

Molecular Release by the Rotaxane and Pseudorotaxane Approach

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In memory of Sir James Fraser Stoddart





The controlled release of target molecules is a relevant application in several areas, such as medicine, fragrance chemistry and catalysis. Systems which pursue this implementation require a fine-tune of the start and rate of the release, among other properties. In this scenario, rotaxane- and pseudorotaxane-based systems are postulated as ideal scaffolds

1. Introduction

Rotaxanes and pseudorotaxanes are a type of molecule having at least a linear component encircled by a cyclic one, which have turned out to be useful in the preparation of molecular machines.^[1] Although the first statistical synthesis was reported more than five decades ago,^[2] the development of new synthetic strategies towards rotaxanes is still a hot topic of research nowadays.^[3,4] The interest of the research community within different chemistry areas in these molecules is mainly due to the possibility of being able to control the motion of the components of these intertwined architectures at will,^[5] besides other properties conferred by the mechanical bond.^[6] The vast versatility of advanced properties offered by these molecules has led to the development of a wide range of applications, including catalysis^[7] and functional materials,^[8] among other implementations.^[1]

In this scenario, the preparation of controlled release systems has benefited from advances in rotaxane chemistry. Indeed, different strategies of molecular release have been implemented using the rotaxane and pseudorotaxane approach, allowing to fine-tune the delivery parameters. The successful accomplishment of this application requires a rational design of the intertwined molecule, incorporating active units in at least one of the components of the rotaxane or pseudorotaxane. Thus, by applying an external stimulus, the system can be varied, allowing the release of the molecular cargo. These modifications to the system can be addressed in several ways. The controlled release can be achieved by appending the fragment to be released using a temporary bond that is broken when the external input is applied. A different possibility involves the motion of one component, e.g. shuttling of the macrocycle, thus facilitating the delivery of the target compound. Besides the mentioned strategies, there are other tricky options that embrace the previous transformation of one of the interlocked components to release a new molecule in a final step.

This short review highlights different options of molecular release using rotaxanated-based systems, showing the relevance of the employment of this type of mechanically interlocked molecules (MIMs) and related systems for such implementation. The examples included herein have been to accomplish a precise cargo release, due to the special features provided by the intertwined arrangement. This short review covers advances towards the controlled release of different molecules using rotaxane- and pseudorotaxane-based systems, both in solution and in the solid state.

selected based on the relevance and the type of release approach. In order to establish a simplified classification of the types of systems, two categories have been defined: (i) systems in which rotaxanes and pseudorotaxanes act as discrete molecules to promote the release of the target molecule in solution; and (ii) systems in which rotaxanes and pseudorotaxanes are molecular scaffolds within a material backbone operating as active units to facilitate the release of the molecular cargo. Although the above-mentioned classification is selected, there are other options to classify these systems, such as the origin of the target molecular cargo (linear or cyclic counterparts) and the distinction on whether the process requires bond cleavage or only conformational changes of the intertwined scaffold.

2. Controlled Release Using Rotaxanes and Pseudorotaxanes as Discrete Molecules

This section includes examples which involve the employment of rotaxanes and pseudorotaxanes as discrete molecules in order to accomplish the smart delivery of target molecules. The examples discussed herein take place in solution, releasing the molecular cargo to the medium once the proper stimulus is applied.

2.1. Rotaxane and Pseudorotaxane Systems for Medical Applications

The application of controlled release of molecules in medicine is highly relevant, particularly the delivery of drugs in specific organs following the application of an external or internal stimulus.^[9]

Rotaxane architecture offers a major advantage for controlled drug release, the protective effect of the macrocycle on the surrounding unit.^[10] Furthermore, the vast possibility of functionalization both in the thread and macrocycle paves the way to a precise control over the release process. One of the earliest examples of a rotaxane system used to deliver an anticancer drug involves the employment of the interlocked system 1 which is constituted by a pyridine-functionalized macrocycle and an imidazolium-based thread (Figure 1).^[11] The thread features two different stoppers: (i) one stopper having attached the anticancer drug paclitaxel through an ester bond; and (ii) the other end with hydrophilic motifs to improve biocompatibility. Indeed, this rational design of the stoppers enhances aqueous solubility and also improves the pharmacoki-

