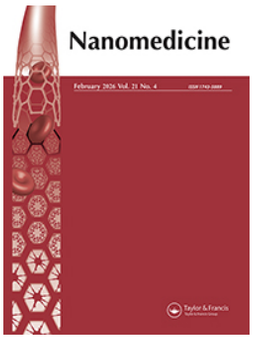
Designing drug delivery systems: the impact of structural order and disorder for optimized therapeutic outcomes



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REVIEW

Designing drug delivery systems: the impact of structural order and disorder for optimized therapeutic outcomes

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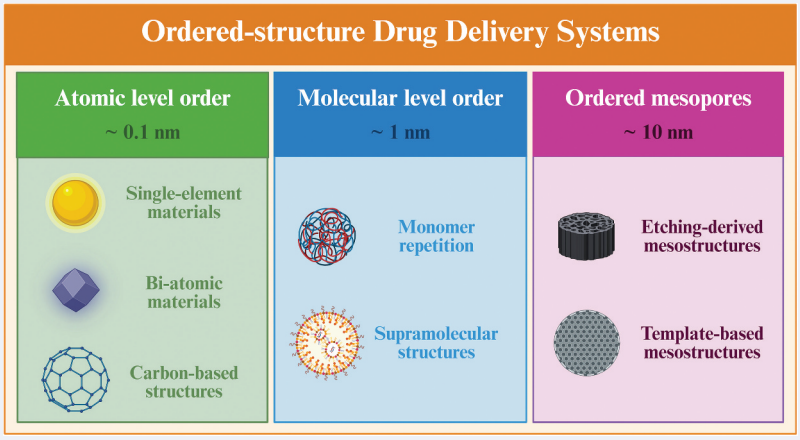
ABSTRACT

The implementation of drug delivery systems in nanomedicine aims to improve the efficacy, safety and stability of therapeutic substances within the body, while controlling their rate and time of release. While numerous reviews over the years have thoroughly summarized the most recent advances and applications of drug delivery systems, to the best of our knowledge none has ever approached the topic by focusing on the impact of their structural order on both drug loading and the resulting therapeutic outcome. In this review, we aim to highlight the importance of considering the intrinsic properties of the carriers in terms of atomic, molecular and supramolecular order. Indeed, each level of order enables specific interactions between the carrier and cargo, leading to unique properties of the resulting nanosystems. Depending on the final application, the choice of a specific drug delivery system can therefore significantly influence the therapeutic effects. Thus, our work aims to facilitate the design of drug delivery systems by elucidating which level of intrinsic material order is most appropriate for a given clinical challenge. The literature search included PubMed and Scopus covering the period from January 2000 to July 2025.



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Nanoparticles; drug delivery system; ordered systems; porous nanoparticles; cancer therapy

1. Introduction

In the context of nanomedicine, Drug Delivery Systems (DDS) are nanometric carriers capable of transporting diverse therapeutic compounds by exploiting various strategies and employing many different materials, including lipids, polymers, and inorganic materials [1]. DDS have been extensively studied for their capability to enhance the pharmacological properties of conventional drugs. This is achieved through various mechanisms, including: modifying their pharmacokinetics and biodistribution, improving solubility of poorly soluble free drugs, protecting drugs from rapid degradation in vivo, and enhancing targeting delivery [2].

However, despite initial excitement in the early 2000s, progress in terms of clinical translation has slowed. Over the years, many reviews have documented the limited clinical approval of novel nanomedicines, including DDS, by major regulatory bodies (Food and Drug Administration – FDA or European Medicines Agency – EMA). A recurring conclusion from these analyses highlights the market dominance of lipid-based nanomedicines over complex systems that populate preclinical studies [1,3,4]. This dominance is largely due to the high effectiveness of these lipid-based products, which has consequently led research and many reviews to focus on type of DDS, specific drugs, or pathology addressed, rather than focusing on the material composition and structure.

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Article highlights

- Structural order is fundamental to the final properties of Drug Delivery Systems.
- Materials ordered at the atomic level are more suitable for dual therapies and nanotheranostics.
- Materials ordered at the molecular level are extremely versatile and modular.
- Ordered porous materials present excellent drug loading capabilities but lower versatility than molecular level ordered materials.
- The intended application determines the most suitable level of order required by the Drug Delivery System

Therefore, exploring a novel perspective could allow for a deviation from conventional classifications and promote new considerations that may lead to alternative, more effective solutions.

This review provides a panoramic overview of recent advancements in preclinical nanomedicine-based DDS. The literature review was initiated with a search across the Scopus and PubMed databases, targeting size categories of drug delivery nanosystems combined with keywords such as "crystalline" or "ordered." Given that the concept of "order" is infrequently categorized explicitly, requiring thorough article analysis, a two-stage selection process was implemented: (i) in-depth content analysis of retrieved articles was performed to confirm relevance and the degree of ordering discussed, and (ii) citation tracking was used to identify additional relevant works cited by the selected papers. We specifically examine the crucial relationship between carriers' drug-hosting capability and their intrinsic material order, defined here as the property of being composed of repeated, ordered units. From the fundamental atomic level to complex mesoporous structures, we will explore how this order impacts material properties, paving the way for synergistic therapies and enabling broad-range therapeutic drug delivery. We believe this novel classification will provide enhanced insight into how hierarchical structural arrangement can directly or indirectly impact the properties and functionality of nanocarriers. This approach is particularly crucial in a landscape where increasingly complex new materials are blurring traditional definitions.

2. Atomic-level order

At the most fundamental scale, the repetition of building blocks in a system aimed at drug delivery can be found at the atomic and molecular level. Indeed, atoms, when bonded one another may form nanoparticles that can be used as potent platforms to deliver drugs. In this case, the order is not a feature that directly affects the ability of the particle to carry a small molecule or a generic drug: it rather represents the reason why the specific molecule possesses peculiar properties and becomes of interest in the biomedical field.

In this direction, inorganic nanoparticles (NPs) (i.e., metal, metal-oxide, semi-conductor nanomaterials not based on carbon) have proved to be powerful tools for precision drug delivery and theranostics. Depending on their chemistry, they can possess intrinsic therapeutic properties, such as magnetic responsiveness [5–7], optical activity [8,9], ROS generation [10–13], ion dissolution effects [14], and radiosensitizing properties [15]. These crystalline structures can offer therapeutic benefits either on their own or when combined with external or internal stimuli [7,16]. Beyond their inherent qualities, the surface chemistry of inorganic NPs allows for further functionalization and drug adsorption [17]. While initially recognized as stand-alone drug delivery systems, recent advancements highlight the role of inorganic NPs in achieving synergistic effects when combined with other materials. For example, hybrid NP drug delivery systems often leverage the photothermal activity of metal nanoparticles to enhance drug delivery [18]. Still, drug absorption in these systems may be relatively poor. The mechanistic basis for this phenomenon is the limited interatomic space. Due to the tight packing of the atoms, the drug cannot be effectively encapsulated within the nanoparticle; consequently, drug absorption is restricted to the nanoparticle's surface. Therefore, amorphous polymeric coating on crystalline core NPs typically facilitates drug loading and release, while preventing major drawbacks such as aggregation [17,19].

At the atomic level, carbon-based materials can also offer significant potential in drug delivery due to the hybridization of their bonds, leading to structural versatility and potential for chemical functionalization. These properties allow the formation of structures possessing internal cavities suitable for drug loading.

While the intrinsic atomic order of these materials does not directly affect their cargo-loading capability, it provides chemical and physical properties that make them suitable for efficient drug delivery (Figure 1).

2.1. Metal and metal oxide NPs

Most of the metal NPs (MNPs) currently studied for biomedical applications are based on Au, Ag, or Cu; other less commonly adopted metals include palladium, titanium and zinc. As metal-based nanomaterials, they share common features such as easy synthesis and functionalization [20], photothermal properties [10] and NPs dissolution under predetermined condition [21], which in the case of Ag, for example, imparts antibacterial properties [22,23]. For drug delivery purposes, MNPs can be functionalized directly with active biomolecules or with specific linkers [24,25], such as acid-sensitive linkers [26]. Another interesting example is represented by cobalt-modified silver NPs functionalized with Cisplatin (CoAg@Cis), where Ag NPs are used to stabilize Co NPs, which provide magnetic properties, but suffer from poor stability. This combination of metals and anti-tumoral drug proved to be effective to reduce cell viability in vitro tumor models [27]. Covalent binding of active compounds is not the only way to load drugs on MNPs. For example, Ag NPs have been used as DDS to enhance paclitaxel (PTX) cytotoxic activity against cancer cell line models [28]. AgNPs-PTX demonstrated superior and selective anticancer activity on lung cancer models in vitro, limiting the toxicity in healthy models, while also providing antimicrobial activity. In a recent study published

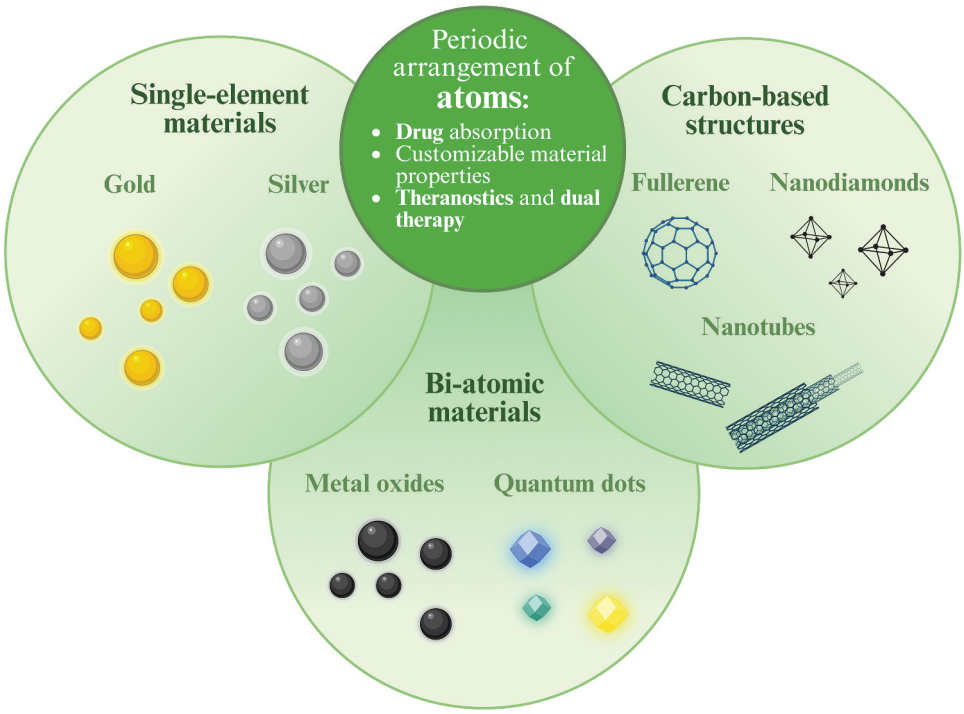

Figure 1. Summary of materials featuring a periodic arrangement of single atoms. Created with Biorender. https://BioRender.com/ovz6xe5.

by Jakhmola et al., a one-pot green reaction allowed the authors to obtain Au NPs decorated on the surface with Doxorubicin (DOX) and Curcumin through the complexation with Au^{3+} ions during the synthesis [29]. This interesting approach not only allows for a greener synthesis, without the use of toxic chemicals and heating, but also enables the loading of two active compounds whose release can be triggered upon ultrasound stimulation, a noninvasive and nondestructive treatment.

Besides MNPs, metal-oxide NPs (MONPs) have gained considerable success in recent years as powerful tools in biomedicine due to their inherent physicochemical properties. MONPs based on Fe [30], Mn [31], Gd [32] prove useful in both diagnostics and theranostics by leveraging their superparamagnetic properties in magnetic resonance imaging (MRI). Iron oxide NPs (IONPs) are extensively studied in the field of nanomedicine. Main applications include iron deficiency treatments, MRI contrast agents, and local hyperthermia [3,33,34]. IONPs and their application in drug delivery have also been explored, often in combination with coating materials such as polyvinyl alcohol, human serum albumin and polyethylene glycol that improve stability and drug loading [35–37]. However, another interesting application of IONPs magnetic properties is in the successful loading of metal-based therapeutics such as Cisplatin. Kuznetsova et al. [38] adopted a combination of polyethylene glycol (PEG)-stabilized Fe_3O_4 NPs and ionic liquid to efficiently load Cisplatin onto the NPs. After loading, NPs can be separated magnetically for purification and further analysis, while in human serum, protein corona formation hinders the drug leakage, allowing for cytosolic release of the therapeutic drug. Inorganic metal oxide and semiconductor NPs may possess unique properties that enable multimodal therapies, possibly in combination with drug loading and release. Cerium oxide, for example, has been studied for its ability to change oxidation state; this property can be exploited in biomedicine to mimic redox enzymes, contributing to the homeostasis of free radicals [39,40]. In 2018, Yao et al. successfully developed cerium-based upconverting NPs that simultaneously allow photodynamic therapy triggered by near infrared (NIR)-light and overcome hypoxia in cancer cells [41]. Cerium oxide is able to autocatalytically convert H_2O_2 into H_2O and O_2, thereby enhancing the photodynamic effect. This hollow NPs have loaded with DOX to deliver chemotherapeutic in combination with NIR-light stimulation inside cells. Another example of crystalline inorganic NPs serving as powerful tools in nanomedicine are Zinc Oxide (ZnO) NPs. This semiconductor nanomaterial possesses unique properties such as strong catalytic activity [42,43], UV-absorption [44], antibacterial activity [45], anticancer activity [46–48], and reactive oxygen species (ROS) generating ability highlighted in other reviews [49–51]. Its chemical surface also makes it a favorable candidate for drug adsorption, making it a good candidate for drug delivery [52,53]. It has been demonstrated through Density Functional Theory (DFT) calculations that the coordination of OH- groups in quercetin with ZnO NPs' surface allows for simple drug loading and selective release upon acidic conditions [54].

