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Review article

Systems for stimuli-controlled release: Materials and applications

Marion Bruneau[a,b,c], Simona Bennici[a,b,*], Jocelyne Brendle[a,b], Patrick Dutournie[a,b], Lionel Limousy[a,b], Sylvain Pluchon[c]

[a] Université de Haute-alsace, CNRS, IS2M UMR 7361, F-68100 Mulhouse, France
[b] Université de Strasbourg, France
[c] Agro Innovation International, 35400 Saint Malo, France

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ABSTRACT

The design and development of delivery controlled systems of molecules of interest has attracted great interest over the last years. pH variation, light irradiation, temperature increasing, variation of the redox potential and the application of a magnetic field are among the most widely used stimuli that can be used to induce the release of an active molecule in a medium. The dominance of pH and photo-controlled release is clearly highlighted by the numerous articles published in these fields as well as all the related applications. In the case of pH-controlled release, two main parameters govern the release: the solubility of the active molecule in the releasing medium and the stability of the carrier materials. In the photo-controlled release, the carrier needs to contain a photo-sensible functionality; this stimulus can be successfully applied in the medical field when red light, that is able to penetrate the human tissues, is used. A large panel of applications of controlled release can be identified in the pharmaceuticals, agriculture, cosmetics, chemistry and dyes industry fields. More recently, biological, enzymatic, and mechanical (ultrasounds, stretching, shear stress) stimuli have been developed for target applications, in particular for drugs and hormones release. Consequently, many types of materials (polymers, silica, oxides, MOF…) can be used as carrier in relation to their compatibility with the active molecule and the type of releasing medium. This review aims to gives a useful overview on the materials, applications and mechanisms implied in stimuli-controlled release.

1. Introduction

Controlled-release of active molecules is an important process developed in many fields such as pharmaceutical [1–73], agriculture [74–84], cosmetics [85], dyes [86–103], chemistry [104–110].

The controlled active molecule delivery technology has progressed over the last decades, with the development of oral sustained, self-regulated, long term and nanotechnology based release systems. Different stimuli can be applied to induce the release such as variations in pH [1–12], temperature [4,11,24,34–36], redox potential [6,24–26], light irradiation [44–55], application of a magnetic-field [69–73], mechanical constrains [111–114] or biological stimulation [115–118]. In this review, a special attention is paid to the design of stimuli-responsive systems able to deliver an active molecule as well as to the mechanisms involved in the release process.

2. Materials

In this section, the materials used for stimuli-controlled release are presented. For stimuli-controlled release, various carrier materials such as nano or mesoporous silica, oxides, Metal Organic Framework (MOF), polymers, carbons or biomolecules have been developed. Moreover, different material shaping has been tested like core-shell structures, structure composed of a core containing the active molecule coated by another material which allows to slow down the diffusion process, or host-guest structures, where the active molecule is adsorbed, caged or linked to the host material. The type of carrier compounds, modifications, encapsulation procedures and conditions, as well as the type of applied stimulus, are gathered in Table 1.

3. pH-controlled release

pH-controlled release allows the delivery of one or several active molecule(s) occluded in a carrier material through a change of the pH of the medium.

Silica can be used as pH-controlled carrier with or without modifications [1–9,86–90]. In 2010, Yang et al. [1] have used mesoporous silica nanotubes, coated with multilayered polyelectrolytes, to control

* Corresponding author at: Université de Haute-Alsace, CNRS, IS2M UMR 7361, F-68100 Mulhouse, France.
E-mail address: simona.bennici@uha.fr (S. Bennici).

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Table 1
Materials used for stimuli-controlled release.

Type	Material	Modifications	Encapsulation procedure	Conditions	Stimuli	Ref
Silica-based	Mesoporous silica		Contact with carrier in water	(25 °C/24 h/dark/pH = 7.5)	pH	[2]
			Contact with carrier in acid	(25 °C/8 h/pH = 2.3)		[86]
			In situ synthesis			[7,8]
			Incubation with carrier	(12 h)		[9]
					Light	[106]
		Fe_3O_4 particles	Contact with carrier in water	(25 °C/48 h/dark)	pH	[5]
		Zn	Contact with carrier in HEPES	(12 h/pH = 7.4)	pH/redox	[6]
		Spiropyran	Contact with carrier in PBS	(25 °C/24 h/dark)	Light	[58]
		Poly(4-vinyl pyridine)	In situ synthesis	(25 °C/60 h)	pH	[87]
		Polyethyleneimine/Cyclodextrin	Contact with carrier in PBS	(pH = 7.4)		[88]
		Poly(2-(diethylamino)ethyl methacrylate)	Contact with carrier in water	(25 °C/14 h)		[89]
		Carbohydrate-protein	In situ synthesis		pH/glucose	[90]
		Enzyme/glutaraldehyde			Glucose level	[119]
		Cyclodextrin	Contact with carrier in PBS/DMF	(25 °C/72 h/pH = 7.4)	Enzyme	[115]
			Contact with carrier		Biological response	[120]
	Mesoporous organosilica	Molybdenium sulfide	Contact with carrier in PBS	(37 °C/5 to 72 h/pH = 7.4)	Light	[50]
	Silica nanotube	Polyelectrolyte	Contact with carrier in HCl	(25 °C/10 h/dark/pH = 2)	pH	[1]
	Hybrid silica nanoparticles		Contact with carrier in water	(4 °C/24 h)	pH/temperature	[4]
	Laponite® (synthetic clay)			(25 °C/24 h)	pH	[3]
	Li-fluorohectorite (clay)			(25 °C or 65 °C/4 h or 24 h)	Temperature	[65]
	palygorskite	Iron oxides/ethylene oxide/propylene/amino silicon oil	In situ synthesis			[82]
Oxides-based	Graphene oxide	Chitosan/carboxymethyl cellulose/Ca^{2+}	Contact with carrier in water	(25 °C/24 h/dark)	pH	[13]
		Encapsulation agent/surface modifier		(25 °C/24 h)		[14]
				(25 °C/10s/shake)		[15]
		DNA/aptamer	Contact with carrier in water/DMSO	(25 °C/24 h)	ATP	[116]
	Iron oxide	Sodium alginate/hydroxyapatite	Contact with carrier in dichloromethane	(50 °C/1,5 h/ultrasound)	pH	[16]
		[2′-(imino-ethylene-imino)acetyl]/polyethylene glycol	Contact with carrier in ethanol	(25 °C/5 h)		[41]
		Polymersomes	In situ synthesis		Magnetic field	[69]
		Silica nanoparticles				[70]
		Gelatin				[72]
		Liposomes	Contact with carrier in NaOH solution	(60 °C/pH = 7.8)		[71]
		Poly(vinyl alcohol)	Contact with carrier in PBS	25 °C/pH = 7.4		[73]
	Copper/zinc superoxide dismutase	Poly(ethylene glycol)/poly(L-lysine)	In situ synthesis		Biological response	[121–123]
	Manganese oxide	Bovin serum albumine/methacrylic acid/acrylamid/enzyme	CONTACT with carrier in PBS	37 °C/pH = 7.4	Glucose level	[117]
MOF	MOF-Zn		Active molecule as ligant	(85 °C/72 h)	pH	[10]
			In situ synthesis	(70 °C/72 h)		[11]
				(130 °C/72 h)		[12]
Carbon	Carbon nanotube	Chitosan	In situ synthesis	(pH = 7.4)	pH	[18]
		Titanium/polypyrrole			Electric field	[124]
Metals	Silver nanoparticles		Contact with carrier in water	(25 °C/2 h)	pH	[40]

(*continued on next page*)

Table 1 (*continued*)

Type	Material	Modifications	Encapsulation procedure	Conditions	Stimuli	Ref
Polymers	Alginate	Protamine/silica	Contact with carrier in water	(25 °C/72 h)	pH	[91]
		N-isopropylacrylamide/*N*-hydroxymethylacrylamide	In situ synthesis	(37 °C/6 h)	pH/temperature	[35]
		Chitosan	Contact with carrier in water	(25 °C/0.5 h)	pH	[21]
		Poly(lactic-co-glycolic acid)	In situ synthesis		Ultrasound	[125]
			Contact with carrier in water	(25 °C/0.5 h)		[126]
	chitosan	κ-carrageenan	Contact with carrier in PBS	(25 °C/2 h)	pH	[19]
		Bone ash/glycidyl methacrylate/poly(ethylene glycol)diacrylate		(25 °C/72 h/pH = 1.2 or 7.4)		[22]
		Glycolipid	Contact with carrier in ethanol	(25 °C/20 min)	Redox	[68]
	Poly(ethylene glycol)-based polymers	Poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate)	Contact with carrier in DMF/DMSO	(25 °C/0.5 h/dark/pH = 7.4)	pH	[25]
		Methacrylate/folic acid	Contact with carrier in DMSO	(25 °C/4 h)		[29]
		Dimethacrylate	Contact with carrier in dichloromethane	(80 °C/18 h)	Light	[51]
		3,6-dichloro-1,2,4,5-tetrazine	In situ synthesis			[59]
		Polymethacrylate			Temperature	[110]
		Poly(β-amino ester)/poly(ε-caprolactone)	Contact with carrier in PBS	(2 °C/6 h)	pH/temperature	[34]
		Diglycidyl ether/cystamine	Contact with carrier in water	(25 °C/24 h)	pH/redox	[26]
		Phenylboronic acid	In situ synthesis		ATP	[127]
		Poly(L-glutamic acid)	Contact with carrier in water		target receptor	[118,128]
	Methacrylate-based polymers	Methacrylic acid	Spray coating		pH	[74]
			Contact with carrier in alkali solution	(25 °C)		[75]
		Magnetite	Contact with carrier in water	(25 °C/24 h)		[39]
		2-hydroxyethyl methacrylate		(25 °C/24 h)		[20]
		Polystyrene	In situ synthesis			[23]
		Ethylene glycol dimethacrylate/ethylene glycol dimethacrylate	Contact with carrier in water	(4 °C/48 h/dark/pH = 5.5–6)		[33]
		Methacrylic acid/folic acid		(25 °C/24 h/dark)	pH/temperature/redox	[24]
		Ferrocene	Contact with carrier in acetone	(25 °C/12 h)	Redox	[102]
	Polylactic acid-based polymers	N-isopropylacrylamide	In situ synthesis	(25 °C/4 h/dark)	Temperature	[66]
		Poly(ethylene glycol)	Contact with carrier in DMC	(25 °C/30s/vortexed)	pH	[32]
		Liposome	In situ synthesis			[31]
			Contact with carrier in water		Shear stress	[111]
	Polyelectrolytes	Ferrocene	Exchange of layers		Redox	[103]
			Contact with carrier in water	(25 °C/pH = 3)	pH	[104]
	Coumarin-based polymers		Contact with carrier in acetonitrile	(25 °C/20 h)	light	[53]
			In situ synthesis			[77]
				(55 °C/3 h)		[78]
		Nitroimidazole/chitosan				[48]
		tert-Butyldimethylsilyl chloride	Contact with carrier in methanol	(25 °C/96 h)		[52]
		Pentaerythritol/isocyanate	in situ synthesis			[98]
	Spiropyran-based polymers	Polyglycerols			light	[57]
		Poly(dimethylaminoethyl methacrylate)	Contact with carrier in DMF	(25 °C/20 min)	pH/light/temperature	[92]
		Carbon nanotube	Chelation		Light	[105]
			Contact with carrier in toluene			[101]