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Figure 1. Operation mode of rotaxane 1 for the controlled release of paclitaxel.^[11] Biproducts from hydrolysis reactions are omitted for clarity.

netic profile of the drug delivery system. The macrocycle also features a self-immolative linker which prevents the release until an enzymatic-triggered input initiates the process. Thus, the macrocycle protects the anticancer drug during systemic circulation, preventing premature release mediated by plasma esterases. Upon internalization into cancer cells, β -galactosidase initiates a cascade of reactions, which includes rupture of the ester bond between the self-immolative linker and the β -galactose unit, two 1,6-elimination reactions and saponification of the ester bond mediated by an esterase. This sequence of reactions leads to the controlled opening of the macrocycle and the subsequent liberation of the anticancer compound. Preclinical evaluations show an exceptional stability of these



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approach.

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rotaxanes in plasma, contrasted by their responsiveness to

intracellular enzymatic activity. The biological assays carried out

with this interlocked controlled release system revealed a good

replication of the therapeutic efficacy of free paclitaxel while

reducing systemic toxicity, showing a higher selectivity index

for cancer cells compared to normal ones. Noteworthy, the

obtained selective activation in cancer cells overexpressing β -

galactosidase underscores the potential of these systems to

target malignancies with minimal impact on healthy tissues.

Thus, a significant advantage over traditional chemotherapy

agents is obtained when using the drug-release by the rotaxane



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Adrian Saura-Sanmartin is currently a Postdoctoral Junior Leader ("la Caixa" Foundation) researcher at Universidad de Murcia. His research is focused on mechanically interlocked molecules and smart materials. The goal of developing site-specific chemotherapy treatments to minimize damage to normal cells is a major focus of researchers in the field. A related example employed a pillar[5]arene-based [2]rotaxane mitochondria-targeting unit as a controlled release system, which delivers an anticancer drug in cancer cells due to their more negative potential of the mitochondrial membrane compared to that of the normal cells.^[12]

Small variations in the design of any of the rotaxane components acting as the controlled release system led to considerable changes in the method of release, thus allowing for modulation of the cargo delivery. An illustrative example of this issue is the employment of rotaxanes 2 as molecular cages to regulate the binding of DNA, cytotoxic effects and the cellular uptake of Pt(II)-salphen complex.^[13] These rotaxanes consist of a bipyridine-based macrocycle surrounding a thread which features a Pt(II)-salphen unit along with an ester-based bulky group (Figure 2). The ester motif is responsible for dethreading,^[14] thus allowing the release of the platinum complex, which is a compound well known for its selective targeting of G-quadruplex (G4) DNA, positioning it as a promising candidate for cancer treatment. Initially, the macrocycle inhibits the binding of this metal complex to G4 DNA. The interlocked controlled release systems work sequentially through a two-step cleavage operational mode that requires two different inputs, having two distinct controlled release processes depending on the design of the cleavable stopper: (i) in the case of rotaxane 2a, where pivalic (Pv) ester scaffolds which respond to esterase are used in the aryl ester-based stopper, the release of the target complex occurs through a sequential esterase-triggered hydrolysis of the pivalic ester bond, followed by the hydrolysis of the aryl ester; and (ii) the release of the target anticancer complex takes place through a two-steps protocol, involving exposure to light followed by enzyme-assisted hydrolysis, when rotaxane 2b having photoresponsive nitroveratryl (Nv) motifs incorporated into the aryl ester-based stopper is employed. Notably, in vitro cell viability assays on osteosarcoma cells were accomplished using these rotaxanes, showing improved cell permeability compared to their non-interlocked counterparts and an enhanced inhibition of cancer cell growth. Remarkably, the light-controlled release strategy led to a precise spatiotemporal control over localization of the platinum compound and cytotoxicity. Thus, these intertwined architectures are postulated as ideal candidates to precisely accomplish a temporal control of therapeutics by manipulating their physicochemical properties.

