characterized by the fact that they attempt to implement rational and tailored design at the smallest levels (molecular, atomic). There is a trend towards more complex structures and combinations of materials (composites). The field of nanocarrier-based drug delivery systems is particularly benefiting from this development. In general, nanocarriers are used for the targeted application of a wide variety of active ingredients (Chariou et al., 2020). With their help, the transport, the site of action, the release quantity, and the duration of exposure to the active ingredient can be influenced. But the active ingredients themselves can also be protected by the carrier on their way to the site of action. For agricultural purposes, nanocarriers have been used for several decades (Kah et al., 2013). In medicine, the first applications were approved as early as the 1990s (Chariou et al., 2020). In the scientific literature, however, the term "nanocarrier" appeared relatively late with the beginning of this century (Figure 1). The Figure below shows the trend between 2010 and 2020, whereby the number of published scientific articles using the term "nanocarrier" has increased significantly. This trend seems to be continuing so far.

Figure 1: Number of scientific publications in which the term "nanocarrier" appears in the title, abstract or keywords.

Search query with term "nanocarrier" in the Web of Science™ Core Collection (status 26.04.2023).

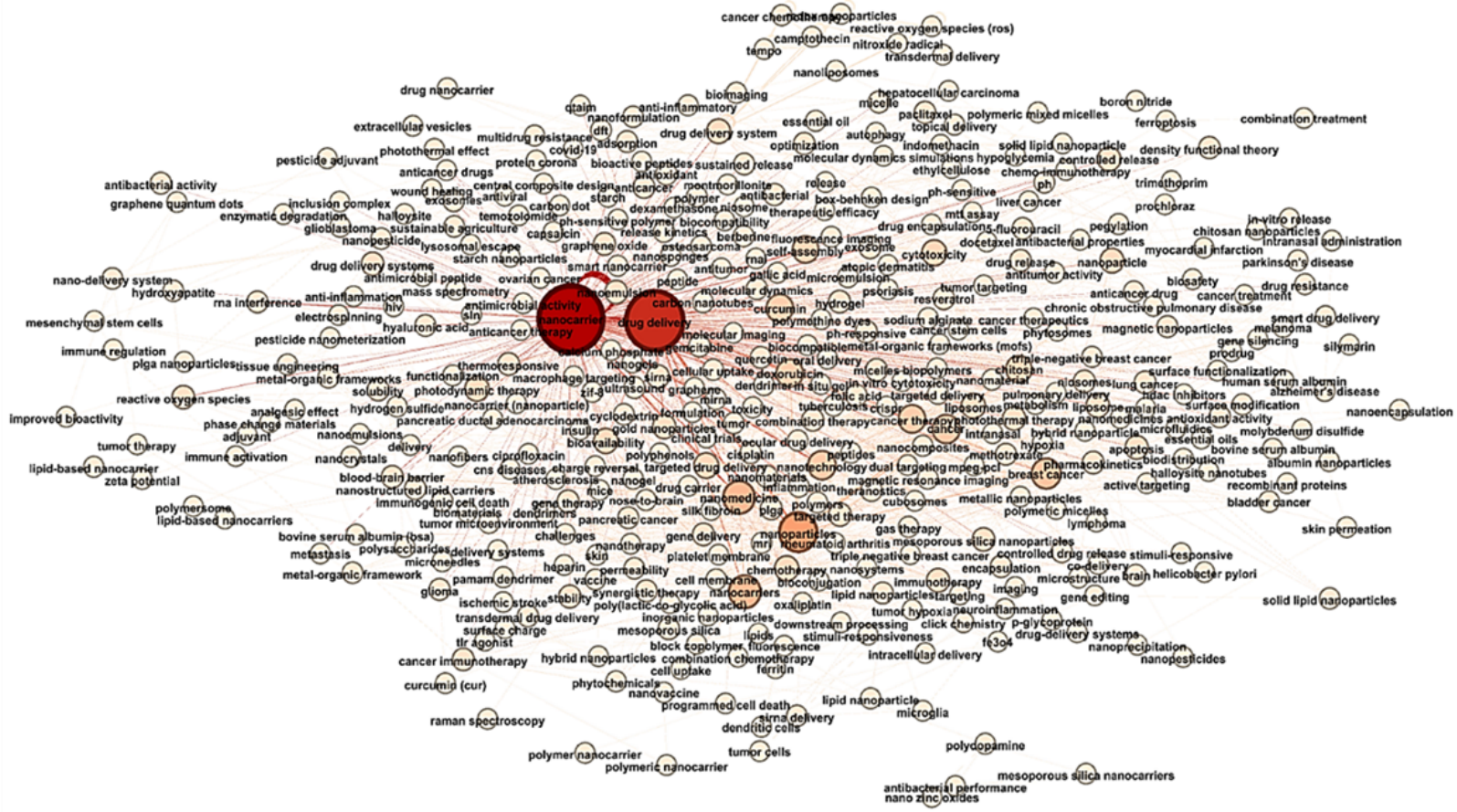


Source: own illustration, BOKU.

The field of nanocarriers is very diverse. This applies to the materials used, which range from inorganic nanoparticles to viruses, as well as to the functionalities and surface properties enabling a “carrier” system. In addition to the simple carrier function, protection against degradation (colloidal stability) or better solubility, targeted transport is also possible with many systems. Nanocarriers can be used to transfer not only active ingredients such as drugs, but also enzymes or nucleic acids (DNA, RNA). In this regard, Chariou et al. (2020) stated that they "[...] observed a shift away from the development of nanocarriers for small-molecule reactants and towards the delivery of peptides, proteins and nucleic acids". For example, a very complex approach aims to use plant viruses transferred to crops with the help of aphids to achieve at least transient genetic modification of plants. This concept is known as “insect allies” and described in more detail in Pfeifer et al. (2022). The highly heterogeneous carrier materials entail that a narrow size range cannot be given for the entire field of nanocarriers. Accordingly, Chariou et al. (2020) extend the definition limit of nanomaterials beyond 100 nm to up to 1000 nm for their conducted literature review about nanocarriers. Regarding current research on nanocarriers, the terms used in the publications indicate that mainly medical applications represent the current research focus (). The term "drug delivery" appears in this context with almost the same frequency as the search term "nanocarrier" used for the research shown in Chapter 2.1. Presumably, not least the successful use of a liposomal nanocarrier to protect RNA vaccines in the Covid-19 pandemic gave the research field an additional boost.

Figure 2: Network representation of the keywords of all publications in the period 1.1.2022-24.8.2022 in which the term "nanocarrier" appears in the title, abstract or keywords. Only keywords that are mentioned in at least two publications were considered. The size of the nodes, the strength of the colouring and the strength of the connections between the nodes correspond to the frequency of their use or the frequency of their common mention in the publications.

Search query with term "nanocarrier" in the Web of Science™ Core Collection.



Source: own illustration, BOKU.

Few terms in the current scientific literature indicate agricultural use of nanocarriers. It is possible that nanocarriers used in agriculture are referred to differently. Chariou et al. (2020) suggest that in the agricultural sector, the term "nanocarrier" is avoided so as not to affect public acceptance of nanoscale carrier systems.

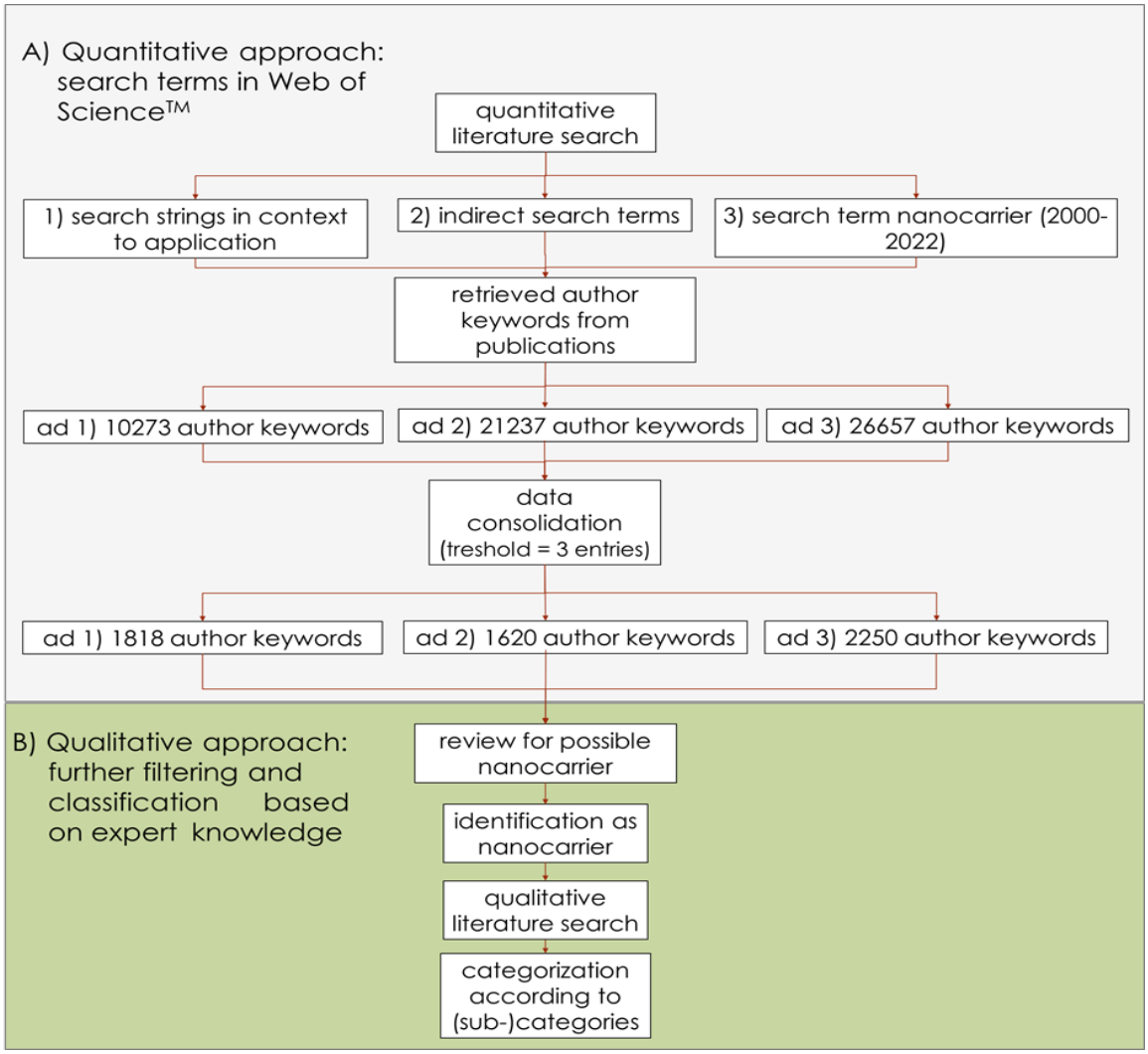
The list of identified carrier types presented in this report does not claim to be complete. The large number of designations and the dynamic development in this field of research make it difficult to obtain a complete overview. New types of nanocarriers are constantly being published in the literature, although it is difficult to determine whether these are genuine innovations or whether a new name is only intended to give the impression of innovation. This becomes particularly clear in the almost unmanageable field of those vesicular carriers that are designated with the suffix "some". The prototype of these "somes" is considered to be the liposome (see detailed description below). Liposomes are lipid-based, self-assembling structures with a double membrane that were first described in the 1960s. In the meantime, there is a multitude of names for liposome-like structures, which differ mainly in the addition of further components. However, carriers with the suffix "some" are also described, which do not have a vesicular structure and thus differ greatly from liposomes, as well as structures which are not based on lipids, but are made of polymers, for example. In their review, Apolinário et al. offer an overview of the broad and heterogeneous field of "some" and propose a rational classification (Apolinário et al., 2021). But also other, partly very fanciful terms for nanocarrier types are often not used uniformly and interchangeably, such as "beads", "spheres" or "capsules". This makes a clear description and classification difficult. The present work represents an approach for a possible categorization of the different nanocarrier on basis of their material origin and is intended to provide assistance in finding one's way through the maze of different designations, functionalities, materials and areas of application.

This report provides an overview of the field of nanocarriers in the following chapters. First, the underlying search strategy (Chapter 2) and the working definition of nanocarriers used to narrow the search scope (Chapter 3.1) are explained. The identified types of nanocarriers are presented in Chapter 3.2 followed by the assignment to the state of development in chapter 3.3. Chapter 3.4 is dedicated to the use of nanocarriers in their main areas of application. The topic of biodegradability of nanocarriers is discussed in the last chapter of the study results (Chapter 3.5), as this property is attributed to many carrier materials in the literature and to explain this often vaguely defined term in more detail.

2 Methodological approach

To characterize the field of nanocarriers and describe the different types of carriers, all carrier types used so far and those under development had to be researched and classified in a systematic way. Scientific literature, patent databases and other information available on websites were used as sources of information for the systematic research. Figure 3 shows the applied methodological approach to collect, filter, review and analyze the literature in the field of nanocarriers. This approach allowed to categorize and subclassify the complex carrier systems with a focus on their material composition and possible areas of application. The search method consists of a quantitative (Figure 3A) and a qualitative (Figure 3B) approach. The quantitative approach consisted of software-assisted literature research and import of the retrieved keywords into an Excel-database. These keywords were subsequently filtered based on expert knowledge and a more in-depth literature search using the snowball principle to identify those representing terms of nanocarriers. Furthermore, for some applications, the search term-based screening for keywords representing nanocarriers had to be complemented by an additional qualitative search. The qualitative search approach (Figure 3B) allowed to add and filter missing NC-specific keywords, which were finally added to the keyword list obtained from the quantitative part (Figure 3A). This combination made it possible to include as many NC-relevant studies as possible in our literature search to be able to carry out a nanocarrier classification (Chapter 2.2) at the end.

Figure 3: Methodological quantitative (A) and qualitative (B) approaches to filter, review and analyze the field of nanocarriers to be able to perform a categorization. (NC: nanocarrier)



Source: own illustration, BOKU.

2.1 Quantitative approach: search terms in Web of Science™

The aim of this methodological approach was to gain an all-encompassing overview of the nanocarrier field. All sub-headings within the following section refer to the respective box in Figure 3A:

"Quantitative literature search":

The first step was a quantitative literature search in the literature database *Web of Science™ Core Collection* (WOS). The overall goal of this quantitative literature search was to retrieve keywords from peer-reviewed publications that are related to nanocarrier.

For all queries the WOS search field "topics" was used, which refers to all publications with the keyword in the title, abstract, the author keywords and the KeyWords Plus®. In the query results, research articles, literature reviews and early access articles were chosen as document types.

"1) Search strings in context to application", "2) Indirect search terms", "3) Search terms for nanocarrier (2000-2022)":

Since many studies do not use the term "nanocarrier", three different searches were applied that enabled to retrieve a collection of as many studies as possible that deal with nanocarrier, even though these publications avoid nominating nanocarriers as such:

"1) Search strings in context to application" were referred to four areas of applications (publication period investigated: 1st January 2022 to 2nd November 2022): medicine/pharmacy, food/food supplements, agriculture/nanoagrochemicals and cosmetics. The search strings were composed of at least two search terms that were combined by the "and"-function. Nanocarriers, which are applied in medicine/pharmacy, were accessed by search strings containing "nano", "carrier" and one of the following five search terms: Diagnosis, disease, drug, targeted delivery and therapy. For agriculture/nanoagrochemicals, the search strings involved "nano" and one of the following nine search terms: Agrochemical, clay, crop, fertilizer, fungicide, herbicide, insecticide, pesticide, and plant. For cosmetics, the search string contained "nano", "carrier" and "cosmetics".

"2) indirect search terms" were related to indirect descriptions of nanocarriers via the function and research scope (publication period investigated: 1st January 2022 to 2nd November 2022). These indirect search terms were determined by the snowball principle within a qualitative literature survey. Each of the following indirect search terms was used for a separate search in the *Web of Science™ Core Collection*: Carrier-mediated transportation, controlled release, delivery system, delivery vehicle, drug carrier, drug delivery, encapsulation, microencapsulation, nanoencapsulation, nanofluidic devices, sustained release, targeted delivery, transdermal drug delivery, vesicular carrier, and vesicular delivery systems.

"3) Search term nanocarrier (2000-2022)" contained the term "nanocarrier" (publication period investigated: January 1st 2000 to December 31st 2022). This strategy aimed to find and screen most of the studies that have been reported about nanocarriers within this period (Figure 3).

"Retrieved author keywords from publications":

Author keywords were retrieved form publications that were accessed by the three different search terms as described above. 10273 author keywords were retrieved from "1) search strings in context to application", 21237 from "2) indirect search terms" and 26657 from "3) search term for nanocarrier (2000-2022)".

"Data consolidation (threshold = 3 entries"):

To process the large amount of author keywords in the following qualitative procedure (Figure 3B), author keywords that were mentioned less than three times were excluded from further evaluation in order to select more general names of nanocarriers. The data consolidation was performed automatically by a custom-made script using the software *LabVIEW* (National Instruments, U.S.) that executed the following steps: 1) Author keywords were checked for exact identity (except for capitalization), 2) identical author keywords were cumulated, and 3) their frequency was determined. After data have been consolidated, retrieved author keywords were reduced to 1818 author keywords within „1) search strings in context to application", to 1620 author keywords within „2) indirect search terms" and to 2250 author keywords within "3) search term for nanocarrier (2000-2022)".

2.2 Qualitative approach: further filtering and classification based on expert knowledge

Aim of this methodological approach was to filter and classify the author keywords that were achieved by the previous search terms (Figure 3A). All sub-headings within the following section refer to the respective box in Figure 3B.

"Review for possible nanocarrier":

Consolidated author keywords (Figure 3A) were initially reviewed by expert judgement for possible nanocarrier. Relevant author keywords were marked and further investigated within the next step. Table A1 in the appendix lists retrieved author keywords from publications that were obtained by the three different search terms as described in Figure 3A: "1) search strings in context to application", „2) indirect search terms", „3) search term for nanocarrier (2000-2022)". The author keywords in Table A1 were already consolidated (Figure 3A) and reviewed for possible nanocarrier (Figure 3B).

"Identification as nanocarrier":

The selection of possible nanocarrier in the previous step was further refined by a qualitative check based on patent information retrieved from the database *SciFinder*^{n} and the literature database *Web of Science™ Core Collection*. This step led to a list of names of nanocarrier.

"Qualitative literature search":

The list of identified nanocarrier were completed by qualitative literature search.

"Categorization according to (sub-)categories:

Nanocarrier that were retrieved by author keywords and the qualitative literature search were assigned to chemical categories and sub-categories (see Chapter 3.2). In addition, the nanocarriers were described by a number of criteria. For a comparative characterization of the nanocarrier, the following (sub-)categories and criteria were applied:

1. Generic term for carriers
2. Chemical category of the carrier
3. Chemical sub-category of the carrier
4. Material used for the nanocarrier
5. Active ingredient of the nanocarrier (by example)
6. (potential) Application area of the nanocarrier (medicine/pharmacy, food/food supplements, agriculture, cosmetics and other applications)
7. Properties of the nanocarrier
8. Example of the nanocarrier
9. Advantages of the nanocarrier
10. Disadvantages of the nanocarrier
11. State of development (see paragraph below)
12. Mode of drug release

Within each generic term for carriers, the categories were accessed by a further qualitative literature survey. Missing nanocarriers have been added if they were not yet listed in the database so far. The characterization based on the criteria was carried out using examples of the respective nanocarrier type. The criterion "state of development" (SOD) was determined by applying a scale with three grades that derive from the nine Technology Readiness Levels (TRL). This simplification and grouping of the developmental stage into either TRL 1-3, TRL 4-6 or TRL

7-9 was necessary due to vague description (uncertainty) and the paucity of information on the TRL. We hereby followed the approach of Jankovic and Plata (2019). In this work, the TRL definition was only used as a first orientation and, therefore, deliberately referred to as "state of development" (SOD). This should enable a prevention of misunderstandings and "pseudo-accuracies". For this study, the SOD was defined as follows:

- SOD 1-3 represents a formulated concept of the nanocarrier type
- SOD 4-6 represents the development in laboratory and testing of the prototype
- SOD 7-9 represents usage, availability and close to market penetration

3 Results

3.1 Working definition for nanocarriers

To separate the research area of this work from related technologies, a working definition was derived from the current general understanding of nanocarriers in the scientific literature. The working definition refers to the primary function, size, and key features of the carrier:

Nanocarriers are carrier systems for active ingredients whose external dimensions are smaller than 1000 nm in at least one dimension (Chariou et al., 2020). They are used, among other things, for protection, targeted transport to the site of action and sustained release of an active ingredient. The specific functionalities and characteristics of a nanocarrier can affect persistence, interactions, and fate in the environment of the carrier material itself as well as of the transported active ingredient.