2.2. Quantum dots

Beyond metal oxide NPs, Quantum Dots (QDs) represent another class of semiconductor nanocrystals with nanometric dimensions (typically between 1 and 10 nm), based on many different materials. Their exceptional luminescence, coupled with peculiar optical and electrical properties, makes them

particularly suitable as luminescent probes in various biomedical applications and, more recently, in drug delivery systems [55,56]. These zero-dimensional NPs have a greater surface-to-volume ratio compared to conventional NPs with diameter larger than 10 nm. Therefore, they have been employed for drug loading via chemical and physical adsorption, including hydrophobic interactions and π-π stacking (non-covalent interactions) [57–61]. For example, Su et al. developed red emissive carbon QDs with amino modification, which successfully loaded DOX by π-π stacking. The presence of nitrogen functional groups enabled the QDs to penetrate cell nuclei for optimal drug delivery [60]. In another work, authors achieved methotrexate loading onto manganese and nitrogen-doped carbon QDs. While Mn-doping allows the QDs to be used as an MRI contrast agent, methotrexate is an anticancer drug with competitive binding to folate receptors that can also be used as a targeting agent for cancer cells [59]. In another example, Ag_2S QDs were utilized to create a smart DDS for chemo-photodynamic therapy [61]. In this work, the Ag_2S served as a photosensitizer, triggered by NIR light, while forming a host-guest interaction with pillar [6]arene (CP6) molecules and self-assembling into ordered 100 nm structures. The QD surfaces were modified with alkyl chains, enabling both hydrophobic interaction with DOX and supramolecular chemistry with CP6 molecules. The system was able to produce strong ROS generation upon irradiation with NIR light and smart release in acidic environment.

2.3. Carbon based nanostructures

Among the emerging nanomaterials in the field of drug delivery, carbon-based nanostructures (CBNs) are undoubtedly significant [62,63]. Known for their ordered and crystalline architectures, where carbon atoms are arranged in a specific and repeated pattern [64], CBNs are characterized by massive surface-to-volume ratio, endowing them with superior capability to incorporate drugs of various nature. A large variety of CBNs are presented in scientific literature as possible drug carriers, but while the possible strategies of drug incorporation may vary depending on the structure, all CBNs require functionalization strategies to decrease their intrinsic cytotoxicity [65] and improve colloidal stability in biological solution [64].

2.3.1. Fullerenes

The first class of CBNs considered for drug delivery application are fullerenes. Fullerene has been extensively studied across various research fields over the past years [66]. However, it has only recently gained attention as a drug carrier, due to recent advancements in its synthesis and functionalization strategies that allows it to overcome its natural insolubility in water-based solution [67]. Its structure, consisting of sp^2 carbons forming a highly symmetrical cage with different sizes (C60, C76, etc [68]), can be exploited for cargo transport in biological environment. The cargo of fullerenes can be divided into two main groups: drugs and bioactive molecules, or nucleic acids and genetic material. PTX and DOX [69,70] are among the most extensively studied drug molecules in the development of new drug delivery strategies. These drugs were encapsulated in functionalized fullerenes using with two principal strategies: covalent [71–73], or non-covalent [74] bonding. For instance, the surface of C60 can be oxidized with concentrated nitric acid to introduce carboxylic groups, enabling non-covalent conjugation with DOX via π-π stacking and hydrophilic interactions [75–77]. Beyond these, other drugs have been explored as potential cargo for functionalized fullerenes. Examples include chloroquine [78] for COVID-19 treatment, hydroxyurea [79] for anticancer therapy, ibuprofen [80], carbamazepine and phenytoin [81] for antiepileptic treatment. More naïve drugs have also been investigated, such as the plant alkaloid Piperlongumine as a potential drug delivery system for the treatment of highly metastatic lung cancer [82], or folk medicine alkaloid berberine [83] as an anticancer drug.

Fullerenes are also widely proposed as gene therapy agents, serving as carriers for various forms of genetic material, such as plasmid DNA [84,85], small interfering RNA [86–88], micro RNA [89–91], and oligonucleotides [92–94]. Cationic fullerenes are particularly important for controlled gene delivery due to their low immunogenicity, affordability, and high efficacy. Cationic groups facilitate electrostatic interactions with negatively charged nucleic acids, enabling complexation and cellular uptake [92,95].

Even though many strategies have been investigated to overcome biocompatibility issues while preserving its intrinsic properties and ensuring effective loading of cargos, including hydrophilic ones, further research is still needed to achieve improved stability, reproducibility, and long-term toxicity profiles [92,95,96]. New frontiers of fullerene research for drug delivery are moving toward more complex, and multifunctional delivery system, where fullerene is targeted and biodegradable over time [97–100].

2.3.2. Carbon nanotubes

In the field of ordered carbon structures for drug delivery, carbon nanotube must be mentioned. Two types of carbon nanotubes can be distinguished: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). Both types are structured as graphene sheets rolled into hollow cylindrical nanotube structures. The walls are composed of carbon atoms arranged in hexagonal patterns, while the curved, tubular ends incorporate carbon pentagons [100]. Their ordered carbon structure presents the same limitation described above, i.e., poor solubility [101,102] and biocompatibility [103–105]; thus, functionalization strategies need to be adopted [106–109]. The most common ones rely on covalent or non-covalent bonding with functional groups. Covalent bonding of the CNT surfaces can increase hydrophilicity and solubility in aqueous media, while also extending circulation time in plasma and increasing the number of reactive sites for further conjugation with therapeutic molecules or targeting ligands. The most common strategy for covalently functionalizing CNT surface consists in oxidizing CNT walls with strong acid. Noncovalent bonding relies on Van der Waals forces, π–π stacking, hydrophobic

interactions, or electrostatic binding between the CNT surface and different molecules, ensuring minimal damage to the original CNT structure and its electronic properties [96].

The cargo, whose nature can also in this case range from common chemotherapeutic drugs to active molecules, genetic material, and even more complex compounds, can be either be absorbed on the CNT surface [110–112], or be located inside the hollow structure [113–115]. In both cases drug release occurs in response to a specific stimulus, making CNTs stimulus-responsive structures that enable temporal and spatial controlled drug release. pH sensitive delivery is one of the most studied drug delivery mediated by CNT [116–120]. Other common release triggers include temperature-triggered [121,122], or redox-responsive [123–125] or near-infrared-responsive [126–129] mechanisms. Less common examples include enzyme-responsive [130–132] and multiple-responsive [133–135] drug delivery CNT-based systems. Therefore, CNTs have emerged as highly promising platforms for advanced drug delivery. Their exceptional physicochemical properties, coupled with remarkable drug loading capacities and versatile functionalization capabilities, position them at the forefront of innovation. Significant progress has been achieved in surface engineering, enabling enhanced biocompatibility, precise targeted delivery, and sophisticated stimuli-responsive drug release mechanisms [136].

A special subgroup of SWCNTs is represented by carbon nano-horns, which deserve to be mentioned as a platform for drug delivery. Nano-horns possess a horn-shaped nanostructure constructed from sp^2 carbon sheets [137], essentially a single-layered graphene sheet structure wrapped in a conical shape [138]. Their tight cage construction and elongated structure make them a high-aspect-ratio fullerene subclass, allowing for a good comparison with single-walled carbon nanotubes [139]. Their conical structure makes them more biocompatible, and they are under scientific investigation to replace SWCNTs [140]. This opens possible new frontiers for this niche material in the drug delivery research area [141].

2.3.3. Carbon nanodiamonds

Research literature on carbon-based ordered structures for drug delivery also comprehends less common and more specialized materials, such as carbon nano diamonds.

Nanodiamonds (NDs) are a relatively recent subject of study in the drug release research field. NDs typically exhibit a faceted truncated octahedral structure made of carbon atoms, characterized by electrostatic fields on their facet surfaces. In biomedical applications, two primary types of nanodiamonds are distinguished based on their synthesis methods: detonation nanodiamonds (DNDs) and high-pressure high-temperature nanodiamonds (HPHT NDs) [142]. They are suitable for biomedical application, and specifically for drug release purposes, due to their strong structural integrity and functionality in biological environment [142–144]; their excellent chemical inertness and stability, which shields encapsulated or adsorbed drugs from degradation by external factors; their small size and high surface area, which provide a substantial capacity for drug adsorption and loading; and their intrinsic biocompatibility [142]. This last aspect can be related to their different C-atom hybridizations, i.e., sp^3 [145]. NDs are proposed as drug delivery platforms for different nanomedicine areas, ranging from anticancer therapy [146–148] and gene delivery [92] to bone-targeted drug delivery [149,150], and even HIV treatment [151,152]. Their large applicability is related to the ease of bonding drug molecules to NDs both chemically and physically, augmenting their delivery abilities [153]. They are emerging as a promising candidate for multimodal bioimaging due to their optical and spectroscopic properties, which are related to their defects and

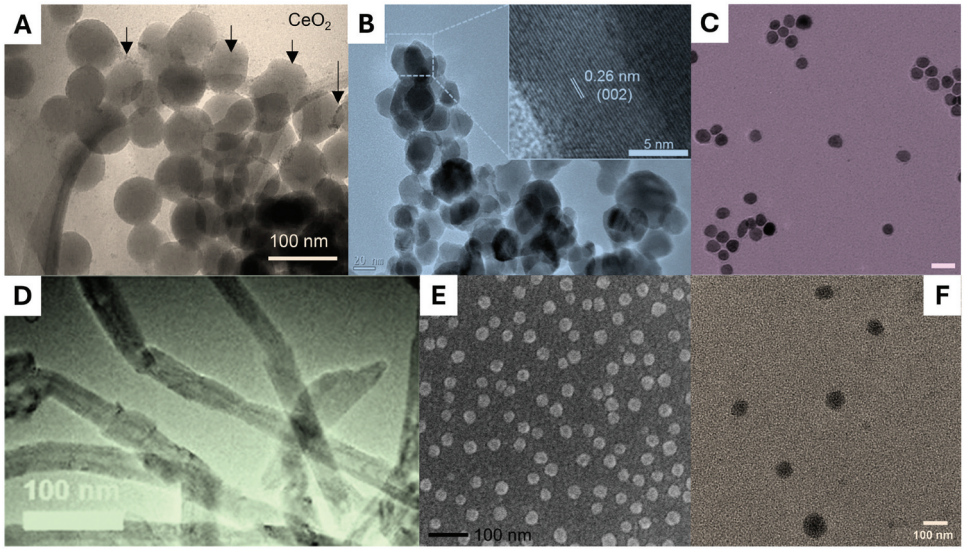

Figure 2. Examples of atomic-ordered nanostructures analyzed through electron microscopy characterization. The images are reproduced with permission, showing: (A) cerium oxide [39], (B) zinc oxide [54], (C) iron oxide [36], (D) carbon nanotubes [129], (E) carbon nanodiamonds [149], (F) silicon quantum dots [58].

admixtures in the crystal lattice [154], making them innovative platforms for theranostic applications [155–158], i.e., combining drug release and imaging.

2.4. Core findings

The above-mentioned carbon nanostructures, MNPs, MONPs, and QDs share an ordered structure at the atomic level as the main feature (Figure 2).

This crystalline structure of inorganic nanomaterials provides them with intrinsic therapeutic and diagnostic properties crucial for biomedical applications. While their lattice does not offer internal drug loading space, except for hollow structures, their high surface-to-volume ratio and versatile surface chemistry are paramount, enabling diverse drug loading strategies and functionalization for enhanced and synergistic drug delivery systems (Table 1). Indeed, current research efforts are focusing on hybrid theranostic systems. In these systems, an inorganic crystalline core is retained to provide therapeutic properties, while an amorphous coating is frequently employed to enhance the overall drug loading capacity.

3. Molecular-level ordered drug delivery systems

Beyond atomic-level order, this section highlights the significance of molecular-level order in the design of drug delivery systems. In particular, the section addresses drug delivery systems characterized by a highly ordered internal structure that arises from the repetition of molecular-scale building blocks. The molecular periodicity can range from the covalent concatenation of monomers into polymeric chains to the supramolecular self-assembly of amphiphilic macromolecules, such as fatty acids (Figure 3). Organic molecules represent the main class of ordered systems for drug delivery capable of self-assembling into drug-loading structures; they are generally characterized by high versatility and structural customizability.