Another significant goal in the field of medicinal chemistry is the development of radiotracers which can be employed as probes for cancer biomarker imaging. Rotaxane-based radiotracers have turned out to be suitable scaffolds to target biomarkers of disease in vivo.[15] Indeed, rotaxanes have been proposed as an innovative alternative to the traditional design of radiolabeled monoclonal antibodies for their application in Positron Emission Tomography (PET). This approach aims to overcome the limitations associated with such antibodies, including their prolonged circulation in the bloodstream, slow metabolism and excretion, which could help minimize patient exposure to ionizing radiation. Thus, [4]rotaxane 3 is positioned as a system for adjusting pharmacokinetics of cancer-targeted radiotracers (Figure 3).^[16] This interlocked system is constituted by two cucurbit[6]uril (CB6) macrocycles, a β -cyclodextrin macrocycle, having an aminoazepine bond with the amine groups of lysine residues on the onartuzumab monoclonal antibody, and a thread having two metal complexes with the chelating agent desferrioxamine B acting as stoppers. One of the metal complexes is radiolabeled with ⁸⁹Zr, which emits radiation detectable by PET, enabling the monitoring of the distribution of the drug. The other metal complex is stabilized by a non-radioactive Fe atom that contributes solely to structural stability. The monoclonal antibody positioned at the β -cyclodextrin unit specifically targets the c-MET receptor, a protein overexpressed in certain tumors. The results obtained show that incorporating the monoclonal antibody into a rotaxane scaffold preserves its tumor uptake specificity for MKN-45 tumors and significantly reduces its accumulation in other key organs which are involved in protein excretion, such as kidneys. This is reflected in a shorter effective half-life compared to covalent onartuzumab complexes. The interlocked structure allows the introduction of additional metabolic degradation pathways that are not available to conventional



Figure 2. Operation mode of rotaxanes 2 for the controlled release of Pt(II)-salphen complex.^[13] Biproducts from photocleavage and hydrolysis reactions are omitted for clarity. Abbreviation codes: Pv = pivalic; Nv = nitroveratryl.

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Figure 3. Chemical structure of [4]rotaxane 3 employed as radiotracer.^[16] The different bond ruptures that led to distinct release mechanisms are shown in red.

radiopharmaceuticals, optimizing its pharmacokinetic profile. Interestingly, different release mechanisms are possible using this system: (i) rupture at positions 1–4 leads to the delivery of semirotaxane species, where the macrocycles dethread due to the loss of stoppers, thus releasing radioactive fragments that are rapidly eliminated; (ii) cleavage at position 5 involves the hydrolysis of the aminoazepine bond, generating a [⁸⁹Zr]-containing byproduct, which is quickly excreted via hepatobiliary and renal pathways; and (iii) rupture at position 6 involves the opening of the β -cyclodextrin cyclic component, resulting in a secondary metabolite that also exhibits a very short half-life.

2.2. Rotaxanes and Pseudorotaxanes as Nanoreactors

The use of rotaxanes as nanoreactors is an interesting application in the field of molecular machinery.^[17] These systems work by changing one of the interlocked components and subsequently releasing a new molecule, just by adding fragments while the motion of the components proceeds or taking place in the confined environment of the space within the macrocycle, which can promote chemical transformations of the encircled functionalities.

The stereoselective synthesis of β -lactams,^[18] which is a hot topic in the pharmaceutical industry, has been achieved using benzylic amide rotaxane-based nanoreactors.^[19] This reaction involves cyclization of interlocked *N*-(arylmethyl)fumaramide threads in a basic medium, with the polyamide macrocycle acting as both an activator and a stereodifferentiating agent, ultimately yielding *trans*- β -lactams in a diastereoselective manner. When a dibutylamido stopper is placed at the thread, a dethreading process can be undertaken, thus releasing the biologically active non-interlocked β -lactam. Besides the diastereoselectivity in the formation of the nitrogen-containing five-

membered heterocycle, enantioselectivity over the process can also be achieved when chiral elements are placed at the intertwined counterparts. Thus, when a benzylic amide macrocycle having one methyl group with R configuration encircling a nonsymmetric N-(arylmethyl)fumaramide is employed as the nanoreactor system 4, the cyclization of the threaded functionality triggered by cesium hydroxide and the subsequent dethreading reaction leads to the isolation of the enantioenriched β -lactam **5** (Figure 4).^[20] In this reported example, the small methyl substituent on the macrocycle is responsible for the symmetry breaking of the rotaxanes, enabling efficient chirality transfer via the mechanical bond from the macrocycle to the thread. Therefore, this reported example clearly shows the controlled release of newly generated molecules within the cavity of the macrocycle of these intertwined molecular architectures.