We define as nanocarriers all structures or substances that do not primarily bring about the intended effect of an active ingredient, but in which it is enclosed up to the site of action or with which it is connected (this also includes covalent bonds). The nanocarrier is able to sustain its structure even without the ingredient, i.e., a surface modification of the active ingredient is not considered as a nanocarrier in the sense of this definition. Furthermore, passive or active mobility belongs to the tasks of a nanocarrier. Site-stable nanoscale carrier structures are therefore excluded from the definition (sensor surfaces, materials for affinity chromatography, etc.).

The authors of this study are aware that there are carrier types larger than 1000 nm. However, the present work is oriented at a cut-off in accordance with the above definition to keep the focus on comparably small structures.

In this study, the term "nanocarrier" includes entire nanocarrier-based systems in the size range of 1-1000nm. Here it is important to note that a nanocarrier system consists of an active ingredient that is transported through the nanocarrier, and the carrier structure itself. Nanocarrier systems also include surface functionalization and other surface modifications (e.g., for stabilization) to deliver an active ingredient specifically to its destination (controlled/targeted delivery). The term "nanocarrier" used in this study thus refers to the entire nanocarrier system.

3.2 Types of nanocarriers

The comprehensive, systematic literature search conducted for this study resulted in a large number (412) of indications or equivalent terms for nanocarriers, which are used in the literature. After a first analysis of the nature of these carriers, 132 different generic terms for carriers could be identified[1] (see Table A 2 for the full list of identified carriers). The carriers were characterized according to the following criteria – this categorization approach is shown on the example of “nanodiamonds” (S. Chauhan et al., 2020):

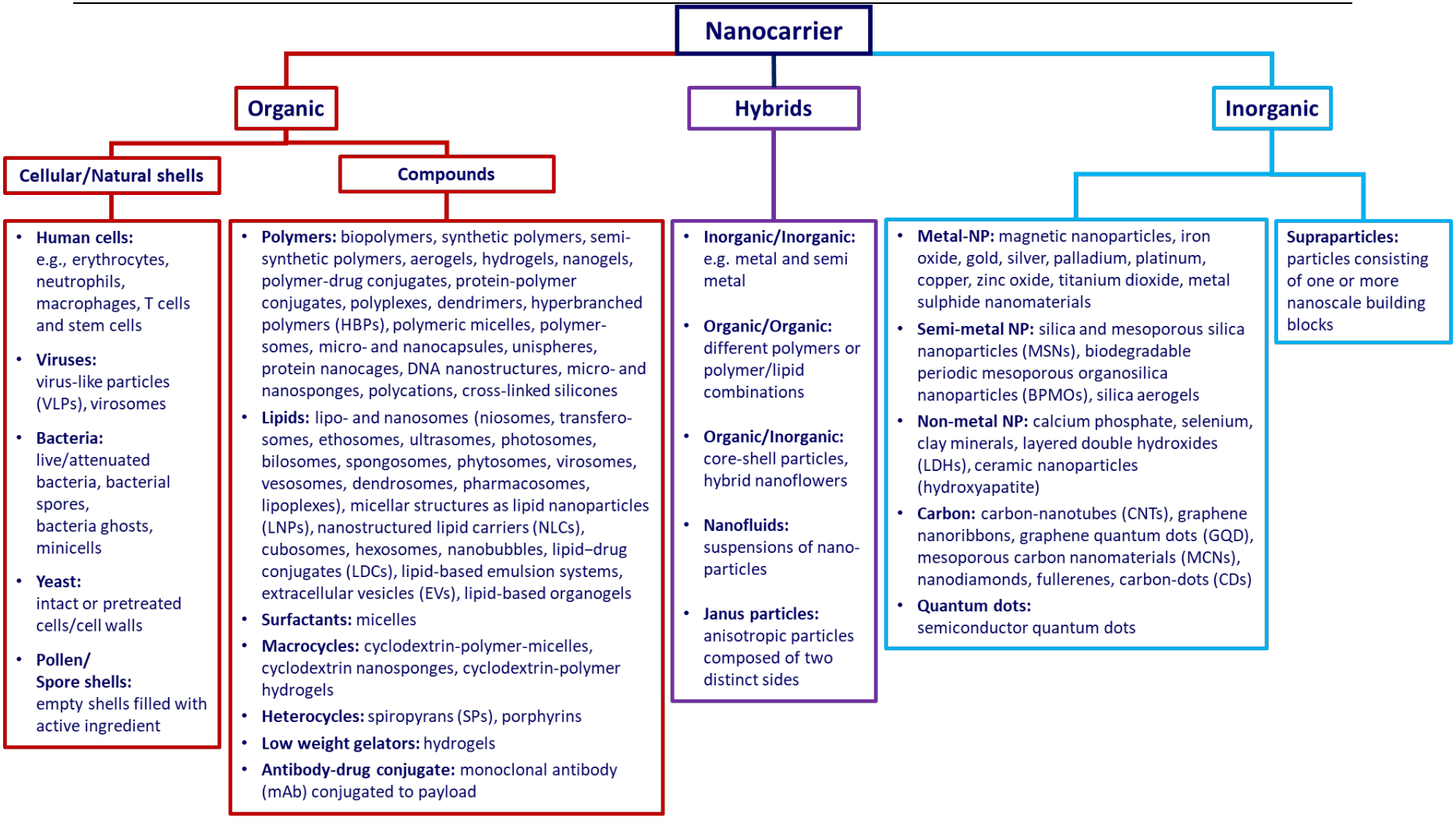
- **Generic term for carriers:** nanodiamonds
- **Chemical category of the carrier:** inorganic

[1] The complete database of identified carriers can be downloaded under https://bokubox.boku.ac.at/#0fef35095cf8ba48b05281f4f8808f45“

- **Chemical sub-category of the carrier:** carbon-based
- **Material used for the nanocarrier:** carbon; core-shell structure with inner diamond core and outer graphite shell for binding functional groups)
- **Active ingredient of the nanocarrier:** Doxorubicin hydrochloride, proteins (antigens, antibodies, immunoglobulin)
- **(Potential) application area of the nanocarrier:** medicine/pharmacy
- **Properties:** adjustable surface area
- **Example of nanocarrier:** (not available)
- **Advantages:** chemically inert, high hardness and thermal conductivity
- **Disadvantages:** possibly influence on structure and function of attached proteins
- **State of development:** allocated to 7-9, already applied to medical devices
- **Mode of drug release:** (not available)

Origin and chemical composition of nanocarriers represent comparatively clear criteria, enabling a systematization. Based on the literature analysis, a corresponding scheme including major classes and subdivisions of nanocarrier types is shown in Figure 4.

Figure 4: Schematic representation for the categorization of nanocarrier types by material type and structure.



Source: own illustration, BOKU.

Most nanocarriers, which are mentioned in the literature, are either made of organic or inorganic substances. In addition to these two groups, there are also hybrid structures in which organic and inorganic substances are combined to achieve properties that meet the requirements of specific applications. Supraparticles are listed as another class because they represent clusters of individual particles (organic, inorganic or hybrid) that can combine to form a supraparticle but can also dissociate in response to a stimulus. The various nanocarrier types are described in more detail in the following chapters.

3.2.1 Organic

On the one hand, organic nanocarriers include those on a cellular basis or consisting of natural envelopes of pollen and spores, and on the other hand, organic nanocarriers can also be made from a wide range of organic compounds (Figure 4).

3.2.1.1 Human cells-based

Cell-mediated drug delivery systems are explored in nanomedicine, in which **erythrocytes, neutrophils, macrophages, T cells and stem cells** are used. According to Choi et al. (2023), cell-based systems have clear advantages over conventional delivery systems. In addition to being biodegradable and well tolerated by the human body, they are less immunogenic and cytotoxic. Depending on the cell types used for delivery, the target tissue and the properties of these delivery systems can be very specific (Choi et al., 2023).

Erythrocytes, for example, have a high loading capacity and can carry payloads such as different drugs as well as contrast agents for imaging. Due to their reversibly deformable membrane, it is possible to encapsulate active ingredients using mechanical techniques. The long half-life of erythrocytes also allows sustained release of the cargo. Their properties as carriers for the transport of various active pharmaceutical ingredients such as antiviral and anti-inflammatory drugs, antigens, nucleic acids, peptides and enzymes have been explored since 1973. However, the use of erythrocytes as drug carriers has some limitations, especially their inability to migrate across the vascular endothelium to release the cargo. Therefore, immune cells and stem cells are increasingly explored as extravascular cell-based delivery systems. (Choi et al., 2023)

Stem cells in particular are potentially suitable for cell-based drug delivery. They are able to survive in cancerous environments and they tolerate chemotherapeutic agents. Moreover, they show regenerative, anti-inflammatory, and immunomodulatory properties. Stem cells have been used primarily for the regeneration of diseased tissue and in cancer therapy, but the use of stem cells as drug carriers presents several obstacles according to Choi et al. (2023), including infection, immunogenicity, tumorigenicity, poor retention after transplantation, and low drug loading efficiency. The suitability of live cells for targeted delivery of active ingredients has been investigated in several clinical trials (Choi et al., 2023).

3.2.1.2 Virus-based

Virus-like particles (VLPs) are an emerging nanocarrier platform offering great advantages. They are biocompatible, easy to functionalize and they exhibit morphological uniformity. The size of VLPs ranges from about 10 nm to over a micron, and these carriers exhibit different morphological structures. The principles used to package viral RNA or DNA within the viral capsid, based on supramolecular self-assembly and disassembly processes, can also be utilized to encapsulate active ingredients. Incorporation of zinc phthalocyanine, CdSe/ZnS quantum dots, gold nanoparticles and magnetic material has been reported. In addition to the process of

disassembling and reassembling of the viral capsid to encapsulate the cargo, the active ingredient, e.g., the anticancer drug doxorubicin can also bind covalently to specific reactive sites on the capsid proteins. VLP platforms can be modified with polymers (e.g., PEG) in order to reduce their immunogenicity and increase their half-life in the host. (Ma et al., 2012)

The internal cavities and external surfaces of a variety of viruses can be chemically and genetically modified to allow covalent attachment of drug molecules and various cell- or tumor-targeting ligands, such as folic acid or antibodies (Ma et al., 2012). For example, the Cowpea chlorotic mottle virus (CCMV), the Cowpea mosaic virus (CPMV), the Red clover necrotic mosaic virus (RCNMV), the Tobacco mosaic virus (TMV9), the Turnip yellow mosaic virus (TYMV), the Brome mosaic virus (BMV), the Human polyomavirus, the Hibiscus chlorotic ringspot virus (HCRSV), the alphaviruses, and the MS2 and M13 bacteriophage have been explored for drug delivery purposes (Ma et al., 2012). Ma et al. (2012) emphasize the importance of a comprehensive assessment of the toxicity and biodistribution of VLPs in vivo before testing them for medical applications.

Virosomes are restructured viral envelopes explored as carriers for large molecules such as nucleic acids, genes, or drugs. They are composed of membrane lipids and viral spike glycoproteins. Initially, liposomes of purified influenza spike proteins were used to fabricate virosomes, and subsequently, several other viral species, including Sendai virus, Semliki Forest virus, vesicular stomatitis virus and Sindbis virus, were investigated. To deliver active ingredients into the cytoplasm of host cells, virosomes fuse with their endosome or plasma membrane. Virosomes may be applied by a variety of routes such as topical, oral and transdermal to achieve drug delivery. (Shende & Basarkar, 2019)

3.2.1.3 Bacteria-based

Bacteria may be used in medicine for the delivery of for drugs against cancer and as vectors for gene therapy. According to Patyar et al. (2010) live, attenuated or genetically modified non-pathogenic bacterial species are being investigated for anticancer therapy, either for direct tumoricidal effects or for delivery of drugs, cytotoxic peptides, therapeutic proteins or prodrug-converting enzymes to solid tumors (Patyar et al., 2010).

Some bacterial species have a predilection for proliferation and accumulation within tumors and exhibit beneficial characteristics such as motility, the ability to simultaneously carry and express multiple therapeutic proteins, and can be eliminated by antibiotics (Patyar et al., 2010). Anaerobic bacteria, such as species belonging to the genus Clostridium, thrive in cancer tissue that is low in oxygen and destroy it, while perish on contact with the oxygen-rich sides of the tumor, consequently they would be harmless to healthy tissue. Besides bacteria of the genus *Clostridium* also *Salmonella typhi*, *Bifido bacterium*, *Salmonella choleraesuis*, *Vibrio cholerae*, *Listeria monocytogenes* and *Escherichia coli* are being explored for drug delivery, for example (Pandey et al., 2022). Since bacteria are not able to destroy all tumor tissue, they are combined with chemotherapeutics (Patyar et al., 2010). Genetically modified bacteria express a specific therapeutic gene, such as interleukin-2 for the treatment of liver cancer. **Bacterial spores**, a dormant form of bacteria, are also interesting candidates to target cancer. These spores of anaerobic bacteria are highly resistant and can survive in environments that are rich in oxygen, although no proliferation is possible there. On the contrary, the dead and oxygen-poor areas inside tumors provide favorable conditions for these types of bacteria, allowing spores to germinate and bacteria to multiply (Patyar et al., 2010). Bacteria can also be sensitive to a

variety of stimuli, such as chemicals, pH, light, and temperature (Shende & Basarkar, 2019). Bacterial therapy has still some major problems to overcome, such as toxicity, incomplete tumor lysis and the potential for DNA mutations. However, clinical trials are underway for several bacterial-based drug delivery systems for cancer treatment (Pandey et al., 2022).

"Bacteria ghosts" are hollow, empty and **non-living** envelopes of genetically modified gram-negative bacteria such as *Escherichia coli*. Although unable to multiply, they show all the favorable structural, immunogenic and bioadhesive properties because of proteins present on their surface. Therapeutic agents such as nucleic acids, antigens and proteins can be encapsulated within these cellular envelopes. (Shende & Basarkar, 2019)

"Minicells" are achromosomal microparticles that are usually the consequence of aberrant cell division in bacteria and that contain membranes, ribosomes, RNA and proteins but cannot multiply. Minicells are under investigation as delivery vesicles for drugs, vaccines and RNA in medicine. For example, *Escherichia coli*-derived minicells can be used as a cost-effective and scalable technology for dsRNA production and encapsulation in one single step in which the microbes first produce the dsRNA and then the minicells. (Islam et al., 2021)

3.2.1.4 Yeast cells-based

Yeast cells are eukaryotic cells and suitable for the encapsulation of both hydrophobic and hydrophilic active ingredients due to their phospholipid membrane. They are cheap and abundant ingredients in food and are widely used for fermentation in the food industry (Tan et al., 2021). The most important yeast cell used in the development of delivery systems is *Saccharomyces cerevisiae* or baker's yeast. The inner plasma membrane and the rigid cell wall are the main cell components used for encapsulation. The encapsulation process using yeast cells is relatively simple and low-cost. Only the yeast, water and the active ingredient are needed, and the use of further additives is not necessary (Tan et al., 2021). According to Tan et al. (2021) the solution of the active ingredient (aqueous or organic solvent solution) is mixed with the yeast cells (in the form of live, wet or dried, plasmolyzed or non-plasmolyzed) or the aqueous suspension of yeast walls for several hours at an adjusted temperature (usually 20-60°C). Particularly in the food industry, yeast cells appear to be suitable for the protection, encapsulation and controlled release of active ingredients such as flavors or other hydrophobic substances (Tan et al., 2021).

3.2.1.5 Pollen and spore shells

Pollen and spore shells are naturally derived microcapsules (1-2 µm) consisting of an inner layer (intine; mainly cellulose) and an outer layer (exine; protein sporopollenin) with several beneficial properties. They are uniform in size and are resistant to alkaline solutions, acids and temperatures of up to 250°C. Pollen and spore shells have the ability of encapsulating and releasing active substances in a controlled manner and to enhance their bioavailability. Empty shells can be easily filled with a liquid active substance by simple mixing, as the shell is porous. The production is simple and cheap. By protecting the active substances against oxidation, storage stability can be increased. (Diego-Taboada et al., 2014)

3.2.1.6 Polymer-based

Polymeric nanocarriers have attracted considerable attention for the delivery of active ingredients and drugs because some polymers enable the design of structures that can be water soluble, biocompatible, stable during storage and can even be designed to be biodegradable

(Mitchell et al. 2021). Disadvantages include an increased risk of particle aggregation and toxicity. Therefore, only a small number of polymeric nanocarriers are currently FDA approved and in clinical use (Mitchell et al., 2021). There are various ways to produce a polymeric nanocarrier system. The active ingredient can be either encapsulated in the internal cavity of the carrier, integrated in the polymer matrix, chemically conjugated to the polymer, or bound to its surface. As Mitchell et al (2021) point out, this allows for the delivery of various active ingredients, including hydrophobic and hydrophilic compounds, as well as substances with different molecular weights, such as small molecules, biological macromolecules, proteins and vaccines. A variety of different natural and synthetic polymers can be used for nanocarrier formulations.

Building blocks for **biopolymers** include proteins, such as albumin, fibroin, ferritin, vault protein, gliadin, elastin or soy protein and polysaccharides, such as heparin, chitosan, carboxymethylchitosan, chitin, alginate, carageenan, xanthan, cellulose, carboxymethylcellulose, starch, gum arabic, hyaluronic acid, dextran, zein, gelatin, lignin, pectin, collagen, gellan or fucoidan. Natural polyesters, such as polyhydroxyalkanoate (PHA), amidines, such as guanidin, glycosides, such as glycyrrhizic acid or nucleic acids (DNA, RNA) are also under research for the use as biopolymer-based nanocarriers.

Many **synthetic polymers** can be used as carrier materials, for example polylactic acid (PLA), poly(lactide-co-glycolide) acid (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), polysebacic acid anhydride (PSA), polymethacrylates (Eudragit® - anionic copolymer of methacrylic acid and methyl methacrylate), poly(2-(dimethylamino)ethyl methacrylate (PDMAEMA), 2-(dimethylamino)ethyl methacrylate (DMAEMA*), poly(alkyl cyanoacrylate*) (PACA), polyethyleneimine (PEI), polyamidoamine (PAMAM), polyethylene oxide, polypropylene oxide, poloxamers (block copolymer of ethylene oxide and propylene oxide), polyethyleneimines, tocopheryl polyethylene glycol succinate (TPGS), poly(epsilon(ε)-caprolactone), polyurethanes, silicone (polyorganosiloxanes).

Semi-synthetic polymers, such as gelatine modified with methyl acrylamide are also investigated for polymeric nanocarriers.

Aerogel is an extremely light material consisting of 99.98% air by volume, exhibiting high porosity and outstanding strength. This biopolymer-based material has advantageous mechanical, morphological, and pharmaceutical properties that make it attractive for biomedical and drug delivery applications. Drug release from the aerogel can be controlled by adjusting the pore size of the aerogels and the pH that triggers release. Biopolymer-based aerogels belong to a class of materials with a wide variety of functional groups, linear and branched copolymers, and are responsive to various stimuli such as pH and temperature. (Abdul Khalil et al., 2023)

Hydrogels are three-dimensional networks of hydrophilic polymers that swell in contact with water and have a high level of water retention (Mahmood et al., 2022). Synthesized from biopolymers, hydrogels can have different properties for different applications and have been widely applied in medicine, for example, as transdermal drug delivery systems. Hydrogels are flexible and versatile materials and they can also react stimuli-responsively if they contain the corresponding functional groups (pH-sensitive temperature-sensitive, electrosensitive and light-responsive gels) (Mahmood et al., 2022). Hydrogels can be crosslinked physically by non-covalent interactions, chemically by covalent bonds, or by a combination of both (Buwalda et al.,

2017). Crosslinked hydrogel particles are also called **nanogels** and there are various natural and synthetic polymers suitable to synthesize nanogels (Khan et al., 2022).

