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Polymers as controlled delivery systems in agriculture: The case of atrazine and other pesticides

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ABSTRACT

The exponential growth of world population of the last years increases the necessity to optimize the technologies associated to the agricultural sector. In this direction a smart use of pesticides is able to guarantee high productivity, avoiding problems related to their losses with consequent pollution issues. An extremely promising solution is represented by slow-release pesticides that are able to increase pesticides efficiency, lowering their application frequency, preserving the environment but still satisfying the requirement of the plants. So, in the last years, research efforts were dedicated to the development of materials that, at the same time, are cheap, environmental friendly and biodegradable. The aim of this review is to focus on polymeric devices used as slow release systems of pesticides. In particular strong attention will be dedicated to different polymers and different formulation strategies in order to understand the high amount of possibilities and performances of these devices.

1. Introduction

Global food production in the last half a century benefitted from the intensive use of pesticides, fertilizers, water, and energy. Pesticides play a key role in enhancing crop production [1] by eradicating, repelling or mitigating any pest and they are usually classified based on their intended target organism. However, it is estimated that almost 90 % of the pesticides actually are lost due to their degradation, photolysis, evaporation and surface runoff, and only 0.1 % are finally deposited on the harmfully biological targets [2,3]. Thus, they became a source of concern due to the large proportion released into the environment as a potential hazard [4]. Not only this, in some cases pesticides suffer from insufficient target specificity, nontarget effects, and poorly timed application [5]. Pesticides include a wide range of herbicides, insecticides, fungicides, rodenticides, and nematicides. Approximately 2 million tons of pesticides are used each year, out of which 47.5 % are herbicides [6,7]. Among these a good example is represented by atrazine, a synthetic herbicide widely used in several crops, and is one of the most consumed pesticide in the world with an annual consumption of 70,000 to 90,000 tons [8]. However, it represents a big environmental risk due to its low biodegradability and, the long half-life in water coupled with its moderate solubility is a potential hazard also to human health, as atrazine can easily migrate into groundwater and subsequently into food [9]. To overcome these problems, with atrazine and pesticides in general, different controlled release formulations (CRF) or controlled release systems (CRS) have emerged and are being proposed as an effective way to improve the utilization of pesticides via prolonging the effective duration, reducing the pesticide dosage, saving manpower and energy as well as having a reduced toxicity [10–14]. These particular pesticide formulations are designed to be both environmentally friendly and safe for use, while also being responsive to their surrounding micro-environment. They exhibit an intelligent and sophisticated behaviour that results in a more precise and controlled release profile [3].

Typically, a carrier is used to deliver the pesticides as it aids in refining selectivity and effectiveness, pesticides are encapsulated within and this enhances their safety and handling [15]. The CRS can be classified into two main categories: matrix and reservoir systems. The former is the most suitable and widely used method, the pesticide is dissolved in the material, that it is processed to the required shape. The latter, is obtained most notably by a method of microencapsulation, small particles (solid, liquid, or gaseous) are coated with a thin coating [16]. Materials such as clay minerals, siliceous materials, polymers, and a variety of organic an inorganic materials have been explored for their feasibility in pesticide formulations [17]. Due to the low cost, free availability, nontoxicity, and biodegradability of natural polymers, they are preferred as pesticidal carriers. The aim of this review is to describe the main systems and techniques used to achieve the controlled or sustained release of atrazine and other pesticides focusing on their applications. As already anticipated the carriers considered will be mostly the biodegradable ones, with an emphasis on natural biopolymers as they tend to be preferred to synthetic ones thanks to them being more eco-friendly and cost-effective [18]. Indeed, the focus in the last few years shifted from

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synthetic biopolymers and, more importantly, from petroleum-based polymers to natural occurring ones.

2. Mechanisms of controlled release of pesticides

Before delving into each CRS type and the materials used, it is of key importance to understand the mechanisms of how a pesticide molecule is transported through the matrix into the surrounding environment in a slow or controlled manner. In general, it is assumed that CRS of pesticide will behave the same as CRS of drugs, on which many studies have been carried out [3]. Following what is commonly known in literature the release rate can be controlled either by diffusion, degradation or osmosis. Fig. 1 shows the four possible release mechanisms: diffusion-controlled release of pesticide through water-occupied pores, direct diffusion through the polymer, degradation-controlled pesticide release and solvent controlled release of pesticide due to osmotic pressure.

For the most part, diffusion is the main release mechanism and it occurs through the water molecules that occupied the pores and relies on the porous structure of the matrix.

Going more into details, water seeps through the coating layer and by filling the pores shifts the active ingredient (AI) towards the surface, as this process takes some time it results in a controlled release (Fig. 1) [21]. AI outflow is also influenced by factors such as the thickness of the membrane and its solubility in water. The release rate follows a zero-order kinetic and the model assumes that the physical attributes and dimensions of the system do not change throughout the release (no loss of bulk polymer or degradation). Moreover it also assumes the absence of burst release. The self-diffusion coefficients can be estimated through NMR [22]. Osmosis-controlled release and swelling-controlled release is based on osmosis, the total flow of water across a selective membrane governed by a pressure gradient by the membrane itself. In Fig. 1d the molecules move towards the environment owing to the pressure gradient, the controlling parameters are the diffusion coefficient of the AI and the relaxation of the polymer chain [23].

In the same way, due to hydrostatic pressure, water absorbing matrices are used for water-soluble pesticides for their swelling behaviour. After being placed in water or buffer, the solvent diffuses into the polymer network causing swelling and volume expansion. The swelling behavior is characterized by two moving fronts: (i) the swelling interface which moves inward; and (ii) the polymer interface which contacts water and moves outward. The release of the cargo is determined by the rate of chain relaxation and/or the drug diffusion rate through the polymeric system [24]. Another type of diffusion occurs through polymer diffusion (Fig. 1b), and it is controlled by solute motion through the matrix. The release is augmented, in general, by the porosity of the matrix that can increase the surface area suitable for AI dissolution. So, in this case the diffusion rate also relies on the physical parameters of the pesticide like the size, morphology and water solubility [3]. Finally, the release caused by surface erosion or degradation of the polymer matrix (Fig. 1c) can be described through Hopfenberg's model where the zero-order surface release of the AI determines the rate-limiting step of release. This zero-order process is essentially a combination result of dissolution and erosion processes at the polymer surface. Therefore, this empirical equation is appropriately applied for the surface-eroding particles since this model assumes that the release rate is controlled by the dissolution process on the surface. Biodegradable polymers such as polyesters are an example of this type of release, as they are expected to release the pesticide through hydrolytic or enzymatic degradation. Surface erosion in general is preferred, as the erosion kinetics are reproducible and thus can be controlled. Moreover, with only surface erosion water sensible AI are protected. Bulk erosion on the other hand is less predictable and does not protect the pesticide from the environment, making it suboptimal for a controlled delivery [3].

2.1. Types of controlled release systems

Controlled release systems for pesticides can be classified according to their structure. As shown in Fig. 2 it is possible to find particles, films, capsules, emulsions, layered systems, hydrogels, porous beads, and fibres.

Capsules have been and still are widely used in pesticide delivery and play a key role in the development of CRS. The pesticide is coated onto the material, usually natural or synthetic polymers, and then released continuously. The capsules can be of different dimensions depending on the application, indeed the first commercially available CRS of a pesticide was microencapsulated methyl parathion, in 1974 [14]. As briefly mentioned above, encapsulation can reduce toxicity, mask odour, improve stability and efficacy by decreasing the required pesticide while also potentially reducing environmental pollution [30,31].

Furthermore, encapsulated active ingredients usually have a longer half-life as they are protected from external factors, such as sun and rain [14]. Several other systems different from capsules have been developed and proposed, such as silica, clay/organoclay, emulsion, nanometals, hydrogels, and waxes [10,32–35]. The following sections will give a description and examples for the controlled release of pesticides in a wide range of systems from nanoscale to hydrogels.

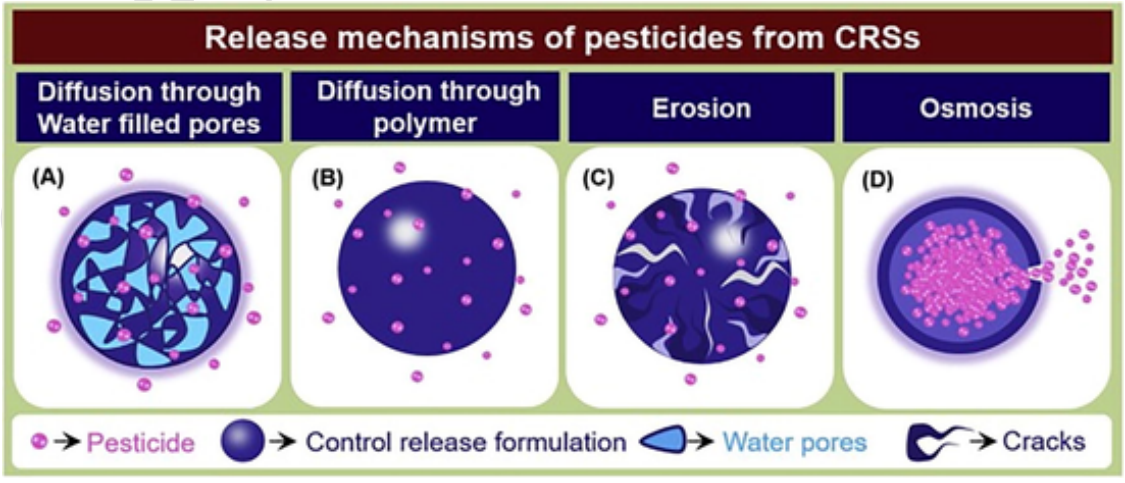

Fig. 1. Schematic illustration of release mechanisms of pesticides from CRSs. (a) Diffusion of pesticide through water-filled pores, (b) Direct diffusion through the polymer, (c) Pesticide release due to polymer degradation, (d) Pesticide movement due to osmotic pressure. Reprinted with permission from Elsevier [3].