3.1. Polymers

Polymers are macromolecules formed by repeating monomer units connected by covalent bonds along the main chain [159]. Their structure can be highly variable, resulting in linear, branched, or cross-linked geometries depending on various factors, such as the nature of the monomers or the type of polymerization [160]. The utility of polymers as drug delivery systems lies in their capacity to entrap drug molecules among their branches. The polymer chains' order and crystallinity are key determinants of drug loading. Specifically, ordered branches facilitate a more controlled drug loading profile due to regular inter-chain spaces, though they characteristically offer less volume for drug storage than amorphous polymers. Additionally, the tight and ordered packing of these polymers effectively retards the drug release, thus enabling enhanced control over the release kinetics [161,162].

Among the various types of polymers, there are also copolymers, which represent a class of macromolecules formed by two or more different monomers inserted within the same polymer chain [163]. Depending on the order of the monomers, they can be classified as block copolymers, formed by blocks of monomers covalently connected to each other, alternating copolymers, in which the monomers alternate within the polymer chain, or random copolymers, where there is no specific order in which the monomers are alternated [164]. These structural differences give polymers different physical and chemical characteristics that can be modulated during the material synthesis phase to obtain a polymer with specific characteristics for its intended use.

In the field of controlled drug delivery, research began in the 1980s and is currently one of the most active branches of biomedical research. Polymers allow for improved pharmacokinetics and longer circulation times compared to free drugs, improving targeting to the tissues of interest [165].

A variety of polymers are used for drug delivery. A first subdivision concerns the interaction between the drug and the polymer. Specifically, polymer-based DDS can be divided into polymer-drug conjugates (PDCs) and nanoparticles [166]. The main difference concerns the interaction between the drug and the carrier: in PDCs, there is a stable covalent bond between the polymeric structure and the drug, overcoming the problem of burst release; for this reason, the drug must have free functional groups that can be conjugated to the polymeric structure [167]. In the case of nanoparticle systems, however, the drug is encapsulated or adsorbed within the structure, maintaining the two components as distinct entities.

Another possible subdivision concerns their origin, which can be natural or synthetic. Natural polymers include chitosan, alginate, hyaluronic acid, gelatin, cellulose, and dextran. The most commonly used synthetic polymers include polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), their copolymer polylactic-coglycolic acid (PLGA), and PEG [166].

Drug loading and release are dependent on several factors depending on the intrinsic characteristics of the polymer. Ordaz et al. demonstrated that polymer thickness and molecular weight, for example, influence diffusion in polymer film systems from the nanometer scale up to larger [168]. Chen et al. also showed how free volume, or the empty space between polymer chains, positively influences drug diffusion [169]. Increasing the free volume increases the space within the structure, thus allowing greater diffusion of the drug into the surrounding environment. Another characteristic that influences diffusivity is the polymer's glass transition temperature (Tg). Specifically, above the Tg, increasing chain mobility facilitates drug diffusion, increasing its release. Conversely, at lower temperatures, diffusion is limited [170]. Molecular weight can also be related to drug release kinetics. In particular, Jeong et al. showed how, in semicrystalline polymers such as PCL, increasing molecular weight is directly related to a decrease in the structure's crystallinity with a relative increase in amorphous structure, thus creating a coarser microstructure that increases drug diffusion [171].

3.1.1. Synthetic polymers

Synthetic polymers have gained increasing success over the years due to the possibility of structural engineering and modulation of their chemical and physical properties.

Table 1. Overview of nanocarrier-drug conjugates and loading strategies for inorganic NPs and carbon-based nanostructures.

Carrier	Drug	Drug loading method	Application	Ref
Nanoparticles				
Niosomes (NIOs) containing spherical gold nanoparticles (AuNPs)	Paclitaxel (PTX)	PTX thin-film hydration method and co-incorporation of AuNPs	*In vitro* drug delivery in breast cancer cells (MCF-7) combined with photothermal therapy	[18]
Transactivator of transcription (TAT) peptide-modified gold nanoparticle platform (TAT-Au NP)	Doxorubicin and Gd^{3+}	Covalent drug conjugation via hydrazone chemistry	*In vivo* drug and contrast agents delivery in mice bearing intracranial glioma xenografts (U87, U251, GBM43, GL261)	[26]
Bimetallic nanocomposites CoAg (magnetic cobalt core with an AgNPs shell)	Cisplatin	Drug loading by incubation in aqueous medium	*In vitro* drug delivery in breast cancer cells (MCF-7) and colorectal cancer cells (HCT)	[27]
Silver nanoparticles (AgNPs)	Paclitaxel	Drug loading via adsorption with sonication-assisted mixing	*In vitro* drug delivery in breast cancer cells (MCF-7), lung carcinoma cells (A549) and brain glioma cells (C6)	[28]
Human serum albumin (HSA) coated iron oxide nanoparticle (HINP)	Doxorubicin	Drug adsorption in organic solvent	*In vitro* drug delivery and *in vivo* efficacy study in a breast cancer xenograft model (4T1)	[36]
CeO_2/monodispersed spherical silica (Sil) and CeO_2/halloysite (Hal) nanotube	Curcumin and Cisplatin	Drug loading by solvent evaporation (Curcumin) and via aqueous adsorption (Cisplatin)	*In vitro* drug delivery in breast cancer cells (MCF-7)	[39]
Cerium oxide nanoparticles (CNP)	Chloroquine (CQ)	Simple mixing of drug and NPs in aqueous media	*In vitro* drug delivery in breast cancer cells and in spheroids (MDA-MB-231 and MDA-MB-468)	[40]
Zinc oxide nanocrystals (ZnO NCs)	Sorafenib and Vismodegib	Sequential drug adsorption from organic solvent	*In vitro* drug delivery to pancreatic cancer cells (BXPC-3)	[52]
ZnO nanoparticles	Quercetin	Drug loading via adsorption from solution	*In vitro* drug delivery in breast cancer cells (MCF-7)	[54]
ZnO quantum dots (QDs)	Doxorubicin	Drug loading via adsorption from solution	*In vitro* drug delivery in breast cancer cells (MCF-7)	[57]
Silicon quantum dots (SiQDs) functionalized with inorganic silica mesoporous nanoparticles (MNs)	Doxorubicin	Drug loading via aqueous adsorption from solution	*In vitro* drug delivery in colon cancer cells (HT-29 and HCT116)	[58]
Manganese nitrogen dual-doped carbon quantum dots (Mn-, N-CQD)	Methotrexate	Drug adsorption from a mixed solvent system	*In vitro* drug delivery in breast cancer cells (MCF-7)	[59]
Carbon nanotubes				
C60 fullerene	Doxorubicin	Drug loading via non-covalent adsorption assisted by sonication	*In vivo* drug delivery in tumors and metastasis of Lewis lung carcinoma in mice (LLC)	[69]
Fullerene-paclitaxel conjugate	Paclitaxel	Covalent drug conjugation via carbodiimide chemistry	*In vitro* drug delivery in human epithelial lung carcinoma A549 cells	[73]
C60 fullerene	Piperlongumine	Drug loading via hydrophobic adsorption	*In vitro* drug delivery in Lewis lung carcinoma cells (LLC) and *in vivo* efficacy study in tumors and metastases	[82]
C60 fullerene	Berberine (Ber)	Drug loading via non-covalent complexation	*In vitro* drug delivery in T lymphoblast cells (CCRF-CEM)	[83]
Fullerene-based nanocomplex	siRNA	Self-assembly via electrostatic interactions	*In vitro* drug delivery in B16F10 mouse melanoma cells and *in vivo* pulmonary delivery	[87]
Tetra[4-(amino)piperidin-1-yl]-C_{60} (TAPC)	Heavy chain ferritin (HFn)	Non-covalent self-assembly of TAPC with HFn, followed by a sequential, hierarchical self-assembly of additional HFn	*In vitro* drug delivery in glioblastoma and hepatocellular carcinoma cells (U87MG and HepG2), *in vivo* drug delivery in orthotopic glioma mouse model and metastasis mouse model	[97]
Methacrylic acid (MAAc) functionalized multi-walled carbon nanotubes (MWCNTs-MAAc)	Resveratrol	Drug loading via adsorption from solution	*In vivo* drug delivery in rats with radiation-induced enteropathy	[114]
MnO_2-coated hexachlorocyclotriphosphazene-curcumin-bis (4-hydroxyphenyl)-disulfide (HCCP-CUR-HPS)-functionalized magnetic multiwalled carbon nanotubes (M-MWNTs)	Paclitaxel (PTX) and Curcumin (CUR)	Sonication-assisted co-adsorption (CUR) and adsorption from organic solvent (PTX)	*In vitro* drug delivery in cervical cancer cells (HeLa)	[120]

(*Continued*)

Table 1. (Continued).

Carrier	Drug	Drug loading method	Application	Ref
Hyaluronic acid-modified single-walled carbon nanotubes (SWCNTs-HA)	Doxorubicin (DOX) and Gd^{3+} ions	Covalent drug conjugation via oxime chemistry (DOX) and metal ion complexation (Gd^{3+})	*In vitro* drug release in breast cancer cells/MCF-7 and *in vivo* efficacy study in combination with photothermal therapy in mice bearing subcutaneous sarcoma tumors (S180)	[124]
Injectable near-infrared (NIR) photothermal responsive drug-loaded multiwalled carbon nanotubes (DMWCNTs)	Paclitaxel (PTX) and vascular endothelial growth factor (VEGF)	Drug co-loading via adsorption	*In vitro* drug delivery in nerve stem cells(NSCs) and *in vivo* efficacy tests involving rats with hemisectioned spinal cord injury	[129]
Amphiphilic chitosan derivative-coated single-wall carbon nanotubes (CNT) encapsulated in a thermo/pH sensitive nanogel (CS/PNIPAAm@CNT)	Doxorubicin (DOX)	Adsorption from organic solvent (DMSO) with base-assisted conversion of Doxorubicin.	*In vitro* drug delivery in combination with near-infrared irradiation in cervical cancer cells (HeLa)	[134]
pH sensitive poly(ethylene glycol) – doxorubicin (PEG – DOX) on single-wall carbon nanotubes (SWNTs)	Doxorubicin (DOX)	Covalent drug conjugation via hydrazone bond formation	*In vitro* drug delivery in combination with near-infrared irradiation in cervical cancer cells (HeLa)	[135]
Nanodiamonds				
Nanodiamonds (NDs)	Usnic Acid (UA), 5-Fluorouracil (5-FU) and Curcumin (CUR)	Covalent drug conjugation via carbodiimide coupling chemistry	*In vitro* drug delivery in breast cancer cells (MCF-7) and liver cancer cells (Hep-G2)	[147]
Nanodiamonds (NDs)	Alendronate (Alen)	Sequential covalent conjugation via carbodiimide chemistry	*In vitro* drug delivery in MC3T3-E1 osteoblast-like cells and *in vivo* accumulation in bone tissues of nude mice	[149]
Nanodiamonds (NDs)	Mitoxantrone	Drug loading via adsorption in basic aqueous solution.	*In vitro* drug delivery in triple negative breast cancer cells (MDA-MB-231)	[153]
PEGylated nanodiamonds (NDs)	Doxorubicin (DOX) and folate (FA)	Covalent drug conjugation via hydrazone linkage	*In vitro* drug delivery in cervical cancer cells (HeLa) breast cancer cells (MCF-7), liver cancer cells (HepG2), Chinese hamster ovary cells (CHO), in vivo efficacy and toxicity studies in mice bearing HepG2 tumors	[155]

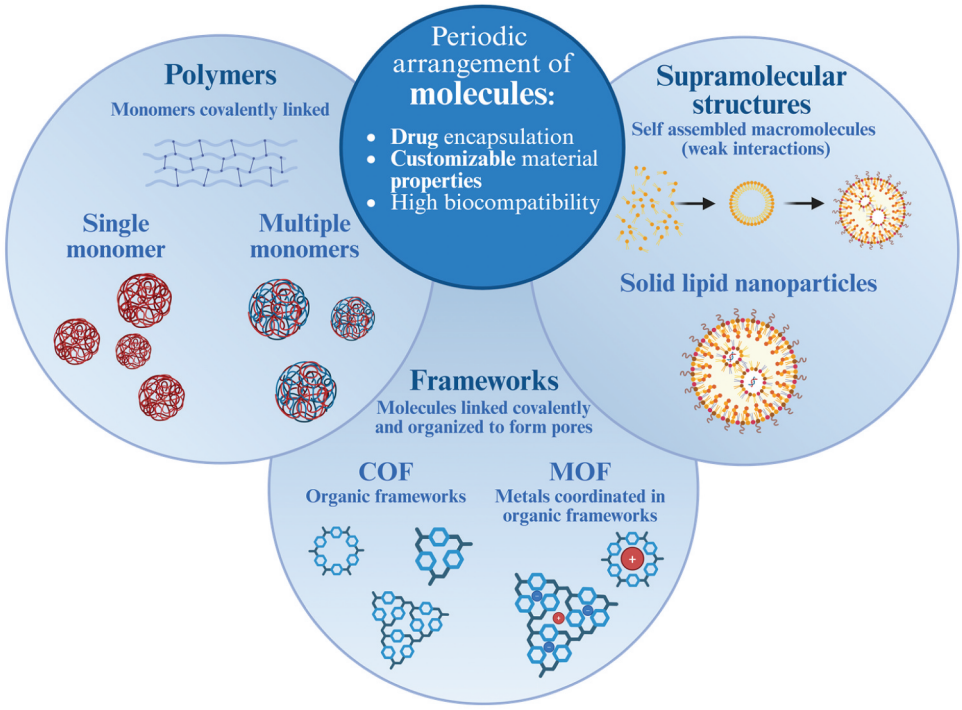

Figure 3. Summary of the most exploited materials that present periodic arrangement of molecules, covalently or weakly bound. Created with Biorender. https://BioRender.com/ibpmnrj.