It is pertinent to highlight supramolecular catalysis using cyclodextrin derivatives in this section, such as the early example involving the utilization of a β -cyclodextrin-modified



Figure 4. Operation mode of rotaxane-based nanoreactor 4 to yield β -lactam 5 through a two-steps protocol involving a base-promoted cyclization and a thermal dethreading.^[20] Tetralactam macrocycle from dethreading is omitted for clarity.



diphosphane to capture an alkene-based substrate and release regioselectively a hydroformylated product through the formation of a pseudo[1]rotaxane.^[21] Several examples of supramolecular catalysis following this pioneering strategy have been reported.^[22]

2.3. Rotaxanes and Pseudorotaxanes as Profragrances

The scent industry is another potential area where controlled release systems turn out to be highly useful. The aim here is to increase the persistence or longevity of the aroma, so that the consumer perceives the organoleptic properties unchanged or for a longer period. These systems which allow a sustained release of the fragrance or the storage until a stimulus is applied are known as profragrances.^[23]

The employment of rotaxanes as profragrances has been accomplished by placing a scent-based stopper at the linear component of the intertwined compounds **6** (Figure 5).^[24] These interlocked controlled release systems bear a benzylic amide macrocycle encircling a fumaramate-based thread which features a volatile alcohol fragrance attached by an ester bond. The incorporation of the fragrance within the interlocked systems improves the stability of the scent, thus reducing its volatility.

Consequently, these rotaxane profragrances serve as excellent frameworks for storing fragrances while preserving their organoleptic characteristics. A series of thermal or photochemical dethreading processes, followed by treatment with



Figure 5. Chemical structure of the interlocked profragrances 6, $^{[24]}$ employed for the controlled release of alcohol-based scents. The different substituents of the fragrance-based stopper are indicated in the blue box.

pig liver esterase (PLE) allow the release of the fragrance. The PLE treatment induces an enzymatic hydrolysis in the presence of potassium dihydrogen phosphate as a buffer and Arquad as a surfactant. The alteration of the steric properties of the end groups of the thread (either dibutyl- or dibenzylcarboxamido) allows the release rate of the target fragrance to be fine-tuned. Thus, the enzymatic release of scents at room temperature from profragrances **6a** with a butyl stopper only needs the enzymatic hydrolysis as the stimulus, while the system having a benzyl stopper (**6b**) operates through two sequential inputs, temperature increase followed by enzymatic hydrolysis in order to deliver the volatile compounds. Therefore, the rational design of the thread components allows modification of the scent release mechanism.

2.4. Rotaxanes and Pseudorotaxanes for Allosteric Release

The allosteric effect enables remote regulation of the properties of the system by the binding of an effector to a specific site on the structural backbone of a molecule, which is known as allosteric site. This effect has also been employed in rotaxane systems, including the reversibly assembly of a semirotaxane system^[25] and the study of the interplay of allosteric and chelate cooperativity to obtain multivalent pseudorotaxanes.^[26]

The allosteric release mechanism in rotaxanes turns out to be a novel approach to detaching a macrocycle while retaining the interlocked structure, as has been reported using rotaxane 7 as the controlled release system.^[27] This intertwined architecture is constituted by a CB6 cyclic component and a linear counterpart having two ammonium sites, an isobutyl stopper and an adamantane motif as the other ended-group (Figure 6). The adamantane motif acts as stopper for CB6 and as allosteric site for cucurbit[7]uril (CB7), which has the role of allosteric trigger. The process hinges on the strategic use of electrostatic repulsion between both macrocycles. The operation mode starts with CB7 binding to the adamantane-based allosteric site placed at the thread, leading to the intertwined species 8. This site, which is positioned away from the primary station of CB6, causes a conformational strain in the system. The binding event increases the energy of the interlocked system, forcing CB6 to overcome the kinetic barrier of its isobutyl stopper which leads to a dethreading process, giving 9 as the new intertwined architecture. Since the initial arrangement is destabilized once CB7 occupies the allosteric site due to the proximity to CB6, which generates a strong electrostatic repulsion, it is possible to fine-tune the stability of the system by slightly modifying the structure. Thus, the adjustment of the distance between the allosteric site and the primary binding site allows control over the release rate. This method paves the way for advanced noninvasive controlled release devices.