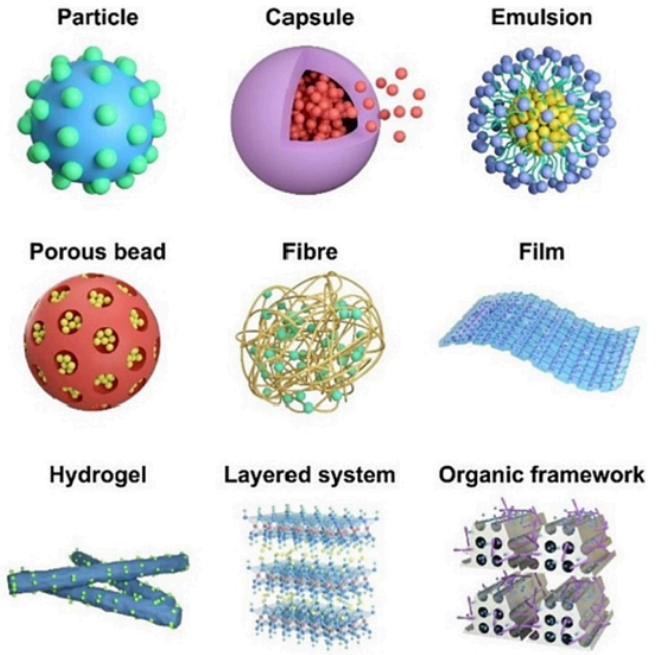

Fig. 2. Types of controlled release systems. Reprinted with permission from American Chemical Society [14].

2.2. Nano based systems

The term "nano based system" indicates a structure whose size is below 100 nm in at least one dimension, according to IUPAC. They are designated with a nano prefix, and are claimed to exhibit novel properties associated to the small size of their components [32]. The agricultural sector has seen an astounding increase in the use of nanotechnology as well as nanomaterials to manage better crop production [36]. The potential resides in the high surface/volume ratio, the wide range of available materials, and the fact that nanoparticle size is usually the driving force in their colloidal behaviour and increased relative surface area [37,38]. Moreover, in the case of nano porous structures they possess ordered pores and large pore volumes. They can be synthesized as inorganic, organic, and inorganic–organic hybrids with tunable porous structures and morphologies [39,40]. Nanoparticles, nanocapsules, and nanospheres are the most frequently synthesized nanosystems where the AI can be entrapped, encapsulated, or attached to NPs. For instance, a nanocapsule delivery system loaded with two AIs, validamycin and thifluzamide, to prevent and control rice sheath blight was developed by Cui et al. The nanocapsule system is based on a W/O/W double emulsion combined with high pressure homogenization. Once loaded with the pesticides it showed a mean particle size of 260 nm.

Their findings demonstrated that the bioactivity of the dual-functionalized system was significantly better than that of the commercial formulations as the dual-functionalized system displayed a clear synergistic effect between the two AIs improving the bioactivity and the nanocapsules showed better spreading performance with their sustained controlled release [41]. Also avermectin (AVM) can be encapsulated into nanocarriers to improve its biological activity. In this direction Chen and coworkers reported the synthesis of zein modified nanoparticles to encapsulate AVM through hydrophobic interactions. Zein was modified by dialdehyde carboxymethyl cellulose (DCMC), making a conjugate (Z-DCMC) that is more hydrophilic than zein. Dynamic light scattering analysis showed that the nanoparticles had an average particle size of 68 nm. Moreover, AVM encapsulated in Z-DCMC exhibited enhanced biological activity with the lethal concentration (LC_{50}) decreasing from 199.89 to 106.41 mg/L compared to non-encapsulated AVM. In addition to this, the wettability and protection from UV light increased and the final release rate is a "first order" release driven by electrostatic interactions between carrier and cargo [42]. In another recent study by Wang et al. multifunctional avermectin/polysuccinimide with glycine methyl ester nanoparticles (AVM-PGA) were prepared. Like in the previously cited paper the biological activity went up, using an in vitro releasing test the mortality rate of *Plutella xylostella* was almost 100 % after 48 h, while for free AVM it was only 51.5 %. Moreover the release, driven by Fickian diffusion, was significantly more efficient as the nanoparticles showed a better uptake and transportation performance. Additionally, the PGA performed a good growth promoting effect on rice [43] in terms of plant fresh weight and height with a dramatic difference at 6.25 μg/mL respect to control group. The effect of particle size on the sustained release properties and biological activity of AVM was also investigated. The delivery system was prepared by emulsion polymerization using PLA, with a decrease in particle size the release rate and biological activity increased due to the increased surface are and enhanced adhesion and penetration. It also showed good anti-photolysis properties and stability as already seen above [44].

An other category widely studied is represented by mesoporous hollow silica nanoparticles (MSN). They have received considerable attention owing to their controllable mesoporous structure, large pore volume, easy surface modification and intrinsically large cargo loading content [45]. Early studies by Li et al. and Liu et al. synthesized and characterised hollow silica nanoparticles loaded with avermectin and validamycin. In both paper MSN were prepared through a sol–gel route [46].

The first research demonstrated how the shell thickness has a significant impact on avermectin release. Increasing the shell thickness in the range of 5–45 nm led to a more sustained release by decreasing the release rate of the pesticide from MSN, showing that the shell thickness is one of the main controlling factors for the active agent release from such systems [47]. While, for the second one a high loading of the pesticide (36 wt%) was achieved and the release profile from the nanoparticles showed a multi-staged release pattern [48]. However, in both cases the release exhibited an initial burst release, this uncontrolled premature release of pesticides from bare MSNs restricts their application. In this sense recent research proposed surface functionalization of MSN to construct multifunctional pesticide delivery systems. This can provide an alternative for sustained pesticide release responsive to external or internal stimuli [49–53]. Xu et al. modified MSN with carboxymethyl chitosan for sustained azoxystrobin release. They were able to create it through a novel strategy of emulsion-based synchronous pesticide encapsulation and surface modification of MSN with CMCS, that enabled a loading content of 21 %, a better bioactivity against Phytophthora infestans, and a pH-sensitive release [54]. Functionalization of MSN surface can be achieved also through grafting. Indeed, researchers grafted poly(glycidyl methacrylate-co-acrylic acid) (P(GMA-AA)) onto MSN using seeded precipitation polymerization and tested the resulting composite with Abamectin (ABA) loaded as a model pesticide. The release data showed two stages of ABA release: an initial rapid release stage that help ABA to reach a sufficient amount to control the insects target, then the later slow release stage useful for minimizing the amount of ABA that reaches nontarget organisms.

The findings revealed that ABA@MNS@P(GMA-AA) had a high pesticide-loading efficiency of 33 wt% and pH-dependent pesticide release. Furthermore, it also showed to be effective control of rice pest *Cnaphalocrocis medinalis larvae*, and to have a long-term efficacy [55]. Polymer materials and polymeric micelles have been used for some time due to their ability to provide sustained release of the associated active compounds. In particular, as will be seen in a following section, natural polymer materials used as pesticide polymer-controlled release carriers have become a new hot spot. Campos and coworkers developed polymeric nanocapsules based on poly(ε-caprolactone) (PCL) and solid lipid nanoparticles (SLN) that were used as carriers for a mixture of car-

bendazim (MCB) and tebuconazole (TBZ), a systemic benzimidazole fungicide and a triazole class systemic fungicide with a broad spectrum of action respectively. The nanocapsules showed an average diameter of 542 nm, high encapsulation efficiencies were achieved (>99 %), cytotoxicity assays showed that encapsulation of the fungicides decreased their toxicity, and the release profiles of MBC and TBZ were modified when the compounds were loaded in the nanoparticles. Indeed, the researchers did soil layer release experiments, because in this system, interactions may occur with the soil (Fig. 3). Loading of the fungicides into the nanoparticles decreased the amounts of the fungicides available for leaching, thus the possibility of reaching toxic ranges concentrations to non-target organism in the environment is low [56]. In Fig. 3 the comparison with commercial formulation showed the sustained release and better performance of the device produced.