One of the key characteristics for the development of an effective polymer delivery system is related to its in vivo degradation. One technique for making these polymers degradable involves inserting linkages into the polymer chain that are sensitive to hydrolysis or enzymatic cleavage, such as ester bonds [172].

A study conducted by Li et al. on (PLGA), demonstrated a correlation between the rate of hydrolysis and drug administration using rhodamine-B as a model [173]. PLGA, a polymer formed by the monomers L-lactic acid (LA) and glycolic acid (GA), has a monomer ratio that inversely influences the crystallinity of the structure [161]. Furthermore, they demonstrated that ordered PLGA exhibits a slower degradation profile than random copolymers, thus releasing the molecule more gradually. The researchers suggest that the mechanical reason lies in the faster hydrolysis observed with an increased amorphous fraction. This is due to higher water penetration within the pores of the amorphous structure, which is more readily accessible than the tightly packed, ordered crystalline systems. Mechanically, amorphous systems exhibit bulk polymer erosion, meaning degradation takes place throughout the entire nanoparticle (surface and interior). In contrast, the low water permeability in ordered systems causes the degradation to be limited to the surface, which leads to a slower overall release.

Another technique used to achieve controlled degradation and release involves the insertion of redox-sensitive groups, such as thiol or disulfide groups [174,175]. Zhou et al. developed a nanoparticle system consisting of a block copolymer of PEG and PLA containing disulfide bonds (PEG-SS-PLA), used to load PTX. Once internalized by cells, the nanoparticles responded to the high concentration of glutathione present in the intracellular environment, leading to the breaking of the disulfide bonds and subsequent targeted release of the drug into the target cells [176].

PEG, mentioned previously, is one of the synthetic polymers most widely used in drug delivery systems due to its high biocompatibility, water solubility, and electrical neutrality. All of these properties give PEG a “stealth” effect, allowing it to remain in circulation for longer periods, reducing the immunogenicity of the system and thus improving the pharmacokinetics of the drugs associated with it [177].

The molecular architecture of PEG influences the efficiency of drug loading and release. Specifically, the molecular weight of PEG is directly proportional to the density of the hydrophilic layer that forms around the polymer framework. Therefore, the longer the chain, the greater the external barrier. This stabilizes the system, delaying drug release. At the same time, however, it can reduce loading due to increased steric hindrance [178].

In addition to PLGA and PEG, PCL has also received increasing attention for controlled-release applications, due to its stability and slow degradation.

A widely used polymer is PCL, a semicrystalline polymer with ester linkages within its structure that can be hydrolyzed under physiological conditions, making it a promising candidate for in vivo drug delivery [167]. Its slow degradation, producing nontoxic species [179,180], also allows for sustained release over time.

One of the main limitations of PCL is its marked hydrophobicity, which limits its effectiveness with water-soluble molecules. To overcome this limitation, an interesting property of polymers can be exploited: the ability to copolymerize them, thus synthesizing a polymer with intermediate characteristics derived from the constituent copolymers. An example is the study conducted by Sadeghi, in which PLGA-PCL nanospheres sensitive to acidic pH were developed for the release of curcumin (Cur). This phenomenon

can be explained by the protonation of the side chains, which leads to the collapse of the branches and the simultaneous opening of the nanosphere cavities, thus increasing the release of the drug contained within them. Tests conducted on A549 lung cancer cells have demonstrated a good ability to induce apoptosis, superior to that of free Cur [181].

Beyond its use in nanoparticle systems, PCL can also be conjugated with drugs via cleavable linkers, allowing for release at the pathological site. Zhai et al., for example, developed micelles of an mPEG-PCL with an acetal (Ace) bond, used to bind PTX, which is sensitive to acidic pH. In vitro studies showed that the drug-loaded micelles were pH-sensitive, resulting in greater release as the pH decreased. They have also demonstrated greater therapeutic efficacy on breast cancer cells (MCF-7) compared to the free drug [182].

Active targeting is crucial in the development of a drug delivery system. For example, Peng et al. formulated nanocrystalline PCL-PEG worm-like micelles conjugated with Herceptin to specifically target HER2-positive breast cancer cells. These micelles were loaded with PTX, demonstrating effective specificity against HER2-overexpressing tumor cells, reducing tumor size and prolonging survival in a SKBR-3 tumor xenograft model in nude mice [183].

3.1.2. Natural polymers

While research on synthetic polymers remains active, it is increasingly complemented by the use of natural polymers, which offer higher biocompatibility and biodegradability. These materials are particularly attractive for cancer drug delivery due to their favorable permeability, therapeutic potential, and low immunogenicity. They are considered safe and highly adaptable within biological systems. However, the use of natural polymers as drug carriers is challenging because of their broad molecular weight distribution and batch-to-batch variability [184].

Among natural polymers, chitosan is a linear polyamine containing many free amine groups that can interact with negatively charged drugs or encapsulating agents. Chitosan is a semi-crystalline polymer whose physical and chemical properties are influenced by its molecular weight, degree of deacetylation and crystallinity. Swelling, porosity and absorption are influenced by the alignment of the polymer molecular chains and by the method used to synthesize chitosan from chitin [185]. In the anticancer field, drugs are mostly loaded into chitosan nanoparticles by two main techniques: nanoencapsulation, where the drug is entrapped within the polymer matrix during nanoparticle formation [186–188], and surface conjugation, where the drug binds to the outer surface driven by ionic or hydrogen bonding [189]. Furthermore, chitosan is frequently used in combination with other functional polymers to enhance aqueous solubility, biocompatibility, and drug release behavior [190].

These loading methods influence drug localization, release kinetics, and therapeutic efficacy, making chitosan a widely used carrier in targeted cancer drug delivery systems [191]. Chitosan has been explored in combination with sodium alginate, through the development of hydrogel beads prepared by double crosslinking leading to the formation of beads with an inner porous structure [192–194]. Other natural polymers such as alginate [195,196] and gelatin [197,198] have been used in nanoformulation for drug delivery, but very few passively targeted nanocarriers have been accepted for clinical use.

3.2. Molecular frameworks

A molecular framework is a crystalline porous network constructed from repeating molecular building blocks, which collectively form well-defined cavities and channels capable of hosting drug molecules. The pore dimensions are typically of the same order of magnitude as the drug molecules themselves, facilitating the highly controlled inclusion and entrapment of the drug within the framework's pores.

3.2.1. Covalent organic frameworks

A specific subclass of polymers is represented by covalent organic framework.

Covalent organic frameworks (COFs) are microcrystalline porous organic polymeric materials first described by Cote et al. in 2005 [199]. They are composed of strong covalent bonds between different light elements such as carbon (C), nitrogen (N), hydrogen (H), oxygen (O), boron (B), silicon (Si), and sulfur (S) [200], which cross-link into ordered two- or three-dimensional networks [201].

Their modular architecture enables the formation of structures with customizable and well-defined porosities in terms of size and geometry. Due to their ordered structure, large surface area, chemical and thermal stability, defined porosity and the absence of metallic components, these materials can be used in different fields such as photocatalysis [202–204], electrocatalysis [205–207], energy storage [208–210] and in the biomedical field [211,212].

Despite the excellent potential mentioned above, COFs present some limitations in the biological field. Among these is their poor hydrophilicity due particularly to the organic and aromatic nature of the components, thus leading to a limited use in the biological field where the interaction with biological fluids is crucial [213]. A second obstacle concerns the reversibility of the imine bonds (C = N) common in COFs due to their ease of synthesis. This leads to limited stability to hydrolysis, thereby restricting the use of COFs as drug carriers in biological fluids [214]. A novel approach to overcome these obstacles, by improving hydrolytic stability and hydrophilicity, involves the modification of imine bonds into more stable bonds such as secondary amines [215].

Drug treatment of tumors faces several challenges, some of which are low dispersibility in aqueous solutions, low stability, and unregulated drug release. To overcome these limitations, COFs have been used as advanced drug delivery systems due to their crystalline nature, which enables uniform pore sizes and geometries, thereby ensuring uniform loading and well-controlled drug release [216]. The ability to create pores with customized geometries and sizes, along with their large surface area, make COFs excellent drug carriers, enabling the loading of larger amounts of drugs compared to other nanomaterials such as liposomes or polymeric nanoparticles [217].

The group led by Fang et al. in 2015 was among the first to exploit this technology for drug release [218]. They developed a COF for the loading and release of ibuprofen demonstrating not only a good adsorption and prolonged drug release over time but also that the release is dependent on the size and geometry of the framework pores. Indeed, they demonstrated an inverse relationship: while larger pores facilitate greater drug encapsulation, smaller pores correspond to a slower release rate. This latter characteristic represents a significant advantage for applications requiring highly controlled release kinetics. Furthermore, a study conducted by Kaliya et al., demonstrated that COFs can achieve greater loading of drugs, such as gemcitabine, within their structure compared to standard carriers like polymeric or lipid nanoparticles [219].

Another important aspect in drug loading into COFs concerns host-guest interactions. Consistent with the above, Luo et al. demonstrated that covalent triazine frameworks (CTFs), a subclass of COFs consisting of 1,3,5-triazine aromatic rings with planar π-conjugation properties, when based on porphyrins and loaded with drugs, achieved 70% drug release in the first 6 hours, with the remaining drug released more gradually over the following hours [220]. This can be explained by the fact that in the first phase, the drug is released via a concentration gradient or by physical adsorption of the drug into the pores. In the second phase, however, strong host-guest interactions, including hydrogen bonds and π-π stacking interactions, allow the framework to release the drug with slower kinetics.

Several modifications have been made to COFs to obtain a controlled and targeted release of the drug in the tumor target, among these is the development of COFs sensitive to pH variations by exploiting the fact that the tumor microenvironment is generally more acidic than that of healthy cells. Asadi et al. synthesized azine-linked COF (Az-COF), post-synthetically reduced amine-linked COF (Az-AL-COF) and asulfonated version (Az-AL-SO3H-COF) and evaluated their characteristics as drug delivery systems for DOX. The results show that there is a greater release of DOX at acidic pH compared to neutral pH. In particular, a more marked difference is observed with sulfonated COF, probably because the semi-ionic structure of Az-Al-SO3H-COF facilitates the diffusion of DOX and H+ ions, favoring enhanced release of the drug at acidic pH. In addition, sulfonated COF loaded with DOX showed selective cytotoxicity toward tumor cells [214].

To achieve an even more targeted drug release in the tumor environment, double-sensitivity COFs have been developed. For example, the group of Anbazhagan et al. synthesized a COF loaded with DOX sensitive to acidic pH values and to high levels of glutathione (GSH), as GSH is overexpressed in the tumor environment. The results showed that the drug release reached a value of 70% under acidic pH conditions, 80% at high GSH levels and only 20% in a physiological environment, thus showing a high sensitivity of the designed COF [221].

Another technique involves combining photodynamic therapy (PDT) with the release of chemotherapeutic drugs to enhance the therapeutic effect on cancer. In particular, the group of Ge et al. synthesized a hypoxia-sensitive COF due to azo bonds present within the framework in which the photosensitizer chlorin e6 (Ce6) and the hypoxia-activated drug tirapazamine (TPZ) were immobilized. Upon irradiation with near-infrared light, Ce6 was activated by consuming oxygen, inducing severe hypoxia, leading to COF degradation and, at the same time, the release and activation of the drug TPZ, thus leading to tumor cell death in a hypoxic environment [222].

In recent years, an increasing number of research groups are integrating specific ligands into COFs to achieve active and precise targeting to specific membrane receptors, thus improving the spatial distribution of the therapeutic agent [223–225]. The group led by Benyettou in 2024 developed a nano-sized COF (nCOF) conjugated with the RGD peptide to specifically bind to αvβ3 integrins overexpressed in triple negative breast cancer (TNBC) sensitive to acidic pH conditions additionally loaded with DOX. The results show that treatment with nCOF modified with the RGD peptide offers greater efficacy and specificity of treatment compared to unmodified nCOF and free DOX [216].