Although other dethreading reactions of rotaxanes can be considered as controlled release protocols to yield the corresponding macrocycles as the target compound,^[28] these processes have been omitted from this review, except for the above-mentioned example which represents a different concept. In many of the other examples discussed in the previous Review doi.org/10.1002/chem.202500350

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Figure 6. Operation mode of the allosteric release in rotaxane 7.[27]

sections, dethreading processes take place also yielding the macrocycle, but as a byproduct that even is not the target molecule to be delivered.

3. Controlled Release Using Rotaxane- and Pseudorotaxane-based Materials

This section includes examples which involve the integration of rotaxanes and pseudorotaxanes within material backbones in order to accomplish the smart delivery of target molecules. The examples discussed herein take place in the solid-state or at the solid-solution interface. In addition to the classification made in the various subsections of this section, which is based on the type of material, another classification can be made based on whether the controlled release involves bond cleavage or exclusively conformational changes.

3.1. Rotaxane- and Pseudorotaxane-based Nanoparticles

The functionalization of the surface of mesoporous silica nanoparticles with rotaxane-based molecular shuttles lets to smart nanovalves that take advantage of the control of the internal dynamics of these interlocked structures.^[29] The operation of these nanocontainers requires the initial loading of a compound within the pores of the nanoparticles, followed by pore closure with the macrocycles. Upon application of an appropriate stimulus, the macrocycle, which acts as a gate, moves away from the porous surface and allows the release of the encapsulated molecules at will. These rotaxanated nano-

valves operate through two main release mechanisms: (i) dethreading of the macrocycle in order to open the pores; and (ii) shuttling of the macrocycle away from the pores while retaining the interlocked structure. Both mechanisms involve conformational changes, without cleavage of a covalent bond.

An interlocked nanovalve operating through the dethreading mechanism involves the attachment of pseudorotaxanes 10 to the surface of mesoporous silica nanoparticles (Figure 7).^[30] These pseudorotaxanes consist of a cyclobis(paraquat-pphenylene) (CBPQT⁴⁺) macrocycle acting as a mobile gate and 1,5-dioxynaphthalene-based threads as fixed gateposts attached to the surface of the nanopores. In order to accomplish the controlled release mechanism, the loading of the nanopores with tris(2,2'-phenylpyridyl)iridium(III), which is a luminescent guest molecule, is carried out once the threads are anchored to the nanoparticles. The subsequent threading using CBPQT⁴⁺ avoids the releasing of the guest compound by effectively closing the pores. This assembly operates as a redox-controlled nanovalve since a reducing agent triggers the dethreading of the newly reduced CBPQT^{2(•+)} bisradical dication macrocycles, thus reopening the pores to release the molecular cargo. The functionality of the nanovalve was monitored using fluorescence spectroscopy, since the employed iridium-based compound exhibits a distinct emission that diminishes upon encapsulation and reappears after the release takes place. A similar approach has been employed to release rhodamine B from pseudorotaxane-functionalized mesoporous silica nanoparticles in response to a pH modification.^[31]

Besides the above-mentioned stimuli, light has also been employed as the input to promote the release of a guest molecule using rotaxane-based nanoparticles. The example discussed below highlights the use of light as a stimulus, but Review doi.org/10.1002/chem.202500350

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Figure 7. Operation mode of the delivery mechanism of the intertwined nanovalve having attached pseudorotaxanes 10 as the gatekeepers.^[30] For simplicity, only one pore of the silica nanoparticle is shown in the figure.