Ye and coworkers employed a method involving self-assembly to create micelles for diuron encapsulation. These micelles were formed using an amphiphilic carboxymethyl modified chitosan with photo labile 2-nitrobenzyl side groups, referred to as NBS-CMCS. The study observed a remarkable encapsulation efficiency of 91.9 %, indicating the effectiveness of this approach. Furthermore, the sustained release of diuron was demonstrated and under normal circumstances, where incident light was absent, the release of diuron was minimal, suggesting the stability of the micelles. In contrast, under simulated solar irradiation, a substantial release of diuron was observed, with 96.8 % of the entrapped pesticide being released over a 8 h period at pH 7.0 [57]. Polymers are also used as stabilizers in various formulations, Liu et al. proposed a model pesticide, bifenthrin, prepared in nanoparticles by flash nano precipitation. A multi-inlet vortex mixer was developed to provide rapid micro mixing, high supersaturation and rapid bifenthrin nanoparticle nucleation and growth. Several polymeric stabilizers were tested, such as poly(vinylpyrrolidone) and poly(vinyl alcohol) to cite a couple. With a pesticide loading increase from 50 to 91 % nanoparticle size increased from 100 to 200 nm. The stability of the dispersions was followed for more than 12 days. Nanoparticle pesticides could potentially provide higher efficiency, better uniformity of coverage, and less worker exposure than compounds in organic solvents [58]. Finally, nanocomposites are conventionally prepared by combination of an organic polymer matrix and a nano-dimensional inorganic filler. The resulting hybrids can exhibit high durability, high strength, light weight and process flexibility, and are used in transportation, agriculture, aerospace, defence, sporting goods, food manufacturing, packaging and energy infrastructure [16,59]. Sustained release formulations of the insecticide cartap hydrochloride were prepared by Kumar et al. using commercially available poly(vinylchloride) (emulsion and suspension) and carboxymethyl cellulose with clays like bentonite, kaolinite, and fullers' earth. The cartap hydrochloride-sodium carboxymethyl-cellulose-kaolinite formulation provided superior control (3.33 %) of rice leaf folder in field grown rice (*Oryza sativa L.*) [60].

Nanocomposites can also be stimuli responsive. In this direction Chi and corworkers developed novel temperature-responsive sustained-release herbicide particles (TCHP) with a core–shell structure using a nanocomposite consisting of attapulgite (ATP), NH_4HCO_3, amino silicon oil (ASO), poly(vinyl alcohol) (PVA), and glyphosate (Gly). The illustration of the fabrication procedure and mechanism is reported in Fig. 4. Within this structure, ATP had the capacity to attract numerous Gly molecules within micro/nano networks through the formation of hydrogen bonds. Simultaneously, NH_4HCO_3 could generate CO_2 and NH_3 bubbles, creating micro/nano-sized pores in the ASO-PVA shell when exposed to high temperatures, their quantity, and the solubility of the PVA shell could be precisely regulated by adjusting the temperature. Experimental pot tests confirmed the remarkable performance as a CRS at elevated temperatures, an effect in Gly loss mitigation was demonstrated, thus enhancing its effectiveness in managing weeds [61].

In similar direction, using ASO and ATP, Chen et al. proposed a light-responsively sustained-release herbicide particle (LCHP) with core–shell structure loading glyphosate and using azobenzene (AZO) as a photo responsive molecule. A nanonetwork-structured ATP was evenly dispersed within the pores of biochar, creating a porous biochar-ATP composite.

This composite served as a carrier to efficiently load a substantial quantity of both Gly and AZO molecules, resulting in the formation of granules known as porous biochar-ATP-Gly-AZO. Subsequently, ASO incompletely coated these biochar-ATP-Gly-AZO granules, leading to the creation of LCHP, characterized by numerous micro pores within the ASO coating. When exposed to UV–vis light radiation, the AZO molecules underwent transformations between trans and cis isomers, effectively serving as light-induced "stirrers" that facilitated the release of Gly from LCHP through these nano pores. Again, pot experiments demonstrated excellent light-responsive sustained release performance [62].

2.3. Micro based systems

Micro based systems are typically small, spherical structures consisting of a core material encased within a uniform shell. According to IUPAC definition they have a size greater between 0.1 and 100 μm. These microcapsules can have diverse core contents, which may include solids, liquids, gases. Similarly, the protective matrix surrounding them can be customized using a variety of materials, such as metal oxides, organic compounds, inorganic synthetics and biopolymers. Generally, microencapsulation is accomplished by crystallization, solvent evaporation, polymerization, spray-drying, freeze-drying, spray-cooling, extru-

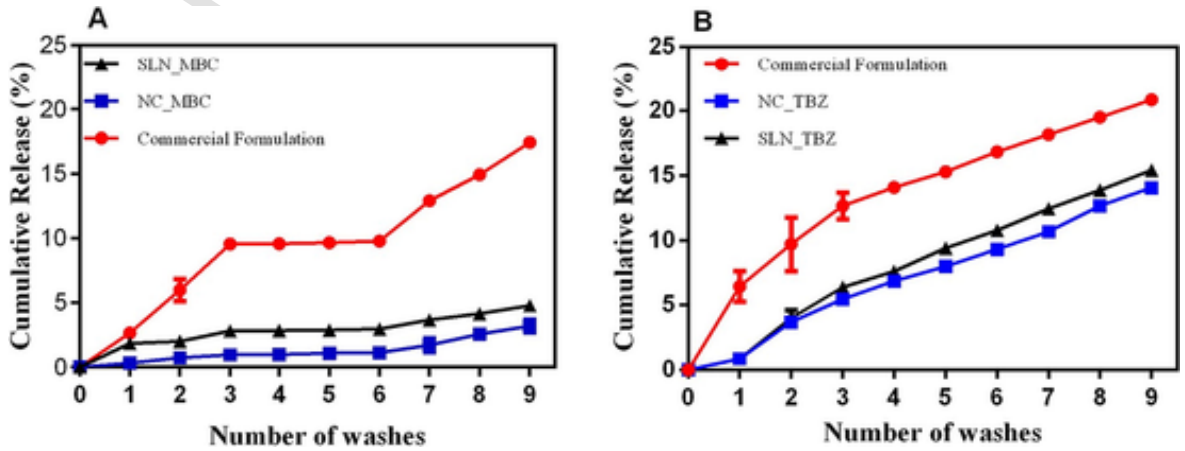

Fig. 3. Cumulative release of (A) MBC and (B) TBZ in suspensions of nanoparticles (NCs and SLNs). Reprinted with permission from Springer Nature [56].

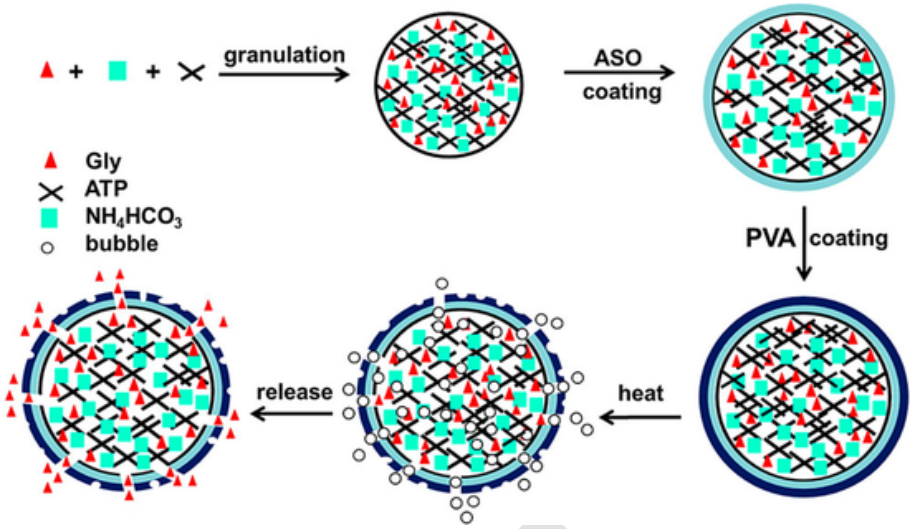

Fig. 4. Schematic illustration of fabrication procedure of TCHP. Reprinted with permission from [61].

sion, emulsification, and photo- techniques [3,63,64]. Microencapsulated pesticides can be diluted with water or liquid fertilizers and sprayed using conventional equipment. It requires less polymeric component per pound of pesticide than monolithic devices and is capable of establishing a constant pesticide release rate. Pesticide release rate can be varied over wide limits by varying microcapsule particle size distribution, wall thickness and wall permeability, and additives such as film forming agents can be added directly to the formulation [16]. Different types of micro based systems exist, such as microsphere coated granules and microcapsules.