3.2.2. Metal organic frameworks

A further step forward in the field of ordered porous materials exploited as drug delivery systems is represented by metal-organic frameworks (MOFs), a class of hybrid crystalline materials composed of coordinated metallic ions and multitopic organic linkers. Their ordered structure allows for fine and precise control on their porosity (ranging from micro to mesoporosity), on the surface area, often exceeding 5000 m^2/g, and on the internal chemistry of the framework. These structural characteristics make MOFs particularly suitable for the encapsulation and controlled release of bioactive molecules, such as conventional drugs, peptides, proteins, and nucleic acids [226–228]. Examples of MOFs exploited as effective DDSs include the MIL100(Fe) and UiO66 structures, whose ordered crystalline structure characterized by large pores and interconnected channels, enables hosting therapeutic molecules of different sizes and natures. This design helps avoid aggregation phenomena or localized accumulation, which may hinder the drug controlled release and therapeutic efficacy [229,230]. MOFs' high intrinsic porosity allows for a significantly superior loading capacity compared to other traditional mesoporous materials, with a loading efficiency frequently exceeding 60% wt without compromising structure stability [231].

MOFs' ability to retain the drug inside the matrix, thus allowing for its controlled release, is due not only to their intrinsic structural properties, but also to the chemical interactions forming within their crystalline pores. These confined spaces favor the formation of hydrogen bonds, π–π interactions, metal coordination, and electrostatic interactions, providing a strong anchoring of the therapeutic molecules and superior stability during their transport and release [232–234].

The modular nature of MOFs further enables the design of stimuli-responsive systems, allowing for drug release in response to specific signals. For example, MOFs like ZIF-8 are pH-sensitive, selectively degrading in the acidic environment typical of cancer cells, thus releasing their cargo in a controlled manner and avoiding systemic side effects [235,236]. Similarly, redox-sensitive MOFs release their payload in the presence of

intracellular glutathione, exploiting this mechanism to selectively target unhealthy cells [237,238]. Other examples involve thermo-responsive or UV-Vis light-activated systems, owing to the incorporation of smart polymers or photocatalytic nuclei, further widening the capabilities for controlled drug release [239–241].

One of the many advantages offered by the deployment of MOFs as DDSs is the possibility of tailored post-synthesis modification. Examples in literature include biocompatible coatings such as PEG and polysaccharides to enhance in vivo stability, or the functionalization with targeting moieties to increase therapeutic specificity, or inclusion in lipid bilayers [242,243]. Furthermore, another interesting possibility is directly co-assemble the drug as an integral part of the MOFs without affecting its ordered crystalline structure, which shows the versatility and the therapeutic potential of these materials [244–247]. Post-synthesis modifications, as well as tailored adjustments during the synthesis process, also enable overcoming one of the critical aspects of the use of MOFs as drug delivery systems, which is their stability in complex physiological solutions. Such strategies include the development of protective coatings, PEGylated core-shell architectures, and the embedding of the crystalline structures within polymeric matrices, enhancing the bioavailability and reducing the cytotoxicity of those MOFs composed of metals prone to prematurely degradation. Conversely, other MOFs, such as structures based on Zr (UiO66) and Fe (MIL100), exhibit considerable intrinsic hydrolytic resistance [248–252].

Recent in-depth investigations demonstrated how MOFs' crystallinity and ordered porosity directly and positively affect the precision and the efficacy of the controlled drug release, opening up new prospects in the design and engineering of smart nanosystems that combine safety, efficacy, and scalability [253–256].

Furthermore, metal-organic frameworks have the potential to be exploited as diagnostic agents, positioning them as effective theranostic nanotools. In fact, the crystalline order of these structures allows uniform incorporation of imaging agents, such as Gd^{3+} and Mn^{2+}, or fluorescent probes, which can be later combined with cytotoxic drugs to obtain a single multifunctional platform. This approach enables therapeutic and diagnostic synergy, which can be further enhanced by functionalizing the system with peptides and antibodies for a highly selective molecular targeting [257–260].

Considering all these aspects, MOFs clearly emerge as one of the most promising classes of materials in drug delivery, due to the combination of engineered structural order, high and homogeneous drug loading, controlled and stimuli-responsive release, and chemical versatility.

3.3. Supramolecular structures

3.3.1. Solid lipid nanoparticles

Lipids are a heterogeneous group of molecules insoluble in water but soluble in organic solvents. Structurally, lipids are composed of hydrophobic hydrocarbon chains and polar head groups and their amphiphilic nature allow them to self-assemble in aqueous environments, forming organized structures [261]. In the context of solid lipid nanoparticles (SLN), recent studies have demonstrated how these characteristics of lipids are fundamental to form stable and functional drug delivery systems [262,263].

SLN are a class of nanocarriers that have acquired significant attention since the early 2000s, in the fields of drug delivery, cosmetic formulation, and biotechnology [264]. These nanoparticles, composed of solid lipids, offer key advantages such as biocompatibility, biodegradability, and low toxicity. SLNs are capable of encapsulating both hydrophilic and hydrophobic drugs and provide controlled-release profiles, overcoming many limitations associated with traditional colloidal carriers. Compared to polymeric nanoparticles and liposomes, SLNs offer greater physical stability, lower production costs, and easier scalability, which makes them attractive for industrial applications [265,266].

SLNs are typically ranging in size from 10 to 1000 nm, consisting of a solid lipid core, an emulsifier, and a water or solvent phase. The solid lipid matrix is composed of physiological lipids, which contributes to reduce acute and chronic toxicity. Various lipids like tripalmin, tristerin, trilaurin, cetylpalmitate, glyceryl behenate, glyceryl monostearate (GMS), precirol are used in the formulation of SLNs [267–271]. The emulsifier, on the other hand, plays a crucial role in stabilizing the formulation by preventing particle agglomeration, influencing the stability and crystal structure [272]. SLNs can be produced using various techniques, including high-pressure homogenization, solvent/emulsion evaporation, phase inversion, microemulsion, and solvent injection methods [273].

The core of the nanoparticles is formed by a solid lipid crystalline structure that plays an important role in how drugs are incorporated and retained. Parameters such as the velocity of lipid crystallization, lipid hydrophilicity and the shape of the lipid crystal influence nanoparticles proprieties [274]. One potential disadvantage of SLNs lies in the use of a lipid matrix made of similar molecules, which tends to form a highly ordered, perfect crystal with few imperfections. Since drugs are usually incorporated between fatty acid chains, between lipid layers, or in crystal imperfections, a tightly packed crystalline lattice can limit drug solubility and reduce loading efficiency [275]. To overcome these limitations, Nanostructured Lipid Carriers (NLCs) were introduced. NLCs are formulated by mixing solid lipids with liquid lipids (such as oils) or by using glycerides composed of fatty acids with varying chain lengths. These modifications create a less ordered lipid matrix with more imperfections and gaps between the chains, which enhances drug solubility and loading capacity, while also reducing the likelihood of drug expulsion during storage [276–278].

It is essential to consider how the solid-state ordering of the lipid matrix determines their behavior under physiological conditions. The crystalline high ordered lattices of the SLN core display low baseline diffusion and slow leaching but drug encapsulation retention can be compromised under physiological stimuli such as acidic pH, elevated temperature, and enzymatic activity, all of which may destabilize the nanoparticle structure. Specifically, pH gradients and protein adsorption can disrupt the surfactant – lipid interface or lead to a protein corona formation [279,280]; mild heating may induce

polymorphic transitions that expel drug molecules [281]; and lipase-mediated lipid hydrolysis that degrades the lipid matrix, leading to a drug release that depends on the degree of crystallinity and the nanoparticles composition [282].

While clinical studies involving SLNs for cancer treatment remain limited, preclinical research is focused in exploring SLN for the controlled and targeted delivery of anticancer drugs. Drug-loaded SLNs can be administered through various routes, including intravenous, subcutaneous, and intramuscular injection, or even directed to specific organs for localized treatment [283]. SLNs are known to accumulate in the tumor microenvironment through passive diffusion via the Enhanced Permeability and Retention (EPR) effect, thanks to their optimal size range [284]. Active targeting strategies have been developed to enhance SLN specificity. By modifying the surface of SLNs with ligands, antibodies, or peptides, the nanoparticles can be functionalized to recognize and bind to specific receptors on cancer cells, improving uptake and therapeutic efficacy [285,286].

Furthermore, stimuli-responsive (triggered) drug release systems are under investigation to enhance the precision of SLN-based drug delivery. These systems rely on internal tumor microenvironment cues, such as acidic pH [287], or external stimuli, including magnetic fields [288], or hyperthermia [289] to trigger drug release at the tumor site.

3.4. Core findings

It can therefore be concluded that polymers represent an extremely versatile class of materials for the controlled delivery of molecules such as drugs, owing to the possibility of chemically modifying them and the ability to synthesize copolymers to overcome specific limitations, especially for synthetic polymers. On the other hand, COFs and MOFs represent a new frontier in the field of drug delivery due to the unique characteristics of modularity, porosity and large surface area, which allow for loading large quantities of drugs and obtaining a controlled and uniform release. Although they present some limitations, the most recent progress confirms their potential in biomedical applications and, in particular, in oncology. Finally, solid lipid nanoparticles (SLNs) represent a highly promising class of ordered materials that are particularly useful to encapsulate and provide controlled release of both hydrophilic and hydrophobic drugs, thus overcoming many limitations of traditional delivery systems (Figure 4). For molecular-level ordered materials, the structural arrangement plays a role heavily dependent on the intended device scope. Ordered materials, such as crystallized polymers and molecular frameworks (MOFs/COFs), are primarily suited for controlled release applications. Their packed structures slow down polymer degradation or mechanically hinder drug diffusion (in frameworks), collectively resulting in a more controlled release profile. However, their reduced internal void spaces inherently leads to a lower drug loading capacity, which is typically higher in non-ordered materials, such as amorphous polymers and the less crystalline inner cores of lipid nanoparticles. In general, these materials exhibit higher biocompatibility than inorganic crystalline nanoparticles. Nevertheless, COFs and MOFs specifically require appropriate stabilization due to their intrinsic hydrophobicity, which, while beneficial for the loading of certain drug molecules, complicates the formation of a stable dispersion for biological use.

Further development of smart, biodegradable, and multifunctional platforms could pave the way for new generation therapeutic systems, combining biosafety and clinical efficacy (Table 2).

4. Ordered, mesoporous delivery platforms

As the dimensions of the repeating structures within a drug delivery system increase beyond the molecular scale, distinct pores begin to form in the material. These pores can be randomly distributed throughout the particle's structure or arranged in ordered, repeating patterns (Figure 5).

A key advantage of ordered porosity is the potential for significantly higher drug loading, the availability of space for pore surface functionalization, and the precise control over surface and morphology parameters that result from the ordered structure. Since these pores are much larger than the interstitial spaces in a dense molecular matrix, they can accommodate not only larger macromolecules (proteins,

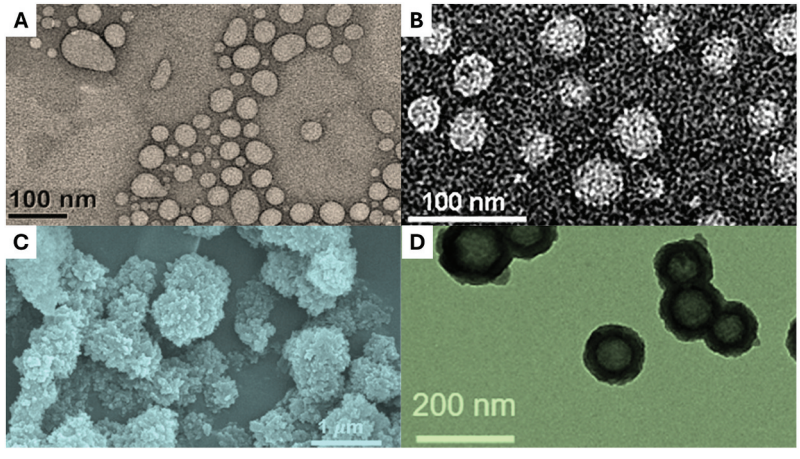

Figure 4. Examples of molecular-level ordered nanostructures analyzed through electron microscopy characterization. The images are reproduced with permission, showing: (A) synthetic polymerosome [174], (B) natural polymerosome [54], (C) covalent organic framework [214], and (D) metal organic framework [239].

Table 2. Summary of drug delivery systems characterized by a molecular periodicity.