also the operation through the shuttling mechanism of the macrocycle, preserving the intertwined architecture. The lightresponsive interlocked nanovalves are synthesized by attaching molecular shuttle 11 to the pores of mesoporous silica nanoparticles (Figure 8).^[32] The rotaxane system has two stations placed at the thread, a fumaramide binding site close to the stopper and a glycylglycine station near the pores. The release mechanism of rhodamine B, employed as a model cargo, hinges on the light-induced isomerization of the photoactive fumaramide station. In the open state, the benzylic amide macrocycle, which acts as a gatekeeper, encircles the fumaramide station, enabling free cargo diffusion into the silica pores. Upon ultraviolet irradiation at 254 nm, the fumaramide undergoes photoisomerization to maleamide, altering its binding affinity, thus inducing the shuttling of the cyclic counterpart towards the peptide-based station. The new position of the macrocycle effectively seals the pores, hence capturing the molecular cargo. Subsequent irradiation at 365 nm restores the system to the open state, relocating the macrocycle to its initial position. This change allows the controlled release of rhodamine B by the reopening of the pores. Interestingly, the process demonstrates solvent-dependent release dynamics, with faster diffusion in dichloromethane compared to water, attributable to the differing solvation effects on the positional stability of the macrocycle. The advantage of this type of interlocked nanoparticles lies in its potential reusability by simply uptaking molecules into the pores and controlling the position of the macrocycle.

3.2. Rotaxane- and Pseudorotaxane-based Polymers

Rotaxane-based polymers arise from the intersection of polymer science and the chemistry of the mechanical bond, turning out to be a cutting-edge area of research in materials science.^[33,34] The advanced properties resulting from this material arrangement allow the development of very diverse applications, being a useful instrument within the synthetic toolbox for the preparation of controlled release systems.

Polypseudorotaxanes made from α -cyclodextrin have been successfully employed for the release of Terbinafine, which is a synthetic allylamine derivative having antifungal activity via inhibition of the enzyme squalene epoxidase.[35] These interlocked systems were prepared by adding α -cyclodextrin to a surfactant dispersion having polyethylene glycol and Terbinafine. The macrocycle interacts both with PEG and the antifungal drug, thus forming the tridimensional polypseudorotaxane stacking structure. By using ex vivo vertical and static penetration models of porcine vaginas, the encapsulation of Terbinafine using micelles and α -cyclodextrin to form an intertwined architecture was tested. The polypseudorotaxane approach offers two main advantages: (i) variations in the concentration of the macrocycle allow to modulate mucoadhesion, resistance to vaginal flow and drug penetration; and (ii) the prolonged drug release of polypseudorotaxanes compared to micelles turns out to be a suitable protocol for treating recurrent infections of vulvovaginal candidiasis.



Figure 8. Operation mode of the interlocked nanovalve having attached rotaxane 11.^[32] For simplicity, only one pore of the silica nanoparticle is shown in the figure.

The employment of self-assembled polyrotaxanes as enhanced drug delivery systems has been reported, using polyrotaxane **12** as the interlocked scaffold and doxorubicin as the model drug.^[36] The intertwined architecture **12** is constituted by a 4-arm star-polymer of ε -caprolactone as the thread, which is encircled with several pillar[5]arenes and stoppered with an adamantane motif (Figure 9). The adamantane motif allows host-guest interactions with a biocompatible β -cyclodextrin derivative functionalized with poly(acrylic acid), which acts as the pH trigger. The newly formed supramolecular polyrotaxane polymer could then self-assemble in aqueous solution to build supramolecular vesicle nanoparticles. When these vesicle nanoparticles are loaded with doxorubicin, an acidic environment leads to the release of the drug. Indeed, cell viability *in vitro* studies were carried out, showing an enhanced



Figure 9. Chemical structure of the polyrotaxane 12 employed as scaffold for the construction of a drug delivery platform. $^{\rm [36]}$

uptake of the drug in the tumor cells. Interestingly, *in vivo* assays revealed a more effective inhibition of the tumor using the doxorubicin-loaded polyrotaxanes-based supramolecular vesicle nanoparticles, indicating that these systems could selectively release the drugs in the pathological sites, thus reducing side effects on healthy organs.