(*continued on next page*)

Table 1 (*continued*)

Type	Material	Modifications	Encapsulation procedure	Conditions	Stimuli	Ref
Polymers	Azobenzene-based polymers		Contact with carrier in DMSO		Light	[54]
			Contact with carrier in DMF	(25 °C/12 h/dark)		[55]
		b-Cyclodextrin	Contact with carrier in PBS	(25 °C/10 min/dark/pH = 8)		[47]
		Liposomes	Contact with carrier in water	(25 °C/pH = 7.4)		[85]
		Attapulgite/biochar/amino silicon oil	In situ synthesis			[79]
		Poly(ethylene glycol)/2,2-di(hydroxymethyl)propionic acid				[100]
		Alginate/poly(ethylene glycol)	Contact with carrier in water	(25 °C/vortexed)		[99]
	Ortho-nitrobenzyl-based polymers	Cyclooctyne/poly(methacrylate)	Contact with carrier in acetonitrile	(25 °C/72 h)	Light	[46]
			In situ synthesis			[49,56]
		Poly(N-isopropylacrylamide)/poly(4-acryloylmorpholine)	Contact with carrier in DMSO	(25 °C/2 h)	Light/temperature	[63]
		Poly(ethylene glycol)	Grafting in DMF	(75 °C/8 h)	Light	[80]
		Carboxymethyl chitosan	Contact with carrier in acteone	(25 °C/10 h)		[81]
		Poly(ethylene oxide)	Contact with carrier in THF	(25 °C)		[94]
		Quinone-methide	Contact with carrier in PBS	(25 °C/10 min/pH = 7.4)		[96]
		Poly(ethylene glycol)/methacrylate	Contact with carrier in THF	(25 °C/12 h)		[97]
	Polydopamine	Poly(N-isopropylacrylamide)	In situ synthesis	(25 °C/24 h)	Temperature	[83]
		poly(2-(dimethylamino)ethyl methacrylate)	Contact with carrier in alcohol	(25 °C/50 h)		[84]
	Polyurethane	Azobenzene	In situ synthesis		pH/light/temperature	[93]
			Contact with carrier in DCM/DMSO	(25 °C/10 min)	Light	[95]
	Acrylic acid-based polymers	κ-carrageenan	Contact with carrier in water	(0 °C/25 h)	pH	[30]
		Poly (styrene sulfonate)		(25 °C/15 min)		[76]
		Cellulose	Contact with carrier in PBS	(25 °C/48 h)		[17]
	Acrylamide-based polymers	Poly(Maleic anhydride-β-cyclodextrin)	Contact with carrier in water	(25 °C/8 h)	pH/temperature	[36]
		Polytetramethylene ether glycol	Contact with carrier in alcohol	(25 °C/72 h)	Temperature	[64]
		Proteins	In situ synthesis		Enzyme	[129]
	Poly-L-lysine	Hyaluronan			pH	[37]
		Poly(allylamine)/poly(styrene) sulfonate/hyaluronic acid			Stretch	[130]
	Polyester dendrimer	Cyclic acetals of 2,4,6-trimethoxybenzaldehyde	Contact with carrier in Chloroform	(25 °C/12 h/dark)	pH	[28]
	Electrospun fibers (Eudragit® L100)		In situ synthesis			[42]
	Tetrathiafulvalene				Redox	[109]
	Galactose	(Trifluoromethyl)-phenyldiazirine/cyclooctyne	Contact with carrier		Light	[45]
	Phenolic Schiff base derivative		In situ synthesis			[107]
	Ruthenium nitrosyl complex		Contact with carrier in ethanol	(4 °C/12 h/dark)		[61]
	Dithiazolylethene	Metallic complexs	In situ synthesis			[131]
	Poly(caprolactone)-based polymer	Cellulose/polyester			Stretch	[132]
			Contact with carrier in water	(25 °C/7 days)	Ultrasound	[133]
	Elastomer	Alginate/polylactic acid	In situ synthesis		Stretch	[112]
			Injection in the solid			[113]
	Commercial micelles Pluronic P105		Contact with carrier in PBS	(25 °C/pH = 7.4)	Ultrasound	[134]
	Poly(lactide-co-glycolide)			(4 °C/12 h)	Biological response	[135]
Biomolecules	Liposomes	Nanostructured lipids	Contact with carrier in water	(37 °C/0.5 h)	Light	[60]
			Contact with carrier in PBS	37 °C/pH = 7.4	Shear stress	[114]
			Contact with carrier in water		Temperature	[136]
						[137]
	Lipide nanocapsule		In situ synthesis		Biological response	[138]
	Peptide/lipid				Enzyme	[139]
	Organo-phosphorous hydrolase	Hexahistidine/poly(ethylene glycol)/poly(L-glutamic acid)			Biological response	[140]

Abbreviations: DCM, dichloromethylene; DMC, dimethyl carbonate solution; DMF, Dimethylformamide; DMSO, Dimethyl sulfoxide; HEPES, 4-(2-hydroxyethyl)-1 piperazineethanesulfonic acid; PBS, Phosphate-buffered saline; THF, Tetrahydrofuran.

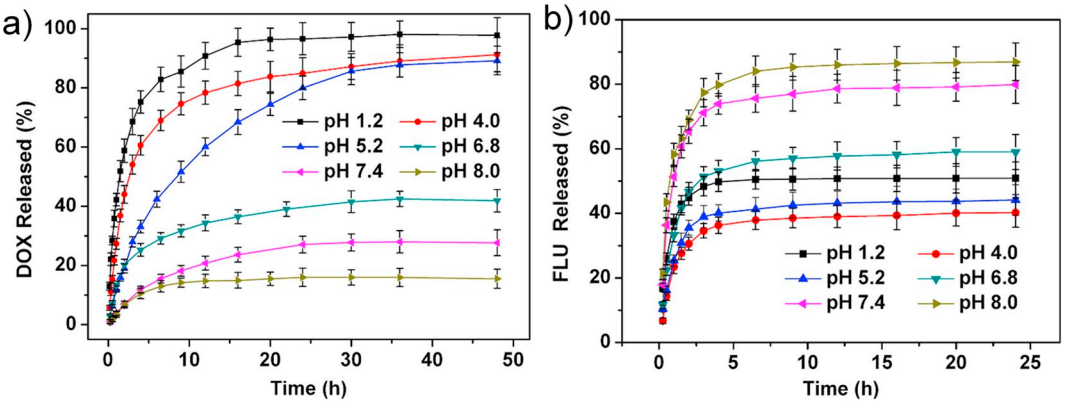

Fig. 1. DOX (a) and FLU (b) release from modified silica nanotubes as a function of time and pH.
Reproduced with permission from Yang et al. [1].

the release of anticancer drugs (Doxorubicin hydrochloride (DOX), a positively charged molecule, and sodium Fluorescein (FLU), a negatively charged molecule). The amount of released molecule between pH = 1.2 and pH = 8 was measured by UV spectrophotometry. DOX was easily and almost completely released after 15 h at pH = 1.2. Both the amount and the release rate (slope of the curves in Fig. 1), resulted to be lower at higher pH (only around 10% of the active molecule was delivered after 48 h at pH = 8 (Fig. 1a)). Indeed, at lower pH values, the amine groups of the DOX molecule become positively charged and the anions in the solution compensate the charges. An increase of the osmotic pressure takes part and, consequently, additional water can enter into the material. The swelling of the host material allows to solubilize the drug. On the contrary, the amount of FLU released was the highest (~90% in 24 h) at pH = 8, and decreased at acidic pH (35% at pH = 4) (Fig. 1b). This specific behavior is due to the presence of COO^- groups that, also in this case, contribute to the augmentation of the material charge, and, by increasing the osmotic pressure, promote the swelling and the increasing of the amount of water present in the material.

One year later, in 2011, Barat et al. [2] used mesoporous silica (MCM-41) with organized structure as carrier to perform the controlled release of folic acid (FA). The release kinetics resulted to be fast, as shown by the high value of the slope of the curves in Fig. 2a. After 15 min, only 15–20% of FA was released at pH = 2, while at pH = 7.5 > 90% of FA was already released (Fig. 2a). This releasing behavior is due to the solubility of folic acid that is very small at low pH. The addition of an excess of 3-[2-(2-aminoethylamino)ethylamino] propyl-trimethoxysilane in the initial mixture allowed to slow down the releasing process of FA (Fig. 2b). This compound forms a pH-sensitive barrier that affect the release of this active molecule.

In a recent study, Zea et al. [86] investigated the pH-controlled release of sodium phosphomolybdate ($Mo_{12}Na_3O_{40}P$), a compound that presents anticorrosive properties. The molecule was adsorbed on the surface of spherical nanotanks of mesoporous silica with organized structure. The “pH” stimulus was then chosen because the corrosion phenomenon is mainly due to pH variations. The amount of phosphomolybdate released was quantified by ICP-OES (Inductively Coupled Plasma - Optical Emission Spectroscopy). The results show a weak release of molybdate and phosphate ions at pH < 9. At very high pH, the release becomes important with the highest value (around 100 mg of Mo per gram of nanoparticle) measured at pH = 13 (Fig. 3). The same authors also tested the effect of the encapsulation of charged nanospheres by an electrolyte layer: polydiallyldimethylammonium chloride (PDDA). The results show that the active molecule was strongly encapsulated in the carrier at a pH < 9 and that no release was detected. These results also indicate that neither the mesoporous silica nor the electrolyte layer are stable at very basic pH.