Polymer-drug conjugates, also known as polymeric prodrugs, are drug delivery systems formulated to incorporate therapeutic agents into polymers using selected functionalities (Alven et al., 2020). According to Alven et al. (2020) they are composed of three units: 1) solubilizing unit 2) targeting moiety and 3) the therapeutic agent, which are incorporated into the polymeric backbone. Targeting moieties are, for example, folic acid, antibodies, sugars, or peptides. The therapeutic agent is usually incorporated into the polymeric backbone via a linker and amine, alcohols, or carboxyl groups are suitable functional groups for the conjugation of the active agent, for example. Polymer-drug conjugates can be synthesized using branched or linear polymers. Polyaspartimide, poly(malic acid), poly(vinyl pyrrolidone), poly(ethylene glycol) (PEG), and poly(vinyl alcohol) polymer (PVP) are examples of linear polymers, while poly(amidoamine) and poly(ethyleneimine) polymers are example of branched polymers. Polymer-drug conjugates improve the bioavailability of the therapeutic agent, and they are biodegradable. They also reduce the toxicity of the drug and improve its stability and solubility. With this type of nanocarrier, sustained and controlled drug release is feasible, which makes it possible to overcome drug resistance problems. (Alven et al., 2020)

Protein-polymer conjugates are also interesting candidates under investigation for drug delivery as of their precise binding interactions and limited negative side effects. They can improve the bioavailability of encapsulated hydrophobic drugs, protect drugs from hydrolysis, enzymatic or chemical degradation, reduce toxicity and provide sustained release. However, proteins often exhibit poor stability, rapid clearance, and immunogenicity, which limit their clinical use. Conjugation of a polymer to a protein can help to overcome these problems by increasing the stability of the protein and the circulation time. The attachment of polyethylene glycol (PEG) to a protein is an example of a protein-polymer conjugate (Stevens et al., 2021). The use of a stimuli-responsive polymer, such as poly(N-isopropylacrylamide) (PNIPAM), allows for controlled drug release. (Stevens et al., 2021)

Vectors are important in gene therapy, but the commonly used viral vectors have some immunological disadvantages. Non-viral vectors such as **polyplexes** are therefore under investigation as a promising alternative (Khan et al., 2022). Polyplexes consist of a (preferable cationic) polymer conjugated with DNA. A variety of cationic polymers have been investigated such as polyethylenimine (PEI), poly-L-lysine (PLL), polyamidoamine (PAMAM) and poly (2-dimethylaminoethyl methacrylate) (PDMAEMA) (Rohan et al., 2019). Polyplexes are biocompatible and interesting for drug and gene delivery in cancer therapy, because they can be decorated with ligands to target overexpressed membrane proteins of cancer cells (Khan et al., 2022).

Dendrimers are polymeric nanocarriers with arborescent architecture (Chariou et al., 2020; Mitchell et al., 2021). They consist of a central core with radially oriented branching repeating units, which end in chemical groups that can be functionalized (Chariou et al., 2020). The cargo can be encapsulated in the core or conjugated to the surface (Chariou et al., 2020). Some polymeric dendrimers are currently under clinical trials (Chariou et al., 2020). Dendrimers can be used to deliver a wide variety of agents, but are most commonly studied for the delivery of nucleic acids and small molecules (Mitchell et al., 2021). The so-called “Star Polycation” (SPc) is

a cationic dendrimer that has four peripheral arms functionalised with amino acids (for a detailed description see below).

Hyperbranched polymers (HBPs) are highly and randomly branched macromolecules. Like dendrimers, they have a 3D spherical structure that makes them attractive for use in drug delivery. HBPs exhibit low intrinsic viscosity, low tendency to chain entanglement, smaller hydrodynamic radius, good solubility, and high degree of branching resulting in a high number of terminal functional groups. These properties make HBPs more advantageous than linear polymers. Like dendrimers, HBPs contain internal cavities that make them suitable for encapsulating varying sized compounds. (Kavand et al., 2020)

Polymeric micelles are spherical vesicles formed by amphiphilic block copolymers with alternating hydrophilic and hydrophobic segments. The ratio of active ingredient to the block copolymers determines their properties (Chariou et al., 2020). They are of interest for medical applications, and several nanocarriers of this type are currently tested in clinical trials. Micelles are also in development as promising nanocarriers for the encapsulation of pesticides (Chariou et al., 2020). To optimize the properties and overcome some of the drawbacks of single micelles, it is possible to combine two or more different amphiphilic polymers into so-called "mixed micelles" (Cagel et al., 2017). They exhibit improved thermodynamic and kinetic stability, increased drug loading capacity, more precise size control, and easier ways to incorporate different modifications. **Polyion complex (PIC) micelles** have a core-shell structure. The core consists of a polyion complex and the hydrophilic shell is formed by a neutral copolymer that acts as a stabilizer (Kalinova & Dimitrov, 2022). In addition to synthetic charged block copolymers, a variety of hydrophilic macromolecules such as peptides, proteins, nucleic acids, or oligonucleotides can be used. They form spontaneously in aqueous solution under conditions of thermodynamic equilibrium, which is one of their main advantages (Kalinova & Dimitrov, 2022).

Polymersomes are vesicular structures formed by self-assembly of amphiphilic copolymers. In addition, optimization of the vesicular membrane can help to tailor polymersomes for different applications, e.g., as drug delivery vehicles or in the form of an artificial organelle. The size of polymersomes ranges from tens of nm to µm, and the potential areas of application are primarily in cancer therapy, diagnostics and vaccines. Polymersomes can encapsulate hydrophilic, hydrophobic, and amphiphilic molecules, and due to their thick and tough membrane they show a better stability than other vesicles. (Zhang & Zhang, 2017)

Microcapsules (or **nanocapsules**) are spherical particles ranging in size from 50 nm to 2 mm that are capable of encapsulating an active ingredient (Singh et al., 2010). It should be noted that the terms microcapsules and microspheres (or nanocapsules and nanospheres) are often used interchangeably. In addition, some related terms such as "microbeads" and "beads" are also used interchangeably. A wide variety of natural and synthetic polymers can be used for microencapsulation, but generally, hydrophilic polymers, hydrophobic polymers or a combination of both are used (Singh et al., 2010). Encapsulation in microcapsules or microspheres allows for controlled release of an active ingredient and also the targeted delivery to the desired site of action (Singh et al., 2010). Microspheres of natural origin, such as the so-called “Elespher”, are composed of algae extract and are used in cosmetics (Patravale & Mandawgade, 2008). Active ingredients are released by diffusion from the sphere or when they break after application to the skin. **Unispheres** are small, colored cellulose beads. They are

considered as a polymeric alternative to liposomes in high surfactant formulations such as shampoos (Patravale & Mandawgade, 2008).

Protein nanocages are another type of polymeric nanocarriers with potential applications in biomedicine. They are formed by the self-assembly of natural or synthetic protein subunits into a cage-like structure with three surfaces that can be functionalized: the interior, the exterior, and the intersubunit space between the protein subunits. Therapeutic and diagnostic agents can be loaded into the interior of nanocages, while their exterior surfaces can be modified to enhance their biocompatibility and to enable targeted delivery of the cargo. Protein nanocages exhibit interesting properties, such as biocompatibility, functional diversity, biological production, and flexibility of design through protein engineering, making them of interest for various applications. (Bhaskar & Lim, 2017)

Stimuli-responsive polymeric nanocarriers have received considerable attention for targeted and controlled drug delivery (Lombardo et al., 2019). Depending on their specific design, responsiveness to different stimuli can be realized, including physical (e.g., temperature, light), chemical (e.g., redox, pH), and biological (e.g., enzymes). **Thermosensitive micelles** are the most extensively studied. They consist of polymers with thermoresponsive blocks, such as PNIPAM. These polymers change their properties in aqueous solution, resulting in a destabilization of the micellar structure, allowing controlled drug release (Lombardo et al., 2019). **pH-responsive polymeric nanocarriers** are of particular interest in the therapy and diagnosis of cancer and have been intensively studied over the last two decades (Rao et al., 2018). The specific tumor microenvironment is considered an ideal trigger for the selective release of chemotherapeutic agents in the tissues and within the cells of tumors (Rao et al., 2018).

From a chemical perspective, nucleic acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are polymers composed of monomers called nucleotides (Australian Academy of Science, 2017). **DNA nanostructures** have shown potential for drug delivery due to their predictability and programmability (T. Wang et al., 2022). They can be considered as “smart” drug delivery vehicles, because of their ability to perform complex tasks, such as targeted delivery of agents to the desired site of action and stimuli-responsive release of the cargo. Computer-aided software has been invented for the design of DNA nanostructures (Hu et al., 2020). DNA nanostructures, such as the so-called “analogic China map” structure, dolphin-like structure, DNA tweezer, DNA box, DNA polyhedron, etc., have been developed. The **DNA origami** technique can be used to create even more complex and sophisticated structures with precisely tailored sizes and diverse structures (Hu et al., 2020). DNA origami can also serve as a template for forming crystal superlattices and constructing inorganic nanostructures. In addition, the unique addressability of DNA origami allows precise control over the location of the cargo, which can be used for super-resolution optical imaging and precise arrangement of the cargo (Hu et al., 2020). The complex structure of **DNA origami "nanorobots"** is based on the manipulation of a long strand of DNA by binding it to shorter "staple" strands (Douglas et al., 2012). They could be used to deliver cargos such as gold nanoparticles or fluorescently labeled antibody fragments. The design of these nanorobots allows them to open in response to molecules released by specific cell surface proteins (Douglas et al., 2012). **RNA nanostructures** are also promising candidates for use in gene therapy in nanomedicine, as they allow the attachment of functional units, such as aptamers or small interfering RNAs (siRNA), and combinations thereof (Høiberg et al., 2019).

Nanosponges are three-dimensional (3D) porous structures made from cyclodextrins or biopolymers such as ethyl cellulose. They are interesting for cancer therapy and drug delivery because of their narrow size distribution and high entrapment efficiency (Iravani & Varma, 2022). They protect active ingredients from degradation and improve the solubility of lipophilic therapeutic agents. In addition, they can be magnetized to achieve appropriate magnetic properties (Iravani & Varma, 2022). **Microsponges** consist of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, antifungal, and anti-inflammatory agents (Kaity et al., 2010). Microsponge sizes range from 5-300 µm in diameter, and they can be synthesized using methacrylic acid/ethyl acrylate copolymer (Eudragit®) (Kaity et al., 2010).

Gene delivery has gained much attention in biomedical research. The safety risk associated with the use of viral vectors makes **polycations** an interesting alternative due to their better safety profile and ability to interact more effectively with cells (Modra et al., 2015). They also exhibit greater stability compared to other non-viral vectors. Typical polycations, such as poly-l-lysine (PLL), polyethyleneimine (PEI), PEG, poly-2-dimethylaminoethyl methacrylate, and natural polysaccharides, such as chitosan, have been shown to have the ability to condense plasmid DNA (pDNA), which is an important requirement for gene delivery (Modra et al., 2015). Scientists have developed and patented a polymeric transport vehicle made of cationic synthetic polymers specifically designed to transport dsRNA for the use as spray suspensions of pesticides in agriculture (Li et al., 2019). This so-called "**star polycation**" (SPc) is prepared from inexpensive, commercially available chemicals. The starting material is pentaerythritol, which initiates the polymerization of DMAEMA. Other chemicals required for the synthesis are bromo-2-methylpropionyl bromide, triethylamine and the solvent tetrahydrofuran (Li et al., 2019). Polymerization takes place under a nitrogen atmosphere. The final product is a white powder after lyophilization. SPc is a cationic dendrimer with four peripheral arms functionalized with amino acids. Nucleic acids can be bound to SPc by mixing and adding an emulsifier such as Tween 20 (Z. Wang et al., 2022). The resulting complexes can be more easily taken up by cells via endocytosis (Linyu et al., 2021).

Common silicone fluids such as dimethicone are widely used in cosmetic products. A common property of silicone polymers is their high permeability, which makes them suitable for controlled release applications and accounts for their widespread use in transdermal delivery systems. **Crosslinked silicones**, such as elastomers and adhesives, have only recently been used in cosmetic formulations and are suitable for drug delivery. Silicone elastomers are cross-linked solid polymers capable of entrapping the cargo within the matrix. (Patravale & Mandawgade, 2008)

3.2.1.7 Lipid-based

Lipid-based nanocarriers are typically spherical platforms, formed by self-assembly and are the most frequent class of nanocarriers in approved nanomedicines. They are easy to synthesize, can carry high amounts of active ingredients, and their physicochemical properties can be controlled to modify their characteristics (Mitchell et al., 2021).

The most important type are **liposomes**, which are composed of phospholipids, that can form unilamellar, multilamellar and plurilamellar vesicular structures. The amphiphilic nature of liposomes allows them to carry and deliver both hydrophilic and hydrophobic substances (Liu et al., 2022). Their stability is modfied by size, surface charge and modification with ligands or

polymers. Liposomes can also be functionalized to create, for example, PEGylated or glycolyted liposomes (Liu et al., 2022). Nano-sized liposomes are referred to as **nanosomes** (Thach et al., 2019).

"Stealth liposomes" are second generation liposomes that circulate longer in the blood due to the addition of polyethylene glycol (PEG) as a stabiliser. Targeting with monoclonal antibodies, peptides, growth factors, glycoproteins, carbohydrates, or receptor ligands is also possible. Modifications with synthetic polymers such as polyvinylpyrrolidone (PVP), polyacrylic acid (PAA), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) covalently linked to poly(2-methyl-2-oxazoline) or to poly(2-ethyl-2-oxazoline) are also under investigation. (Immordino et al., 2006)

Changes in the composition and structure of conventional liposomes have led to new classes of lipid vesicles with flexible and ultradeformable properties, such as **niosomes** (nonionic surfactant combined with cholesterol), **transfersomes** (phospholipids and surfactant), or **ethosomes** (phospholipids and ethanol) (Hua, 2015). **Ultrasomes** are specialized liposomes that encapsulate a UV endonuclease enzyme and are used in cosmetic products to aid in the repair of UV damage to the skin (Creative Biolabs, 2023b). **Photosomes** encapsulate the enzyme photolysase extracted from the marine alga *Anacystis nidulans* and are incorporated into sun care product to protect the sun-exposed skin *(Creative Biolabs, 2023a)*. **Asymmetric Oxygen Carrier System (AOCS) liposomes** consist of a perfluorocarbon core and a shell formed by a monolayer of phospholipids. Their function is to carry oxygen into the skin (Patravale & Mandawgade, 2008). **Yeast-based liposomes** are also used in cosmetics to repair and oxygenate the skin (Patravale & Mandawgade, 2008). **Bilosomes** are modified niosomes that also contain bile salts (Rehman et al., 2020). Sponge-like liquid crystalline nanodelivery systems made of amphiphilic lipids and surfactants are called **spongosomes** (Zou et al., 2017) and **phytosomes** are complexes between a phospholipid and botanical derivatives such as catechin or quercetin (Patravale & Mandawgade, 2008). **Lipofectamine** is a common transfection reagent and consists of a 3:1 mixture of (2,3-dioleoyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium trifluoroacetate) and 1,2-dioleoyl-*sn*-glycerophosphoethanolamine. The lipid subunits of Lipofectamine form liposomes in an aqueous environment, in which the transfection cargo is encapsulated. Lipofectamin increases the transfection efficiency of RNA or plasmid DNA and significantly improves the stability and efficiency of dsRNA (Yang et al., 2022). Another form of liposomes are **virosomes**, which are reconstituted from viral envelope phospholipids with the nucleocapsid removed (Asadi & Gholami, 2021). Virosomes are currently undergoing preclinical and clinical testing for use in vaccines (Asadi & Gholami, 2021). **Vesosomes** are liposomes in which smaller liposomes can be encapsulated and liposomes encapsulating dendrimers are referred to as **Dendrosomes** (Paleos et al., 2013). Both systems are currently being investigated for drug delivery. Recently developed lipid drug delivery systems are so called **pharmacosomes** (Pandita & Sharma, 2013). They are nanoscale colloidal vesicles or a hexagonal arrangement of colloidal drug dispersions covalently attached to the phospholipid. **Lipoplexes** are defined as the complexes between nucleic acids and cationic lipids. They have been successfully studied in the cytosolic delivery of microRNA (miRNA) in cancer therapy (Zhang et al., 2022). "**Nanotopes**"®, unlike ordinary liposomes, have only a monolayer membrane of a phospholipid (i.e. lecithin). These nanocarriers have a very small particle size (20 – 40 nm) and better stability compared to liposomes (Montenegro, 2014).

Other lipid-based nanocarriers are **lipid nanoparticles (LNPs)**. Unlike conventional liposomes, LNPs form micellar structures within the core of the particle. They typically consist of cationic or ionizable lipids, phospholipids and cholesterol (Mitchell et al., 2021). **Solid lipid nanoparticles (SLNs)** have a monolayer membrane and a solid core of complex glyceride mixtures, purified triglycerides and waxes, stabilized by polymers or surfactants (Oliveira et al., 2022). SLNs stabilized by multiple phospholipid layers are called **emulsomes** (Bolat et al., 2023). Lipophilic drugs can be encapsulated within their solid lipid core and the drug release can be prolonged (Bolat et al., 2023). **Nanostructured lipid carriers** (NLCs) present an aqueous and oily phase and they are formulated using physiological and biocompatible solid (e.g., lauric acid, stearic acid and cocoa butter) and liquid (e.g., glycerol, miglyol 812, corn oil and oleic acid) lipids as well as surfactants (Oliveira et al., 2022). **Cubosomes** and **hexosomes** are self-assembled non-lamellar liquid crystalline nanoparticles similar to SLNs (Yaghmur & Mu, 2021). Their colloidal stabilization in water usually requires an efficient stabilizer. They belong to the family of structurally tunable nanoparticles encapsulating internally inverted non-lamellar liquid crystalline phases or micellar phases, which are referred to in the literature as **ISAsomes** (Internally Self-Assembled Somes) (Yaghmur & Mu, 2021).

Nanobubbles are nanometer-sized bubbles (10–200 nm) consisting of a shell made of polymers, phospholipids, or proteins with unilaminar composition, and a core formed by a less soluble gas. Nanobubbles can be utilized for gas delivery applications, and more recently they have also been studied in relation to drug and gene delivery (Sutradhar Nitai et al., 2022).

Lipid–drug conjugates (LDCs) are a type of drug delivery system in which the drug molecules are modified with covalently bound lipids. This modification alters drug properties such as lipophilicity. Depending on the chemical nature of the drugs and lipids used, different conjugation strategies and chemical linkers can be used to synthesize LDCs (Irby et al., 2017).

Microemulsions, nanoemulsions, SMEDDS (self-microemulsifying drug delivery system) and **SNEDDS** (self-nanoemulsifying drug delivery system) are **lipid-based emulsion systems** that can increase the solubility of water-insoluble active substances. They also show additional advantages such as improved permeability, protection against pre-systemic metabolism, ease of manufacture and production upscaling (Dhaval et al., 2022). **Double emulsions** are "emulsions of an emulsion" such as a water-in-oil emulsion dispersed in water, and are often referred to as "multiple emulsions" (Sagalowicz & Leser, 2010). Double emulsions are of interest as delivery systems in food products. Unstable hydrophilic active ingredients can be dissolved in water droplets within the oil droplets protecting them from the external aqueous phase of the food product (Sagalowicz & Leser, 2010). **Pickering emulsions** are stabilized by solid particles and do not contain surfactants (Tai et al., 2020). This type of emulsion is of particular interest for oral drug delivery due to its good stability and biocompatibility. The oral bioavailability of poorly soluble compounds, such as curcumin, can be increased several-fold by using Pickering emulsions (Tai et al., 2020).