For the latter a lot of researchers during the last 20 years dedicated attention to their utilization and specialization as a source for releasing pesticides [65]. In this direction Li and coworkers, for example, developed starch microcapsules at high production rate as a carrier for avermectin (AVM). The method used to prepare the microcapsules was a premix membrane emulsification method (PME) that allowed to fabricate uniform microcapsule with a controllable size with final PDI < 0.1. They investigated the effects of structure, size distribution, and pesticide content of the carriers on the release behaviour. It was demonstrated that the ~0.7 μm microcapsule with 47 % of AVM exhibited the fastest release rate in an early stage followed by sustainable AVM release up to 97 % fraction over a period of 2 weeks. Furthermore, mathematical analysis suggested that the release mechanism involves non-Fickian and Case-II diffusion depending on the size and AVM content [66]. Case-II diffusion is an extreme case of non-Fickian diffusion, the relationship between the rate of diffusion and the concentration gradient is not linear, it is often observed in polymers and other materials where the diffusion process is hindered or sustained by factors such as polymer chain relaxation [67]. Different materials were used for microcapsules production. Recently Zhao and coworkers developed CMC based microcapsules as carrier system for AVM delivery. In particular, they synthetized multi-stimuli-responsive AVM polyurea microcapsules (AVM@CM-SS-PU) by interfacial polymerization with modified carboxymethyl cellulose CMC-SS-NH_2 as the wall material and hexadecane as the temperature-responsive core. The obtained microcapsules showed diameters of approx 3.90 μm and the encapsulation efficiency of AVM was around 88 %. The release system obtained is able to guarantee sustained release of the pesticide with release rate that increases with temperature. Moreover, the photostability was 5-times higher than that of a normal AVM solution, in fact the insecticidal activity stayed at 50 % after 180 min of UV irradiation compared to a decrease to 13.3 % for the commercial formulation. Then, the high insecticidal activity and biosafety was demonstrated [68].

AVM was also used by Suraphan et al. alongside chlorantraniliprole (CAP), a selective insecticide, to build a codelivery microcapsule system to create a synergistic effect between the compounds and enhance drug efficiency and decrease usage. A porous polylactide (PLA) microcapsule formulation was employed for this purpose, by double emulsion method with premix membrane emulsification method (PME) the AVM/CAP-loaded porous microcapsules (AVM /CAP P-MCs) were produced with prolonged sustained release, high loading content and entrapment efficiency, as well as good light and thermal stability. Compared with the commercial AVM and CAP, AVM microcapsules and CAP microcapsules, the AVM /CAP co-delivery system showed a superior bioactivity against *Plutella xylostella* [31]. Before testing the co-delivery, some of the same authors did research both on CAP and PLA. In fact, they constructed CAP microcapsule formulations with a high loading content via solid in oil in water (S/O/W) double-emulsion method combined with PME. The microcapsule formulations with good light and thermal stability showed a significantly sustained release for a long period alongside increased bioactivity with respect to commercial CAP formulations [69]. As anticipated, in another paper they used PLA to fabricate three kinds of carriers including microspheres, microcapsules, and porous microcapsules for controlled delivery of Lambda–Cyhalothrin (LC) produced via PME. Various microcapsules with a high LC content, as much as 40 %, and tunable sizes, from 0.68 to 4.6 μm, were constructed by manipulating the process parameters. The possibility of "manipulating" the systems is of great importance to achieve the precisely desired release. Indeed, compared with technical LC and commercial formulations, the microcapsule systems showed a significantly sustained release of LC for a longer period. The LC release triggered by LC diffusion and matrix degradation could be optimally regulated by tuning LC contents and particle sizes [70]. Other biodegradable polymers used to produce microcapsules and microspheres, among many others, are polydopamine (PDA), poly(hydroxybutyrate) (PHB), poly(ε-caprolactone) (PCL), and poly(hydroxybutyrate-valerate) (PHBV).

PDA is an excellent polymer for microcapsules owing to its good adhesion, biodegradability, UV resistance, and fairly simple preparation process. However, most preparation methods rely on either etching the hard templates using harsh acid/solvent or on soft templates containing toxic solvents/emulsifiers, that are not environmentally friendly [71–73]. Tang and coworkers developed PDA microcapsules templated by Pickering emulsions stabilized by cinnamoyl chloride modified cellulose nanocrystals (CNC) for essential oil and pesticides encapsulation. The essential oil (turpentine) was used as a botanical pesticide as well as solvent for the herbicide (2,4-D). The system showed a sustained re-

lease behaviour with a reduced toxicity and improved encapsulation efficiency, constituting an effective and promising approach for pest control [74]. Takei et al. used a combination of PLA and PCL to immobilize and encapsulate acetamiprid using a O/O emulsion with a solvent evaporation method. This enabled a large releasable amount, around 89 %. It is interesting to note that the authors initially developed PLA based microspheres, but that resulted in a low amount of releasable pesticide, around 18 %. This may have been due to a tight structure and a high hydrophobic microclimate. The incorporation of PCL of lower molecular weight than PLA into the PLA microspheres resulted in the looser structure and less hydrophobic microclimate [33]. Both PHB and PHBV are biodegradable, inexpensive and their high crystallinity allows a decrease in the speed of degradation if compared to PLA and PGA homo- and copolymers [75–78]. Grillo and coworkers used these two promising polymers to develop microparticles containing ametryn to both improve its action and reduce environmental toxicity. The preparation method involved a W/O emulsion using the emulsion/solvent evaporation method. The average sizes of the PHB and PHBV microparticles were 5.92 ± 0.74 μm and 5.63 ± 0.68 μm, respectively. The release behavior of ametryn underwent modification when it was encapsulated within the microparticles, resulting in a slower and more sustained release pattern compared to the straightforward release of pure ametryn.

When ametryn was combined with PHB and PHBV microparticles, there was a notable reduction in the amount of herbicide released within the same time frame, decreasing to 75 % and 87 % respectively. For both types of microparticles (PHB and PHBV), the release mechanism for ametryn was governed by diffusion processes characterized by anomalous transport governed by diffusion and relaxation of polymer chains, non-Fickian case-II transport [79]. Micro emulsions have also been extensively used for encapsulating hydrophobic and hydrophilic AIs, prepared by the interfacial and in-situ polymerization method, and the reported sizes vary from 20 to upper limits between 100 and 500 μm [80,81].

An example was given in 2017 by Wang and colleagues, in their study emamectin-benzoate (EMB) slow-release microspheres were prepared by the microemulsion polymerization method using PLA as a carrier (Fig. 5). Samples showed uniform spherical shapes with an average diameter of 320.5 ± 5.24 nm and good dispersity in the optimal formulation with the polymeric stabilizer poly(vinyl alcohol) (PVA) and composite non-ionic surfactant polyoxyethylene castor oil (EL-40). Stabilizer and surfactant were chosen after a study of their effect on particle size and dispersity of EMB. The system showed excellent anti-photolysis performance, stability, and controlled release properties. Indeed, the release went on for more than 250 h with respect to the 80 h of a commercial solution [82]. As seen for nano based systems silica matrices and composites are fairly diffused. For the former there are quite a few examples, thanks to the large surface area, good biocompatibility, and high drug loading capability as explained in the previous section. Guo et al developed an enzyme-responsive emamectin benzoate (EMB) microcapsule based on a copolymer matrix of silica–epichlorohydrin-carboxymethylcellulose. The synthesis is quite complex with a few steps, from the synthesis of amino-functionalized silica microcapsules to the synthesis of epichlorohydrin modified car-

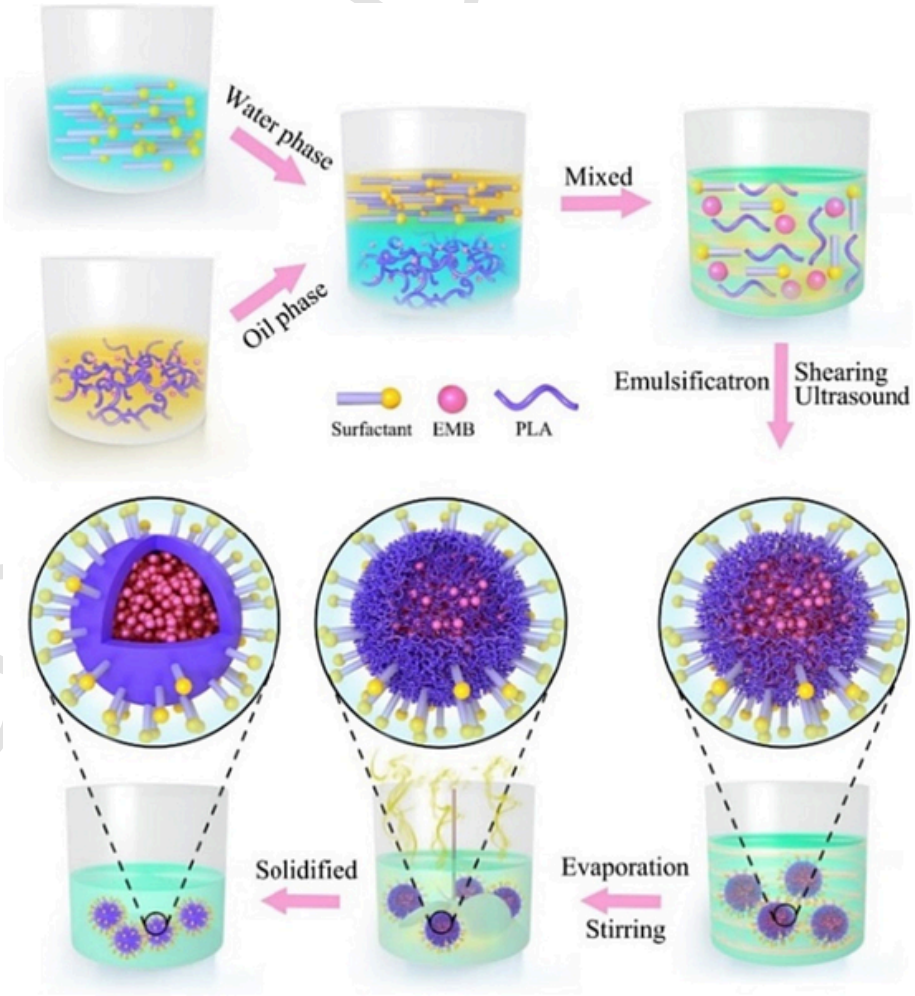

Fig. 5. Schematic description of preparing the EMB slow-release microspheres. Reprinted with permission from Springer Nature [82].

boxymethylcellulose (EMC) and finally the synthesis of the copolymer matrix via centrifugation.