In 2017, Roozbahani et al. [3] studied the controlled release of Dexamethasone (an anti-inflammatory and immunosuppressive molecule) using Laponite® as a carrier. The release process was studied in a PBS solution (Phosphate Buffered Saline) at pH = 5.4 and 7.4, at 37 °C, and the concentration was followed by UV–visible spectrophotometry. The results have shown a higher release of the Dexamethasone in acidic medium (Fig. 4b) compared to neutral pH (Fig. 4a). The influence of the pH during encapsulation shows also an influence on the release extent (Fig. 4), in particular when performed at pH = 5.4. In physiological medium, the intercalation of Ca^{2+} or K^+ cations is favored to the detriment of Dexamethasone (positively charged), which induces its release into the medium. These cations may subsequently be substituted by H^+ ions.

Materials based on graphene or iron oxides at different oxidation states can also be used as carriers for pH-controlled release [13–16].

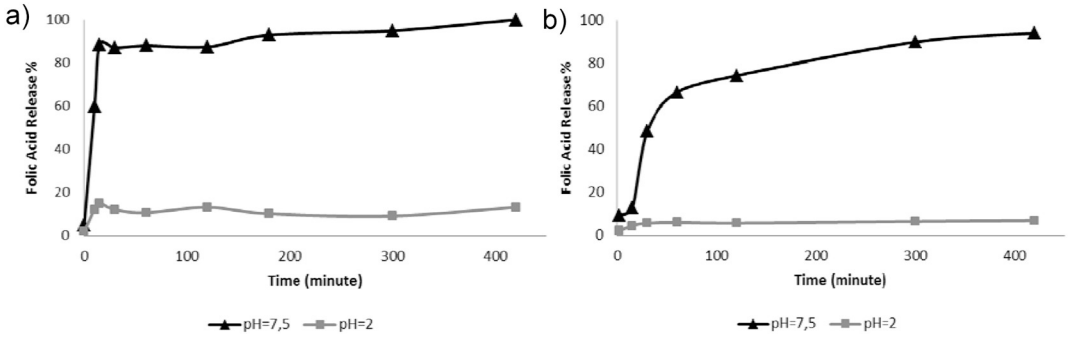

Fig. 2. Release of folic acid from a mesoporous silica as a function of pH without (a) and with (b) 3-[2-(2-aminoethylamino)-ethylamino]propyl-trimethoxysilane into the initial solution.
Reproduced with permission from Barat et al. 2011 [2].

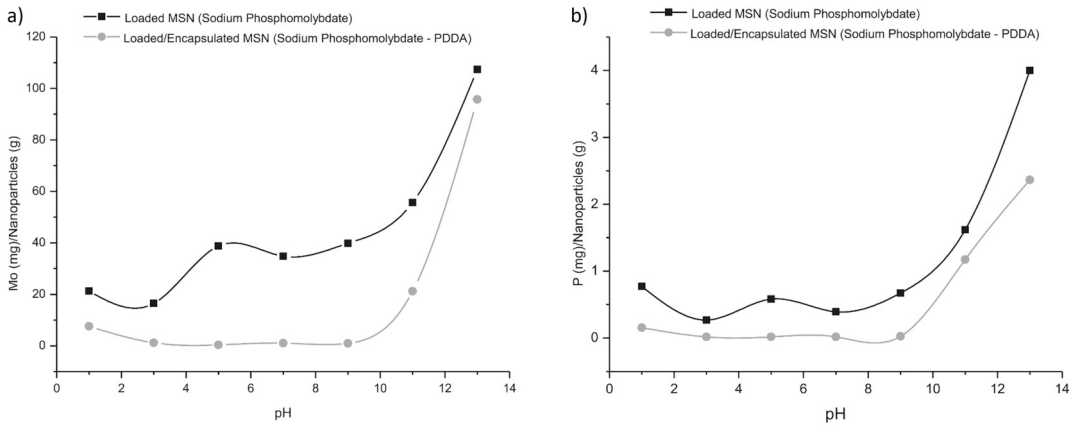

Fig. 3. Release of Molybdate (a) and Phosphate (b) ions from a mesoporous silica as a function of pH.
Reproduced with permission from Zea et al. 2018 [86].

For example, Aliabadi et al. [14] and Wang et al. [13], used modified graphene oxide for controlled release of 5-fluorouracil (5FU), a molecule with anticancer properties.

In the first study [14], the kinetics of release was tested in PBS medium at 37 °C at two different pH (5.8 and 7.4), and the quantification of the active molecule concentration was carried out by UV–visible spectrophotometry. The release of 5FU is progressive with a maximum reached after 120 h. The released quantities were variable depending on the pH of the medium. At pH = 7.4, the released amount was of 59% and at pH = 5.8 of 74% (Fig. 5). The release behavior is dependent on the concentration of H^+ ions in the medium. These release profiles can be indeed related to the degradation profiles of the carrier. The authors therefore concluded that the crucial factor in the release of 5FU is the stability of the carrier.

Wang et al. [13] produced, a hybrid aerogel composed by chitosan/carboxymethyl cellulose/Ca^{2+}/graphene oxide (CS/CMC/Ca^{2+}/GO) by electrostatic assembly. The release of active molecule was tested in PBS medium at different pH and at human body temperature (37 °C). The results were obtained by estimating the quantity released by UV–visible spectrophotometry. The release results to be higher at neutral pH (68% after 600 min) than at acidic pH (Fig. 6). The variation of the release amounts as a function of the pH could be attributed to the swelling ratio of the compound.

In 2017, Manatunga et al. [15] performed the controlled release of molecules with anti-cancer properties (curcumin and 6-gingerol, which are hydrophobic molecules) thanks to an innovative carrier, i.e. iron oxide nanoparticles covered by a bi-layer of sodium alginate and hydroxyapatite. In this study, the release was the highest at pH = 5.3 (Ace medium: medium buffered with acetate) for the two anticancer agents,

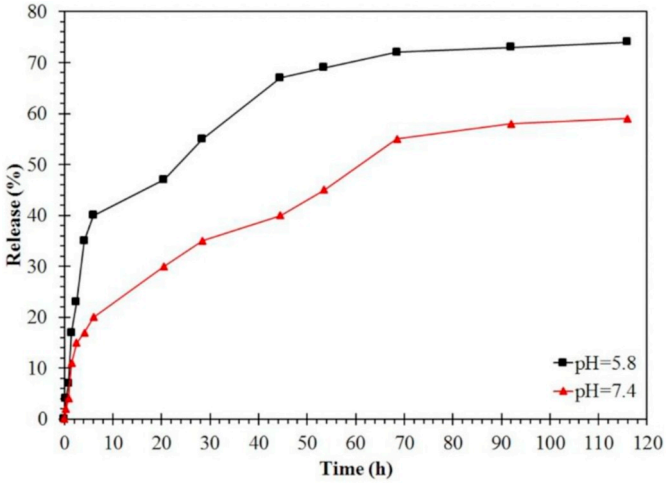

Fig. 5. Release of 5FU encapsulated in a graphene oxide as a function of time and pH.
Reproduced with permission from Aliabadi et al. 2018 [14].

with a ratio of 100% after 180 h. At pH = 7.4 (PBS medium: medium buffered with phosphate), the release was less effective, with 40–50% of the molecule released after 180 h, as can be seen in Fig. 7.

Numerous studies have shown that it is possible to release drug-active molecules or dyes by "pH stimulus" from carriers based on organic polymers [17–39,74–76,91–93,104]. For this purpose, different types of carriers have been developed: core-shell structures [23,24,31] or host-guest

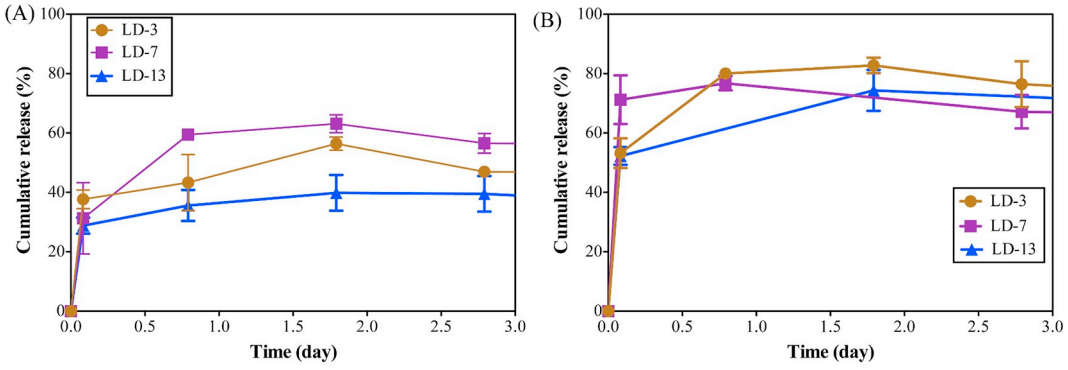

Fig. 4. Release of dexamethasone adsorbed on Laponite® at 37 °C as a function of pH and time at pH = 7.4 (A) and pH = 5.4 (B) (LD corresponds to the Laponite®-Dexamethasone compound and the number corresponds to the pH of encapsulation).
Reproduced with permission from Roozbahani et al. 2017 [3].

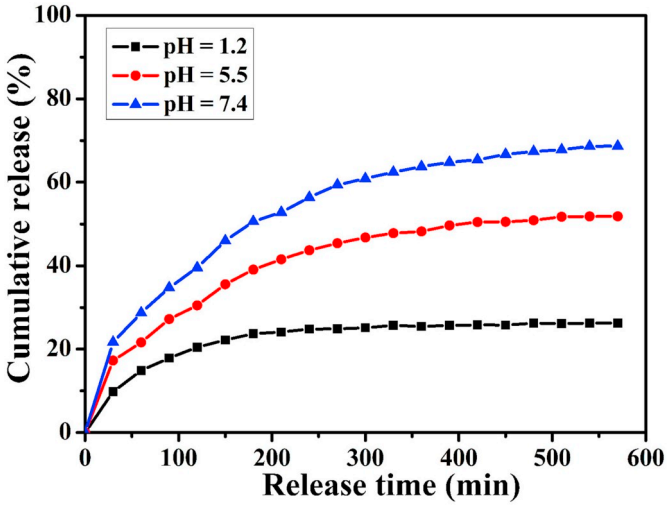

Fig. 6. Release of 5FU encapsulated in an aerogel as a function of pH and time. Reproduced with permission from Wang et al. 2017 [13].

structure such as nanospheres [20], capsules [21,76,91,93,104], hydrogels [17,22,30,34,36,75], micelles [25–29,32], nanoparticles [19,31]…

Among the others, Li et al. [24] used core-shell microspheres to carry out the controlled release of doxorubicin hydrochloride (DOX), an anticancer. The core, being sensitive to the variation of pH, is the element that drives the controlled release. The results of the tests, carried out without the addition of GSH (Glutathione: pseudotripeptide) in the release medium, showed that after 30 h, at pH = 7.4 and at room temperature, only 10% of DOX were released, against approximately 20% at pH = 5.5 (Fig. 8). The high release at low pH has been explained by the decomposition of the polymer microspheres.