Cells release extracellular vesicles under both physiological and pathological conditions. These can be detected in all body fluids, including blood, urine, saliva, breast milk and tear fluid. Cell-derived **extracellular vesicles (EVs)**, such as exosomes or endosomes, act as mediators of many (patho)physiological processes. EVs are produced by cells but are not cells themselves. For this reason, in the present categorization they are classified as lipid-based nanocarriers rather than cellular ones. They are phospholipid based and therefore comparable to liposomes, but are

composed of a mixture of different lipids and proteins. EVs can be isolated from cell cultures, blood plasma, bovine milk and plants. They are being explored in medicine for the delivery of therapeutic agents to specific cells or tissues due to their intrinsic ability to migrate to their organ of origin (homing ability). (Herrmann et al., 2021)

Lipid-based **organogels** are also being investigated as delivery systems. Organogels are non-glass thermoreversible semi-solid systems in which an organic liquid phase is entrapped in a three- dimensional cross-linked network. Organic solvents or oils can be used as the liquid phase. The structuring network can be formed by self-assembly of low molecular weight or polymeric organogelator molecules. For the purpose of drug delivery, biocompatible gelating molecules such as lecithin, sorbitan monostearate and amino acid derivatives are generally the most suitable. Organogels are promising for the use as depot formulations following parenteral extravascular injection. (Bastiat et al., 2010)

3.2.1.8 Surfactant-based

In addition to polymers also amphiphilic **surfactant** molecules also form **micelles** above the critical micelle concentration and poorly soluble or insoluble active ingredients can be solubilized within their hydrophobic core. The use of surfactants to enhance the solubility of poorly water soluble substances is a very common approach in which the active ingredient is mixed with a surfactant to form a stable concentrate, which is then added to the concentrate to an aqueous medium. In this method, micelles spontaneously form. Polysorbate 80 is an example of a non-ionic surfactant, that is widely used in the cosmetic, food and pharmaceutical industries, and is also suitable for micellar encapsulation, for example, of curcumin. (Wang & Sukumar, 2020)

3.2.1.9 Macrocycles-based

Macrocycles are molecules and ions that contain a ring of twelve or more atoms. They can enclose drugs in their ring-shaped structure, preventing drug degradation by creating a steric barricade, making interesting for drug delivery. The macrocycle's cavity can also be modified to control the drug release and the host-guest complexation. The most studied macrocycles are cyclodextrins, cucurbiturils, calix[n]arenes and pillar[n]arenes. In particular, cyclodextrin-based inclusion complexes and hydrogels have been extensively investigated and are already in use. (Trotta et al., 2022)

Cyclodextrins are cyclic oligosaccharides consisting of 6 or more units of α-1,4-linked D-glucopyranose units produced from starch by the action of cyclodextrin glucosyltransferase, via enzymatic degradation and intramolecular rearrangement reaction (Trotta et al., 2022). In medicine, α-, β-, and γ-cyclodextrin subunits are of particular interest and are used in drug delivery systems for cancer and gene therapy as well as in diagnostics, imaging, biosensors, and medical devices. Because of their amphiphilic nature with a hydrophobic core and a hydrophilic shell, a variety of drugs, especially lipophilic molecules, and compounds with a poor water solubility, can be entrapped in cyclodextrins (Trotta et al., 2022). The 3 parent cyclodextrins can be further modified or functionalized, and thousands of different derivatives have been proposed in the literature, particularly for pharmaceutical uses, but also for applications in the food industry (Morin-Crini et al., 2021). Delivery systems based on cyclodextrins have many advantages, ranging from higher encapsulation efficiency, better solubility, greater

bioavailability, stimuli-responsiveness, sustained or controlled release, site-specific action, biocompatibility to protection of drugs from degradation (Trotta et al., 2022).

Cyclodextrin-polymer micelles enhance stability and allow the design of stimuli-responsive micelles (Saji, 2022). **Cyclodextrin nanosponges** are a versatile porous network of crosslinked cyclodextrins. They are described in the literature as biodegradable and exhibit superior properties compared to bare cyclodextrins such as improved controlled drug release and stability (Saji, 2022). Injectable **cyclodextrin-polymer hydrogels** based on PEG, polycaprolactone, polyether urethane, hyaluronic acid or polysaccharides can potentially deliver both hydrophilic and hydrophobic drugs. NIR-responsive hydrogels have attracted considerable research attention (Saji, 2022) Cyclodextrins are widely used in applications such as medicine/pharmaceuticals, cosmetics, textiles, household products, and in pesticide formulations (Morin-Crini et al., 2021).

3.2.1.10 Heterocycles-based

Spiropyrans (SPs) belong to the family of so-called photochromic molecular switches and have recently gained attention as potential nanocarriers due to their biocompatibility. its structural feature is the presence of a benzopyran (chromene) moiety linked to another heterocyclic moiety, typically an indoline. SPs can reversibly change their conformation between a closed (hydrophobic spiropyran) and an open form (hydrophilic merocyanine). This can be induced by various stimuli, such as light, pH, heat, and the presence of metal ions. (Bio)polymers, inorganic nanoparticles and carbon nanomaterials functionalized with SPs have been investigated as delivery systems. (Fagan et al., 2021)

Porphyrins are another class of heterocyclic molecules, that have gained attention in nanomedicine for imaging and therapy. They are composed of four conjugated pyrrole rings arranged in a cycle. Various porphyrin-based nanocomposites have been explored, such as gold nanoshells/PLA, loaded with doxorubicin and porphyrin attached to the surface. These composites exhibit good colloidal stability and prolonged blood circulation. Many porphyrin-based composite materials also show favorable fluorescence and photoacoustic properties, which are interesting for simultaneous imaging and therapy applications called “theranostics”. A drawback of porphyrins is their low water solubility, and various nanoparticles have been investigated to transport the hydrophobic porphyrin molecules in biological media. (Rabiee et al., 2020)

3.2.1.11 Hydrogels based on low weight gelators

Gelators are substances capable of forming a gel. Hydrogels based on low weight gelators, include 3,4,5-trihydroxybenzoic derivatives, poly(N-isopropylacrylamide), amphiphilic gemini imidazolium, sugar functionalized naphthalimide, amphiphilic bis-imidazolium and fluorinated bolaamphiphile with thymine glycosylated polar groups. For example, hydrogels based on low weight gelators haven been investigated for the transport of drugs across the skin barrier. In addition, pH-responsive hydrogels have been developed to deliver various anti-inflammatory drugs. (Saji, 2022)

3.2.1.12 Antibody drug-conjugate

Antibody drug conjugates (ADCs) represent a combination of chemotherapy and immunotherapy. This emerging class of drugs consists of a monoclonal antibody (mAb) conjugated to a drug via a chemical linker that is directed against a target antigen on the surface

of cancer cells. This approach reduces systemic exposure and therefore potential adverse effects. The safety and efficacy of ADCs depend on the careful selection of the components and the manner in which the mAB is linked to the cytotoxic cargo (Khongorzul et al., 2020).

3.2.2 Inorganic

Nanocarriers based on inorganic materials are promising drug delivery platforms. They are capable of efficient loading and controlled release of drugs, extended circulation, improved biocompatibility and desirable pharmacological profiles (Khan et al., 2022).

3.2.2.1 Metallic nanoparticles

Metal nanoparticles (MNPs) are potent carriers for the delivery of various therapeutic agents such as antibodies, nucleic acids, chemotherapeutics, and peptides (Chandrakala et al., 2022). Many MNPs such as silver, gold, palladium, titanium, zinc, and copper nanoparticles exhibit enhanced tunable optical properties, and their surface can be easily functionalized to conjugate targeting moieties or active biomolecules through H-bonding, covalent bonding, and electrostatic interactions (Chandrakala et al., 2022). A large variety of different drugs can be delivered by MNPs to enhance the therapeutic efficacy.

Magnetic nanoparticles are important in biomedicine, particularly for drug delivery. Their inherent magnetism allows for targeted drug delivery (Kianfar, 2021). Magnetic drug delivery is a technique in which magnetic carriers are controlled by the application of magnetic forces to deliver drugs to the desired site in an organism. Various magnetic drug delivery systems (MDDS) have been developed specifically for the treatment of cancer and neurological disorders (Aslam et al., 2021). Some of the commonly used magnetic nanoparticles include maghemite (Fe_2O_3), magnetite (Fe_3O_4), iron oxides, metal alloys, rare earth minerals, and transition materials. Ferromagnetic nickel and cobalt or antiferromagnetic chromium nanoparticles are less popular due to their toxicity, which requires an impermeable coating (Aslam et al., 2021). For the use in drug delivery magnetic nanoparticles are functionalized with antibodies, proteins, carbohydrates, and other similar molecules that allow for a targeted delivery of drugs to the desired site of action by binding to a receptor on the cell membrane. Magnetic nanoparticles tend to agglomerate due to their high surface energy and dynamic dipole–dipole interactions. Therefore, surface modification with polymers, gold, silica, lipids, amino groups and other organic substances is generally required (Aslam et al., 2021).

Iron oxide nanoparticles (IONPs), especially the **superparamagnetic iron oxide nanoparticles (SPIONs)**, are interesting carriers for the delivery of various anticancer drugs (Khan et al., 2022). IONPs are used in cancer therapy for magnetic hypothermia treatment (MHT), drug delivery of chemotherapeutics and also for gene therapy. Due to their versatility, they can be functionalized with various targeting agents such as transferrin, aptamers, HA, folate, and peptides (Khan et al., 2022). IONPs represent the majority of inorganic nanocarriers approved by the FDA (Mitchell et al., 2021).

Gold nanoparticles (AuNPs) are interesting nanocarriers in medicine due to their inertness, stability, low cytotoxicity, and biocompatibility. AuNPs can be used in cancer treatment such as photothermal therapy, radiofrequency therapy and drug delivery applications (Khan et al., 2022; Song et al., 2016). For example, AuNPs functionalized with a chemotherapeutic agent have demonstrated the ability to destroy cancer cells, and they can also be functionalized with various

other molecules, such as PEG, thioalkyltetra(ethylene glycol)lyated trimethylammonium, poly(L-aspartate), 3-mercaptopropionic acid, tumor necrosis factor-alpha, and photocleavable and zwitterionic thiol ligands (Khan et al., 2022). AuNPs as nanocarriers have also been synthesized in micellar amphiphilic copolymers, and so-called gold "nanoflowers", coated with two layers of silica for the purpose of drug loading and NIR photothermal therapy for the treatment of oral cancer have also been developed (Song et al., 2016).

Silver nanoparticles (AgNPs) have been developed as nanocarriers for the delivery of anticancer, antibacterial, antiviral, antifungal and antioxidant agents (Hussein & Abdullah, 2022). AgNPs exhibit low toxicity, high thermal stability, and low volatility, making them suitable for drug delivery. Conjugation with biomolecules enhances their pharmaceutical properties (Khan et al., 2022), particularly, surface functionalization with targeting molecules, or coating with biodegradable and biocompatible polymers (Hussein & Abdullah, 2022). In addition, silver itself has anticancer activity (Gomes et al., 2021).

Palladium nanoparticles (PdNPs) exhibit anti-bacterial and cytotoxic pharmacological properties and their high porosity makes them suitable for drug delivery. The therapeutic drug can be indirectly conjugated to the PdNPs through a linking molecule. (Chandrakala et al., 2022)

Platinum nanoparticles (PtNPs) are under research in nanomedicine and pharmaceutics. Their large surface area makes them interesting for many biomedical applications, and they also exhibit antimicrobial, antioxidant and anticancer properties. However, one of the drawbacks of PtNPs is their toxicity, and it is a challenge to design and develop biocompatible PtNPs for cancer therapy. (Chandrakala et al., 2022)

Copper nanoparticles (CuNPs) have unique physical, chemical, electrical, and optical properties, low cost, and availability, and they exhibit good antibacterial properties. Transferrin (Tf)-templated copper nanoclusters (Tf-CuNCs) show enhanced luminescence. They have been developed for targeted delivery and bioimaging purposes. Curcumin-capped CuNPs are also being investigated as potential inhibitors of human breast cancer cells. (Chandrakala et al., 2022)

Zinc oxide nanoparticles (ZnO NPs) are a promising nanocarrier for cancer therapy and the treatment of diabetes and inflammation. The combination of ZnO NPs and the anticancer drug daunorubicin showed a significant reduction in cytotoxicity and an increased cancer cell targeting. ZnO NPs capped with gum arabic represents a nanodelivery system with high cytocompatibility. Nanocurcumin-zinc oxide nanoparticles, encapsulated in chitosan, are useful for the treatment of diabetes mellitus, and have shown no toxicity in experimental animal studies. (Chandrakala et al., 2022)

Titanium dioxide (TiO_2) is a semiconducting metal oxide that could be used for drug delivery systems, especially in cancer therapy, due to its chemical stability, low toxicity and low cost. Various nanostructures of TiO_2 such as TiO_2 NPs, TiO_2 nanotubes, TiO_2 matrices, TiO_2 capsules and TiO_2 whiskers have been developed as nanocarriers for various anti-cancer drugs. (Chandrakala et al., 2022)

Metal sulphide nanomaterials (MeSNPs), such as nickel sulphide or copper sulphide, are a novel class of metal-containing nanomaterials with high biocompatibility, and unique

physicochemical properties making them of interest for cancer therapy, and drug delivery. (Chandrakala et al., 2022)

Some metallic NPs can act as **radiosensitizers** due to the high energy absorption and enhancement of the photoelectric effect. Reactive oxygen species (ROS) are generated in the vicinity of the NPs during irradiation. Therefore, potential applications in nanomedicine include not only drug delivery but also the combination of cancer therapy and radiotherapy. The combination of a radiosensitizer and a chemotherapeutic drug can help to prevent damage to the healthy tissue and to improve the dose−response curve. Radiosensitizers that have been intensively studied include **gold, tungsten, gadolinium** and **hafnium oxide NPs (HfO_2 NPs)**. HfO_2 NPs for the treatment of soft tissue sarcoma are in the second phase of clinical trials. (Sherstiuk et al., 2021)

3.2.2.2 Semi-metallic nanoparticles

Silica nanoparticles, and mesoporous silica nanoparticles (MSNs) are versatile biodegradable nanocarriers with a high loading capacity that improve efficacy and reduce side effects of drugs. Their surface can be easily modified. There are several synthesis methods to synthesize MSNs in different particle sizes and with variable pore sizes. MSNs can be functionalized with non-toxic polymers such as PEG to prolong the blood circulation time, and to increase the stability in blood fluids. PEG modification also helps prevent immune response and particle aggregation. MSNs can also be designed for stimulus-responsive drug delivery, and they can be passively or actively targeted. In passive targeting, MSNs accumulate in solid tumors. In active targeting, MSNs are equipped with a targeting ligand that interacts with a receptor. MSN nanocarriers can also be delivered to the target site by specific stimuli, either internal (endocytosis, pH changes, presence of glutathione, and redox sensitivity) or external (light, magnetism, and ultrasound). (Khan et al., 2022)

Biodegradable periodic mesoporous organosilica nanoparticles (BPMOs) are another type of recently developed nanocarriers for targeted drug delivery. An organic bridge between two or more silicon atoms gives this material the property of enhanced biodegradability in biological systems. The periodically ordered pores of BPMOs have nanometer-thick walls. Several degradation methods have been investigated, such as redox, pH, enzymatic activity, and light. One study demonstrated accelerated degradation of BPMOs under redox conditions compared to mesoporous silica nanoparticles without redox-sensitive bonds. Since there are only a few studies demonstrating *in vivo* degradation of BPMOs, further investigation of this issue is needed, e.g. by animal excretion studies. (Chinnathambi & Tamanoi, 2020)

A special class of porous materials are **silica aerogels**. They could be used for oral drug delivery systems. Silica aerogels improve the stability of drugs and their dissolution rate (Guenther et al., 2008).

3.2.2.3 Non-metallic nanoparticles

Calcium phosphate nanoparticles (CaP-NPs) are considered ideal nanocarriers, especially for cancer therapy. They are particularly suitable for pH-responsive drug delivery because they are stable at physiological pH and able to dissolve at lower pH, resulting in rapid drug release. CaP exhibit good biocompatibility and are non-toxic. (Khan et al., 2022)

Clay minerals belong to the nanolayered silicates. Their good biocompatibility, high specific surface area, chemical inertness, colloidality, and thixotropy makes them interesting for carrier applications. In medicine, nanoclays have been developed as drug carriers for the delivery of

antibiotics, antihypertensives, antipsychotics, and anticancer drugs. Clay minerals, particularly **montmorillonite, kaolinite and halloysite** are used for controlled and targeted drug delivery, and these materials can enhance drug dissolution due to their surface charge (Khatoon et al., 2020). The intercalation of ions into the interlayer space or surface modification alters the properties of nanoclays and makes them more suitable for drug delivery. Hematological, biochemical and histopathological animal studies have shown montmorillonite to be nontoxic (Khatoon et al., 2020). Halloysite nanotubes (HNTs) can bind synthetic and biological components such as chitosan, gelatin and alginate. These nanocarriers exhibit enhanced loading capacity and allow for the controlled release of drugs, proteins and DNA (Khatoon et al., 2020). HNTs have also been shown to be interesting carriers for the slow release of a model active ingredient (vinylene carbonate (VC)) in lithium batteries (Ahn et al., 2022). The encapsulation of VC in HNTs improved the cycling stability of the battery.

Layered double hydroxides (LDHs), are solids with positively charged layers and charge-balancing anions in the interlayer space. Various active ingredients such as genes or drugs can be incorporated into their framework. They have been investigated as nanocarriers for the controlled release of several non-steroidal anti-inflammatory drugs (Viseras et al., 2010). Systems of LDHs and dsRNA, called "BioClay", were also developed as a carrier system for dsRNA in sprayable crop protection products against insect pests (Rank & Koch, 2021).

Selenium nanoparticles (Se NPs) have emerged as promising nanocarriers for biomedical applications due to their degradability, high bioavailability, stability and drug encapsulation capacity. Despite the toxicity of elemental selenium and especially selenium salts, Se NPs have been widely used for direct anticancer treatment and pathogen killing or clearance in host cells due to their potent ability to induce apoptosis or autophagy by regulating reactive oxygen species (ROS). (Lin et al., 2021)

Ceramic materials, such as **hydroxyapatite (HAP)** conjugated with calcium phosphates, silica, alumina, zirconium, iron oxides, carbonates, and titanium dioxide are used for various biomedical applications (Sharma et al., 2022). These ceramic nanoparticles exhibit high mechanical strength, pH and temperature resistance, high stability, high loading capacity, and flexibility in hydrophobic and hydrophilic systems, making them desirable for drug delivery applications. For example, folic acid conjugated and PEG-functionalized HAP NPs have been developed for the delivery of the anticancer drug paclitaxel, hollow mesoporous HAP NPs for pH-responsive nanocarriers, and HAP microspheres for the sustained delivery of doxycycline hydrochloride (Khan et al., 2022). Zinc and magnesium-doped HAP-urea nanohybrids were synthesized as slow-release fertilizers for nitrogen delivery to wheat and rice crops (Sharma et al., 2022).

3.2.2.4 Carbon-based nanomaterials (CBNs)

Due to their structural dimensions and physical properties, carbon-based nanomaterials (CBNs) are recognized as potential nanocarriers in medicine and agriculture. However, all carbon-based nanocarriers can have side effects or exhibit toxicity, limiting their potential applications. In addition, the formation of a protein biocorona on the surface of CBNs can alter their properties, the biodistribution, pharmacokinetics, cellular uptake, toxicity, and clearance. Although, modification of the surface with e.g., functional groups, molecules and polymers may enhance their dispersibility, and biocompatibility, and render them more suitable for biomedical applications. According to their structure, CBNs are categorized as carbon nanotubes, graphene,

mesoporous (activated) carbon, nanodiamonds, fullerenes, and carbon dots. (Debnath & Srivastava, 2021)

Carbon nanotubes (CNTs) are cylindrical structures and can be classified as **single-walled (SWCNTs), double-walled and multi-walled (MWCNTs)** based on their number of layers. Functionalization with natural or synthetic polymers and therapeutic molecules improves dispersibility, biocompatibility and reduces toxicity. CNTs exhibit many interesting properties such as large surface area, high stability, and they can bind a wide variety of therapeutics, including DNA, enzymes, antibodies, and drugs. SWCNTs have been found to be good carriers for small interfering RNAs. CNTs can be used as efficient photothermal agents due to their strong NIR light absorption capability. MWCNTs functionalized with thermosensitive polymers can be used for temperature-responsive release of bioactive substances. (Debnath & Srivastava, 2021)

Graphene is composed of a single layer of carbon atoms. This material exhibits superior properties such as a large surface area, excellent thermal conductivity, optical transparency, and high and elastic strength (Debnath & Srivastava, 2021). **Graphene nanoribbons** are prepared by cutting graphene sheets into fine tiles with a high aspect ratio. Graphene oxide nanoribbons have great potential for use in drug delivery, cancer therapy and DNA applications. **Graphene quantum dots (GQD)** can be prepared by cutting graphene sheets into pieces in the size range of 2-20 nm. They are used in biomedical applications due to their very small size, excellent photostability and high dispersibility and are also considered non-toxic. Surface modifications with polymers help to make graphene materials more compatible with biological systems. They can respond to stimuli for controlled drug release (Debnath & Srivastava, 2021). The surface of graphene oxide can be modified with various polymers. This material is being explored for use as a nanocarrier for pesticide delivery in agriculture (Zhu et al., 2022).