In the end, they obtained microcapsules that had a remarkable loading ability for EMB (about 35 % w/w) and could protect it against photo- and thermal degradation effectively.

Furthermore, they displayed a cellulase stimuli-responsive properties, a good bioactivity against *Myzus persicae* together with less genotoxicity than EMB at technical grade [83]. Another study by Xu and coworkers showed two types of microcapsules containing cyhalothrin: pesticide encapsulated in silica (SiO_2) microcapsules and silica modified with *N*-isopropyl acrylamide (NIPAM) and bis-acrylamide (MBA). The process involved the creation of a silica shell through the hydrolysis and polycondensation of tetraethyl orthosilicate under alkaline conditions. Subsequently, the single-shelled silica microcapsules were modified with triethoxyvinylsilane and cross-linked with NIPAM and MBA through free radical polymerization.

Both single- and double-shelled microcapsules exhibited high loading capacities for cyhalothrin, with the double-shelled microcapsules achieving better control over release. This improved control was likely due to a combination of diffusion and erosion mechanisms. Importantly, the microcapsules demonstrated prolonged persistence compared to cyhalothrin emulsifiable concentrate [84]. For what concerns composites Wilpiszewska et al. proposed the preparation of novel microparticles based on high substituted carboxymethyl starch (CMS) containing sodium montmorillonite (MMT) by crosslinking with Al^{3+}. CMS was obtained from two sources: native potato starch and amylopectin. The hydrophilic CMS/MMT composite systems were used for the herbicide isoproturon, they achieved a good encapsulation efficiency of around 75 %, and the release rate from the composite in water was drastically reduced if compared to commercial isoproturon. More specifically about 95 % of the herbicide was released after approximately 700 h from the composite, whereas the commercial counterpart achieved this in approximately 24 h. More importantly, after a series of eight irrigations, only about 10 % of the loaded isoproturon leached from the composite, suggesting that the CMS/MMT carriers have the potential to reduce the leaching of herbicides, thereby mitigating environmental pollution [85].

2.4. Hydrogels

Hydrogels are cross-linked networks of hydrophilic polymers able to absorb a large amount of water and aqueous solutions due to the presence of hydrophilic functional groups. They can be stimuli-responsive towards temperature, pH, and enzymes [86]. The presence of crosslinks in their three-dimensional structure preserves the stability of swollen hydrogels and makes the grafting insoluble in a solvent due to electrostatic interaction and the hydrogen bonding strengthens the polymer [87,88]. Depending on the application hydrogels mechanical strength can be fine-tuned depending on the starting co-monomers.

Mechanical strength can also be induced by physical crosslinking, creating a double network structure, and incorporating inorganic nanomaterials into the hydrogel [34,89,90]. Using hydrogels as CRSs in agricultural application can be advantageous, formulation methods are straightforward and less strict requirements mean an eventually easier commercialization of the end product [34]. Additionally, hydrogels can be synthesized utilizing various natural polysaccharides, that are preferred to synthetic ones, making the structure biodegradable and environmentally friendly, thus ideal for a release in soil [3]. Thanks to their properties to attain large amounts of water, controlled release of agrochemicals and change their behaviour with environmental change they gained the attention of the researchers to use them as a solution of agricultural problems, without affecting the environment and fertility of soil. As a matter of fact, they were used as an efficient water management tool, to increase the porosity of the soil by holding large amounts of water for a prolonged period, which reduced the need of irrigation, lowered the erosion of soil and thus increased the fertility of soil itself [91,92]. So, the application of hydrogels as CRSs for pesticides can serve a double function, the release of the loaded compound and the water management of its surrounding environment. One recent paper, by Saruchi et al., developed a biodegradable hydrogel of a natural polysaccharide aloe vera and vinyl monomer acrylic acid with ammonium persulfate-glutaraldehyde used as the initiator-cross-linker system. The pesticide used was dichlorvos loaded by immersion of the hydrogel in a solution containing the compound. The synthetized hydrogel had a maximum swelling of 756 %, and a maximum biodegradation in soil of 90 %, 94 %, and 93 % in case of soil burial, composting and vermicomposting methods. Furthermore, the release curve of the pesticide, from release tests in soil, showed a sustained release with a maximum value of 1000 ppm after 44 h. The release kinetics is non-Fickian and dichlorvos release rate depends on the relaxation time of the hydrogel matrix. More importantly, together with the release profile, the second function of the hydrogel was studied.

The water retention period prolonged from 11 to 20 days and water content of clay soil and sandy loam soil was increased to an extent of 6.1 % and 5.79 %, respectively [93].

Xiang et al. proposed a dual-action pesticide-loaded hydrogel with the capacity to significantly induce plant resistance against tobacco mosaic virus (TMV) infection and promote plant growth.

They produced an alginate-lentinan-amino-oligosaccharide hydrogel (ALA-hydrogel) by coating the surface of an alginate-lentinan drug-loaded hydrogel (AL-hydrogel) with amino-oligosaccharide using electrostatic action (Fig. 6). Lentinan (LNT) is a neutral polysaccharide ex-

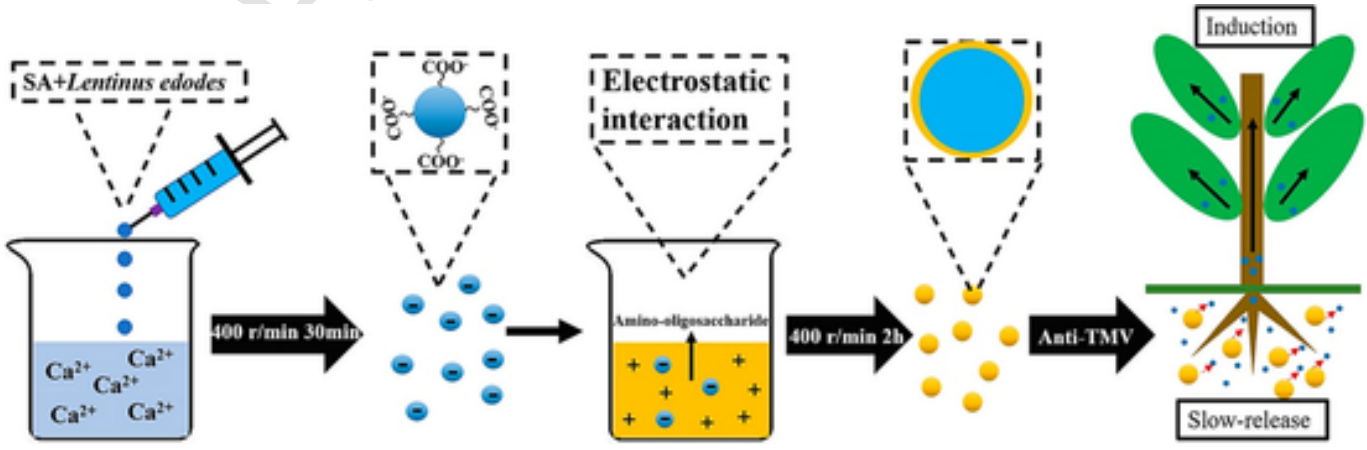

Fig. 6. Schematic representation of the synthesis of ALA-hydrogel and the induction of plant resistance. Reprinted with permission from American Chemical Society [94].

tracted from the fruiting body of *Lentinus edodes* and has superior antifungal and antibacterial activities, thanks to the amino oligosaccharide the release of LNT was sustained and the release time much longer respect to AL-hydrogel. This is due to the fact that the denser network obtained using amino-oligosaccharides can retard the release of LNT. Morever it was found that the ALA-hydrogel in the soil exhibited the ability to induce plant defences against TMV and promote plant growth by increasing the release of calcium ions to promote *Nicotiana benthamiana* growth, thus ensuring long term induction [94].

The above-mentioned technique of creating double networks to enhance hydrogels properties was used by Wang and coworkers in a study to construct several stretchable double-network nanocomposite hydrogels, which were used to control the release of λ-cyhalothrin.