Mao et al. [20] and Jia et al. [23] reported on the use of 2-(diethylamino)ethyl methacrylate (DEAEMA), as constituent of their polymer, to achieve the controlled release of drugs.

The first team [20] described a complete release from the molecularly imprinted polymers (MIPs) after 18 days. These results indicate that the release is faster at acidic pH (pH = 5.2 > pH = 6.4 > pH = 7.4) (Fig. 9). The authors assumed that the "pH-sensitive" release is due to the decomposition of the hydrogen bonds (−OH···NC− and −NH or $-NH_2$···O═C−), because of the protonation of −CN and −NH groups in acidic media (Fig. 10).

Jia et al. [23] synthesized a core-shell structure for the release of ibuprofen, an anti-inflammatory. The results showed that at pH = 7.5 the release extent is very low (< 10%) and increases with the acidity of the medium (about 40% at pH = 5.3 and more that 70% at pH = 3.4) (Fig. 11). Jia et al. [23] have also elucidate the mechanisms of release. Between pH = 7 and 5, the affinity of the carrier with water increases and the hydrophobic material become hydrophilic, due to the formation of protonated tertiary amine groups. The hydrophilic form allows then the incorporation of water and the release of the active molecule takes place by dissolution. Between pH = 5 and 3, the swelling of the carrier allows the release of the active molecule in the solution.

Alginate (Na or Ca) is also used as a carrier to achieve controlled release of different molecules [21,35,91].

He et al. [91] in 2015, succeeded to release four solutes (dyes) of different molecular weights from hybrid capsules, "Ca-alginate/protamine (protein)/amorphous silica". The best release was observed at neutral or basic pH compared to that performed at acidic pH. The capsules network loose its structure when the pH is > 4.5, thus letting the solutes of different molecular weights being released in the solution. The molecules characterized by a low molecular weight were more easily released.

Acevedo-Fani et al. [21] studied the release of the folic acid contained in a "alginate/chitosan" carrier. The results showed that release was the highest at pH = 7, reaching 100% in 400 min, against 20% at pH = 3 (Fig. 12). This can be explained by the solubility of folic acid, that results to be very low at acidic pH.

Using a polymer functionalized with spiropyran, Jiang et al. [92] achieved the controlled release of coumarin 102. The release was tested at different pH by analyzing the concentration of coumarin 102 in the medium by UV–visible spectrophotometry. The results showed that the release of coumarin 102 is the best at acidic pH. The order of the maximum release amount was the following: acidic pH (55%) > basic pH (25%) > neutral pH (3%) (Fig. 13). The high release rate of coumarin 102 at acidic pH is due to the swelling of the polymer.

Metal-organic-frameworks (MOF) materials have been recently identified as carriers for pH-controlled delivery of active molecules [10–12].

As an example, MOFs were used as a carrier by Gao et al. [10] for pH-controlled release of ibuprofen. The concentration of ibuprofen, during the release tests carried out in PBS (Phosphate Buffer Saline: buffered phosphate buffered saline) medium, was measured by UV–visible spectrophotometry. The release was more effective at pH = 5 than at pH = 7.4. The ibuprofen release is facilitated when the MOF is used in mono-nanosheet form, rather than as multi-nanosheets (Fig. 14). In this case, ibuprofen is adsorbed on the mono-layer of MOF, the release is linked to the degradation of the MOF in the acid medium, which induces an anion exchange between the phosphates of the PBS medium and the ibuprofen adsorbed on the MOF sheets.

Concerning the "pH-controlled" release, two main parameters generally

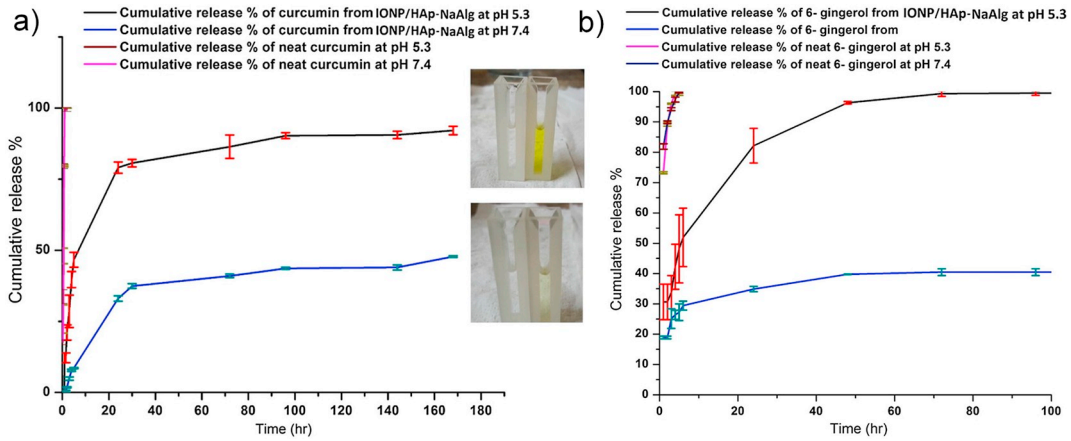

Fig. 7. Release of curcumin (a) and 6-gingerol (b) from modified iron oxides as a function of pH and time. Reproduced with permission from Manatunga et al. 2017 [15].

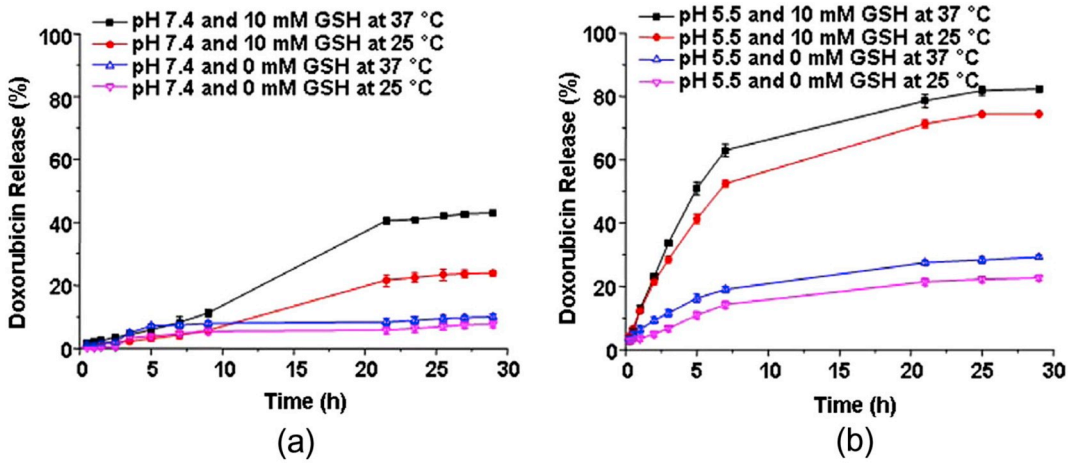

Fig. 8. Release of DOX at pH = 7.4 (a) and 5.5 (b) from organic microspheres of core-shell structure as a function of time and the presence of GSH.
Reproduced with permission from Li et al. 2014 [24].

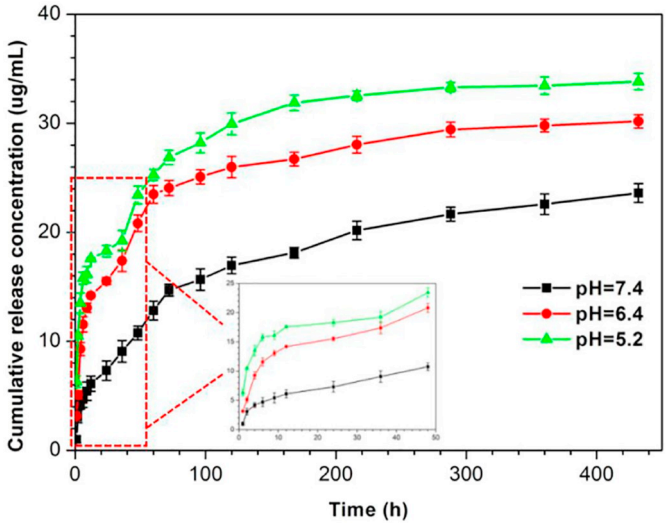

Fig. 9. Release of vancomycin from hybrid nanospheres as a function of pH and time.
Reproduced with permission from Mao et al. 2017 [20].

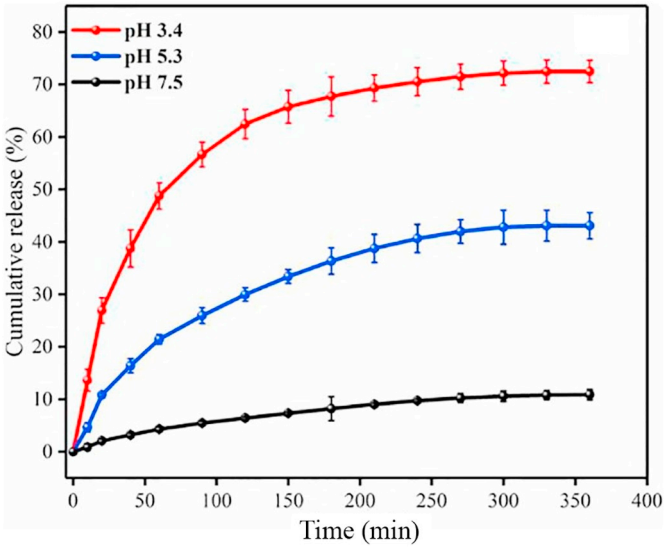

Fig. 11. Release of ibuprofen from an organic core-shell structure as a function of pH and time.
Reproduced with permission from Jia et al. 2017 [23].