Mesoporous carbon nanomaterials (MCNs) are promising carriers for poorly soluble drugs. MCNs are also known as **activated carbon** (AC). AC is a type of carbon material with a turbostratic structure, rich surface functional groups, micropores and a high specific surface area. AC has been explored as a nanocarrier for sustained drug delivery due to its many advantageous properties such as low cost, commercial availability, non-toxicity, and high absorbability. AC is also a potentially environmentally friendly pesticide carrier due to its reported non-toxicity. (Yang et al., 2019)

Nanodiamonds are a heterogeneous family of carbonaceous nanoparticles that vary in size, shape or surface potential depending on the method of preparation (Swati Chauhan et al., 2020). They have a core-shell structure with a diamond inner core and a graphitic outer shell (Swati Chauhan et al., 2020). Nanodiamonds are very flexible in terms of surface modifications, and they show high biocompatibility, making them interesting candidates for drug delivery and cancer therapy. Nanodiamonds can be functionalized with a targeting molecule, such as a tumor-specific antibody. They accumulate primarily in tumor tissue and interfere with drug efflux from cancer cells (Benson & Amini, 2020).

Fullerenes are an allotropic modification of carbon, and their family includes several spherical atomic C_n clusters. Fullerene C_{60} ("bucky balls") is the most common and best-studied fullerene. Functionalized fullerenes are of interest in the field of biomedicine as nanocarriers; for example C_{60} fullerenes functionalized with glycine were found to be suitable for drug encapsulation and delivery. (Debnath & Srivastava, 2021)

Carbon dots (CDs) are the newest member of the CBN family. They are quasi-spherical carbon allotropes with very small particle sizes <10 nm. They exhibit several interesting properties such as water dispersibility, conductivity, low toxicity, and biocompatibility. CDs are promising candidates for drug delivery and through surface functionalization with polymers drug efficacy and reduced toxicity can be achieved. As a result, these materials are intensively studied in medicine for gene-, chemo-, and antibiotic therapy. (Debnath & Srivastava, 2021)

3.2.2.5 Semiconductor quantum dots

Semiconductor quantum dots (SQDs), along with perovskite QDs, carbon QDs (CQDs) and graphene QDs (GQDs), are nanocrystals with unique photoluminescence properties and high photostability (Pavlicek, Neubauer, et al., 2023). They are typically made of metal chalcogenide and can be classified into groups based on their components: 1) core-type QDs such as CdS, ZnS, InP and CdTe, which have uniform internal compositions, 2) core-shell QDs, which have different molecules as the core and a shell covering them; for example, CdSe as the core and ZnS as the shell, 3) alloyed QDs, which consist of alloys of two different semiconductors (Badıllı et al., 2020).

QDs can easily pass through cell membranes. This property, together with their high specific surface area, which provides multiple attachment sites for drug targeting, makes them suitable for drug delivery (Pavlicek, Ehmoser, et al., 2023). The surface of QDs needs to be modified with ligands to introduce them into biological systems and to make them water-soluble and biocompatible. QDs can be considered as effective tools for microenvironment-targeted drug delivery (Badıllı et al., 2020). QDs have optical properties that also make them suitable for imaging applications (Khan et al., 2022). pH-responsive drug delivery systems for controlled release have been reported, for example based on ZnO QDs conjugated with polymers or CdTe QDs modified with PEG to mitigate their toxicity (Khan et al., 2022).

3.2.3 Hybrid systems

Lipid and polymer-based nanocarriers are the most promising types of delivery systems in medicine that are currently in clinical trials or already on the market. However, each system has its drawbacks, which can be overcome by combining them into hybrid nanocarriers. These hybrid systems show the advantages of different organic and inorganic structural components. Core shell hybrid nanoparticles made of different oils, metal oxides, organic, and inorganic components have a multilayer structure. Lipid-polymer, polymer-inorganic, metal (gold, silver, or iron)-polymer, silica (SiO_2)-based, and polymeric hybrid systems have been the most widely studied as nanocarriers. Hydrophilic polymers, such as PEG, can impart stealth properties to nanoparticles, but do not enhance or impart new functionality to nanoparticles. For this reason, coatings with PEG are often not regarded as hybrid systems. Similarly, nanoparticles conjugated with targeting ligands are not considered hybrid systems (Madni et al., 2017).

Hybrid systems are being explored for gene and drug delivery, phototherapy, tissue regeneration, vaccines, antibacterials, biomolecule detection, imaging probes, and “theranostics” (Seaberg et al., 2021).

3.2.3.1 Inorganic/inorganic hybrid systems

Only one example of an inorganic/inorganic hybrid nanocarrier system could be found in the literature. Li et al. developed a novel NIR laser-triggered nanocarrier based on a core of gold

nanorods and a shell of mesoporous silica capped with reversible single-stranded DNA valves (Li et al., 2013). The valves were opened or closed by switching the laser on and off to control the release amount of cargo molecules. With the reported nanocarriers, controlled delivery of the cargo could be possible, allowing the treatment of diseases with a precise dosage of a drug at a desired time in a specific area (Li et al., 2013).

3.2.3.2 Organic/organic hybrid systems

Organic/organic hybrid systems consist of either the combination of two or more polymers, or polymers and lipids. Lipid/polymer hybrid nanocarriers consist of a drug-containing polymeric core and a lipid shell. In addition, the surface of the lipid shell can be modified with different materials. Since a wide variety of polymers and lipids are suitable for this type of nanocarriers, lipid/polymer hybrid systems can theoretically be prepared to carry any therapeutic moiety or active ingredient. (Madni et al., 2017)

Examples of organic/organic hybrid systems are PLGA/modified chitosan, PLGA/phosphatidylcholine/stearic acid, PLGA/lecithin, PLGA/PEG/dextran sulfate, PLA/didodecyldimethylammonium bromide/cetyltrimethylammonium bromide, PLGA/glyceryl tripalmitate, PLA/chitosan, or chitosan/hyaluronic acid (Madni et al., 2017).

3.2.3.3 Organic/inorganic hybrid systems

Inorganic/organic hybrid systems typically have an inorganic core and an organic shell, but an inorganic shell can also be applied to an organic core. The most commonly used inorganic building blocks include metals, such as gold or iron oxide nanoparticles, inorganic compounds such as zinc oxide (ZnO) nanoparticles, calcium phosphate (CaP) nanoparticles, and porous structures such as mesoporous silica nanoparticles, and metal-organic frameworks (MOFs). Organic building blocks include polymers and copolymers, lipids, clays, dendrimers and isolated cell membranes, as well as carbon derivatives, such as graphene oxide (GO), fullerene (C_{60}), carbon nanotubes (CNTs), and graphene quantum dots (GQDs), which can exhibit properties similar to both organic and inorganic systems. (Seaberg et al., 2021)

For example, an inorganic shell of gold nanoparticles provides physical and chemical stability to the polymeric core of lecithin loaded with a therapeutic drug (Madni et al., 2017). Metallic nanoparticles with sizes <100 nm typically respond to different stimuli. Inorganic/organic hybrid systems with a metallic core can be used for thermotherapy of cancer, because when a magnetic field is applied, the resulting heat destroys the cancer cells (Madni et al., 2017). Inorganic nanoparticles also respond to infrared light and ultrasound waves. This makes such systems interesting for “theranostic” applications (Madni et al., 2017). Another example of such hybrid systems is the combination of the lipid bilayer of liposomes and inorganic components. While liposomes have a high loading capacity and protect the encapsulated cargo from degradation, inorganic components can provide magnetic targeting, imaging, biocompatibility, and photothermal drug release capabilities (Madni et al., 2017; Seaberg et al., 2021). For example, chemotherapeutics can be encapsulated in gold-liposome hybrids for drug delivery applications (Seaberg et al., 2021). Biocompatible AuNPs have also been used in combination with polymers, such as chitosan, polyvinylpyrrolidone (PVP), and polypeptides for drug delivery purposes (Seaberg et al., 2021).

Organic–inorganic hybrid nanoflowers are flower-like hybrid nanoparticles that have been recently developed. They have attracted much interest due to their simple synthesis, high

efficiency, and enzyme stabilizing ability. Most combinations include copper–protein, calcium–protein, and manganese–protein hybrid nanoflowers, copper–DNA hybrid nanoflowers, and capsular hybrid nanoflowers. The polymers used can be, for example, chitosan, amylase, and albumin. (Lee et al., 2015)

3.2.3.4 Nanofluids

Nanofluids are a term for suspensions of nanoparticles, that could be used for direct heat transfer enhancement in many industrial applications, heat exchangers, transportation, electronics, and biomedical and food industries. Nanofluids have also been considered for drug delivery and antibacterial therapeutics. However, the implementation of these types of nanocarriers in biomedical applications is challenging and requires further research. (Sheikhpour et al., 2020)

Nanofluids can, for example, contain dispersed magnetic nanoparticles such as SPIONS or magnetite (Fe_3O_4) and can be used as nanocarriers in cancer therapy or for hypothermia methods. The application of Fe_3O_4-based nanofluids in targeted MRI has been investigated. Nanofluids of some metals and metal oxides exhibit antibacterial activity, and the antibacterial efficacy of a trimetallic Au/Pt/Ag-based nanofluid has been shown for different bacterial strains. Fe_3O_4/oleic acid nanofluid has been explored for the controlled delivery of various agents such as antibiotics. (Sheikhpour et al., 2020)

3.2.3.5 Janus nanoparticles

Janus nanoparticles (JNPs) are anisotropic particles composed of two distinct sides that differ in chemical nature, and/or polarity on each side. This type of particles, such as nanocorals and micro/nanomotors, have many advantageous properties such as dual functionality and anisotropic nature, and they are interesting for potential applications in materials science and biomedicine. Due to the presence of different functional groups and different chemical compounds on the two distinct sides, JNPs can be designed to fulfil different needs simultaneously in drug delivery, such as loading two drugs, having different targeting ligands, or carrying imaging agents. In addition, the site-selective modification of each side of the particle allows for the combination of different agents within a single particle without significant interaction between them, leading to their versatile potential use in “theranostics”, for example (Rahiminezhad et al., 2020).

The use of JNPs for drug delivery is increasingly being investigated. Potential applications of JNPs in drug delivery include co-delivery of two drugs with opposite solubility, chemo-photothermal combination therapy, stimuli-responsive, and real-time monitored dual drug release, active-targeted delivery, “theranostics”, bioimaging, and enzyme-controlled stimuli-responsive drug delivery (Rahiminezhad et al., 2020).

Examples of JNPs being explored for drug delivery include polymeric JNPs composed of PLA/PGA, which are capable of simultaneously carrying a hydrophobic and a hydrophilic drug. Janus silica nanocomposites represent a further multifunctional carrier for dual-drug delivery. These JNPs are composed of UCNP@SiO_2@mSiO_2@PMO (UCNP = upconversion nanoparticle = NaGdF4: Yb, Tm@NaGdF4, mSiO2 = mesoporous silica, PMO = periodic mesoporous organosilica). They contain core@shell@shell structured UCNP@SiO2@mSiO_2 nanospheres and PMO single-crystal nanocubes. Other types of JNPs are Gold-silica, Au-silica, PS-silica, PAA/PDMAEMA, or PS-PAA JNPs, for example. (Rahiminezhad et al., 2020)

Micro- and nanomotors are micro- or nanoscale devices capable of converting chemical or external energy into movement and force (Rahiminezhad et al., 2020). **Janus micro- or nanomotors** have unique asymmetric structures and integrate different functional materials on two sides, and they could provide a new concept for the development of actively delivering drug carriers (Lee et al., 2015). For example, a self-propelled Janus nanomotor based on mesoporous silica nanoparticles was fabricated and used as a carrier for the delivery of a model drug (Lee et al., 2015; Rahiminezhad et al., 2020). For the nanomotor, mesoporous silica nanoparticles (65 nm) were spread on a silicon slide and coated with chromium (Cr) and finally platinum (Pt), as a catalytic layer. The silicon wafer was then sonicated, and Janus-mSiO_2 nanomotors were released (Rahiminezhad et al., 2020). This nanomotor was driven by oxygen as a driving force produced by the decomposition of hydrogen peroxide. The surface of Janus-mSiO_2 nanomotors was also modified with an egg phosphatidylcholine bilayer containing phospholipids modified with folic acid as a targeting ligand (Rahiminezhad et al., 2020). Virus-based nanomotors, consisting of brome mosaic virus and cowpea chlorotic mottle virus capsids half coated with catalytic platinum were also developed (Rahiminezhad et al., 2020).

3.2.4 Supraparticles

Defined and dispersed structures formed by clusters of nanoparticles can be termed "supraparticles". In the field of particle research and development, however, there is no coherent nomenclature for the different types of supraparticles: "The term has been most often used for either particle systems comprising two or more types of nanoscale building blocks to form particles with complex nature, or for particles made from a single type of nanoparticle arranged into more complex structures" (Wintzheimer et al. 2021, p. 5095). Supraparticles are entities that have been created from colloidally dispersed nanoparticles as starting materials. (Wintzheimer et al., 2021)

In many fields of science and technology, such as colloid chemistry, soft matter physics, powder technology and pharmaceutical and food sciences, a crucial attempt is made to control the the size, shape and morphology of these structures. The design of supraparticles is flexible, and a very large number of different structures can be assembled with a small number of building blocks by varying basic design criteria, such as connectivity (density, fractal dimension, order and disorder, or shape), composition (homocomponent versus hetero/multiple- component), and distribution (different phases within the particles, core-shell, or capsule architecture). (Wintzheimer et al., 2018)

By combining individual nanoparticles into more complex supraparticle entities, **three new and unique types of properties,** and thus functionalities can be achieved that cannot be achieved with individual nanoparticles (Wintzheimer et al., 2021):

Coupling – the strong interaction between electrons in nanoparticles within a supraparticle due to their close proximity;

Emergence – arises from a specific structure within the supraparticle rather than from intrinsic properties of the individual building blocks;

Colocalization – specifies that different nanoparticles with distinct properties in a supraparticle form a distinguishable common entity with either combined or superimposed properties that can be moved, as well as removed, concentrated, and observed individually.

These new functionalities can be exploited in various applications, such as agricultural delivery systems or medicine. For example, functional supraparticles synthesized by the self-assembly of alkylamine modified nanodiamonds with have been explored as potential nanocarriers for anticancer drugs (Yu et al., 2019). A pioneering example of supraparticles for agricultural delivery systems are supraparticles composed of biogenic silica particles and cellulose nanofibrils (Wintzheimer et al., 2021).

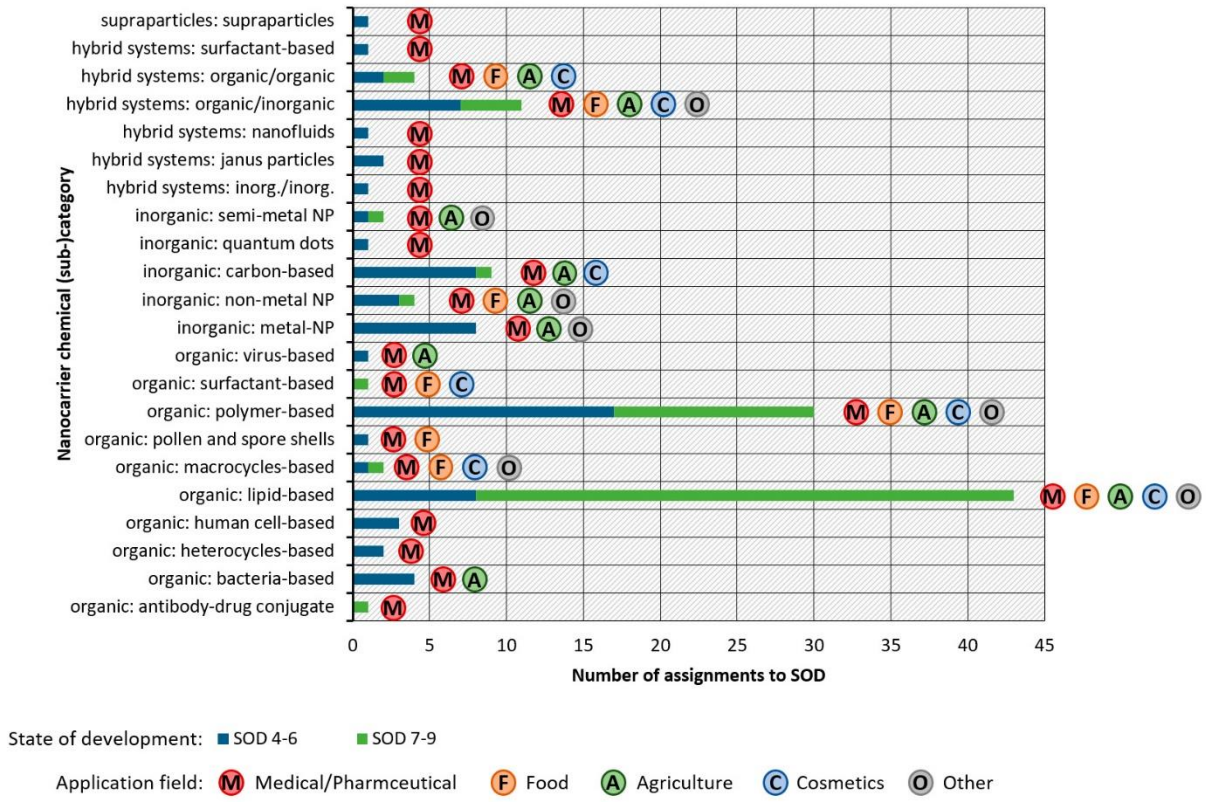
The use of supraparticles, which are typically in the microscale size range, may help to overcome health or environmental concerns arising from the use of nanoparticles. Supraparticles still offer the advantages of nanomaterials while increasing the particle size, which may allow easier and safer handling and less material loss. (Wintzheimer et al., 2021)

3.3 Assignment to the state of development

Nanocarriers have already been used for decades, e.g., in agriculture and medicine (Chariou et al., 2020). However, the number of nanocarrier concepts and the diversity of application areas continues to grow. For a comparably precise analysis of the development status of all nanocarrier types, it is necessary to go beyond screening and analysis of the scientific literature and patent databases and to conduct specific investigations in the fields of industrial research and development on the innovation status of the individual nanocarrier types. Such an effort goes beyond what could be done in the present study. However, the literature review and previously described, and characterized types of nanocarriers enabled to assign a nanocarrier type to a certain SOD (c.f. definition in Chapter 0). The indications of areas of application obtained in this process were also evaluated. The main areas of application are the use of nanocarriers for medical or pharmaceutical purposes, for food, agriculture, or cosmetics. Other application areas in which only a few nanocarrier types could be used or are already used are veterinary medicine, electrochemistry, household products and textiles. The result of the classification of SOD and application area is shown in Figure 5. Applications of nanocarriers are discussed in detail in Chapter 3.4.

Figure 5: Types of nanocarriers incl. potential application fields assigned to their state of development (SOD).

The category "Other" for application fields includes veterinary medicine, electrochemistry, household products and textiles.



Source: own illustration, BOKU.

State of development 1-3 represents an existing formulated concept of the nanocarrier type. No nanocarrier could have been assigned to this level. This creates the impression that all relevant nanocarriers have already past this concept phase and no subsequent nanocarrier will follow. However, this is probably not the case. We experienced poor data availability and possibilities for the identification of nanocarriers in this early development stage. It must be stressed that it is challenging to assign a nanocarrier type to a certain SOD. For example, Jankovic and Plata (2019) have also been confronted in their market study on engineered nanomaterials with this challenge, as they divided the TRLs 3-9 into three newly defined levels, whereas TRL 1-2 was excluded from their classification approach (Jankovic & Plata, 2019).