To produce the hydrogels, hydrophobic derivate of sodium alginate (Ugi-SA), polyacrylamide (PAM) and montmorillonite (MMT) were utilized. The utilization of Ugi-SA and the incorporation of MMT demonstrated significant enhancements in the properties of hydrogels. These improvements were observed in various aspects, including tensile properties, pesticide-loading efficiency and sustained release performance. Indeed, the hydrogels achieved remarkable maximum fracture strain and loading efficiency, reaching values of 2000 % and 81.30 %, respectively. Along with it, the hydrogel containing 5 % MMT content exhibited the lowest cumulative release percentage of pesticide, at only 6.68 % over a period of 87 h [95]. The addition of other components together with hydrogels, creating hydrogel composites, were also studied and under investigation. In this direction Sakar and Singh developed pH sensitive hydrogel composites to release thiamethoxam, an insecticide, loaded through an ex-situ encapsulation technique. Specifically, biopolymeric clay hydrogels composites, synthesized from crosslinking of carboxymethyl cellulose with citric acid in the presence of bentonite, were used. The release of thiamethoxam from the developed formulations was studied in water (pH 7–11). The kinetics study showed the release followed Gallagher–Corrigan equation with an immediate burst release phenomena and higher release rate of thiamethoxam was observed at alkaline pH than neutral condition (pH 7.0) [96]. The same authors recently published a paper in which they synthetized a pH sensitive, boric acid crosslinked carboxymethyl cellulose hydrogels for the triggered release of boron and thiamethoxam. They demonstrated the fast release of boron and Thiamethoxam in high pH solution as compared to acidic pH and shown the potential use of this CRS in plant rhizospheric zone of soils with problem such as acidic soils and alkaline soils [97]. The fabrication of pH-sensitive hydrogel composites was also researched by Xiang and coworkers.

In their work, a pH-responsively controlled-release chlorpyrifos (PRCRC) was developed using a nano-system consisting of chlorpyrifos (CPF), polydopamine (PDA), attapulgite (ATP), and calcium alginate (CA). To obtain the final structure CPF was absorbed in the PDA-modified ATP (PA) through hydrogen bonds and electrostatic attraction, then combined with CA to form PRCRC through cross-linking reaction, wherein PA acted as the skeleton. It was observed that PRCRC spheres tended to collapse in alkaline solution promoting the release of CPF. The pH-responsively controlled release performance was proved by the control efficacy test on grubs. Furthermore, the system could effectively protect CPF molecules from degradation under ultraviolet light and the PA-CA hydrogel possessed a benign biocompatibility on Escherichia coli and foxtail millet, showing a high biosafety [98].

2.5. Environmental/stimuli responsive CRS

Although controlled-release formulations can achieve gradual release, such release processes are not necessarily “smart” or controllable because of the complexity of the environmental conditions and limitations of the carrier materials [14]. Environment responsive delivery systems are made up of stimuli-responsive materials of polymeric origin, some examples can be found in the CRSs of the previous sections but, given the importance, a more in-depth description will be given here along with various studies on the subject. These materials have received considerable attention for being capable of delivering a payload under specific microenvironment conditions in a steered, tunable, and personalized manner [99]. In Fig. 7 different types of stimuli responsive CRSs are reported, as can be seen they can be pH, light, temperature, and enzyme responsive. Additionally, there are some others, more niche systems, that respond to environmental stimuli such as redox potential, electric/magnetic field strength, and ion strength. A key feature of these polymers is their reversibility in response to stimuli. In fact, when exposed to specific signals or stimuli, these polymers undergo macroscopic transitions that alter their surface properties and solubility [100]. Stimuli-responsive CRS exhibit sensitivity to the cues generated by pests and exhibit intelligent responses by releasing AIs to effectively manage and control pests [101,102]. Photoresponsive materials have the unique ability to undergo physical changes in properties like color, conductivity, and solubility, or engage in chemical reactions such as photolysis, dimerization, polymerization, and isomerization when exposed to light energy. These distinctive properties can be achieved by incorporating photosensitive groups into the main chain or side chain of polymers [14,103]. For instance, Atta and coworkers developed a nanopesticide formulation using fluorescent photo-responsive organic nanoparticles containing perylene-3-ylmethanol. They were employed to control the release of 2,4-dichlorophenoxyacetic acid (2,4-D) that proceeds under illumination. Bioassay experiments demonstrated that this nanoformulation effectively delivered 2,4-D into plant tissues and enhanced herbicidal activity [104].

pH-responsive CRSs are made up of polymers whose properties could be manipulated by changing environmental pH. In this case the change of pH influences solubility, conformation and structures by attenuating ionic, hydrogen, and hydrophobic bonds resulting in a reversible micro phase separation or self-organization phenomenon [105]. In 2022, Zha and coworkers developed sodium alginate hydrogels (SAH) loaded with glyphosate in dopamine-modified attapulgite (DA-Gly) to construct pH responsive controlled release microspheres. The release of Gly and the swelling of the hydrogel exhibited distinct patterns based on the pH conditions of the surrounding environment. In an alkaline solution with a pH of 8.5, both the Gly release rate and the hydrogel swelling rate were significantly enhanced, reaching their peaks at 60 % and 26 %, respectively, within 70 and 24 h. Conversely, in both acidic (pH = 5.5) and neutral (pH = 7.0) solutions, the release rate was only 20 %, and the swelling rate was less than 15 %. Both DA-Gly and SAH-Gly contributed to the stability of Gly, protecting it from the effects of ultraviolet (UV) rays and temperature fluctuations. It was then observed that DA-Gly and SAH-Gly reached their maximum Gly concentrations after 28 and 32 h, respectively, and then completely degraded within 200 h in soil [106]. Similarly, Chen et al. grafted alginate on the surface of anisotropic silica (SiO_2-x) via Ugi reaction, to obtain a modified SiO_2-x that is more sensitive to pH if compared to pristine SiO_2-x (SiO_2-1, SiO_2-2, and SiO_2-4). Three stable liquid paraffin-in-water emulsions were prepared with Alg-SiO_2-1, Alg-SiO_2-2, and Alg-SiO_2-4. The pH of the emulsion played a crucial role in determining its stability. From the pH range of 2.0 to 6.2 it was observed that emulsions became more stable due to interactions between polymer chains that led in the formation of a three-dimensional network. As the pH of the emulsion increased particle charge increased, in turn increasing stability thanks to electrostatic interactions. However, at a pH of 9.0, the emulsion's stability decreased as particle charge diminished, making the emulsion more prone to droplet coalescence and separation. λ-cyhalothrin, was used as a model drug and embedded into the emulsions.

It was demonstrated that increasing emulsion pH from 3.0 to 8.0 decreased cumulative drug release from the emulsion from 99.7 % to 13.5 % [107]. An other interesting example can be found in a 2015 paper by Kumar that synthesized nanocapsules containing acetamiprid,

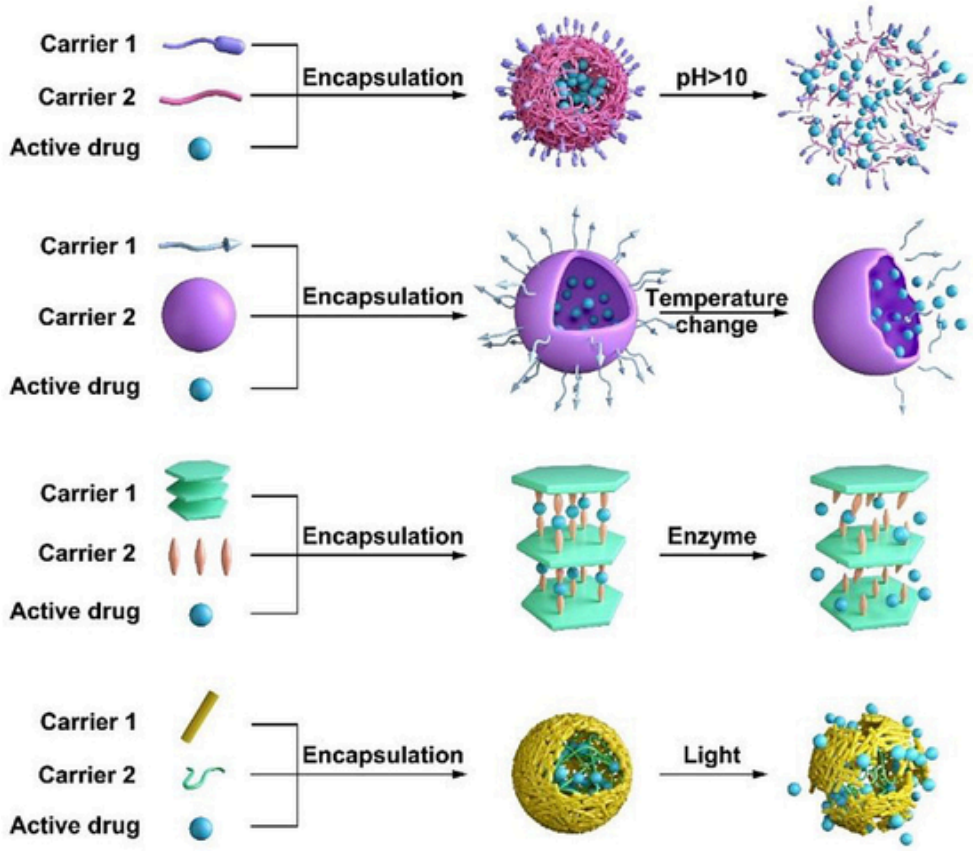

Fig. 7. Different types of smart-response pesticides. Reprinted with permission from Americal Chemical Society [14].