Carrier	Drug	Drug loading method	Application	Ref
Polymers				
PLGA-PCL-Cur	Curcumin	Double emulsion (W/O/W) solvent evaporation technique	*In vitro* drug delivery to lung cancer cells (A549)	[181]
ABA type amphiphilic block copolymers consisting in PDS, and PNIPAM/PTEGMA	Doxorubicin	Co-precipitation followed by dialysis purification	*In vitro* drug release in cervical carcinoma cells (Hela), with minimum toxicity to normal cell s(C2C12)	[174]
aminoglucose (AG)-conjugated, redox-responsive nanomicelles from a single disulfide bond-bridged block polymer of polyethylene glycol and polylactic acid (AG-PEG-SS-PLA)	Paclitaxel	Polymeric micelle formation via solvent exchange and dialysis	*In vitro* drug accumulation and retention in multi drug resistance lung cancer cells (A549), *in vivo* tumor growth inhibition in nude mice bearing A549/ADR xenograft tumors	[176]
Functionalized poly(ethylene glycol)-poly(ε-caprolactone) (mPEG-PCL) diblock polymer with an acid-cleavable acetal (Ace) linkage (mPEG-PCL-Ace-PTX)	Paclitaxel (PTX)	PTX conjugation to the polymer through an acetal bond	*In vitro* drug delivery in breast cancer cells (MCF-7)	[182]
Herceptin-conjugated, PCL-PEG worm-like nanocrystal micelles (PTX@PCL-PEG-Herceptin)	Paclitaxel (PTX)	Oil-in-water emulsion followed by solvent evaporation. Herceptin conjugation via reductive amination	*In vitro* drug delivery to HER2-positive breast cancer cells (SKBR-3)	[183]
thiolated chitosan nanoparticles (CRC-TCS-NPs/5-FU-TCS-NPs)	Curcumin and 5-fluorouracil	Ionic gelation with drug loading and BSA surface coating	*In vitro* drug delivery in colon cancer cells (HT-29 and IEC 6), *in vivo* pharmacokinetics and biodistribution in a Swiss Albino mouse model	[187]
Inorganic/organic hybrid alginate/CaCO3 nanoparticles	Doxorubicin (DOX) and Paclitaxel (PTX)	Solvent evaporation from organic solvent (PTX) and aqueous adsorption (DOX)	*In vitro* drug delivery in cervical carcinoma cells (HeLa) and breast cancer cells (MCF-7/ADR)	[196]
Core/shell structural magnetic mesoporous silica nanoparticles (MMSNs) coated in gelatin	Paclitaxel (PTX)	Entrapment through equilibrium adsorption process followed by desolvation/ crosslinking procedure to graft gelatin	*In vivo* drug delivery by external magnetic field in mice bearing mouse sarcoma subcutaneous tumors (S180)	[197]
Covalent organic frameworks				
3D PI-COF-4 and PI-COF-5	Ibuprofen, captopril, caffeine	Physical absorption within the pores	General drug delivery	[218]
2D imine-linked COF	Gemcitabine	Physical absorption within the pores	*In vitro* pancreatic cancer cells (Mia-PaCa-2 and PANC-1) drug delivery	[219]
Dox@Az-AL-SO_3H-COF	Doxorubicin	Electrostatic and zwitterionic interaction	*In vitro* breast cancer cells (MDA-MB-231) drug delivery	[214]
TCOF-DOX-PEG	Doxorubicin	Electrostatic and hydrogen bonding interaction	*In vitro* cervical carcinoma cells (Hela) drug delivery	[221]
TB-COF-P@CT	Chlorin e6 (Ce6) and tirapazamine (TPZ)	Physical absorption within the pores	*In vitro* and *in vivo* responsive delivery in breast cancer models (4T1)	[222]
Alkyn-nCOF-cRGD	Doxorubicin	Impregnation at neutral pH	*In vitro* and *in vivo* targeted therapy of triple-negative breast cancer (MCF-7 and MDA-MB-231)	[216]
Metal organic frameworks				
Zirconium-based Metal organic framework (Zr-MOF)	Doxorubicin (DOX)	Drug encapsulation via diffusion into MOF	*In vitro* drug delivery in breast cancer cells (MCF-7)	[227]
Metal – organic framework (MOF) MIL-100	Doxorubicin (DOX)	Drug encapsulation via physical adsorption into MOF	*In vitro* drug delivery in breast cancer cells (MCF-7) and *in vivo* biodistribution in nude mice	[229]
Nickel-based metal-organic frameworks (Ni-MOFs)	Carfilzomib (CFZ)	Drug loading via pore impregnation	*In vitro* drug delivery in lung cancer cells (A549), breast cancer cells (MCF-7), neuroblastoma cells (SH-SY5Y) and *in vivo* efficacy in rats	[231]
Isoreticular metal-organic frameworks (Ni-IRMOF-74-II to -V)	Single-stranded DNA (ssDNA, 11–53 nt)	Drug uptake via physical adsorption	*In vitro* delivery and transfection in four mammalian immune cells, primary mouse immune cells ($CD4^+$ T cells, RAW264.7) and human immune cells (THP-1)	[232]
Zeolitic imidazolate framework (ZIF-8)	Doxorubicin (DOX)	Drug loading via pore impregnation	*In vitro* drug delivery in mucoepidermoid carcinoma of human lung (NCI-H292), human colorectal adenocarcinoma (HT-29), and human promyelocytic leukemia (HL-60) cell lines	[233]
Hollow porphyrinic metal-organic framework (H-PMOF) nanoparticles	Doxorubicin (DOX) and indocyanine green (ICG)	Drug loading via physical adsorption	*In vitro* drug delivery in breast cancer cells (4T1) and *in vivo* efficacy study in combination with near-infrared laser irradiation in 4T1 tumor-bearing mice	[239]
MIL-101-Fe metal organic framework	Methotrexate (MTX)	Drug loading via pore impregnation from organic solution.	*In vitro* pH-triggered drug delivery in cervical cancer cells (HeLa)	[245]
Fe metal-organic framework	5-Fluorouracil (5-FU)	Drug loading via physical adsorption	*In vitro* drug delivery in ovarian cancer cells (A2780) and human liver cancer cells (HL-7702) and *in vivo* efficacy in mice bearing A2780 tumors	[246]

(*Continued*)

Table 2. (Continued).

Carrier	Drug	Drug loading method	Application	Ref
Methoxy poly(ethylene glycol)-folate (PEG-FA)-stabilized zeolitic imidazolate framework ZIF-8	Verapamil hydrochloride (VER) and Doxorubicin (DOX)	One-pot synthesis of the MOF and encapsulation of the drugs	*In vitro* drug delivery in melanoma cells (B16F10) and breast cancer cells (MCF-7) and *in vivo* efficacy in mice bearing melanoma tumor model (B16F10)	[247]
Composites of γ-cyclodextrin (γ-CD)-based MOFs (CD-MOFs) and polyacrylic acid (PAA)	Ibuprofen (IBU) and Lansoprazole (LPZ)	Drug entrapment by co-crystallisation	*In vitro* drug release in macrophage cells (J774)	[250]
Bio-MOFs structure consisting of Gd-MOF surrounding a core of Fe-DOX nanoparticles	Doxorubicin (DOX) and indocyanine green (ICG)	In Situ formation of metal-drug coordination polymer nanoparticles	*In vitro* drug delivery in combination with near infrared irradiation in breast cancer cells (4T1) and *in vivo* therapeutic assessment in nude mice bearing 4T1 tumors	[257]
Lipid nanoparticles				
Solid lipid nanoparticle (SLN)	5-Fluorouracil (5-FU)	Adsorption through suspension in water mixture and high pressure homogenization	*In vitro* and *in vivo* drug delivery in colorectal cancer (HCT-116)	[285]
pH-sensitive cationic polyoxyethylene (PEGylated) SLNs	Camptothecin (CPT)	Encapsulation within the lipid matrix using hot homogenization followed by ultra-sonication	*In vitro* and *in vivo* drug delivery in human lung carcinoma (NCI-H358, CRL5802, CL1-5), human colon carcinoma (HCT-116) and human hepatocellular carcinoma (HCC36).	[287]
Magnetic solid lipid nanoparticles (mSLNs)	Doxorubicin (DOX)	Encapsulation within the lipid matrix using emulsification dispersion-ultrasonic method	*In vitro* drug delivery in breast cancer cells (MCF-7)	[288]
Solid lipid nanoparticles co-loaded with gold nanorods (AuNRs-loaded SLN)	Mitoxantrone	Encapsulation within the lipid matrix using emulsification dispersion-ultrasonic method	*In vitro* drug delivery in breast cancer cells (MCF-7)	[289]
Red blood cell-membrane-coated NLC (RBCm-NLC)	Paclitaxel (PTX)	Melt emulsification and extrusion	*In vitro* drug release in lung carcinoma cells (NCI-H1299) and *in vivo* tumor-targeted therapy against sarcoma (S180)	[278]
Nanostructured lipid carriers (NLCs)	Paclitaxel (PTX)	Hot melt homogenization followed by ultrasonication	*In vitro* drug dcelivery in breast cancer cells (MCF-7)	[277]
Solid lipid nanoparticles (SLNs)	clozapine	hot homogenization followed by ultrasonication method	*In vivo* drug delivery and pharmacokinetic analysis in Wistar rats and Swiss albino mice	[271]
Solid lipid nanoparticles (SLNs)	Ibuprofen (IBU)	Hot melt homogenization and crystallization	*In vitro* drug delivery in colorectal adenocarcinoma cells (CaCo-2)	[270]

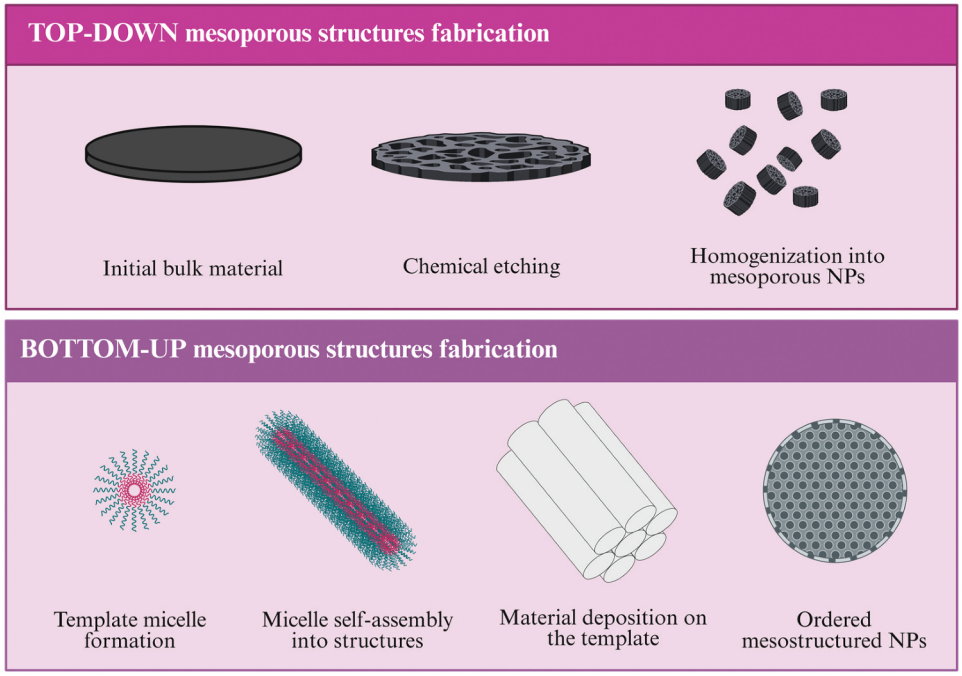

Figure 5. Two primary strategies for creating ordered mesoporous drug delivery systems: top-down erosion of macroscopic material; bottom-up template-guided growth of material. Created with Biorender. https://BioRender.com/uqlwvel.

antibodies) but also the necessary surface functionalization, substantially increasing the encapsulation efficiency and the variety of exploitable moieties [290]. However, a significant drawback of this porous structure is that it can also lead to a much more rapid drug release than non-porous systems, which typically release their cargo more slowly by desorption or material erosion. The restricted diffusion of molecules within the small pores inherently retards the drug release. Furthermore, this limited exchange with the external medium also results in a reduction of potential drug degradation caused by the environment.

Fabricating structures with both micropores (pores < 2 nm) and mesopores (pores in the 2–50 nm range) significantly restricts the choice of suitable materials. This constraint has led academic research to focus on materials that offer precise control over both chemistry and morphology. The result is that the materials must possess a modifiable matrix capable of generating internal pores. This requirement necessitates either the use of amorphous materials, which can adopt virtually any form, or the deliberate creation of holes within a crystalline material to permit a custom generation of pores that would otherwise be structurally unattainable. Consequently, in mesoporous systems, disordered and ordered structures coexist to form composite architectures suitable for drug delivery. As a result, silicon-based materials have emerged as the most promising candidates. The main alternative, in some cases, is carbon-based materials. Indeed, as discussed previously in this review, the highly versatile chemistry of carbon enables extensive customization of both surface properties and morphology. This capability can be leveraged to design smart, environment-responsive mesoporous carbon nanoparticles for drug delivery [291]. Despite their significant promise, the practical application of nanoporous carbon particles is still limited, probably due to the complex functionalization required to achieve biocompatibility and consequently *in vivo* exploitability [292].

Mesoporous titania [293–296], zinc oxide [297–301] and iron oxide [302] were used as potential drug delivery platforms, both in particle and film form. Despite the relatively low availability of studies, the great premises of the material make them worth mentioning, However, in these systems, the porous structure is typically not ordered, both because the aim of the studies does not require such order and because the highly ordered crystalline structure of the crystal inherently hinders pore formation, meaning pores must often be created through disruptive methods to achieve mesoporosity.