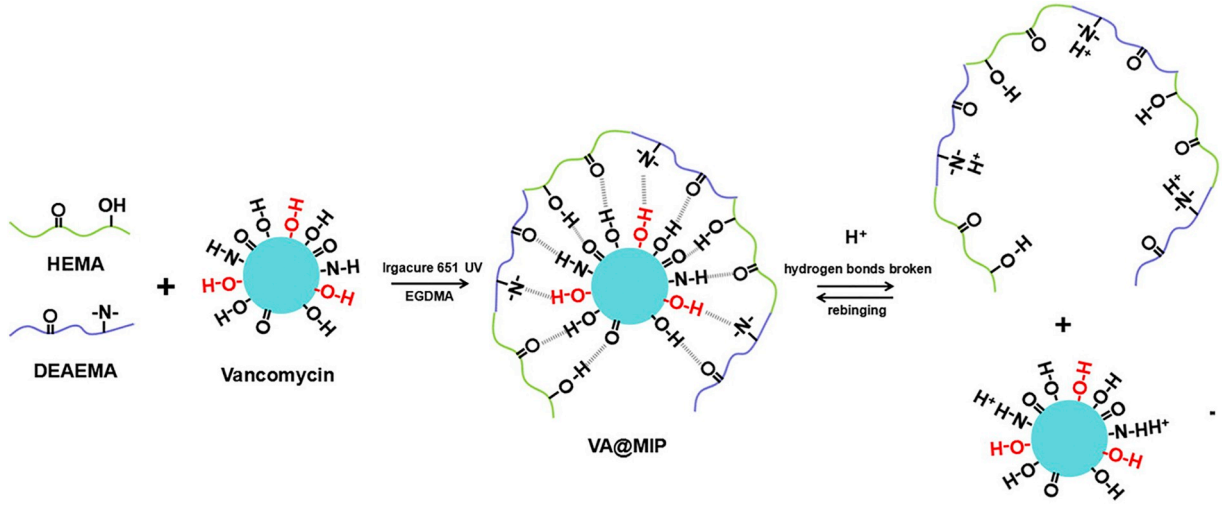

Fig. 10. Scheme of the synthesis of nanospheres and the release of vancomycin.
Reproduced with permission from Mao et al. 2017 [20].

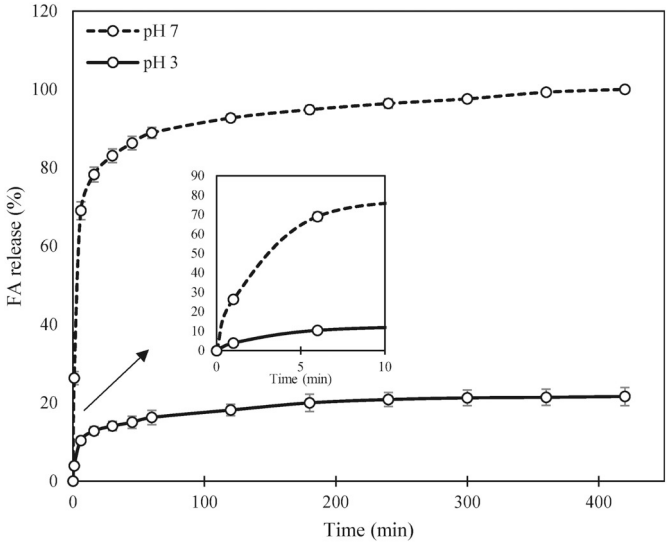

Fig. 12. Release of folic acid from an alginate/chitosan support according to pH and time.
Reproduced with permission from Acevedo-Fani et al. 2017 [21].

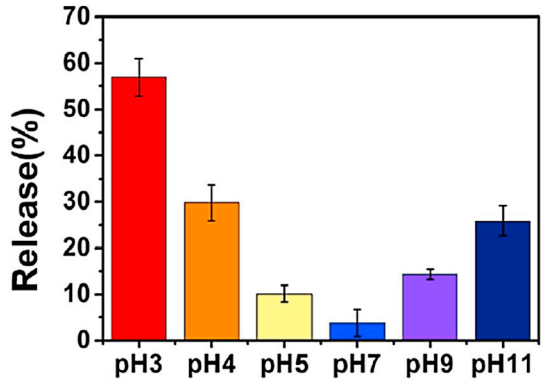

Fig. 13. Release of coumarin 102 from a spiropyran functional polymer as a function of pH.
Reproduced with permission from Jiang et al. 2016 [92].

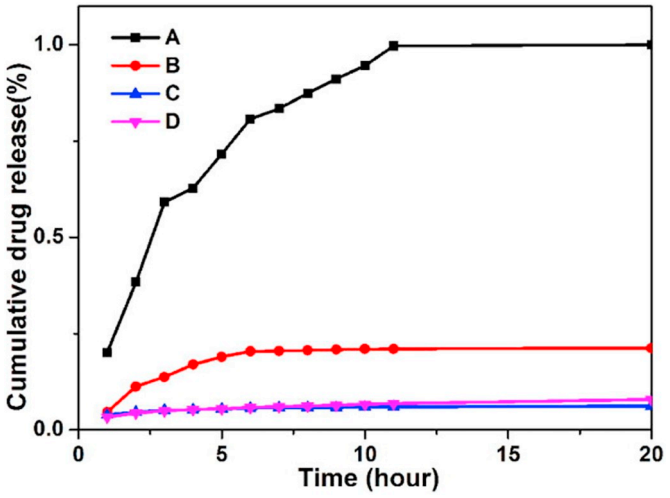

Fig. 14. Release of ibuprofen as a function of pH and time from a zinc MOF: (A and B) 1 nanosheet and multi-nanosheet at pH = 5 (C and D) 1 nanosheet and multi-nanosheet at pH = 7.4.
Reproduced with permission from Gao et al. 2017 [10].

regulate the release processes of active molecules. The first parameter is the solubility of the active molecule. Indeed, in several studies, the releasing process is possible only when the active molecule is soluble in the release medium [2,4,7,21,28,75]. At the pH where the solubility of the molecule is the highest, the release rate and/or amount will be maximized. The stability of the carrier is the second crucial property. Some substrates undergo more or less marked hydration phenomena depending on the pH, a swelling phenomenon can be then take over, allowing the release of the occluded molecules [1,13,15,17,19,23,29,30,33,35,36,74,75,87,89,92]. Other carriers can degrade completely or partially [5,8,10–12,14,16,18,20,22,24–26,31,32,37,39,41,76,86,88,90,91,104] or dissolve [6,9,15,27,42] at certain pH (acidic or basic) to release the active molecules. Some carriers can also permit the exchange of the active molecules occluded with the ions present in the solution, where the release takes part [3]. It is therefore important to choose the carrier, not only depending on the targeted active molecule that will be incorporated, but also on its stability as a function of pH.

This stimulus is widely used in the fields of medicine, agriculture, depollution of water and soils, and can be applied to a broad range of pH, molecules and carriers. Moreover, this system can be simply implemented. The drawback linked to the pH stimulus is the impossibility to put in place a “On-Off” system; indeed, the release is continuous, whatever the pH is, but it takes place at a large extent and at high rate at the target pH.

4. Photo-controlled release

The photo stimulus allows to control the release of active molecule(s) occluded in a carrier material by irradiation with different light sources. Ultraviolet radiation is widely used to start the releasing process by inducing the degradation of the carrier [45,46,49,51–53,57–59,63,78–80,85,93–101,107]. Other studies have shown that it is also possible to photo-release molecules using infrared [47,56,60,96], laser [50,60] (visible monochromatic amplified radiation of very high energy) or visible [44,48,54,55,58,61,77–79,81,101,105,106] lights. Two types of photo-controlled systems can be identified. In the first type, called “ON-OFF”, the release take place only in the presence of light [44–48,53–55,57–59,61,77,80,92–95,98–101,105,131]. In this category, some release systems are also reversible, either in the dark [100] or under a specific wavelength different from that used during release [47,54,55,57,92,101,131]. In the second type, the liberation is continuous, but accelerates in the presence of light [49–51,56,60,63,78,79,85,96,97,106,107].

A review of Xiao et al. [141] reports on studies based on photo-releasable molecules and the relative carriers (generally polymers). Four photoactive molecules, frequently used in polymer synthesis, have been identified: ortho-nitrobenzyl [44,46,49,51,63,80,81,94–97], coumarin [48,51–53,77,78,98], azobenzene [47,54,55,79,85,93,100], and spiropyran [56–58,101,105]. These molecules are integrated in the polymer matrix and their sensitivity to light allows the delivery of the eventually occluded molecules. The induced modifications can be of several types: degradation of the polymer, degradation of the bond between the photosensitive polymer and the active molecule, change of polarity of the polymer… Despite the different characteristics of the various polymeric carriers and active molecules, a common property can be identified: the presence, in each active molecule/polymer couple, of groups sensitive to UV rays (high energy) or to a specific monochromatic radiation.

As mentioned above, coumarin is a photosensitive molecule, studied by Jiang et al. [98] and Gao et al. [77] for photo-controlled release of a dye [98] (2-anilino-6-dibutylamino-3-methylfluoran, ODB-2) and an insecticide [77] (fipronil). In these two studies, modified coumarin, was used as carrier.

In the first study [98], coumarin-modified microcapsules were used as “photocages”. In this study, ODB-2 dye was used as fluorescent probe to follow the releasing process. The release was tested only under UV radiation at two specific wavelengths. The results showed that the release is effective only at 254 nm and not at 365 nm. Such a system can

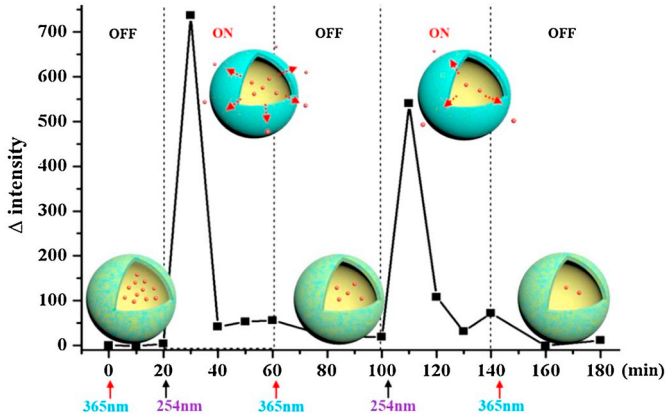

Fig. 15. Schematic diagram of the release of ODB-2 from coumarin-modified microcapsules with an on-off system.
Reproduced with permission from Jiang et al. 2017 [98].

be therefore defined as an "ON-OFF" type (Fig. 15). The mechanism is related to the decreases of the crosslinking of the material once irradiated that allows the release of the dye.