prepared by polyelectrolyte complexation of two natural, non-toxic, biodegradable, and inexpensive macromolecules, alginate, and chitosan to achieve a pH-controlled release. Encapsulation efficiency was found to be 62 %, the release tests were done in vitro at three different pH. The maximum release was observed at pH 10, followed by pH 7 and 4, respectively. Furthermore, if compared to commercial formulation in soil a controlled release pattern was demonstrated and it followed a non-Fickian release mechanism [108]. Temperature-sensitive delivery systems represent an extensively researched category of stimuli-responsive polymers in the realm of drug delivery applications. These systems exhibit sensitivity to temperature changes and adapt their macroscopic structure accordingly in response to external temperature shifts. The delicate balance between the hydrophobic and hydrophilic groups within thermo-responsive polymers means that even a minor temperature fluctuation can induce significant alterations in their properties and behaviour. Their most characteristic parameter is the critical solution temperature, as they can be categorized into two classes according to their response to a change in temperature. The first is of polymers which undergo a sol–gel transition when heated above a certain temperature known as lower critical solution temperature (LCST), while the second is of polymers that precipitate and undergo phase alteration below a certain temperature called the upper critical solution temperature (UCST) [109,110]. Indeed, Shen and coworkers developed thermo-responsive microcapsules prepared with a polydopamine (PDA)-g-poly(N-isopropylacrylamide) (PNIPAm) multifunctional layer to release emamectin benzoate. The preparation of the microcapsules occurred through grafting of the amino-terminated PNIPAm onto the PDA layer in aqueous solution. Kinetic study of emamectin benzoate release showed that the microcapsules exhibit sustained- and controlled-release properties.

Not only that, but the multifunctional layer could also release emamectin benzoate with ease when the temperature was below the LCST. In contrast, when the temperature increases above the LCST, the release rate is reduced demonstrating an excellent thermo-sensitivity [111]. PDA and PNIPAm was also used in a previous work by Xu to produce stimuli-responsive PDA microspheres that were capped with PNIPAm thermosensitive polymer shell. In the resulting core–shell PDA@PNIPAm hybrid system, the PDA core provided excellent temperature and NIR-light sensitivity as well as high loading capacity, while the PNIPAm applied as both a thermosensitive gatekeeper and a pesticide reservoir, for this study imidacloprid (IMI) was chosen as the model pesticide. The results showed that the core–shell PDA@PNIPAm nanocomposites had a high loading capacity and good temperature- or NIR-controlled release performance. Indeed, the structure underwent phase transition in water at a temperature above 32 °C and more importantly, if exposed to NIR-light irradiation with an 808 nm laser at 2 W/cm^2 it could efficiently convert the photo energy into thermal energy and subsequently increase the temperature. The fastest drug release behaviour was observed at 40 °C and up to 64.3 % of the encapsulated IMI was continuously released over a 5 h timeframe. In general, when the PDA@PNIPAm nanocomposites were exposed to irradiation with NIR light, the IMI release was greatly enhanced and, significantly reduced when the external trigger (NIR light) was turned off. This is because of the increase of temperature above the LCST, rapidly shrinking the volume size of the nanocomposites, and finally squeezing out the loaded IMI into the external media. [112]. Xu and coworkers fabricated dual-responsive chitosan copolymer (CS-g-PDMAEMA) through free radical graft copolymerization with 2-(dimethylamino) ethyl 2-methacrylate (DMAEMA) as the vinyl monomer. An emulsion chemical cross-linking method was used to produce pyraclostrobin microcapsules by in situ entrapping the pesticide. The researchers obtained an encapsulation efficiency of 65 % and the pesticide-loaded microcapsules showed a pH- and thermo-responsive release. Indeed, the release

of pyraclostrobin was higher in acidic medium and with an increasing temperature (Fig. 8).

Moreover, it was demonstrated a higher utilization efficiency, thanks to an improved photostability under UV irradiation and lower acute toxicity in the start of the release with respect to the pyraclostrobin technical concentrate [113].

Plants have a natural defense mechanism as they release protective enzymes when attacked by herbivorous insects. The design of pesticide encapsulation materials that quickly hydrolyses in the presence of these enzymes, to induce release, could lead to more timely and effective pest control. Enzyme-responsive materials include polymers, nanoparticles, and hydrogels. Polymers respond either physically or chemically to the stimulus caused by interaction of pest with the plants [114]. Crop damage from pests often involves enzymes like cellulase, pectinase, and protease. Using enzyme-responsive mechanisms to release drugs or pesticides can offer a precise and intelligent method to combat harmful organisms [14,102]. In this direction Liang developed esterase-responsive mesoporous silica chitosan nanoparticles made from covalent chitosan. The pesticide prochloraz was encapsulated in the pores using a silane coupling agent. The nanoparticles had high loading efficiency (25.4 % (w/w)), exhibited good photostability and demonstrated esterase- and pH-triggered controlled release behaviour.

Notably, in temperature ranges of 25–50 °C, changes in the cumulative release rates varied from 18.92 % to 34.21 % after 30 days. When applied as a preharvest treatment in agriculture, they displayed superior antifungal activity against citrus diseases compared to prochloraz emulsifiable concentrate. Moreover, the toxicity to zebrafish was drastically reduced more than 6-fold if compared to technical prochloraz [51]. Successively, in 2020, some of the same authors proposed a novel redox and α-amylase dual stimuli-responsive pesticide delivery system. It was produced by bonding functionalized starch with biodegradable disulfide-bond-bridged mesoporous silica nanoparticles which were loaded with avermectin (avermectin@MSNs-ss-starch NPs). The nanoparticles had a loading capacity of 9.3 % and good photostability given by starch attached covalently on the mesoporous silica nanoparticles. The results showed that less than 9 % of the loaded avermectin (AVM) was released from avermectin@MSNs-ss-starch NPs after continuous incubation for 7 days, indicating the good encapsulation capability of the grafted starch. The addition of α-amylase results in increased release of AVM. The cumulative release amounts of AVM reached up to 72.2 % after 7 days, confirming the remarkable α-amylase responsive pesticide release properties. Furthermore, the redox-responsive release was tested, with the addition of glutathione (2 mM), the cumulative release amount of AVM reached up to 21.7 % after 7 days. By increasing the concentration (8 mM), 51.3 % of AVM was released from the nanoparticles at the same time. An increase in bioactivity was also observed if compared to the AVM emulsifiable concentrate [115]. Kaziem and coworkers synthetized an α-amylase-responsive CRS. The production involved anchoring mechanically interlocked molecules using α-cyclodextrin onto the surface pore rims of hollow mesoporous silica

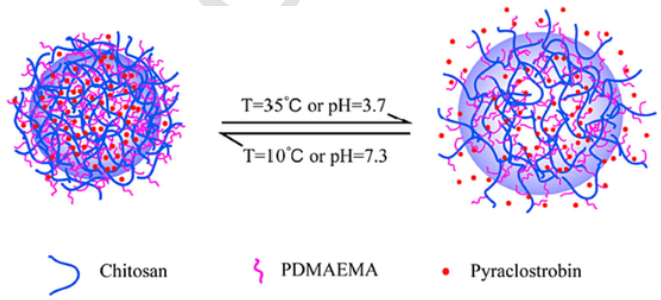

Fig. 8. Schematic illustration of responsive release of pyraclostrobin from Pyr@CS-g-PDMAEMA microcapsule under different thermo and pH conditions. Reprinted with permission from MDPI [113].

nanoparticles. The model pesticide was chlorantraniliprole and with it the CRS achieved an astounding loading capacity of 42 % w/w while also being able to screen it from light and heat. The researchers demonstrated the enzyme responsiveness of the system, release rate of chlorantraniliprole from the nanoparticles could be improved noticeably by addition of external α-amylase [116].

3. CRS for atrazine delivery

To conclude this review on the various types of existing CRS for pesticide it seemed appropriate to analyze more in detail the devices that have been studied for the delivery of the herbicide atrazine. The main problems of atrazine, as already described at the beginning of this review, are related to its low biodegradability and long half-life in water, leading to large amounts persisting in the environment with the consequences severe environmental effects, like migration into groundwater [117]. Several CRSs have been proposed to minimize its impact and optimize so its use. In this direction, a recent work by Fookes and coworkers studied the synthesis and application of silica-based nano- and microparticles with different porous structures for the controlled release of atrazine in order to decrease its potentially harmful effects in the environment. A novel method for producing nanostructured microparticles using a w/o emulsion technique was used and atrazine was encapsulated in the different particles, obtaining higher efficiencies for mesoporous silica nanoparticles [118]. Also poly(ε-caprolactone) (PCL) micro- and nanocapsules were subject of many studies as a potential carrier and release system for atrazine. Triazine herbicides are commonly used in combinations, to increase the effectiveness of weed control. Grillo et al. developed and characterized a system consisting of PCL nanocapsules containing atrazine, ametryn, and simazine, to assess their suitability as controlled release systems that could reduce environmental impacts. The results were remarkable, the sizes of the nanocapsules containing the herbicides were in the range 232–290 nm, encapsulation efficiencies exceeded 84 %, and the formulations remained stable for at least 270 days. Compared to atrazine used in its free forms, genotoxicity tests using different cell types and release tests indicated that the encapsulated formulations were less toxic and demonstrated a slower release. Finally, the mechanism of release was associated with the relaxation of the polymeric chains [119].