State of development 4-6 represents the state of the nanocarrier under laboratory conditions as well as testing phase of the prototype. Most of the identified nanocarrier sub-categories are assigned to this SOD (Figure 5). The largest share is represented by polymer-based nanocarriers (chemical category: organic nanocarrier; see Table 1). Polymer-based nanogels (chemical category: organic nanocarrier), for instance, are assigned to this SOD according to a publication about biomedical applications: "Despite such diversity in their applications, nanogels are not yet a part of clinical use" (Soni et al., 2016).

The second-largest share for SOD 4-6 is represented by lipid-based nanocarriers (chemical category: organic nanocarrier; see Figure 5). Cubosomes, for example, are assigned to this SOD as they have "significant implications for large-scale production […], which currently is a major barrier to the application of cubosomes in the clinic." (Azhari et al., 2016). For carbon-based nanocarriers, such as carbon dots (chemical category: organic nanocarrier) it has been successfully demonstrated that they can be used as trackable drug delivery agents for cancer treatment in an animal model (Zeng et al., 2016). Metal nanoparticles, such as magnetic nanoparticles (chemical category: inorganic nanocarrier), are described as "there are few clinical studies and numerous obstacles to overcome before MDDSs [magnetic drug delivery systems] can achieve therapeutic effectiveness and reach the market" (Aslam et al., 2021). Organic/inorganic nanocarriers, such as covalent organic frameworks (COF) (chemical category: hybrid systems), are assigned to SOD 4-6 because "further optimization in vivo is required for the design of optimal drug-delivery carriers, since findings from in vitro studies do not predict the former's outcomes." (M. C. Scicluna & L. Vella-Zarb, 2020).

A small share of nanocarrier types assigned to SOD 4-6 are bacteria-based nanocarriers, such as non-living bacteria (chemical category: organic nanocarrier), that were "tested [for the] the protective effect of topical application of *Escherichia coli*-encapsulated dsRNA compared to naked dsRNA against single and dual infection by Potato virus X" (Necira et al., 2021). Some of the identified non-metal nanoparticle types (chemical category: inorganic nanocarrier), are also assigned to SOD 4-6. An example is montmorillonite nanoclay (generic term for the carrier: clay mineral/silicate) which "is currently under investigation for its use as a drug carrier system" (Jayrajsinh et al., 2017).

State of development 7-9 represents usage, availability, and closeness to market penetration. Lipid-based nanocarrier types (chemical category: organic nanocarrier; see Figure 5) are most frequently assigned to this SOD. For example, lipid nanoparticles (LNPs) (Table 1), whose "majority […] [is] currently used in clinical applications" (Finn et al., 2018), or bilosomes that are "widely used for the oral delivery of many small molecules like hormones, proteins, vitamins, DNA, and antibodies" (Rehman et al., 2020). Polymer-based nanocarriers (chemical category: organic nanocarrier) are the second most common nanocarriers of this SOD (Figure 5). Nanocapsules (Table 1) for example, are applied "for the treatment of various diseases (including cancer and infections)" (Couvreur et al., 2002). Many of the lipid – and polymer-based nanocarriers are already in use since several years, e.g., liposomes: "several liposomal drug products have been successfully approved and used in clinics over the last couple of decades" (Liu et al., 2022) or PLGA and allylamine-based polymeric carriers approved in 2002 and 2000 (Chariou et al., 2020). This could be because the design of the carrier was comparatively easy to realise because of the experience already gained with these types of materials.

A small share of nanocarrier types assigned to SOD 7-9 is represented by organic/inorganic nanocarriers, such as aquasomes (chemical category: hybrid systems). These nanocarriers have "important medical applications" for the delivery of xenobiotics and antigens (Jagdale & Karekar, 2020). Also, organic/organic nanocarriers are assigned to this SOD, such as bigels (chemical category: hybrid systems) that are "already used as cream analogues, as vitamin E, lycopene, β-carotene and a probiotic delivery system" (Baltuonytė et al., 2022). Antibody-drug conjugates (chemical category: organic nanocarrier) are also assigned to SOD 7-9. These conjugates "have been used in the active-targeting approach since the early 1980s" (MaHam et al., 2009). Also ceramic nanoparticles (non-metal nanoparticles) are already used (chemical category: inorganic

nanocarrier): “Hydroxyapatite (HAP) are […] nowadays used for various biomedical applications” (Khan et al., 2022).

Table 1: List of nanocarrier types assigned to state of development (SOD) 4-6 and 7-9.

SOD 4-6

Chemical category	Chemical sub-category	Generic term
Organic	Bacteria-based	Bacteria (living)
		Bacteria (non-living)
		Bacteria ghost (BG)
		Bacterial minicell
	Heterocycles-based	Nanoporphyrin
		Spiropyrane
	Human cell-based	Erythrocyte
		Immune cell
		Stem cell
	Lipid-based	Cubosome
		Exosome
		Ectosome
		Extracellular vesicle (EV)
		Microvesicle
		Pickering emulsion
		Proniosome
	Macrocycles-based	Supramolecular hydrogel
	Pollen and spore shells	Pollen and spore shells
	Polymer-based	Aerogel (polymer)
		Cross-linked gel
		Dendrimere
		DNA nanostructure
		DNA origami nanostructure
		Hyperbranched polymer (HBP)
		Light-sensitive polymeric nanocarrier
		Nanofiber
		Nanogel
		Polyion complex micelle

Chemical category	Chemical sub-category	Generic term
		Polymer-drug conjugate
		Polyplex
		Protein nanocage
		Spongosome
		Temperature-sensitive polymeric carrier
		Thermoresponsive polymeric carrier
	Virus-based	Virus-like particle
	Yeast cells-based	Yeast cell
Inorganic	Metal nanoparticle	Copper nanoparticle (CuNP)
		Gold nanoparticle (AuNP)
		Magnetic nanoparticle
		Metal sulfide nanoparticle
		Nanowire
		Palladium nanoparticle (PdNP)
		Silver nanoparticle (AgNP)
		Zinc oxide nanoparticle (ZnO NP)
	Non-metal nanoparticle	Aerogel (silica)
		Clay mineral/silicate
		Selenium nanoparticle
	Carbon-based	Activated carbon (AC)
		Carbon nanofibre (CNF)
		Carbon dot (CD)
		graphene oxide (GO) nanosheet
		Graphene quantum dot
		Carbon nanotube (CNT)
		Nanodiamond
		Nanographene flake
	Semi-metal nanoparticle	Titanium dioxide nanoparticle (TiO_2 NP)
	Quantum dots	Quantum dot
Hybrid systems	Inorganic/inorganic	Gold/mesoporous silica nanoparticle nanorod

Chemical category	Chemical sub-category	Generic term
	Janus particles	Janus particle
		Janus-micro- and nanomotor
	Nanofluids	Nanofluid (nanosuspension)
	Organic/inorganic	Covalent organic framework (COF)
		Metal organic network (MOF)
		Nano-conjugate
		Nanoflower
		Nanoshell
		Periodic mesoporous organosilica (PMO)
		Supramolecular metallogel
	Organic/organic	Colloidosome
		Filled microgel
	Surfactant-based	Spanlastic nanovesicle
Supraparticles	Supraparticles	Supraparticle

SOD 7-9

Chemical category	Chemical sub-category	Generic term
Organic	Antibody-drug conjugate	Antibody-drug conjugate
	Lipid-based	Asymmetric oxygen carrier system (AOCS)
		Bilosome
		Double emulsion
		Emulgel
		Emulsome
		Ethosome
		Hexosome
		Isasome
		Lipid conjugate
		Lipid nanoparticle (LNP)
		Lipid-based hydrogel
		Lipofectamine
		Lipoplex
		Liposome
		Liposome (Yeast cell-based)
		Marinosome
		Microemulsion
		Multilamellar vesicle (MLV)
		Multilayered emulsion
		Multi-walled delivery system (MDS)
		Nanobubble (NB)
		Nanoemulsion
		Nanosome
		Nanostructured lipid carrier
		Nanotope
		Niosome
		Pharmacosome
		Photosome
		Phytosome

Chemical category	Chemical sub-category	Generic term
		Solid lipid nanoparticle (SLN)
		Stealth liposome
		Transfersome
		Ultrasome
		Vesosome
		Virosome
	Macrocycles-based	Cyclodextrine (CD)
	Polymer-based	Elastin-like polypeptide nanoparticle (ELP-nanoparticle)
		Elespher
		Micelle (polymer)
		Mixed micelle (MM)
		Multi-layer/core-shell microcapsule
		Nanocapsule
		Nanosphere (NS)
		Nanosponge
		Organogel
		Polycation
		Polymersome
		Silicone vesicles and matrice
		Unisphere
	Surfactant-based	Micelle (surfactant)
Inorganic	Non-metal nanoparticle	Ceramic nanoparticle
	Carbon-based	Fullerene/buckyball
	Semi-metal nanoparticle	Mesoporous silica nanoparticle (MSN)
Hybrid systems	Organic/inorganic	Aquasome
		Gold nanocage
		Superparamagnetic iron oxide nanoparticle (SPION)
	Organic/organic	Bigel
		Glycosphere

The right column of Table 1 lists the nanocarrier types that were used to derive the SOD for the respective chemical (sub-)category. This table provides a more detailed insight into the SOD of each chemical (sub-)category. Some nanocarrier types occur twice within one SOD. Aerogels, for example, are assigned to SOD 4-6 once for polymer-based- and once for non-metal aerogels (Table 1). On the one hand, polymeric aerogels are based on biopolymers such as polysaccharides, proteins, and nucleic acids (Garcia-Gonzalez et al., 2021). These polymeric nanocarriers are assigned to SOD 4-6 because “most of the published articles are related to bench-scale production” (Garcia-Gonzalez et al., 2021). On the other hand, non-metallic aerogels or rather “drug loaded silica aerogels [were] firstly applied as dermal drug delivery systems” (Guenther et al., 2008) and are thus assigned to SOD 4-6.

Another example of multiple entries of a nanocarrier type within Table 1 are liposomes that appear two times in SOD 7-9 (Figure 5). Lipid-based liposomes are based on phospholipids and “have been successfully approved and used in clinics over the last couple of decades" (Liu et al., 2022). In contrast, yeast cell-based liposomes are based on phospholipids derived from yeast cells, from which “a significant number of innovative formulations are now being used in personal care” (Patravale & Mandawgade, 2008). Both nanocarriers are assigned to SOD 7-9.

Micelles can be either based on polymers or surfactants and both are assigned to SOD 7-9 (Table 1). On the one hand, polymeric micelles are either based on polyethylene glycol (PEG), polylactic acid (PLA), polycaprolactone (PCL), polypropylene oxide, polylysine, poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone (Su & M. Kang, 2020). The "FDA [approved] an albumin-based polymeric nanocarrier, Abraxane, which carries an anti-cancer drug, Paclitaxel, for the treatment of breast cancer" (Su & M. Kang, 2020). On the other hand, surfactant-based micelles are made of polysorbate, and they are already available on the market (Feelgood Shop, 2023).

3.4 Applications of nanocarriers

Nanocarriers are of particular interest in medicine and are widely used. This is also the field in which the most intensive research is being carried out. But other areas of application are also inspired by medical research and many types of nanocarriers are used in more than one application area. Nanocarriers are already being used in cosmetics, food and food supplements, agriculture, household products, and textiles. New product developments or applications for approval can be expected.

3.4.1 Medicine

Conventional systemic administration of drugs involves exposure of the entire body. A targeted application is not possible in this way. In addition, depending on the active ingredient, such an application can also have undesirable side effects at the system level. Moreover, 40% of potential active drug ingredients are poorly soluble in water and are therefore not suitable for clinical use (Wang et al., 2019). Medical innovations, such as special delivery systems, aim to selectively transport the active ingredient to target regions of the body, increase cellular uptake of the active ingredients, protect sensitive active ingredients from degradation, and minimize systemic exposure (Marie Christine Scicluna & Liana Vella-Zarb, 2020).

21 nanocarriers have been identified as approved since 1990 in the U.S. and in the EU by the FDA and EMA health authorities and others are in preclinical and clinical testing phases (Chariou et al., 2020). The majority of approved nanocarriers in medicine are liposomes (47%), and the

advantage of these systems is primarily reduced toxicity of the active pharmaceutical ingredient rather than increased efficacy. The drugs used include mainly chemotherapeutics for the treatment of cancer, but also antifungal agents, antibiotics, and hormones**. Lipid nanoparticles**, which are used in the newly developed vaccines against COVID-19, have recently become the focus of public interest. They serve to protect the sensitive mRNA, which codes for the blueprint of the spike protein of the corona virus, from enzymatic degradation.

Liposomal nanocarriers came to market in 1995. The first liposomal drug approved by the U.S. Food and Drug Administration (FDA) was Doxil, which contains the active ingredient doxorubicin for the treatment of cancer. In subsequent years, liposomal carrier systems remained the predominant nanocarriers in medicine due to their efficacy and safety (Su & M. Kang, 2020). By controlling the lipid composition as well as the length of the fatty acid chains of liposomal nanocarriers, their behavior in the event of temperature and/or pH changes can be adjusted. This allows controlled release of the active ingredients under those physiological conditions specific to the site of disease (Chariou et al., 2020). Liposomal delivery systems can significantly improve drug efficacy by stabilizing entrapped drugs, and enhancing targeted uptake in tissues (Su & M. Kang, 2020).

Nanocarriers made of **polymers** are also promising candidates for application in medicine, such as those based on polylactic acid (PLA), polylactic-co-glycolide (PLGA), polyglycolic acid (PGA), polycaprolactone (PCL), polyester, and polyurethane (Chariou et al., 2020; Su & M. Kang, 2020). These polymers can form self-assembled micellar vesicles with a hydrophilic outer layer and a hydrophobic core in which poorly water-soluble drugs can be entrapped (Su & M. Kang, 2020). PLGA is a particularly promising candidate for use as a nanocarrier in medicine. The U.S. Food and Drug Administration (FDA) has already approved a drug for the treatment of cancer based on this delivery system. The only other FDA-approved polymeric nanocarrier is Welchol, an allylamine polymer that encapsulates a drug to treat diabetes and high cholesterol (Chariou et al., 2020). Different approaches are currently being investigated to improve the uptake capacity of polymeric nanocarriers, for example by adding albumin. One such albumin-based nanocarrier approved by the FDA is Abraxane, a drug in which the chemotherapeutic agent paclitaxel for the treatment of breast cancer is transported by the carrier. The milk protein casein or elastin-like peptides can also be components of polymeric nanocarriers in medicine. These functionalization also help protect proteins as active ingredients from degradation in the digestive tract, enabling oral use of protein-based drugs (Su & M. Kang, 2020). Nanocarriers made from natural polymers such as chitosan, sodium alginate, collagen, heparin, or silk are also being developed (Chariou et al., 2020). However, although there are numerous developments in the field of polymeric nanocarriers for medical applications, the number of approvals remains manageable. This is mainly due to the fact that while these systems have an improved safety profile compared to liposomal drug formulations, they do not have higher efficacy (Chariou et al., 2020).

Carbon nanotubes (CNTs) and so-called **carbon dots** are also the subject of medical research, especially for cancer therapy. Due to the small size of these nanocarriers, it is also hoped that these carriers will have an improved ability to cross the blood-brain barrier. However, possible negative effects of these carbon-based transport systems, such as oxidative stress on cells and subsequent inflammatory reactions, hinder their potential application in medicine and make further studies on their safety profile essential (Su & M. Kang, 2020).

Due to their multiple advantageous properties, such as high biocompatibility, drug receptivity, uniformity, easily adjustable size, ease of fabrication, low toxicity and stability in the presence of serum, **Nanogels** are promising candidates in the development of delivery systems in medicine (Su & M. Kang, 2020).

Dendrimers are suitable for applications in the field of medicine, as they can entrap both hydrophilic and hydrophobic drugs with high molecular weight. They increase solubility and improve stability and oral bioavailability of many drugs (Su & M. Kang, 2020). Most dendrimers being developed as nanocarriers for medical applications are based on polyamidoamine (PAMAM) or polypropylenimine units, because they are not recognized by the immune system. Others are based on PEG, polyglycerol, polyglycerol-co-succinate, melamine, or triazine (Chariou et al., 2020).

Hybrid nanocarriers made of different combinations of materials are also the subject of research, such as carbon-based hybrid nanogels or combinations of polymers and liposomes (Su & M. Kang, 2020).

A variety of other different systems and materials are currently being investigated in medical research for their use as nanocarriers, e.g., **quantum dots, graphene, nanodiamonds, various nanoparticles of metals, semimetals, and silicates, supramolecular organogels, DNA nanostructures, pollen and spore envelopes, living human cells, viruses, bacteria, yeast cells, Janus- and supraparticles**. Many of these systems are highly complex and, if they reach market maturity, will have special risk assessment requirements.

In terms of commercialization, the production of nanocarriers on an industrial scale remains a challenge. Several factors hinder progress, such as insufficient uptake capacity of nanocarriers for active ingredients, difficulties in ensuring consistent quality and particle size, or problems in purification (Su & M. Kang, 2020).

The increasing number of applications for approval of nanocarriers in medicine also increases the need for a comprehensive safety assessment of these systems. However, most current assays were developed to study conventional therapeutic agents (Su & M. Kang, 2020). They may therefore have limited applicability to the newly developed delivery systems. In any case, it is important to be aware that the biocompatibility of a single component cannot be a guarantee of the safety of the delivery system as a whole (Su & M. Kang, 2020).

3.4.2 Agriculture

The concept behind the use of nanocarrier systems in the field of agriculture is similar in principle to that of medicine. Nanoagrochemicals are designed to achieve a targeted transport of active ingredients such as pesticides or fertilizers to the desired site of action, but with the major difference that their release takes place in the environment under changeable climatic and geographic conditions and without a specific transport route, such as the bloodstream in medicine (Chariou et al., 2020). Nanocarriers can, on the one hand, be placed on the leaves of plants, where the active ingredients are passively absorbed into the plant via stomata or wounds. On the other hand, they can also be transported in the soil and absorbed through the roots. Currently, agriculture is facing the problem that chemicals are often washed out in the agricultural field and end up in groundwater. Nanocarriers promise to target the dosage of nutrients by releasing them more slowly (plant health management). Future "precision

agriculture" may take advantage of nanocarriers by targeting pesticide and fertilizer delivery. This may also increase the product safety of active ingredients, benefiting groundwater protection, for example. Controlled release could also help improve soil fertility and mineral balance.