In the second study [77], fipronil (an insecticide) was covalently bounded to modified coumarin (Fig. 16). The generated compound can be photo-cleaved with blue light or sunlight, and the release is only possible in presence of light (Fig. 17b). Under blue light irradiation, 50% of the encapsulated fipronil was released in only 11 min, and 80 min was the time required for the almost complete release (Fig. 17a). Sunlight ensured a higher release than the blue light. CO_2 was also released with Fipronil as by-product.

Other organic molecules [45,59,99,107] have been applied in the photo-controlled release under UV irradiation. For example, Chiang et al. [99] used modified sodium alginate hydrogel to release a dye, the Rhodamine B. The release was controlled by UV radiation (at 365 nm) by inducing photo-isomerization that results in the dissociation of the host (hydrogel)/guest (Rhodamine B) complex. UV light provokes the vibration of the bonding of the hydrogel network, thus facilitating the release of Rhodamine B (Fig. 18a). This system is once again an ON-OFF type release system (Fig. 18b).

In 2016, Chang et al. [45] used a carrier based on galactose to release proteins (lectins). Once again, the release took place by irradiation with UV light (at 365 nm) and resulted to be relatively fast, with a released amount of 95% in 30 min.

In 2012, Dai et al. [85] used a CDBA complex (4-cholesterol-4′-(N,N′-diethylaminobutyloxy) azobenzene)-liposome as photo-controlled release carrier of ascorbic acid and catalase under UV radiation. The releasing system was reversible when the carrier/active molecule

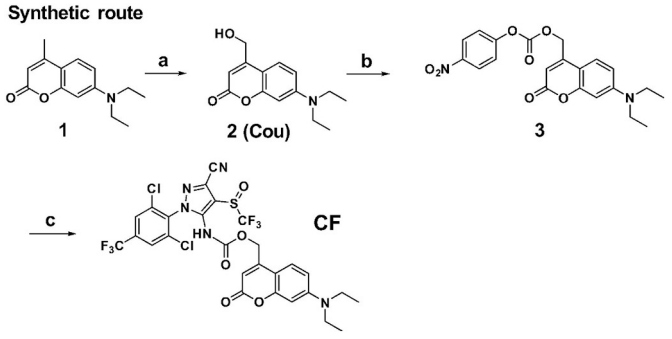

Fig. 16. Synthetic route of the modified coumarin-caged fipronil. 1: 7-(diethylamino)-4-methyl-2H-chromen-2-one; 2: alcohol intermediate; 3: third intermediate; a: SeO2 and NaBH4, CH3OH; b: p-nitrophenyl chloroformate and DIPEA; c: fipronil and DMAP.
Reproduced with permission from Gao et al. 2017 [77].

couple was kept at 37 °C, a very interesting temperature considering that the targeted application was as sunscreen. The release was possible thanks to the trans to cis isomerization of the CDBA during irradiation.

UV irradiation was also used by Zhang et al. [107] in 2010 to photo-release Zn^{2+} ions (ion influencing numerous receptors and channels on the cell surface) from a phenolic Schiff base derivative, used as carrier. In contact with Zn^{2+}, the –OH and -NH groups of the carrier react to form a complex containing the metal element. The release process was indirectly followed by observing the fluorescence emitted by the carrier during the photo-release. Indeed, the complex containing Zn is not fluorescent and an increase in fluorescence makes possible to quantify the decomposed complex portion. The increase in fluorescence was also related to the UV exposure time and consequently the release could be controlled by modifying the UV exposure time.

Other wavelengths than in the UV domain have also been used to photo-release active molecules (visible light [44,48,54,55,58,61,77–79,81,101,105,106], red or infrared light [47,56,60,96], laser [50,60]).

In 2012, Canto et al. [105] used a complex spiropyran-nanotubes of carbons that, irradiated with visible light, was capable to release Zn^{2+} ions. The encapsulation of Zn^{2+} ions is done by a chelation phenomenon and the release is totally controllable by irradiation with visible or UV lights. The irradiation of the material induces a phenomenon of decomposition which allows the release in an "ON-OFF" system.

In 2015, Wang et al. [47] used red light of 60 mW.cm^{-2} power and different wavelengths for photo-controlling the release of proteins (Bovine Serum Albumin (BSA)) contained in a supramolecular azobenzene-based hydrogel. The release was tested in absence of light or by using irradiation lights at 470 and 625 nm. The red light (625 nm) induces a gel-sol transition and the collapsing of the gel structure; the protein occluded in the hydrogel is then released. The use these wavelengths is interesting for medical application because the red light is able to penetrates into the biological tissues. The release results indicate that after 60 min, only 9% of the proteins are released in absence of light, 15% in blue light (470 nm), 45% in red light, and 83% in intense red light.

Finally, Su et al. [50], in 2017, tested the laser irradiation for the photo-controlled release of DOX (an anticancer) encapsulated in the nanosheets of a sandwich-like structure composed of molybdenum sulfide and mesoporous organosilica. The influence of the concentration of the solution, as well as that of the contact time between carrier and solution (5, 24, 48 and 72 h), were taken into account. The release of DOX was dramatically enhanced when exposed to the laser beam at 5 W.cm^{-2}. However, the kinetics was slow, with a released amount of only 8% in 1 h (Fig. 19).

For the photo-controlled release, the carrier material is the component that more often governs the process, because it generally contains the light-sensitive molecule. As the pH-controlled release, photo-controlled release is also widely applied in several domains. The major drawback in photo-controlled release is the use of UV light that is not compatible with medical applications.

Even if the most used stimulus for the photo-controlled release is the UV radiation (short wavelength and very energetic), other lights at different wavelengths can also be used. Particular interest can be given to red light that can be used in the medical field, because of its capacity to penetrate the human tissues, triggering the release of drugs [44,48,54,55,58]. On the other hand, the use of visible light results extremely interesting in the field of agriculture to release active molecules (fertilizers, pesticides, nutrients…) at target moments of the plants' life cycle [77–79,81]. However, the development of new carrier materials, able to set-off the controlled release at different wavelengths in dependence of the different applications, remains still an open issue.

5. Thermo-controlled release

Stimulating the release by inducing a temperature variation is another type of stimulus [4,11,24,34–36,63–66,82–84,92,93,110].

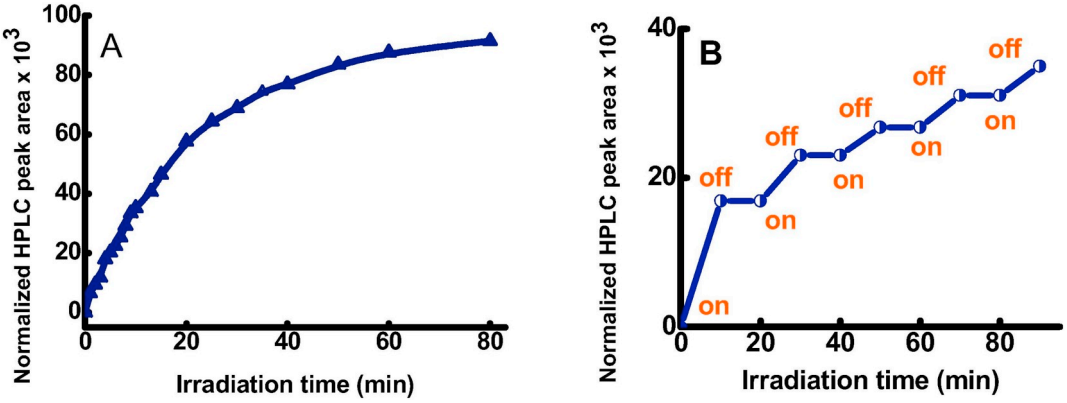

Fig. 17. Release of Fipronil to blue light from coumarin as a function of time (A) and controlled-release according to irradiation (B). Reproduced with permission from Gao et al. 2017 [77].

In 1991, Bae et al. [64] achieved to thermo-control the release of indomethacin, a nonsteroidal anti-inflammatory drug, from a temperature-sensitive polymeric carrier. The releasing process was carried out in PBS solution at pH = 7.4 under constant stirring, at 25 °C and 30/35 °C, and the concentration of indomethacin was followed by UV spectrophotometry. The more effective release (in quantity and rate) was measured at 25 °C. This high performance can be explained by the different permeability between the phases poly(*N*-isopropylacrylamide), denoted poly(NIPAAm) and polytetramethylene ether glycol, denoted PTMEG at the two temperatures. If the permeability of the poly(NIPAAm) phase is negligible at 30/35 °C, and increases at 25 °C, that of the PTMEG phase is maximized at 35 °C. Depending on the intended application, the desired duration of the release can be obtained by mixing different proportions of the two polymers.

As described in Section 3, Li et al. [24] used a core-shell structure for the pH- and thermo-controlled release of Doxorubicin hydrochloride (DOX). The core, being sensitive to pH variations, allows the pH-controlled release. The shell is sensitive to temperature variations and directs the thermo-controlled release. The results showed that the release was higher at body temperature (37 °C) than at lower temperature (25 °C) (Fig. 20). This is explained by the exceed of the lower critical solution temperature (LCST) of the shell, temperature below which the components of the mixture are miscible. The LCST of poly(N-iospropylacrylamide)-*co*-glycidyl methacrylate-co-*N*, *N*-bis(acryloyl)cystamine, the only component constituting the shell is 32 °C in aqueous medium. Below this limit, the microspheres swell. When this temperature is reached, the microspheres loose volume, thus inducing the collapse of the pore structure of the material and the consequent expulsion of the active molecule.

As already mentioned in Section 3, Jiang et al. [92] performed the

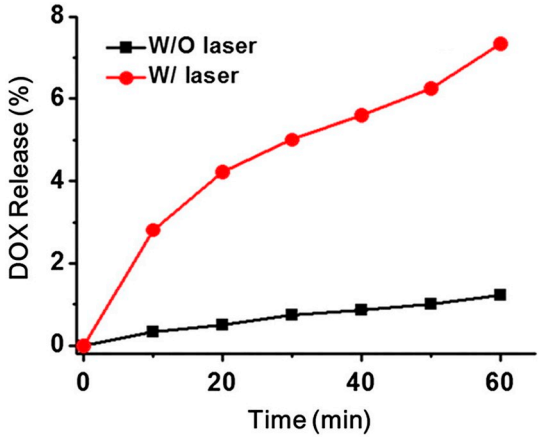

Fig. 19. DOX release from molybdenum sulfide/mesoporous silica nanosheets as a function of time and the presence of laser irradiation. Reproduced with permission from Su et al. 2017 [50].

controlled release of coumarin 102 using a functionalized polymer with spiropyran, as a carrier. The results showed that the release of coumarin 102 was mainly pH-controlled, but the temperature can also play a role in the release: the release is greater at 60 °C than at 25 °C, with an increase of 20% in 120 min. This behavior can be explained by a decrease in the hydrophilicity of the carrier once reached the lower critical solution temperature (LCST) of the copolymer. The increase in temperature therefore induces a contraction of the carrier and the release of the active molecule.