Silicon-based materials, instead, can present a high level of internal order. They effectively address issues of biocompatibility and customizability, making them one of the most promising classes of inorganic systems for drug delivery. The three main types of silicon-based materials used are porous silicon, zeolites, and arguably the most prominent, mesoporous silica.

4.1. Porous silicon

Porous silicon (pSi) particles are an excellent example of ordered porous material, often highlighted for their biocompatibility. The order of the pores in this kind of material is determined by the synthesis approach exploited. Indeed, this is one of the clearest examples of a top-down approach to particles synthesis. A macroscopic silicon wafer is electrochemically etched to create channels in its structure [303]. The result is that the channels are all directed in a single direction parallel to each other. The resulting porous wafer is then crushed, milled and sonicated into nanoscale particles. Despite the main challenge being represented by the high

costs of their synthesis, recent research has also proposed processes that can lead to a gram-scale production of the base material [304]. While this method yields nanoparticles that are less monodisperse in their external morphology compared to those from bottom-up syntheses, they retain a highly consistent and ordered internal pore structure. There are many examples of this in the literature [290] dating back to the 2000s, demonstrating the possibility of carrying hydrophobic [305] molecules to address different medical fields ranging from cancer immunotherapy [306] to Alzheimer's [307] therapy. Research has progressed, including active targeting through peptides, for example in the brain as in the work of Wagoner et al. [308] or by engineering mechanisms to even control the release of multiple moieties (in this case antibodies) in a specific pathway for immunotherapy [309].

4.2. Zeolites

Zeolites are crystalline aluminosilicates, with a three-dimensional framework of silica and alumina tetrahedra that creates a network of well-defined and ordered channels and cavities [310]. This order arises from the structural arrangement of the tetrahedra themselves rather than from the use of templates or etching directionality. There are more than 200 known zeolite types among natural and synthetic structures, with pore dimensions that can vary widely, from a 2–3 angstroms to tens of angstroms [310,311]. Depending on the specific tetrahedral arrangement it is possible to host several kinds of molecules [312,313]. While the primary applications of zeolites are industrial [314,315], their structure presents both advantages and disadvantages in the field of drug delivery [316,317]. Indeed, the pores are smaller compared to other mesoporous structures. This limits the kinds of molecules that can be included in the framework, but also slows down the release of the molecules themselves, which can be released in a more controlled way [310]. For example, the drug diclofenac was released in a sustained manner in the work of De Gennaro et al., exploiting a natural zeolite (Clinoptilolite) [318]. The zeolite, intended for oral administration, was of micrometric dimension and was appropriately surface-modified with cetylpyridinium chloride. The drug loading was performed at physiological pH and yielded approximately 40–60 mg/g of drug. Other natural zeolites, namely faujasite and mordenite, were exploited to host a chemotherapeutic moiety (temozolomide) for glioblastoma treatment [319]. The results were promising in terms of tumor growth reduction in ovo, even if the dimensions of the particles obtained were in the micron range, which probably hinders intravenous administration. Another case of zeolite (Zeolite Y) was intended for anticancer use, and also in this case, despite the coating with organic material might increase its biocompatibility, it is again intended for oral administration [320]. Delving deeper into the literature, it is clear that the zeolites, despite their great promise, find their application mainly in the oral administration [321–324]. This is attributable to the fact that the starting material can be obtained directly from nature, which inherently introduces the possibility of batch-to-batch differences according to the site of material retrieval that require study [325]. Moreover, despite the ordered pores in the system being a clear advantage in terms of sustained release, this also limits the versatility of the system, hindering the use of macromolecules and consequently applications like immunotherapy.

4.3. Mesoporous silica nanoparticles

Currently, the most widely used and promising porous structures for drug delivery are mesoporous silica nanoparticles (MSNs). The great advantage of silica is the possibility of

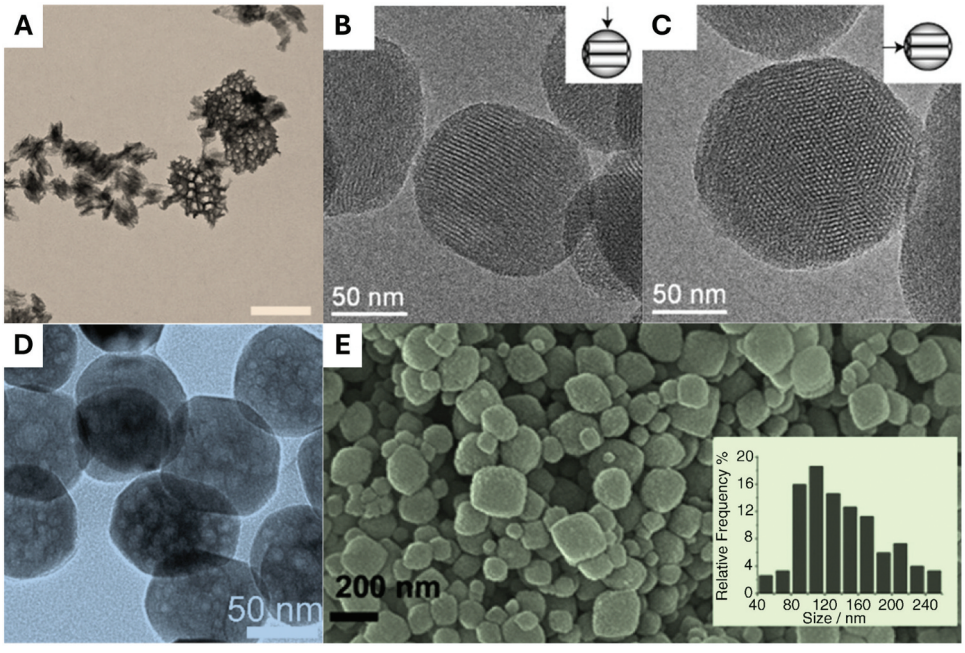

Figure 6. Electron microscopy characterization of representative ordered mesoporous structures. The images are reproduced with permission, showing: (A) porous silicon [304], (B) and (C) mesoporous silica nanoparticles [330], (D) mesoporous iron oxide [302], (E) microporous zeolites [321].

Table 3. Representative mesoporous drug delivery systems.

Carrier	Drug	Drug loading method	Application	Ref
Non-ordered mesoporous nanoparticles				
Mesoporous titania nanoparticles (MTNs)	Doxorubicin	Physical adsorption through immersion in DOX solution	*In vitro* drug delivery in human breast cancer cells (BT-20)	[293]
Ag@SiO_2@mTiO_2 core – shell nanoparticles	Doxorubicin	Physical adsorption through immersion in DOX solution	In vitro drug delivery in human breast cancer cells (MCF-7)	[294]
Yolk – shell gold nanorod@void@mesoporous titania nanoparticles (AuNR@void@mTiO_2 NPs)	Doxorubicin	Physical adsorption through immersion in DOX solution	In vitro drug delivery in human breast cancer cells (MCF-7)	[295]
Mesoporous titanium dioxide nanoparticle (ADH-1-HA-MTN)	Doxorubicin	Physical adsorption through DOX diffusion in an aqueous medium	In vitro drug delivery in human non-small cell lung carcinoma (A549)	[296]
Highly mesoporus spherical 3D ZnO nanoassemblies	Doxorubicin	Physical adsorption through DOX diffusion in an aqueous medium	*In vitro* cervical carcinoma cells (Hela) drug delivery	[297]
Hierarchical core-shell nanoparticles (ZnO-DOX@ZIF-8)	Doxorubicin	Physical adsorption through immersion in DOX solution	*In vitro* pH-responsive drug delivery system for cervical carcinoma treatment (Hela)	[298]
Mesoporous zinc oxide (ZnO) scaffolds coated with drop-cast graphene oxide (GO)	Gemtamicin sulfate (GS)	Physical adsorption through immersion in drug/simulated body fluid solution	*In vitro* drug delivery and supported culture of SaOS-2 osteoblast-like cells	[299]
Submicron-sized mesoporous self-assembled ZnO '*dandelions*'	Doxorubicin and DNA	Physical adsorption through immersion in drug/PBS solution	*In vitro* drug delivery in normal lymphocyte and K562 cancer cells	[300]
Zinc oxide quantum dots (ZnO QDs)	Camptothecin (CPT) and Curcumin	Non-covalent absorption through soaking (CPT) and covalent conjugation (curcumin)	*In vitro* pH-dependent drug delivery in pancreatic cancer cells (BxPC-3)	[350]
ZnO QDs	Doxorubicin	Non-covalent absorption through soaking	*In vitro* pH-dependent drug delivery in human cervical carcinoma cells (HeLa)	[351]
Mesoporous superparamagnetic iron oxide nanoparticles (MSPIONs)	Sorafenib (SFN) and/or brequinar (BQR)	Physical adsorption through immersion in drug/acetone solutions	*In vitro* and *in vivo* ferroptosis therapy against breast cancer (4T1)	[302]
Aluminosilicate mesoporous material (MCM-41)	Diflunisal (Df), naproxen (Np), ibuprofen (Ib) and sodium salt (IbNa)	Soaking procedure	Drug release in simulated intestinal fluid	[317]
Porous silicon				
Porous Si film	Dexamethasone	Impregnation into the porous matrix immediately following etching	Diffusion into phosphate-buffered saline solution	[305]
Porous silicon nanoparticles (pSiNPs)	Sulfonic acid functional group 6-amino-2-naphthalenesulfonic acid (ANA)	Salt-induced adsorption method using calcium chloride ($CaCl_2$)	In vitro and in vivo release in amyloid-beta plaque for plaque disaggregation	[307]
Biodegradable porous silicon nanoparticle (pSiNP)	Brain-derived neurotrophic factor (BDNF) protein	Physical adsorption through immersion in protein/water solution	Protein delivery in *in vivo* traumatic brain injury (TBI) animal models	[308]
Injectable porous silicon microparticles (pSiMPs)	Stimulator of interferon genes (STING) agonist ADU-S100, anti-OX40 antibody (aOX40), and anti-PD-1 antibody (aPD-1)	Non-covalent bonding between pSiMPs and antibodies/ADU-S100 in PBS	Temporally staged drug delivery in *in vivo* animal models of breast cancer (4T1)	[309]
Zeolites				
Zeolites Y (faujasite) and MOR (mordonite)	Temozolomide (TMZ)	Liquid-phase adsorption at controlled pH	*In vitro* and *in vivo* drug delivery in glioblastoma brain tumors (U251)	[319]
Zerumbone-zeolite Y-gelatin composites	Zerumbone (ZER)	Wet impregnation method	Drug release in PBS simulating the gastrointestinal tract conditions	[320]
Zeolites	5-fluorouracil	Wet impregnation method	*In vitro* drug delivery in colorectal cancer cells (Caco-2) monolayers to prove permeation	[321]
Zeolites X and Y	Diclofenac sodium and Piroxicam	Absorption through soaking, with and without filtration	Drug release in pepsin-free simulated gastric fluid	[322]
Microporous zeolites (BEA, ZSM and NaX)	BCS II model drug (indomethacin)	Non-covalent incipient wetness impregnation of the pores	Drug release in simulated gastric fluid, simulated intestinal fluids FaSSIF (fasted) and FeSSIF (fed state) conditions, *in vitro* drug release in Caco-2 cultures	[324]

(*Continued*)

Table 3. (Continued).