The use of pesticides by means of nanocarriers is particularly promising because, although pesticides are effective in small quantities, their uniform application in arable land is difficult, and requires a suitable formulation. In addition, the active ingredients are often unstable under environmental conditions, barely soluble and have a strong affinity to bind to soil particles. To overcome these problems, pesticides have been formulated with polymers or other substances for a long time. But even this method, known as microencapsulation, has its limitations due to the limited chemical and thermal stability of the capsules. For this reason, new nanocarrier systems based on lipids or polymers, for example, are being developed that improve the water dispersibility and bioavailability of the active ingredients and protect the agrochemicals from degrading too rapidly in the environment. (Chaud et al., 2021)

Various **synthetic and natural biodegradable[2] polymers** (see Chapter 3.5) can serve as nanocarriers for agrochemicals, including "nanospheres", in which the active ingredient is uniformly distributed in the polymer matrix, and nanocapsules in which the cargo is encapsulated in the inner core. Such nanocarriers can be made of PEG, PCL, PLA chitosan or sodium alginate and are used to transport various pesticides such as ametryn (a herbicide), atrazine (a herbicide from the chlorotriazine family), acephate (organophosphorus insecticide), emanectin (insecticide), garlic oil, Imidacloprid (an insecticide from the neonicotinoid group), lansiumamide B, Methomyl (insecticide and nematicide), paraquat (bipyridinium herbicide) and simazine (an herbicide from the chlorotriazine group). Nanocarriers made from corn protein (zein) are also being developed for agricultural and have been tested to transport pesticides to protect soybeans from foliar pests. (Chariou et al., 2020)

Micellar nanocarriers consist of amphiphilic surface-active substances that spontaneously form spherical vesicles in water. Hydrophobic substances can be entrapped inside. Most micelles are made of PEG, PLA, PCL, polypropylene oxide, polylysine, or a combination of these substances. Micelles are being developed as promising nanocarriers for agriculture to prevent adsorption of the active ingredient to soil particles. Encapsulated active ingredients include azadirachtin (insecticidal active ingredient from the seeds of the neem tree), carbendazim (fungicide from the benzimidazole carbamate group), carbofuran (broad-spectrum insecticide, acaricide and nematicide from the carbamate group of substances), imidacloprid (insecticide from the group of neonicotinoids), rotenone (insecticide and acaricide), thiamethoxam (insecticide from the group of neonicotinoids), and thiram (fungicide for seed treatment). (Chariou et al., 2020)

Virus-based nanocarriers made of plant viruses and bacteriophages can also offer advantages in agriculture, as they are harmless to humans and domestic animals. They are very mobile in soil and can therefore be used to carry pesticides to the roots of plants. In 2007, the U.S. Environmental Protection Agency approved a nanocarrier based on tobacco mosaic virus to

[2] In the context of environmental risk assessment, biodegradability is an important property of engineered materials that could be released during their use. As there are different understandings of biodegradability and the mention of this property in the scientific literature on nanocarriers does not necessarily correspond to the definitions of biodegradability in the regulatory context, chapter 3.5 is dedicated to this property to address the possible meanings.

transport an herbicide. Red clover mosaic virus is also in development as a nanocarrier for transporting the pesticide Abamectin. (Chariou et al., 2020)

To date, there is no specific regulation for nanocarriers in the field of agriculture because a uniform definition is still lacking. Therefore, it is difficult to determine which nanocarriers actually have already been commercialized. No formulation of pesticides has yet been explicitly marketed with the buzzword "nano." This is probably a strategy of the manufacturers to deal with the unclear regulatory situation and not to jeopardize a public acceptance (Chariou et al., 2020), but probably the sizes of the carrier structures used are also beyond the 100 nm limit as defined in the European Commission's definition proposal for nanomaterials. In the U.S., 42 microencapsulated products, primarily insecticides and herbicides, have been approved by the EPA. Several plant protection products based on capsule suspensions and microemulsions are also approved in the EU. However, information on the size of the capsules or the droplets is not available, so that no statement can be made as to whether these are nanocarriers according to the definition used in this report. Although nanocarriers for agrochemicals represent a promising approach to increase crop yields in an environmentally sound manner, it remains an open research question to what extent the nanocarrier influences effectiveness of the active ingredient, environmental distribution, and mobility, which poses a major challenge for the future risk assessment of complex nanocarrier systems. In addition, testing strategies might have to be adapted and further studies of hazard properties (persistence, bioaccumulation, and toxicity), and environmental fate (exposure including mobility) of the whole nanocarrier systems are needed especially in areas of applications where a release into the environment is intended.

But it is not only novel carrier materials that are being investigated for use in agriculture, but also **new active ingredients** that can be packaged and transported with them and are expected to be more environmentally compatible than conventional pesticides. Special **double-stranded RNA molecules (dsRNA)** tailored to the target organism are expected to control pests in the future by silencing certain genes that are essential for survival (post transcriptional gene silencing). dsRNA can be sprayed onto the leaves of crops. This mechanism, known as "RNA interference" (RNAi), is a natural cellular process that originally arose from virus defence in plants and protects eukaryotic cells from harmful nucleic acids. In agriculture, RNAi can be an effective strategy to control pathogens such as viruses, bacteria or fungi, as well as insects, mites or nematodes (Rank & Koch, 2021). However, RNA molecules are very sensitive and need to be protected against environmental influences such as UV radiation. In addition, they should adhere to the leaf surfaces for a sufficiently long time and not be washed away by rain. Stabilisation to protect against degradation after uptake into the plant cell or into the harmful organism by enzymes (nucleases) or unfavorable environmental conditions (pH) is also essential. Non-encapsulated dsRNA is degraded in the environment within 48 hours (Yang et al., 2022). For these reasons, a number of encapsulation systems, formulations, and delivery forms are being researched and tested (Koch & Petschenka, 2022). Further functionalization can also enable targeted release of dsRNA, for example in a pH-dependent manner, and attractants or baits integrated into the (nano)carriers can improve efficiency and specificity (Rank & Koch, 2021). Many of the nanotechnology-based formulations are inspired by medical research, the development of which was massively stimulated by the use of mRNA vaccines to combat the Covid 19 pandemic (Koch & Petschenka, 2022). Different carrier-systems have been explored for protection and delivery of dsRNA for spray induced gene silencing, such as **guanidine-**

polymers, lipofectamine, peptides, genetically modified bacteria and bacteria "minicells", hydroxyapatite, layered double hydroxides ("BioClay") and gold nanoclusters. Approval has already been sought in the U.S. for an RNAi-based crop protection product. It is expected that companies will seek marketing approval for this technology in Europe as well.

3.4.3 Cosmetics

Various nanocarriers are used in cosmetics to enable the skin penetration of active ingredients, and to increase the solubility of hydrophobic substances, such as vegetable oils, coenzyme Q10 or fat-soluble vitamins. They can also be used to improve the stability of active ingredients, and reduce the amount of active ingredient used (Zhou et al., 2021). The types of nanocarriers used for applications in cosmetics include **micro- or nanoemulsions, liposomes, lipid nanoparticles, so-called "lipid liquid crystals," and polymeric nanocarriers**. Their size ranges from 10 to 1000 nm.

The first carrier system based on **liposomes** was used in cosmetic products in 1986 (Zhou et al., 2021). Improved liposomes, such as **transfersomes, ethanol-containing ethosomes** or **niosomes** made of non-ionic surface-active substances (mainly alkylglycerols in combination with cholesterol) (Kazi et al., 2010) can penetrate the intercellular spaces of the upper skin layer (stratum corneum), which is difficult for active ingredients to penetrate and transport active ingredients to deeper skin layers (Zhou et al., 2021). **Lipid nanoparticles** are colloidal dispersions of a mixture of solid and liquid lipids.

Microemulsions are formed spontaneously when oil, water and an emulsifier are mixed. **Nanoemulsions** are basically conventional emulsions, but with very small droplet size. The small size of the droplets is achieved by high-pressure homogenization with the addition of phosphatidylcholine, but without a synthetic emulsifier to improve skin tolerance.

Polymeric nanocarriers made of biocompatible polymers are also called polymeric micelles, nanohydrogels, nanocapsules or "nanospheres" in the field of cosmetics. They penetrate the skin in the area of the hair follicles and the sebaceous glands and distribute the active ingredients in the skin.

3.4.4 Food and food supplements

A large number of hydrophobic or poorly water-soluble bioactive substances, such as certain vitamins, carotenoids, essential oils, fatty acids or phenolic compounds, are necessary or beneficial for human health. Aromas or flavors used in the food industry are often poorly soluble in water and in some cases also sensitive to higher temperatures or oxidation. With the help of nanocarriers, it is possible to protect highly volatile or sensitive active ingredients, and increase bioavailability, but also to "package" poor-tasting bioactive ingredients such as fish oil (Rezaei et al., 2019).

Cyclodextrins are frequently used for applications in the food industry. These cone-shaped oligosaccharides can trap hydrophobic substances, such as carotenoids, inside and improve their solubility, stability, and bioavailability. This also applies to nanocarriers made from the starch component **amylose**.

Suitable for encapsulating both hydrophilic and hydrophobic substances in food are also **yeast cells** due to their phospholipid-containing membrane. They are food grade, cheap, and the encapsulation process is simple.

Nanogels made of various biopolymers (polysaccharides, proteins) are currently being explored for food application. They are particularly versatile nanocarriers and can entrap both hydrophobic and hydrophilic bioactive substances.

As in medicine and cosmetics, **nanoemulsions** are also finding use in the food sector. They consist of oil (e.g., sunflower, corn germ, olive, or fish oil), water and an emulsifier and act as nanocarriers for hydrophobic substances (e.g., carotenoids or vitamins). Because of the small droplet size, nanoemulsions are transparent and therefore suitable for beverages. Food supplements and functional foods take advantage of multilayer emulsions for the delivery of essential nutrients. Microencapsulated lecithin–chitosan multilayer emulsions, for example, can deliver fatty acids that are essential for the human diet. The multilayer emulsion droplets allow a stabilization of fatty acids in aqueous systems, and deliver the fatty acids via functional foods (Shaw et al., 2007)

Liposomes, nanostructured lipid carriers and **lipid nanoparticles** are also suitable nanocarriers in the food sector, as are **nanofibers** or so-called "**nanosponges**", porous, sponge-like structures based on cyclodextrins in combination with carbonates or anhydrides (Rezaei et al., 2019).

3.4.5 Food contact materials

For extending the shelf life of food, “active” packaging has been developed, that contains natural antimicrobial agents. The efficacy of such packaging can be enhanced through the use of nanocarriers, that allow for the controlled release of antimicrobials (Bahrami et al., 2020). Essential oils, e.g., thymol, eugenol, or coriander essential oil are the most popular antimicrobials for food packaging applications, but due to their vulnerability against environmental stresses and fast release incorporating their free form into food packaging structures (films or coatings) is challenging, and nanocarriers can help to overcome these problems.

Lipid-based nanocarriers, such as nanoemulsions, liposomes and solid lipid nanoparticles, are of particular interest for the use in food packaging because of their ability to enclose both hydrophilic and lipophilic substances, their targeting capability, and their production with natural food-grade materials. In addition, these types of nanocarriers are compatible with most food products. Other **biopolymer nanocarriers, such as chitosan and zein,** are also being investigated as nanocarriers for food packaging applications. (Bahrami et al., 2020)

3.4.6 Veterinary applications

Just as in the field of human medicine, nanocarriers can bring benefits in veterinary medicine to deliver antimicrobials, anaesthetics, antiparasitics, vaccines and antineoplastic drugs to animals, and there are numerous references to relevant research activities in the scientific literature (Carvalho et al., 2020). Nanocarriers may also be incorporated into products for external use, such as disinfectants, hygiene products and cosmetic articles for pets and leisure animals. The main nanocarriers for veterinary applications are based on organic and inorganic particles, such

as **nanoemulsions, liposomes, polymeric micelles and nanoparticles, mesoporous silica nanoparticles, metallic nanoparticles, and dendrimers**. Despite diverse research results, there are still hardly any approved veterinary medicinal products on the market. Only one approved product is mentioned in the literature: a PEGylated protein for the treatment of inflammation in the breast tissue of cows (Chariou et al., 2020), but several other nanocarrier-systems are currently undergoing clinical trials. However, the low yield for this application area may also be due to the fact that different terms are used for veterinary applications of nanocarriers than for the search approach of the present study.

Transported active substances include drugs for cancer treatment (e.g., doxorubicin, paclitaxel, curcumin), anaesthetics (e.g., bupivacaine), drugs for the treatment of leishmaniasis (e.g., oryzalin, paromomycin sulphate, amphotericin B), antibiotics (e.g., amoxicillin, gloxacllin) and also functionalised **gold nanoparticles** for the treatment of breast cancer in dogs have been investigated (Carvalho et al., 2020).

3.4.7 Further Applications

There are some cases where the same type of nanocarrier can be used in multiple applications, such as in medicine, cosmetics, and various consumer products. For example, household products such as **air and textile fresheners** can contain cyclodextrines as carriers. This nanocarrier system, which is already available, partially dissolves in the vapour of the freshener, in which the suspended cyclodextrin molecules bind unwanted odours by forming a complex with their inner part (Helmenstine, 2019). There are also industrial products, such as **lithium-ion batteries** that contain nanocarrier systems to reduce degradation and improve cycling stability, but such specific applications are currently under development, and not applied on industrial scale. For such modified lithium-ion batteries, the active ingredient vinylene carbonate is encapsulated in halloysite nanotubes (Ahn et al., 2022). The system, which comes from therapeutics, facilitates electrochemical stability of the battery by controlled release of the active ingredient. The applications presented above are only a subjective selection and are intended to show that new areas of application can be opened up in the future.

3.5 Biodegradability of nanocarriers

The property of biodegradability is attributed to many nanocarriers and often positively emphasized in the literature. For a better understanding of what is hidden behind this term, which is often vaguely defined and very widely used, some explanations and definitions are given in the following chapter.

The term “biodegradation” describes the process in which a material undergoes “a deleterious change in the chemical structure, physical properties, or appearance” (Williams, 1999 cited in Yang et al. 2021, p. 178). There are several OECD definitions for biodegradability, but the term is often used very generally in literature without a precise definition and there is some confusion among the public about the exact meaning. It is often equated with “compostable” and “bio-based”. One key weakness of use of the term “biodegradable” in literature is that it does not contain any information on the location, timescale and extent of the decomposition process (Yang et al., 2021) and the standard test method used to determine it.

In relation to nanocarriers, biodegradability can mean something different depending on the area of application, because the degradation of a carrier material in medical applications takes place within the human body under different conditions than, for example, in the environment in

agricultural applications. In general, various processes can cause materials to degrade, not least due to their organic or inorganic nature. The degradation of polymers of the polyester and polyanhydride types, for example, is interpreted as “hydrolytic bond cleavage to form water-soluble degradation products that can dissolve in an aqueous environment, resulting in polymer erosion. In this context, the term "degradation" refers to the bond cleavage reaction, whereas "erosion" refers to the depletion of material. Degradation is a chemical phenomenon ; erosion encompasses physical phenomena, such as dissolution and diffusion.” (Tamada & Langer, 1993, p. 552). In contrast, the meaning of degradation in ceramics is interpreted as “decomposition into smaller particles or dissolution into ionic components” (Hench, 2015 cited in Yang et al., 2021, p.178). For biodegradable metals, degradation is a chemical reaction process, i.e. corrosion in a physiologic environment (Yang et al., 2021). Clay minerals, such as layered double hydroxides (LDH) also undergo degradation under environmental conditions. Atmospheric CO_2 and moisture can slowly break down LDH into their ionic constituents such as Mg^{2+}, $Al(OH)_3$, NO_3^-, etc. due to the formation of carbonic acid from CO_2 in water (Mitter et al., 2017).

For example, in one of its publications, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) summarises the **six forms of biodegradation distinguished by the OECD in their testing guidelines for biodegradability** (OECD, 1981b, 1991, 1992a, 1992b, 2001, 2002, 2004a, 2008):

1. “Ultimate biodegradation (mineralisation): The level of degradation achieved when the test compound is totally utilised by micro-organisms resulting in the production of carbon dioxide, water, mineral salts, and new microbial cellular constituents (biomass).
2. Primary biodegradation (biotransformation): The alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance.
3. Readily biodegradable: An arbitrary classification of chemicals which have passed certain specified screening tests for ultimate biodegradability; these tests are so stringent that it is assumed that such compounds will rapidly and completely biodegrade in aquatic environments under aerobic conditions.
4. Inherent biodegradable: A classification of chemicals for which there is unequivocal evidence of biodegradation (primary or ultimate) in any test of biodegradability.
5. Half-life ($t_{½}$): The time taken for 50% transformation of a test substance when the transformation can be described by first-order kinetics; it is independent of the initial concentration.
6. Disappearance time 50 (DT_{50}): The time within which the initial concentration of the test substance is reduced by 50 percent.”

(ECETOC 2013, p. 26)

In particular, the research and development of biodegradable polymeric materials for biomedical applications, such as temporary implants, three-dimensional scaffolds for tissue engineering and delivery systems for controlled and sustained drug release, is progressing rapidly (Song et al., 2018). A variety of natural and synthetic polymers, that can undergo hydrolytic or enzymatic degradation are being explored for biomedical applications. According to Song et al. 2018 “the ideal biodegradable biomaterial should have non-toxic degradation products and be easily metabolized and cleared from the body” (Song et al. 2018, p. 3118). However, no single polymer system can be considered the ideal material for all medical applications equally. Therefore, the current focus is on the development of customized biomaterials for specific medical applications (Song et al., 2018). There are large number of scientific publications and reviews on the use of biodegradable materials as nanocarriers in

medicine is available, but most of them do not provide any detailed information on the methods used to test degradability. For example, it is often not disclosed how long the degradation process takes and which metabolites, or transformation products are produced. In some studies, it is reported that the degradation of a polymer might take a long time. For example, poly(ε-caprolactone) (PCL) is considered a biodegradable polyester, and it is used in the development of biomedical applications. This material can be degraded by microorganisms, but also undergoes hydrolytic and enzymatic degradation. However, PCL shows a slow degradation rate of 2-4 years (Song et al., 2018). The degradation profiles of polymers may also depend on their modifications. The side groups of polyphosphazenes, a new class of inorganic-organic hybrid polymers, can be modified to achieve degradation profiles ranging from a few hours to even years (Song et al., 2018), but this always depends on the prevailing environmental conditions during the test period.

3.5.1 Biodegradation in the human body

In terms of biomaterials for medical purpose, biodegradation refers to the biological processes in the body that cause the gradual breakdown of the material. All biomaterials must be evaluated for biocompatibility, mechanical properties, and biodegradation to determine their suitability for specific medical applications. Biomaterials can be degraded in the body by at least three general mechanisms: oxidation, hydrolysis, and enzymatic mechanisms (Tamariz & Rios-Ramírez, 2013).

In the preclinical phase, a new drug's pharmacokinetic properties are tested in addition to its efficacy. This includes drug absorption, distribution, metabolism, and excretion (ADME). Chemical modifications in the human body include hydroxylation, reduction, and hydrolysis, among others (Issa et al., 2017). These reactions are mediated by proteins that are differentially expressed in different organs. Drug metabolism is defined by Issa et al. (2017) as "the metabolic process in which the chemical structure (parent compound) of a drug is converted into metabolites to facilitate elimination from the body. The principal sites of drug metabolism are the gut and liver due to high levels of metabolic enzymes in these tissues." (Issa et al. 2017, p. 1) Metabolic biotransformation of drugs is a key determinant of elimination and toxicity in humans (Issa et al., 2017).

Drug delivery systems may have a different therapeutic performance than drugs where the active ingredient is in simple solution form. Using an intravenous liposomal medicinal product as an example, the European Medicines Agency (EMA) published a reflection paper to facilitate the approval of such medicinal products and to improve the generation of the relevant quality, non-clinical and clinical data required (European Medicines Agency, 2013). The EMA emphasizes that the principles outlined may also be considered applicable to other novel types of "liposome-like" and vesicular products that may be in development, including those intended to be administered by routes other than intravenous administration. According to the EMA, the specific characteristics of liposomal formulations may have a significant impact on the in vivo pharmacokinetic and pharmacodynamic properties of the active ingredient. The encapsulated cargo may not be biologically available and may be protected from degradation.

4 Conclusion

This report provides an overview of the field of nanocarriers. The literature shows that nanocarrier technology is growing whereby many material combinations (organic, inorganic or hybrid systems), and tailored functionalities are possible. This enables a broad field of applications with high market potential. In terms of the materials used for the design of nanocarriers, a wide range of elements and chemical compounds has been identified. The greatest structural diversity was found in carriers made of organic materials. In addition to synthetic nanocarriers made of inorganic or organic substances, organic materials of natural origin, and even cellular or viral structures are being investigated and in some cases are already being used to create innovative carrier systems for active ingredients. Here, even living, and non-living cellular structures are used as nanocarriers.

This review shows that nanocarriers are developed for and are applied to multiple application areas, such as medicine, pharmacy, cosmetics, food industry (e.g., as food supplements), but nanocarriers can also be used for household products and in electrochemistry. For some applications, the use of nanocarriers could only be identified by using indirect search terms (avoiding the terms “nano” and “carrier”), or by drawing conclusions from the functions and structure of devices or processes (e.g., in the case of batteries). Therefore, despite its broad screening approach, this report represents only a first attempt to cover the whole field of nanocarriers, which can be complemented by future studies. This investigation showed that the application context is not always decisive for the type of nanocarrier envisaged or already in use, as a variety of nanocarrier types play a role in more than one area of application.

An analysis of the state of development proved to be difficult, as the number and variety of different carrier types is too large to draw generalized conclusions about the current innovation stage. Moreover, such estimates lack detailed information about the nanocarrier system and intended purpose from publicly available sources or technical descriptions of patents. Nevertheless, half of the identified nanocarriers – 132 different types in total (status June 2023) – can be assigned to a state of development of 7-9 (usage, availability and close to market penetration), which can be explained by the comparatively long history of this technology, e.g., in agriculture or medicine. The other half of the found nanocarrier types are assigned to state of development of 4-6 (application only on a laboratory scale). Lipid- as well as polymer-based nanocarriers dominate the “mature” types. Some of these carriers have already been used for several years or even decades, in particular medical applications such as vaccines. For most other materials, only a few types of nanocarriers could be identified that are already in use or are close to market penetration.