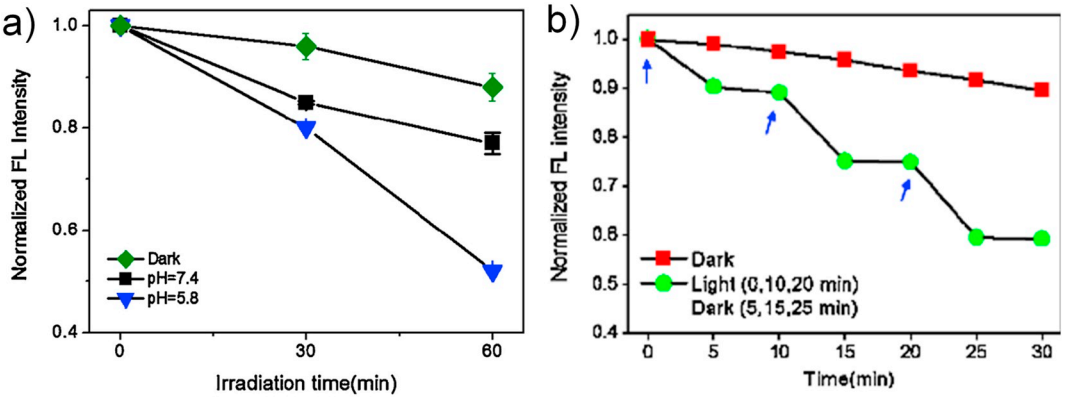

Fig. 18. Release of Rhodamine B from a modified sodium alginate hydrogel as a function of time (a), "ON-OFF" system (b). Reproduced with permission from Chiang et al. 2015 [99].

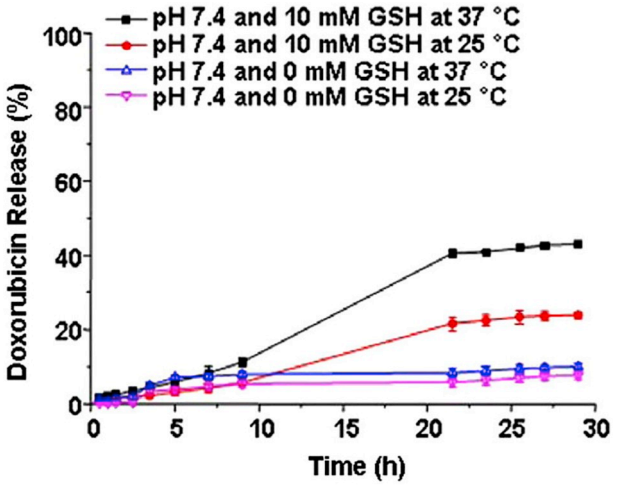

Fig. 20. Release of DOX from an organic core-shell structure as a function of temperature.
Reproduced with permission from Li et al. 2014 [24].

Rivera et al. [65] focused their attention to the thermo-controlled release of ciprofloxacin, a broad-spectrum antibiotic from a commercial Li-fluorohectorite. The release of ciprofloxacin from the composite was carried out in synthetic gastric acid at 37 °C, 50 °C, 65 °C, 75 °C and 85 °C. The release was followed by UV spectrophotometry. The releasing kinetics was much higher at high temperatures (Fig. 21a and b). The authors explain this behavior by the possibility of the active molecule to reach an energy level higher enough to pass over the activation energy barrier needed to release the molecule from the carrier (Fig. 21b).

Some biomolecules, such as thermosensitive liposomes, can also be used as carriers for thermo-controlled release [137]. They are able to release the incorporated active molecules/active principle when the "gel to liquid crystalline" phase transition temperature is reached [136]. During the transition phase there is the formation of "open liposomes" characterized by the presence of pore defects that allow the release of the active molecules.

The "thermo-controlled" release is always linked to the activation energy barrier of the release process. From a physical point a view, the release of the molecule is caused by the change of volume of the material with a variation of temperature and the consequent increase of the permeability of the material [4,24,35,36,64,66,82,84,92], or by a change of physical state (sol-gel transition) [63]. As the stimuli previously described, thermo-controlled release is also an ancient and well established system that is consequently widely used. It has the advantage to be applicable to different types of carriers and active molecules. The major drawback of thermo-controlled release is, as for the pH-controlled release, the impossibility to be implemented in an "On-Off" systems. The release takes over in a continuous way, whatever the temperature, but it is maximized when the target temperature is reached.

6. Redox-controlled release

Other stimuli like the variation of the redox potential [6,24–26,67,68,102,103,108,109,124] can drive the controlled release of active molecules.

For example, Song et al. [103] carried out the redox-controlled release of a dye (Dextran Alexa Fluor® 488) from multilayer films of organometallic polyelectrolytes composed of monolayers of poly(ferrocenylsilane)s (PFSs). To probe the disassembly of PFS films as a function of the redox potential, cyclic voltammograms were recorded. The release of PFSs results to be greater at 0.4 V (highest degree of oxidation) compared to −0.4 V. During the oxidation process, positive charges are introduced into the ferrocene units of the PFS chain. These imbalanced charges induce the disassembly of the polyelectrolyte and thus the release of monolayers of PFSs. In some multilayer films, an anionic dye was then encapsulated by replacing specific layers, in the PFSs at different distances from the surface of the compound, by the dye molecule. The release of the dye was monitored by fluorescence spectroscopy at various oxidation degrees. The results showed that the farther the dye was from the surface layer, the lower the kinetics of release was. At higher oxidation degree, the released amount is bigger. This can be related to the more important disassembly of the multilayer film at high oxidation degrees.

This same stimulus was used by Scheid et al. [102], in 2016, to control the release of malachite green from hollow polymer sphere containing metallic elements. The carrier compound was synthesized by a procedure permitting to obtain "core-shell" type materials. The results showed that, depending on the chosen release solution (water/ethanol solution with or without $FeCl_3$), the release capacity varied. This is explained by the decomposition of malachite green under oxidizing conditions.

For the "redox-controlled" release, the key parameter is to select a redox-sensitive carrier. In the case studies reported in the cited works, the carrier materials contained iron that can present different oxidation states. With the application of an electric field, a redox reaction is then induced. Due to the redox (mainly oxidation) process, the created charge imbalance on the carrier provokes the release. Redox-controlled release is generally based on the use of iron-based carrier. The low

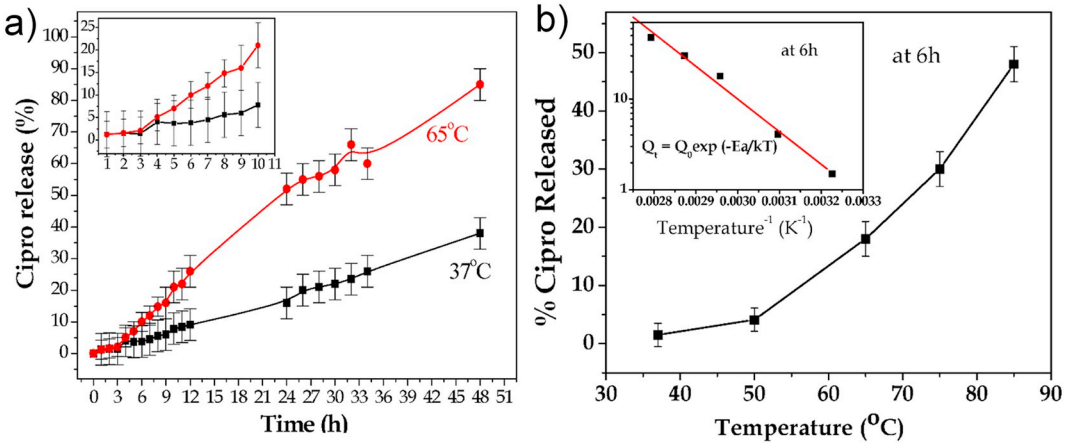

Fig. 21. Release of ciprofloxacin from fluorohectorite-Li as a function of temperature and time (a) and release after 6 h as a function of temperature (b).
Reproduced with permission from Rivera et al. 2016 [65].

choice of carriers types is the main drawback to the implementation of this stimulus. However, due to its versatility "redox-controlled" release is used in several domains.

7. Other stimuli

This section presents the more recent advances in the field of controlled release and the future trends in the domain. Moreover, controlled delivery systems that are seldom applied and their applications are also taken into account.

The first stimuli reviewed is the application of a magnetic field [69–73] to induce the release.

For example, in 2013, Oliveira et al. [69] achieved the release of Doxorubicin (DOX) from polymersomes (polymeric vesicles) using a magnetic field to initiate the release of DOX. The releasing process was carried out in PBS medium at pH = 7.4. The results showed that in the presence of a magnetic field, the release is activated (Fig. 22). Indeed, the application of a magnetic field induces local temperature increases (at the Maghemite level of the carrier) that causes the augmentation of the permeability of the polymersome membrane and the increasing of its porosity.

Ultrasounds stimulation was mentioned by Husseini et al. [134] as way to trigger the release of doxorubicin (DOX) from commercial organic micelles, called Pluronic P105. The results show that the release is not function of the ultrasonic intensity. The releasing threshold was identified at around 0.3 W/cm^2 of power. DOX release is made possible thanks to the cavitation effect, phenomenon also described by Di et al. [125]. Other phenomena have been also described in the literature to be at the origin of the release by ultrasounds. Yohe et al. [133] explained that ultrasounds can induce a pressure variation that provokes the replacement of the air present in the carrier's pores with water, thus allowing the release of the active molecule. For Wang et al. [126] the vibrations of the capsules and the thermal effect induced by ultrasounds are the key parameters for the drug release.

Mechanical stimuli such as stretching [112,113,130,132] or shear stress [111,114] can also be used to start off the release process.