Carrier	Drug	Drug loading method	Application	Ref
Mesoporous silica nanoparticles				
Polymer/mesoporous silica nano-container linked through an acid cleavable linker (DOX@PAA-ACL-MSN)	Doxorubicin	Non-covalent absorption through soaking	*In vitro* pH-responsive drug release in nasopharyngeal carcinoma cells (HNE-1), *in vivo* efficacy studies	[340]
Polymer-coated mesoporous silica nanoparticles (PAH-cit/APTES-MSNs)	Doxorubicin	Non-covalent absorption through soaking	*In vitro* drug delivery in the nucleus of human cervical carcinoma cells (HeLa)	[341]
Mesoporous silica nanoparticles (MSNs)	Doxorubicin	Non-covalent absorption through soaking	*In vitro* drug delivery in human liver cancer cells (HepG2), normal human liver cells (HL-7702) and mouse macrophages (Raw264.7 cells) and *in vivo* tumor therapy (HepG2)	[344]
Peptide-Capped Mesoporous Silica Nanoparticles	Safranin O or doxorubicin	Non-covalent absorption through soaking	Controlled drug delivery *in vitro* in HeLa, MEFs WT, and MEFs lacking cathepsin B cell lines	[346]
Fe_3O_4@mesoporous silica core – shell nanostructure with Au as capping agent	Doxorubicin	Non-covalent absorption through soaking	PH-responsive drug release *in vitro* in human cervical carcinoma cells (HeLa)	[347]
AuNP-capped fluorescein-functionalized mesoporous silica nanoparticles (Au-FMSNs)	^{19}F contrast agent	Non-covalent absorption through soaking	Selective *in vitro* uptake of the nanoprobes in human lung cancer cells (A549) and not in normal ones (MRC-5) for imaging purposes	[348]
Magnetic iron-oxide-cores and mesoporous silica shells	Camptothecin	Non-covalent absorption through soaking	UV-triggered drug release in vitro on Chinese hamster ovarian cells (CHO)	[349]
Poly(L-histidine)-grafted mesoporous silica nanoparticles (MSNs)	Doxorubicin	Non-covalent absorption through soaking, based on electrostatic interactions depending on pH variations	Drug release at physiological and acidic conditions.	[352]
Hybrid mesoporous nanoparticles (PEGylated MSN-*g*-PDMAEA)	Doxorubicin	Non-covalent absorption through soaking	*In vitro* pH-dependent drug delivery in the human hepatocellular carcinoma cell line	[353]

growing this material onto templates (mainly surfactants and called structure-directing agents), which can be suitably tuned to self-assemble into specific pore order inside the material itself. The order of the pores is believed to increase the homogeneity of the distribution of the drug in the particles, leading to a more uniform and controlled release [326]. This approach is mechanistically sound because the controlled dimensions of the pores allow for the achievement of a more stoichiometric drug loading. Given the uniformity of the pores, this ensures precise knowledge of the amount of drug present within the material. Moreover, the tortuous and disordered pore geometry can diminish both drug loading and release speed [327]. The reduction in loading is often attributed to closed channels that fail to connect efficiently to the surface, while the slower release is due to molecules being required to navigate the channels inefficiently. Ordered channels, by contrast, affect release mainly via nanoconfinement, where the narrow pores naturally restrict the bulk movement of small molecules. However, it has been demonstrated that highly ordered and straight channels offer superior loading capabilities compared to random or tortuous channels [328]. The reason lies in the absence of non-accessible regions (dead ends), which ensures that the entire pore volume can be reached for both loading and cleaning. Furthermore, the pore dimension significantly affects both drug loading and release kinetics, with larger pores facilitating a quicker clearance of the internal drug contents. Nonetheless, this order offers superior reproducibility of the release profile. For mesoporous systems, order should be chosen when high-precision controlled release is needed, even if it sacrifices the ability to produce large batches of material. Still, most MSNs do not exhibit a clear order of the pores and, despite the huge and promising literature in this field (mostly covered in many reviews [326,329,330]), we will not focus on this topic that would require a dedicated review alone. However, in certain surfactant concentration conditions, the template used to direct the growth of silica nanoparticles assumes specific conformations. This is the case of CTAB that assists the formation of the honeycomb structure of MCM-41 silica particles. This material was initially synthesized in 1991 by Mobil Oil Corporation [331] for industrial purposes but attracted the attention of many scientists due to its enhanced surface area, pore volume and size, thereby opening up the field of ordered mesoporous materials. However, the first application of MCM-41 in drug delivery is attributed to Vallet-Regi and coworkers in 2001 [332], who managed to include ibuprofen in ordered mesoporous silica particles, achieving a loading capability of about 30%. The control over the pore size, which is enhanced in ordered systems, can also enhance the control over the absorbed molecules in terms of homogeneity of both loading and release. Still, the primary determinant in the control over release is the ratio between the pore size and the molecule's size. The higher the ratio, the faster the release [333]. Also, it has to be considered that, despite the possibilities in terms of surface functionalization and external particle morphology, the internal porous structure, when ordered, may be of three basic kinds: the one similar to the MCM-41 particles, in which the channels are all directed in the same direction (with a small exception of the SBA-15 [334] particles which present pores between the channels). Second, there are MCM-48 particles, where the pore system is three-dimensional and completely interconnected [335]. Finally, there are systems composed of spherical cavities interconnected by means of very small channels or pores [336]. Despite intuition suggesting that an interconnected pore structure should increase the drug incorporation, the real key determinant of controlled release and drug incorporation is surface functionalization [337]. This modification can change the affinity of the surface, which is very large in porous structures, with the drug, thereby increasing or slowing its release [331]. Literature has therefore been focusing on modifications that silica can undergo. It must also be considered that, like other nanoparticles that rely on pores rather than a solid matrix, MSNs suffer from the significant drawback of "burst release," where a large portion of the drug is released immediately upon administration. This issue can be mitigated by capping the pores with surface modifications [338]. These "gatekeepers" are designed to be removed on-demand by a specific stimulus at the target site, allowing for controlled release. Indeed, several works worked on the closing the pores [339] using caps or coatings with polymers [340,341], macromolecules [342–346] and nanoparticles [347–351]. For mesoporous silica and consequently also for ordered mesoporous silica, the most prominent trend in this area is the generation of pH-responsive gatekeepers [341,352,353]. At physiological pH, the pore is closed, while the gatekeeper is dissolved when it encounters the environment in which the drug should be released (e.g., the slightly acidic tumor environment).

4.4. Core findings

Ultimately, the trajectory of ordered porous materials in drug delivery demonstrates a decisive shift from relying on inherent structure alone to engineering sophisticated, functionalized systems (Figure 6).

While materials like porous silicon and zeolites offer well-defined internal order, they face intrinsic limitations in versatility, scalability, or the scope of molecules they can carry. The true breakthrough, therefore, lies with platforms like mesoporous silica nanoparticles (MSNs), where the ordered framework serves as a scaffold for advanced surface chemistry that allows combining a high loading capacity with on-demand release mechanisms (Table 3). Fundamentally, within mesoporous systems, structural order governs the controllability of drug release and loading. The core idea is that the pores act as the definitive mechanism for controlling the performance of the drug delivery system. Although random pores can sometimes exhibit a slower release rate than their ordered counterparts, the main advantage of ordered systems is their significantly higher degree of release control [354]. This benefit, however, comes with the drawback of increased complexity in device fabrication.

5. Conclusions

This review has thoroughly explored the crucial relationship between the intrinsic material order of drug delivery systems and their effectiveness, from atomic to supramolecular scales

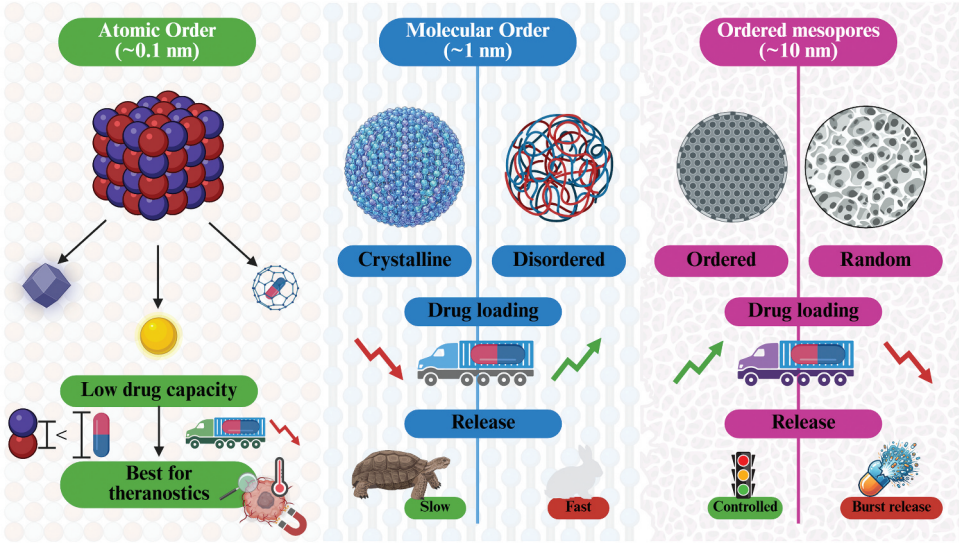

Figure 7. Impact of hierarchical structural ordering across length scales on drug loading, release kinetics, and theranostic performance. Created with Biorender https://BioRender.com/vczj3dx.

(Figure 7). While materials with inherent atomic-level order, like inorganic NPs and carbon nanostructures, offer unique properties for drug interactions and various theranostic applications, their drug-hosting capabilities often rely on surface chemistry and subsequent functionalization. In molecularly ordered systems, such as polymers, COFs and MOFs, their tunable molecular periodicity enables enhanced versatility in both drug loading and release kinetics. Ordered mesoporous platforms, particularly mesoporous silica nanoparticles, combine their high loading capacity with finely controlled release mechanisms. This review offers a fresh perspective on DDS design by highlighting how each level of structural arrangement influences drug delivery mechanisms, release profiles, and overall nanocarrier performance.

Indeed, the choice of a drug delivery carrier's structural order should be guided by the specific aim of its application. Materials with atomic-level order, such as single-element or biatomic nanoparticles, are often used for multimodal therapies. They can act as imaging contrast agents or provide synergistic effects for treatments like thermal ablation or magnetotherapy, while simultaneously delivering therapeutic drugs. Their drug loading capabilities are limited when compared to materials that possess defined porosity but gains features in terms of theranostic applications. Polymers are typically chosen for applications where the carrier's biocompatibility and controlled degradation are the primary concerns. However, structural order plays a distinct role: while it contributes to a slower, more controlled release, the tight packing simultaneously hinders drug loading, leading to superior loading capacity in disordered, amorphous polymeric materials. Furthermore, COFs and MOFs stand out for their unique modularity, which enables precise control over drug release kinetics. Still, their small pore dimensions restrict the variety of molecules that can be incorporated into the particle. Furthermore, their chemical nature frequently hinders water solubility, often requiring chemical modification before they can be effectively utilized as drug delivery systems. When a sustained and prolonged drug release is required, mesoporous materials are particularly effective, due to their high loading capacity and customizable pore structures. In this specific case, structural order serves as a mechanism to precisely control both the loading and the release of the therapeutic agent, thereby enabling precise therapies that necessitate a highly controlled release profile. This information will be crucial for the engineering of future DDS to address complex biomedical challenges using more precise and effective strategies.

6. Future directions

Among all nanomedicines evaluated in clinical trial between 2016 and 2021, liposomal, lipid-based and protein nanoformulations comprised over 78% of the total investigated nanoparticles [4,355]. The clinical dominance of liposomes formulation can be attributed to the intrinsic low-immunogenicity and safety profile of liposomes, as well as their utility in mitigating the toxicity of existing chemotherapeutic agents, such as doxorubicin or paclitaxel. On the other hand, inorganic materials generally face challenges regarding long-term in vivo safety and controlled biodistribution [356].

For instance, while SPIONs were initially authorized for liver imaging, several formulations were withdrawn following safety concerns, including severe lumbar or leg pain necessitating product discontinuation [357].

Furthermore, atomic-level ordered NPs employed in drug delivery frequently exhibit low drug encapsulation efficiency, consequently requiring high dosages to achieve significant therapeutic efficacy. However, their inherent tunability offers specific advantages for applications where other platforms lack capability, such as theranostic and sonodynamic or photodynamic therapy.

Higher-order structures, like polymers and molecular frameworks, offer more favorable drug-to-carrier ratio, serving as potent drug delivery systems.

Still, significant efforts are required to improve *in vivo* biodistribution and stability of these carriers in order to promote their clinical translation.

Similarly, mesoporous delivery platforms have been tailored to maximize drug loading and provide theoretical improvements in drug delivery. Despite this, concerns regarding long-term in vivo accumulation, as well as their limited scalability, hinder their clinical viability.

In general, the high tunability of crystalline structures can be a double-edge-sword.

While high versatility is an advantage, nanomaterials should be carefully characterized in terms of surface and physical properties as these parameters can alter biological functions [356].

Currently, clear causal relationships between crystalline structure variations and biological fate remain undefined.

The lack of comparative studies between ordered architectures and amorphous nanoparticles hinders a clear elucidation of how structural parameters influence degradation rates, stability, protein corona formation, and biodistribution. However, *in vivo* models such as Zebrafish. enable comparisons in terms of toxicity between different type of nanomaterials [23].

Consequently, comparative studies and *in silico* simulations are essential to determine how crystalline structure influences the in vivo fate of nanoparticles.

A machine learning driven algorithm published in 2024 by Mendes et al. [358] offered a blueprint for the panoramic evaluation of advancements in inorganic nanoparticles cancer research. The authors gathered over 700 preclinical studies to comprehensively assess nanoparticles features, applications and outcomes, paving the way for predictive models designed to accelerate clinical translation of inorganic NPs. The study demonstrates the capacity of machine learning algorithms to assist researchers in analyzing large datasets of individual research and identifying common patterns across disparate studies.

Nevertheless, predictive algorithms would benefit from including thorough studies, highlighting also negative results in the database, along with a more standardized way of reporting nanoparticles studies, enabling clearer comparison.

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Author contribution

Alessandro Masoero: writing, editing; Marzia Conte: writing, review and editing; Nicolò Maria Percivalle: writing; Elia Pascucci: writing; Giorgia Savino: writing; Veronica Vighetto: writing; Valentina Cauda: review, editing, funding, supervision; Marco Carofiglio: writing, supervision, conceptualization.

Disclosure statement

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