Rotaxane force actuators,[37] in which the motion of the components occurs through the application of a mechanical force, have turned out to be an ingenious strategy to release target molecules in a controlled manner. The force-controlled release of retro-Diels Alder products has been carried out using rotaxane 13 as actuator (Figure 10).^[38] This intertwined product is constituted by a pillar[5]arene macrocycle threaded by a linear component having a poly(methyl acrylate) (PMA) stopper connected to an oligomer having attached the molecular cargo. The cyclic counterpart is also connected to another PMA chain, thus allowing the activation of this interlocked architecture by a mechanical force. In this system, the mechanical force-activated shuttling of the macrocycle along the thread, which ends with the dethreading of linear molecule 14 and macrocycle 15, leads to the activation and release of the retro-Diels-Alder adducts 16. The molecular cargo release takes place once the macrocycle reaches the cargo-attached sites along its way, due to the pulling of the rigid pillar[5]arene derivative towards the steric obstacles dispersed along the thread. Thus, the macrocycle goes through the steric sites having attached the cargo by



Figure 10. Operation mode of the rotaxane force actuator 13 employed as controlled release system.[38]



mechanochemical breaking the covalent bonds, ultimately releasing the target adducts. Interestingly, this type of interlocked controlled release system is highly efficient both in solution by ultrasonication and in bulk by compression. This system turns out to be highly versatile, since different cargo molecules can be attached as shown by using an organocatalyst, a drug and a fluorescent tag as molecular cargo. A related example has shown that activation by pushing is more efficient and selective than pulling to release a maleimide derivative through a formal retro-[4+2] cycloaddition.^[39] Thus, the controlled release is carried out through the cleavage of labile covalent bonds. This distinct approach paves the way for advanced smart delivery systems where the release of the molecular cargo can be modulated by the applied mechanical force.

3.3. Metal-organic Rotaxane Frameworks

Metal-organic frameworks (MOFs) have also been used as controlled release systems due to the possibility of hosting molecules in their pores and promoting their release by different stimuli.^[40] The incorporation of rotaxanes within MOFs scaffolds allows to integrate the mechanical bond properties into the solid state,^[41,42] thus leading to advanced applications. In this scenario, the employment of **UMUMOF-E-3** as nanodispenser of *p*-benzoquinone has been reported (Figure 11).^[43] This MOF is constituted by units of fumaramide-based rotaxane *E*-17 coordinated to copper(II) paddlewheels.

Indeed, a two-dimensional network of rhombohedral grids

which have the metal nodes connecting E-17 ligands at the vertices is built, featuring water molecules occupying axial positions. These metallogrids create defined channels along one crystallographic axis, providing enough free space for structural transformations, including the isomerization of fumaramide to maleamide triggered by light. When a suspension of crystals of this metal-organic material is irradiated at 312 nm for 8 hours, around 20% of the interlocked fumaramide units are converted into the corresponding interlocked maleamide (Z-17), increasing the pore size of the framework. This porosity change due to conformational changes allows the application of UMUMOF-E-3 as nanodispenser, working through a threesteps cycle: (i) first, the uptake of p-benzoquinone inside the pores is undergone; (ii) then, photoirradiation of the material changes the porosity of the MOF and allows the delivery of the molecular cargo to take place; and (iii) finally, the recovery of the initial material is conducted by thermal treatment, thus allowing to reuse this molecular nanodispenser. The potential reusability of this material positions this system as an appealing platform for the controlled release of molecular cargo.

4. Summary and Outlook

In this short review, the advantages of using controlled release systems based on rotaxanes and pseudorotaxanes have been discussed, showing that the properties conferred by the mechanical bond allow for ingenious modes of operation which ultimately led to smart delivery of target molecules. The highlighted examples have covered a representative collection



Figure 11. Operation mode of UMUMOF-E-3 as nanodispenser.^[43] The key color of the cartoon representatios (belove) is analogous to that of the chemical structures shown in the box and the rhombohedral grid of the crystal structure of the MOF (above).



of release mechanisms, including rupture of a covalent bond, allosteric release, reversible pore sealing of nanoparticles, pore breathing in metal-organic frameworks, supramolecular vesicles, supramolecular polypseudorotaxane gels assembly and pulling/ pushing by mechanical force actuators. One of the main advantages of these systems is the possibility of incorporating the molecular cargo both in the linear and cyclic counterparts, as well as encapsulating the molecule to be released when rotaxanes are part of the entanglement of a material.