Di et al. in 2015 [112] have, for example, developed an elastomer film for the controlled release of Doxorubicin and insulin by stretching. The drugs were encapsulated on a spherical microgel placed at the centre of the elastomer film. When the film is stretched, the spherical microgel turns into an ellipsoid. The surface is then stretched and, as the diffusion that is function of the surface increases, the release process is induced. Moreover, the authors observed that the elastomer possess a higher Poisson's ratio at higher stretching degree that provokes a compression of the microgel fraction: the process is fully reversible. Kim et al. [113] have also used this stimulus to trigger the release of drugs contained in microspheres placed in an elastomer film. For them, the release is induced by the decrease in volume of the microspheres that leads to the expulsion of drugs. Two other teams used the stretching stimulation to release drugs from core-shell structures [130,132]. In these cases, the release is induced by a cracking of the shell under stretching. It is a non-reversible process contrarily to the two first configurations. This stimulus presents several advantages; it can be triggered by the body movement and it can be combine with other devices. For example, if coupled with elastomers, the carrier becomes deformable and can be eventually refilled, which represents an important advantage. Unfortunately, this stimulus is always used for drug release and is not applicable in other fields.

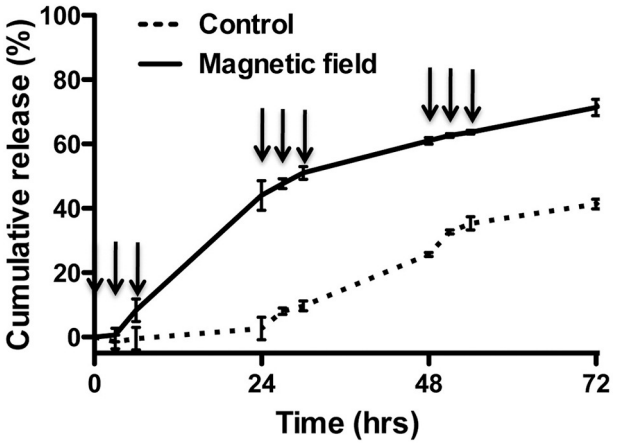

Fig. 22. Release of DOX from Maghemite loaded polymersomes as a function of time and the application of a magnetic field.
Reproduced with permission from Oliveira et al. 2013 [69].

Shear stress was used as stimulus by Korin et al. [111] to release drugs from poly(lactic-*co*-glycolic acid). The idea of this study is to mimic the obstruction of blood vessels. The results showed that shear stress induces a mechanical expulsion of the drug from the carrier. This phenomenon was also observed by Holme et al. [114] that performed drug controlled-release from liposomes. The advantage of this stimulus is related to the possibility of performing drug release into human vessel, but the applications remain limited.

Biological stimuli can also be used to trigger a release process. There are different types of biological stimuli like specific receptors, adenosine-5′-triphosphate (ATP) concentration, glucose level, presence of enzyme…

Jiang et al. in 2018 [118] used receptor-controlled release to trigger delivery of Brain-derived neurotrophic factor from a polymer poly (ethylene glycol)-*b*-poly(L-glutamic acid). The encapsulation of the molecule into the polymeric carrier stabilizes the molecule thus avoiding its degradation. When the molecule comes close to brain vessels, it combines with specific receptors and the release is then observed. This mechanism was also described by Harris et al. [128] by using the same carrier.

ATP (adenosine-5′-triphosphate) was also used as biological stimulus in several studies. For example, Mo et al. [116] developed a DNA-graphene hybrid containing an anticancer drug (Doxorubicin) and an ATP aptamer, a molecule which can combine with ATP. In the presence of ATP, in human body, ATP and ATP aptamer form a complex that causes the dissociation of the carrier and promotes the drug release. The same mechanism was observed by Qian et al. [127] with the ATP-controlled release of doxorubicin.

Glucose level was used as stimulus by Gordijo et al. [117] to start off the release of insulin from nanohybrid particles prepared starting from manganese oxide/Bovine Serum Albumin nanoparticles, coupled with enzymes (glucose oxidase and catalase) in presence of methacrylic acid and acrylamide. In the presence of a high glucose level, the pH decreases and the permeability of the carrier is enhanced consequently promoting the release of insulin. This mechanism of release was confirm by other authors [119,142].

Enzyme can also be used as a stimulus for controlled release. Several types of carrier have been developed for this purpose [143]. For example, Park et al. [115] developed a mesoporous silica/cyclodextrin hybrid to trigger the release of guest molecule after a contact with α-amylase and lipase. The combination of the carrier with these enzymes induces the degradation of the organic part of the carrier. The guest molecule is then free to be release from the degraded carrier (Fig. 23).

The same method was employed by Gu et al. [129] with a polymeric carrier and by Pak et al. [139] with a peptide/lipid carrier. In all these studies, the carrier was degraded by enzymes in human body allowing therefore the release of guest molecules or drugs.

Finally, drugs can also be release by an induced biological response in contact of the carrier be used as adjuvant in vaccines [120]. Adjuvant is in this case used to induce a strong and adapted immune response of the human body leading to the release of the active principle. Others authors have studied nanoparticles as antigen carriers for vaccine delivery [135,138]. In the study of Wendorf et al. [135], poly(lactide-*co*-

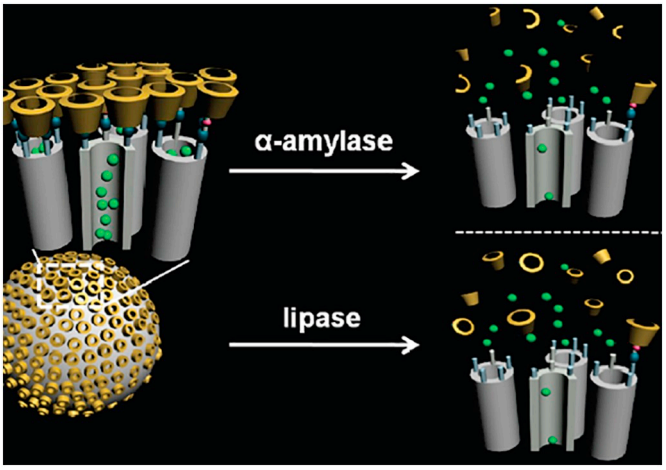

Fig. 23. Mechanism of enzyme-controlled release of guest molecules from mesoporous silica/cyclodextrin carrier.
Reprinted with permission from Park et al. 2009 [115]. Copyright 2009 American Chemical Society.

glycolide) polymers nanoparticles were used for protein antigen adsorption and controlled release. This methodology reduces the amount of excipients. The results are compared with results obtained with aluminium hydroxide. The conclusion of this study is that, after lyophilisation and formulation, the nanoparticles act as an efficient vaccine delivery system. Some nanocages can also be used as carrier or directly as drug; in this case the target molecule become active only when coming in contact with particular tissues of the human body. For example, Jiang et al. [121,122], used copper/zinc superoxide dismutase as carrier for proteins to operate their controlled delivery in the brain. Their formulation allows to reduce infarct volumes and is better tolerated by brain microvessels. With the same type of nanocage, Natarajan et al. [123] try to determine the effects of these nanoobjects in the tuning of glucose and lipid homeostasis in mice. Their formulation improved lipid metabolism without altering glucose homeostasis in mice with a rich fat diet. Efremenko et al. [140] developed a catalytic nanozyme to protect animals from exposure to poisonous organophosphorous compounds. The used spherical nanocage preserves the catalytic activity of the enzyme and it increases its stability. Moreover, the enzyme activity is improved when compared to that of the bare enzyme. In these cases, the active molecule does not need to be release in the medium to be active.

All the stimuli described in this section are promising way to deliver drugs in the human body. They have the advantage to be fully controllable, as the releasing occurs only in the presence of the stimulus. They are “On-Off” systems, but unfortunately their applications remain restrained and only few of them might be implemented in applications in other fields as depollution or agriculture.

8. Conclusion

Stimuli-controlled release is widely used in many fields such as pharmaceuticals, biology, cosmetics, agriculture, chemical and dyes industry… Several stimuli can be applied to induce the release of a molecule of interest from a carrier material: pH and temperature variations, changes in the redox potential, exposure to light, to a magnetic field, or to mechanical forces, interaction with biological compound or biological responses… In this review, the principal stimuli-controlled release and connected mechanisms have been presented.

Fig. 24 summarize the various stimuli described in the literature and the parameters that control the release. The surfaces of the slices of the cake in Fig. 24 give an indication of the extent of application of the different stimuli.

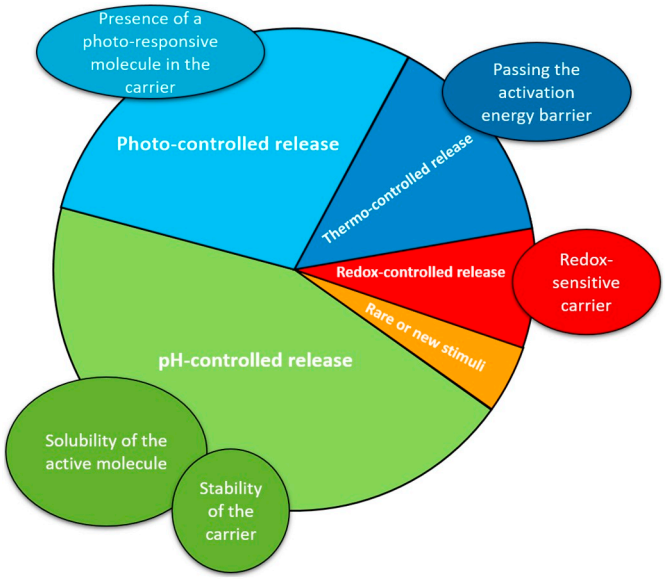

Fig. 24. Scheme of the importance of each stimuli-controlled release and their control parameters.

The pH variation, in green, is clearly the more widely used stimuli to control a release. Indeed, several type of materials can be used as carriers in pH-controlled release and its implementation is generally simple. Photo-controlled release (light blue slice) is also widely used, particularly when performed with UV light. But other wavelengths can be also efficiently applied in specific domains (red light or laser in medical field, visible light in agriculture…). The main challenge connected to photo-controlled release is to develop new carrier materials able to work under irradiation with different wavelengths, in order to be applied to a wider panel of applications. Nevertheless, even if other stimuli-controlled release systems are less widely used, they remain interesting options to be implemented in specific domains.

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Declaration of interest

None.

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