The present study shows that many different types of nanocarriers are currently being researched, and we therefore expect a strongly growing number of nanocarriers to be used in the coming years, based on new concepts in terms of their structural, and material properties. Further forward-looking studies are needed to predict the development of such new conceptions, especially for those which may pose a risk to the environment and human health. In particular, the influence of the nanocarrier system on the efficacy of an active ingredient and its distribution and mobility in the environment must be further researched. A well-founded risk assessment would also have to take into account possible residual risks from the degradation products of the nanocarriers.

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6 Appendix

Table A 1: Retrieved author keywords from publications that were obtained by the three different searches as described in Chapter 2. These author keywords were already consolidated and reviewed for possible nanocarrier systems (see Figure 3 A and B resp.).

1) author keywords retrieved by search strings in context to application	2) author keywords retrieved by indirect search terms	3) author keywords retrieved by the search term "nanocarrier" (2000-2022)
Activated carbon	Adeno-associated virus	5-fluorouracil
Alginate	Albumin Microparticles	Albumin Nanoparticles
Amino zinc NPS	Biosilica nanoparticle	Alginate
Antibody-drug conjugate	Block copolymer	AMD3100
Apoferritin	Carboxymethyl chitosan	Amyloid beta
Arabinogalactan	Carboxymethyl starch	Anti-PEG IgM
Bacteria nanocarrier	Carrageenan	Apoferritin
Bagasse xylan	Chitin	Ascorbic acid
Bilosome	Chitosan hydrogel	Ascorbyl palmitate
Black phosphorus quantum dots	Covalent organic framework	Beta-cyclodextrin
BMSC nano-drug	CuS nanoparticle	Bilosomes
Bovine serum albumin	Diatoms	Black phosphorus
C-60 based-NPS	DNA hydrogel	Block copolymers
Carbon dots	DNA nanotubes	Boron nitride
Carbon nanotube	DNA origami	BSA
Cell-based delivery systems	DNA prism	Calcitonin
Cell-based drug delivery	Double emulsion	Carboxymethyl cellulose
Cellulose nanocrystals	Drug-conjugated hydrogel	Carboxymethyl chitosan
Cellulose nanofibers	Eudragit S100	Casein
Chitosan nanoparticles	FeSe nanoparticles	Ceramide
Chitosan-alginate nanoparticles	Gellan gum	Chitosan nanoparticles
Chitosan-coating	Gelatin-methyacrylate (GelMA)	Chitosan oligosaccharide
Compound carriers	Gliadin	Cholesterol
Copper oxide nanoparticles	Glyceryl monooleate	Chondroitin sulfate
Cubosomes	Glycyrrhizic acid	Clathrin

1) author keywords retrieved by search strings in context to application	2) author keywords retrieved by indirect search terms	3) author keywords retrieved by the search term "nanocarrier" (2000-2022)
Cucumis melo	Gold nanorods	Clay
CuO-NPS	G-quadruplex	Cobalt ferrite
Cyclodextrin	Guar gum	Cubosomes
Dendrimers	Human serum albumin	Cyclodextrin nanosponge
Electrospun fibers	Hyaluronic acid	Cyclosporine A
Emulsomes	IgG fusion proteins	DFT
Exosome	Immuno-niosomes	Docosahexaenoic acid
Extracellular vesicles	Inulin	DOX
Farnesol nanoparticles	Laponite	Ethosomes
Fluorescent silica nanoparticles	Lipid nanoparticles (LNPS)	Eudragit S100
Fullerene	Lipid-drug conjugates	Exosomes
Functionalized magnetic nanoparticles	Lipoplex	Fe_3O_4
GaMOF	Lyotropic liquid crystal	Ferritin
Gold nanocages	Magnetic niosomes	Fucoidan
Gold nanoparticles	Magnetite	Fullerene
Graphene	MCM-41	Gadolinium
Graphene oxide	MgAl-LDH	Gallic acid
Graphene quantum dot	Microbubble	Genipin
Halloysite nanotube (HNT)	Microemulsion	Glycol chitosan
Hexagonal boron nitride nanoparticles	Microgel	Glycyrrhetinic acid
Hollow magnetic nano-spheres	Microporous scaffolds	Gold nanocages
Hollow mesoporous silica nanoparticles	Micro-silica	Gold nanorod
Hydroxyapatite	Milk exosomes	GO-PEG
Hyper-branched polyglycerol	Montmorillonite	G-quadruplex
Iron oxide nanoparticles	MXene	Halloysite nanotubes
Lactoferrin nanoparticles	N-acetylcysteine	Human serum albumin
Lipid-based nanoparticles	Nanocrystal	Hyaluronan
Liposome	Nanoerythrosomes	Hyaluronic acid
Magnetic nanoparticles	Nanoporphyrin	Hydroxyapatite

1) author keywords retrieved by search strings in context to application	2) author keywords retrieved by indirect search terms	3) author keywords retrieved by the search term "nanocarrier" (2000-2022)
Mesoporous silica nanoparticles	Ni1-xCoxFe2O4 NPs	Hyperbranched polymer
Metal-based nanoparticles	Organogel	Ketoprofen
Metal-organic frameworks	Oxidized pullulan	Laccase
Micelles	Pd nanoparticles	Lactoferrin
Microneedles	PDMS	Layered double hydroxide (LDH)
Microspheres	PEG-liposomes	Lecithin
Modified chitosan	PEG-PLA copolymer	Lutein
MOF	PLGA copolymers	Magnetite
Molybdenum disulfides	pNIPAAm	Magnetite nanoparticles
Multi-drug carriers	Poloxamer	Metal-organic frameworks
Multi-walled carbon nanotubes	Poly(methyl methacrylate)	Minoxidil
Nano air-containing liposomes	Poly(vinyl alcohol)	Molybdenum disulfide
Nano-black carbon	Polyacrylamide	Montmorillonite
Nano-bubbles	Polyion complex micelles	mPEG
Nano-clays	Polyketal	mPEG-PLA
Nano-diamond	Polylactic acid	Nanoceria
Nanoemulsion	Polylactide	Nanodiamonds
Nanofluid drug delivery	SBA-15	Nanoerythrosome
Nanogel	Self-assembly	Nanoliposome
Nanogold	Silk cocoons	Nanosponge
Nanohydrogel	Silk fibroin	Niosomes
Nanohydroxyapatite	Silymarin	PAMAM dendrimers
Nano-lipoidal carriers	SLNs	Pectin
Nano-liposome	SNEDDS	Pegylated liposomes
Nano-microplexes	Sodium carboxymethyl cellulose	Periodic mesoporous organosilica
Nanoparticle-in-microparticle system	Spanlastic	PET
Nanosponge	Tannic acid	Phosphorylcholine
Nanostructured lipid carrier	Vaterite	Phytosomes
Nano-transfersomes	Vesosomes	PLA

1) author keywords retrieved by search strings in context to application	2) author keywords retrieved by indirect search terms	3) author keywords retrieved by the search term "nanocarrier" (2000-2022)
Nanovesicles	Virosome	PLGA nanoparticles
Nano-zeolite	Virus-like particles	PLGA-PEG
Nano-Zn particles		Pluronic
New liposome nanoparticles		Pluronic F127
Niosome		PNIPAM
Non-viral gene delivery		Poloxamer
Nuclear targeted peptide (CB5005N)		Poly(amidoamine) dendrimer
Outer membrane vesicles		Poly(epsilon-caprolactone)
PAMAM		Poly(lactic-co-glycolic acid)
PAMAM dendrimer		Poly(N-isopropylacrylamide)
pH-degradable nanogel		Polyamidoamine
Phospholipon		Polyarginine
pH-responsive drug delivery system		Polycaprolactone
Phytosomes		Polydopamine
Pillar[6]arene		Polyethylene glycol
Plant derived extracellular vesicles		Polyethylenimine
PLGA nanoparticles		Polyion complex micelle
PLGA-PEG		Polylactide
Polymer composites		Polymersome
Polymeric micelles		Polyphenols
Polymeric nanocarriers		Polyurethane
Polymeric nanoparticle		Polyvinylpyrrolidone
Polysaccharide nanoparticles		Protein nanocages
Polysaccharides		Protein nanocarrier
Polyurethane		Pullulan
Prussian blue nanoparticles		PVA
Pullulan		Quercetin
Quantum dots		RGD peptide
Selenium		Sepiolite
Selenium nanoparticle		Sialic acid

1) author keywords retrieved by search strings in context to application	2) author keywords retrieved by indirect search terms	3) author keywords retrieved by the search term "nanocarrier" (2000-2022)
Self-assembled PHA granules		Silk fibroin
Silica nanoparticles		SLNs
Silica shell		SNEDDS
Silicon		Sodium alginate
Silicon dioxide nanoparticles		Spanlastics
Silicon-nanoparticles		SPIONs
Silver nanoparticles		Spiropyran
Single-walled carbon nanotube (SWCNT)		Star polymer
Sodium alginate		Starch
Sporopollenin		Starch nanoparticles
Starch ester nanoformulations		Stearylamine
Supramolecular co-nanoassemblies		Superparamagnetic iron oxide nanoparticles
TA-Cu metal-phenolic network		Thermosensitive liposomes
TiO_2 nanoparticles		TPGS
Titanium dioxide		Transferrin
Tocosomes		Triblock copolymer
Transfersomes		Trimethyl chitosan
Vinyl polymers		Triphenylphosphonium
WSSV		Zein
ZIF-67 MOF materials		
ZIF-8		
Zinc nanoparticles		
Zinc oxide nanoparticles		

Table A 2: Identified nanocarrier systems, examples of active ingredients, and their (potential) application areas[3].

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Activated carbon (AC)	2,4-dichlorophenoxyacetic acid sodium	x			x	
Aerogel (polymer)	Paracetamol, ibuprofen, vitamin E, vitamin K3	x		x	x	
Aerogel (silica)	Dithranol				x	
Antibody-drug conjugate	Doxorubicin				x	
Aquasome	Etoposide; insulin, hemoglobin, antigens				x	
Asymmetric oxygen carrier system (AOCS)	Oxygen transport by perfluoro-carbons (PFCs)		x			
Bacteria (living)	Interleukin-2				x	
Bacteria (non-living)	dsRNA	x				
Bacteria ghost (BG)	Doxorubicin				x	
Bacterial minicell	dsRNA	x			x	
Bigel	Ketoprofen	x		x	x	
Bilosome	Calcitonin, cyclosporin A, insulin				x	
Carbon dot (CD)	Doxorubicin				x	
Carbon nanofibre (CNF)	Copper	x				
Carbon nanotube (CNT)	Docetaxel, doxorubicin, methotrexate, paclitaxel, gemcitabine, anti-inflammatory	x			x	

[3] Table A 2 shows only an excerpt from the database of identified nanocarriers. The complete database can be downloaded under https://bokubox.boku.ac.at/#0fef35095cf8ba48b05281f4f8808f45

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
	drugs, osteogenic dexamethasone (DEX) steroids, siRNAs					
Ceramic nanoparticle	Doxorubicin				x	
Clay minerals/ silicate	Amphetamine, naproxen, vitamin B2, dsRNA	x		x	x	Electro-chemistry
Colloido-some	Lipophilic bioactive ingredients such as nutrients, nutraceuticals, vitamins	x	x	x	x	
Copper nanoparticle (CuNP)	Curcumin, doxorubicin				x	
Covalent organic framework (COF)	Ibuprofen, doxorubicin				x	
Cross-linked gel	β-Carotene	x	x	x	x	
Cubosome	Phytantriol, curcumin		x	x	x	
Cyclo-dextrine (CD)	Essential oils, fragrances, flavors, drugs (e.g., prostaglandin E2, piroxicam), catechin		x	x	x	Household products (air and textile fresheners), textiles, food packaging
Dendrimere	Indomethacin, resveratrol, ramipril				x	Veterinary medicine
DNA nano-structure	siRNA, doxorubicin				x	
DNA origami nano-structure	Doxorubicin				x	
Double emulsion	Lipophilic bioactive ingredients, e.g., vitamins	x	x	x	x	
Ectosome	RNA				x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Elastin-like polypeptide nanoparticle (ELP-nano-particle)	Doxorubicin, plasmid-DNA				x	
Elespher® (botanical micro-spheres)	Docosahexaenoic acid (DHA)		x			
Emulgel	Diclofenac				x	
Emulsome	Methotrexate				x	
Erythrocyte	Gluthathione, dexamethasone 21-phosphate, antigens, nucleic acids, peptides, enzymes				x	
Ethosome	Cholesterol	x	x		x	
Exosome	siRNA; anti-inflammatory proteins				x	
Extracellular vesicle (EV)	siRNA, curcumin, antigenes				x	
Filled microgel	Nutrients, nutraceuticals, vitamins			x		
Fullerene/ buckyball	Polyvinyl-pyrrolidone		x		x	
Glycosphere	Retinol		x		x	
Gold nanocage	Erlotinib and doxorubicin		x		x	
Gold nanoparticle (AuNP)	Doxorubicin, DNA, proteins, vaccines				x	Veterinary medicine
Gold/meso-porous silica nanorod	Doxorubicin				x	
graphene oxide (GO) nanosheet	nucleic acids, peptides; antigens				x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Graphene quantum dot	Doxorubicin				x	
Hexosome	Curcumin			x	x	
Hyperbranched polymer (HBP)	Doxorubicin				x	
Immune cell	Paclitaxel				x	
Isasome	Amino acids, peptides, proteins, nucleic acids		x	x	x	
Janus particle	Berberin				x	
Janus-micro- and nanomotor	Heparin				x	
Light-sensitive polymeric nanocarrier	Doxorubicin				x	
Lipid conjugate	5-fluorouracil, heparin, aceclofenac, diclofenac, diminazine diaceturate, curcumin, rifampicin, acyclovir, decitabine, doxorubicin				x	
Lipid nanoparticle (LNP)	Cas9 mRNA and sgRNA				x	
Lipid-based hydrogel	Curcumin	x	x		x	
Lipofecta-mine	Nucleic acids	x			x	
Lipoplex	siRNA				x	
Liposome	Daunorubicin, amphotericin, doxorubicin		x	x	x	Food pack-aging, veteri-nary medicine
Liposome (Yeast cell-based)	Vitamin C		x			

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Magnetic nanoparticle	Doxorubicin, siRNA				x	
Marinosome	Curcumin		x		x	
Mesoporous silica nanoparticle (MSN)	Avermectin, validamycin, DNA, doxorubicin, campothecin, proteins, enzymes, peptides	x			x	Veterinary medicine
Metal organic network (MOF)	Ibuprofen, caffeine				x	
Metal sulfide nanoparticle	Doxorubicin				x	
Micelle (polymer)	Oestrogen, paclitaxel, docetaxel, pesticides	x	x		x	Veterinary medicine
Micelle (surfactant)	Curcumin		x	x	x	
Microemulsion	Propiconazole (fungicide) Banner MAXX, Syngenta	x	x	x	x	
Microvesicle	Enzymes, tumor vaccines				x	
Mixed micelle (MM)	Rhodamine 123 (Rho123), DiR; β-galactosidase (β-Gal); doxorubicin, silybin	x	x	x	x	
Multi-lamellar vesicle (MLV)	Ropivacaine		x	x	x	
Multi-layer/core-shell microcapsule	Vanillin			x	x	
Multilayered emulsion	Omega-3 fatty acids			x	x	
Multi-walled delivery system (MDS)	Peptides, sunscreens		x		x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Nanobubble (NB)	Gas filled units			x	x	
Nanocapsule	Hinokitiol	x	x	x	x	
Nano-conjugate	Pectin-cisplatin	x		x	x	
Nano-diamond	Doxorubicin hydrochloride, proteins (antigens, antibodies, immuno-globulin)				x	
Nano-emulsion	Citral	x	x	x	x	Food pack-aging
Nanofiber (polymeric)	Ibuprofen, paclitaxel, siRNA				x	
Nanoflower	Proteins, enzymes				x	
Nanofluid (nano-suspension)	Doxorubicin, cephalosporin				x	
Nanogel	Hyaluronic acid		x	x	x	
Nanographene flake	(*R*)-ispinesib				x	
Nanoporphyrin	Doxorubicin				x	
Nanoshell (hybrid)	Doxorubicin, paclitaxel, siRNA, DNA				x	
Nanosome	Honokiol, synthetic carbohydrates, peptides/glycol-peptides, engineered enzymes, small anticancer reagents		x		x	
Nanosphere (polymeric) (NS)	Progesterone, doxorubicin, theophylline, salicylic acid, vitamin C		x		x	
Nanosponge (polymeric)	Azelaic acid		x	x	x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Nanostructured lipid carrier	*Passiflora edulis* seeds oil		x	x	x	Food pack-aging, veteri-nary medicine
Nanotope (lipid-based)	Vitamin E		x			
Nanowire (metallic)	DNA (gene therapy)				x	
Niosome	Cisplatin		x	x	x	
Organogel	Diltiazem hydrochloride, curcumin, carotene		x		x	
Palladium nanoparticle (PdNP)	Doxorubicin				x	
Periodic mesoporous organosilica (PMO)	Doxorubicin				x	
Pharmacosome	Any drug having activated hydrogen (-OH, -NH2, -COOH etc.)				x	
Photosome	Photoreactiva-ting light-activated enzyme (photolyase) extracted from *Anacystis nidulans*		x		x	
Phytosome	Quercetin, rutin			x	x	
Pickering emulsion	β-Carotene		x	x	x	Food pack-aging
Pollen and spore shell	Omega3 fatty acids, fish oil, phenols, colourants			x	x	
Polycation	dsRNA	x			x	
Polyion complex micelle	siRNA				x	
Polymer-drug conjugate	Paclitaxel				x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Polymer-some	Paclitaxel, doxorubicin		x		x	Veterinary medicine
Polyplex (polymeric)	DNA (gene therapy), cisplatin				x	
Proniosome	Ibuprofen, captopril, furesamide, levonorgestrel, peptides				x	
Protein nanocage	Fluorescein, RGD 4C peptide, anti-CD4 antibody, doxorubicin	x			x	
Quantum dot	Paclitaxel, doxorubicin				x	
Selenium nanoparticle	Doxorubicin, ciprofloxacin				x	
Silicene nanosheet (SNS)	Paclitaxel				x	
Silicone vesicle and matrice	Aluminum zirconium tetrachloro-hydrex GLY		x			
Silver nanoparticle (AgNP)	Doxorubicin (med), auxins (plant hormones, agriculture)	x			x	Veterinary medicine
Solid lipid nanoparticle (SLN)	Drugs, *Eugenia caryophyllata* essential oil, mRNA	x	x	x	x	Food pack-aging, veteri-nary medicine
Spanlastic nanovesicle	ketoconazole, fluconazole, clotrimazole				x	
Spiropyran	Doxorubicin, ibuprofen				x	
Spongosome	Curcumin, fish oil; *Rucea javanica* oil				x	
Stealth liposome	Doxorubicin				x	
Stem cell	Taxane				x	

Generic term for carriers	Active ingredient (examples)	Agri-culture	Cos-metics	Food/ food supple-ments	Medicine/ pharmacy	Others
Superpara-magnetic iron oxide nanoparticle (SPION)	Paclitaxel, methotrexate, mitoxantrone, doxorubicin; iron itself				x	Veterinary medicine
Supramolecular hydrogel	Dexmethason				x	
Supramolecular metallogel	Doxorubicin				x	
Supra-particles (SP)	Camptothecin				x	
Temperature-sensitive polymeric carrier	Doxorubicin, docetaxel, prednisone acetate				x	
Thermo-responsive polymeric carrier	Doxorubicin				x	
Titanium dioxide nanoparticle (TiO_2 NP)	Gambogic acid, cisplatin, valproic acid, doxorubicin, temozolomide, daunorubicin				x	
Transfer-some	itraconazole		x		x	
Ultrasome	UV endonuclease enzyme		x		x	
Unisphere (polymeric)	Surfactants		x			
Vesosome	Doxorubicin				x	
Virosome	Proteins originating from the virus				x	
Virus-like particle	Nucleic acids (gene therapy), pesticides, doxorubicin				x	Veterinary medicine
Yeast cell	Limonene			x		
Zinc oxide nanoparticle (ZnO NP)	Daunorubicin				x	