In solution, systems that use rotaxanated architecture to achieve advanced release properties of organic compounds offer precise delivery mechanisms. Undoubtedly, the macrocycle offers both a protective effect and allows the release of a certain substance by moving it along the thread or even by a process of dethreading. Although fine-tunable release methodologies have been developed in solution using rotaxanes as the main molecular building backbone, more cutting-edge applications can be obtained in the solid-state by preparing smart materials. In this domain, MOFs are postulated as suitable scaffolds for such implementations mainly due to two strengths of these metal-organic materials: (i) the immense structural variety as a consequence of the possibility of combining a large number of metal salts with a huge diversity of ligands, leaving the imagination of the researcher as the only limitation; and (ii) the ordered structuring of intertwined ligands in a condensed phase facilitates concerted responses leading to a more precisely controlled change of properties. Regarding the controlled release of molecular cargo, MOFs allow the pore size to be modulated both during synthesis and by the pore breathing phenomenon,^[44] which is facilitated by the presence of dynamic organic struts, such as rotaxanes.

When comparing the advantages and limitations in terms of release efficiency and scope of molecular cargo, the incorporation of rotaxanes within materials turns out to be the strategy having a greater potential, although there are some limitations. Indeed, this approach allows a greater number of molecules to be incorporated or encapsulated, without the need to attach the fragment to be released in the structure of the intertwined structure. This makes it possible to incorporate, a priori, a greater number of structures. However, fine control over molecular release can be tricky, as it is more difficult to control certain factors during the rational design of the system, such as the rate of release or even the amount of molecular cargo incorporated within the material. In this scenario, as abovementioned, MOFs offer an advantageous platform to accomplish a fine-tunable controlled release. Within the materials systems, rotaxane force actuators are interesting because the release is controlled by an external mechanical force (pulling or pushing). This allows the applied force to be precisely modulated. However, the major limitation of this method lies in the need to incorporate scaffolds into the rotaxane structure with bonds that are labile enough to cleavage due to the translation of the macrocycle induced by the external force. In contrast, systems operating in solution have the advantage that more works of rotaxanes and pseudorotaxanes have been published in solution than in the solid state or at the solidsolution interface, so there are more options to modulate the release mechanism. This makes it possible to take advantage of the vast scientific knowledge and allows easier follow-up, using a greater number of techniques. However, the structural variety to be incorporated implies that either a covalent bond is formed that can be broken upon application of a stimulus or that a supramolecular assembly is generated due to the complementarity of the different fragments, thus being able to incorporate a more limited scope than in rotaxane-based materials. One of the main disadvantages of systems working in solution is their reusability. For example, architecture that incorporates labile covalent bonds in order to release the fragment can be reused much less often than materials that encapsulate the molecular cargo.

Several advanced modes of operation towards the controlled release of target molecules have been developed to date, but there is still room for innovation and research efforts are needed in order to prepare improved systems. Within this experimental outline, there are two main directions in which future research on the development of such interlocked systems should be focused: (i) the preparation of rotaxanated architecture showing a higher structural complexity; and (ii) the search for new ways of integrating rotaxanes into functional materials.

Regarding the first direction, the synthesis of multi-stimuli responsive rotaxanes,^[45] which allow different operation modes, is particularly relevant. The application of different stimuli allows the properties of the system to be precisely modulated, which would lead to a very fine control over the release of the target molecule. Furthermore, if fine-tuning over the stimuli is possible, enhanced controlled release properties can be obtained.

The second direction can involve two distinct pathways: (i) the development of different methodologies to incorporate rotaxane and pseudorotaxane scaffolds within materials; and (ii) the exploration of new materials into which these intertwined molecules can be incorporated. This second direction is closely related to the first one, since this milestone depends on the structural design of the rotaxane.

The unique properties of rotaxanes and pseudorotaxanes allow to foresee further publications in which these intertwined molecules will be incorporated in other materials, such as covalent organic frameworks, as happened in the case of catenanes.^[46] As a result, new possibilities for releasing the molecular cargo confined in these advanced materials would be accomplished.

In the exploration of new forms of controlled release mechanisms, alternative strategies successfully employed in other fields, such as the development of materials whose formation is reversible,^[47] can lead to interesting properties which can be exploited in conjunction with those provided by the mechanical bond of the rotaxane structure.

Thus, considering the variety of research fields which are involved, as well as the remarkable findings so far, a bright prospect for controlled release systems based on rotaxanes is expected.



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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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