In a subsequent paper, in 2013, they prepared nanocapsules of poly (ε-caprolactone) containing the herbicide atrazine and studied the effect of coating the nanocapsule surfaces using different concentrations of chitosan. Encapsulation efficiencies upwards of 65 % were achieved, depending on the chitosan's concentration, the release curves showed a controlled release which compared to the previous study was altered by the presence of chitosan. The mechanism involved a non-Fickian diffusion alongside the relaxation of polymeric chains [120]. Also Pereira and coworkers studied PCL nanoparticles loaded with atrazine in terms of their herbicidal activity and genotoxicity. The sizes of the unloaded nanocapsules and nanospheres (without atrazine) were 513.0 ± 7.5 and 365.1 ± 0.16 nm, respectively. After encapsulation of the herbicide, there was a decrease in the size of the nanocapsules (483.1 ± 2.5 nm) and an increase in the size of the nanospheres (408.5 ± 2.5 nm), with high encapsulation efficiency at values of 93.4 and 92.7 % respectively. Release tests demonstrated a modified release profile governed by anomalous transport. Furthermore, tests on plants were performed with target (*Brassica* sp.) and non-target (*Zea mays*) organisms, and the nanoparticle formulations were shown to be effective for the control of the target species and did not cause any damage to the non-target organism, clearly displaying an enhanced bioactivity. Other experiments using soil columns revealed that the use of nanoparticles reduced the mobility of atrazine in the soil and by application of the *Allium cepa* chromosome a reduced genotoxicity was demonstrate if compared to the free herbicide [121]. Olivera et al. published two papers in 2015 on the use of PCL nanocapsules as a modified release system for

atrazine (NC + ATZ). In the first paper, a system of NC carrying atrazine at 1 mg/mL was evaluated using Brassica junea as the target plant. Encapsulation efficiency was 86 % and the release profile of atrazine-containing PCL nanocapsules showed a controlled delivery, as the required time for 50 % release ($t_{50\%}$) was approximately 30 h, while $t_{50\%}$ of free atrazine was less than 5 h [122]. Herbicidal activity assays demonstrated the superior bioactivity compared to a commercial formulation.

Indeed, as reported in Fig. 9, the first macroscopic symptoms of atrazine toxicity were observed 3 days after the treatments, but only in leaves that were sprayed with the synthesized CRS. After 7 days, the leaves of the plants treated with nanocapsules containing atrazine at the recommended concentration were mostly necrotic and wilted, with a chlorotic petiole. In addition, by treating the plant with ten-fold diluted CRS (NC + ATZ 1/10) and comparing it with that of commercial atrazine at the recommended dosage, similar symptoms of leaf wilt, yellowing, and necrosis were achieved. This demonstrated that the nanoencapsulation enabled the application of lower dosages of pesticide without any efficiency loss [123].

In a successive paper they studied and demonstrated the efficacy of the same encapsulation method in preventing damages to non-target crops.

The model plant chosen was *Zea mays* L., with a concentration of 1 mg/mL after treatment some parameters such as maximum quantum yield of photosystem II (PSII) and in net CO_2 assimilation rate decreased. However, all these parameters were unaffected 4 and 8 days after the application of encapsulated atrazine. The researchers suggested that the negative effects may have been transient, owing to the ability of the plant to detoxify the herbicide. Regardless of herbicide concentration, atrazine-loaded PCL nanocapsules did not cause any persistent deleterious effects, indicating that this nanosystem could be used as a safe tool in weed control, without affecting the development of the crop [124]. In alternative natural biopolymers like lignin and alginate can be used and in this direction Perez and coworkers proposed alginate-based granules with encapsulated atrazine to obtain a controlled release. Additionally, they studied the effect of incorporation of acid-treated bentonite into the alginate formulation on the release rate of atrazine. Results confirmed the validity of the alginate-based granules but, more importantly, the incorporation of bentonite clearly slowed down the release. Normally, 89.78 % of technical grade product was dissolved in < 6 days, whereas it took at least 108 days to release 93.43 % of alginate granules combined with bentonite [125]. More recently, Busatto and coworkers developed lignin microparticles-in-alginate beads for atrazine-controlled release. Microparticles were prepared by solvent extraction/evaporation and microfluidic techniques. The incorporation of microparticles within alginate beads allowed to reduce the burst release of free microparticles and to extend the release period. Additionally, phytotoxicity results showed that lignin-based formulations are safe according to the parameters evaluated, in contrast with commercial atrazine that resulted phytotoxic [126].

4. Challenges and future perspectives

It is clear that CRSs have a promising future in the agricultural field to address all the problems and hazards normally associated with pesticides.

However, although CRSs have many positive aspects, still careful evaluation is required before using these technologies to protect crop production and to tackle pests. Indeed, regardless of the numerous reports with potential to make an immense impact, the development of CRS including nanopesticides for use in agriculture is still at early stage, as there are still many risks and ethical concerns linked to the proliferation of various formulations. Additionally, the production cost, use and evaluation standards, and large-scale production technology are still problems that need to be tackled. So, CRSs need to be studied and evaluated in terms of their efficiency, toxicity, production scale, composition, degradation behaviour, and cost-benefit, preferably in comparison with the conventional analogues. In this sense the main challenge is the need to arbitrate and assess the bioavailability, durability, and toxicity evaluation of these CRSs in the environment in a better way. In fact, the sufficiency of these data for their use in agriculture still remains a challenge. Some studies have toxicity testing whereas others do not, this calls for the development and deployment of validated techniques to generate enough information on delayed toxicity of these CRS's. In this

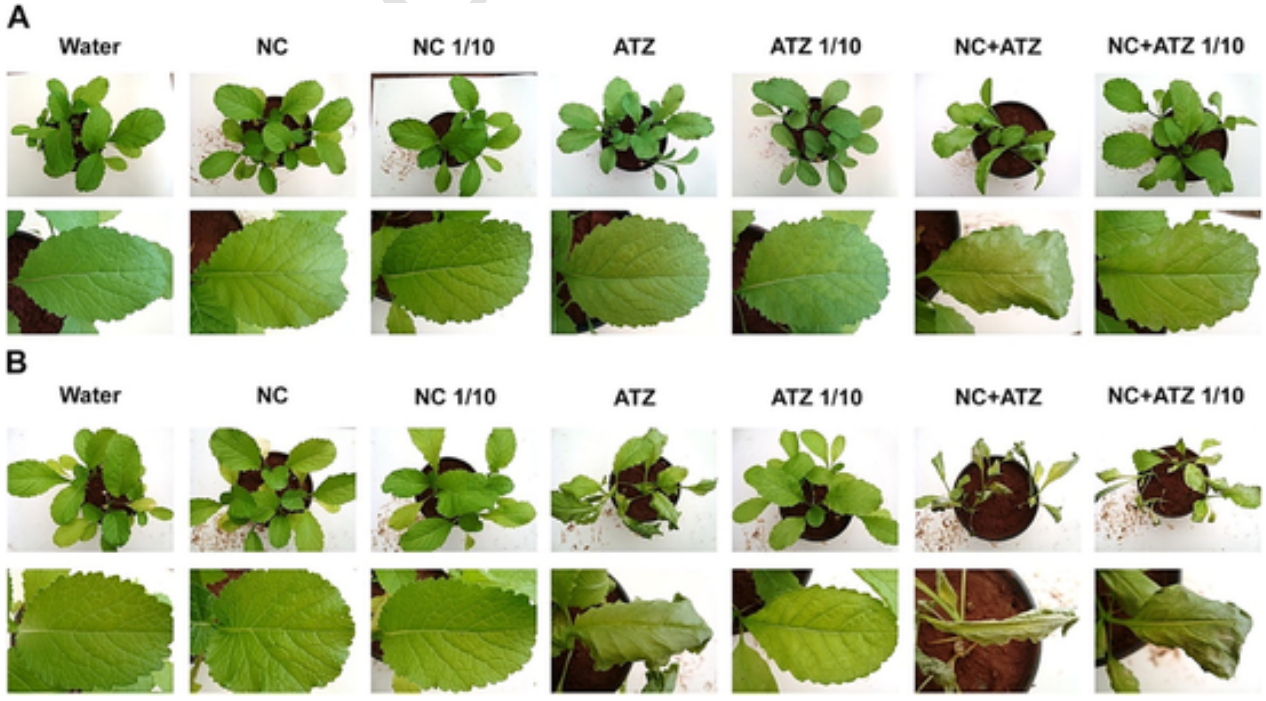

Fig. 9. Symptoms were recorded (A) 3 and (B) 7 days after the plants were sprayed with 3.1 mL of water, empty PCL nanocapsules (NC), commercial atrazine (ATZ), or PCL nanocapsules containing atrazine (NC + ATZ). Reprinted with permission from Public Library Science [123].

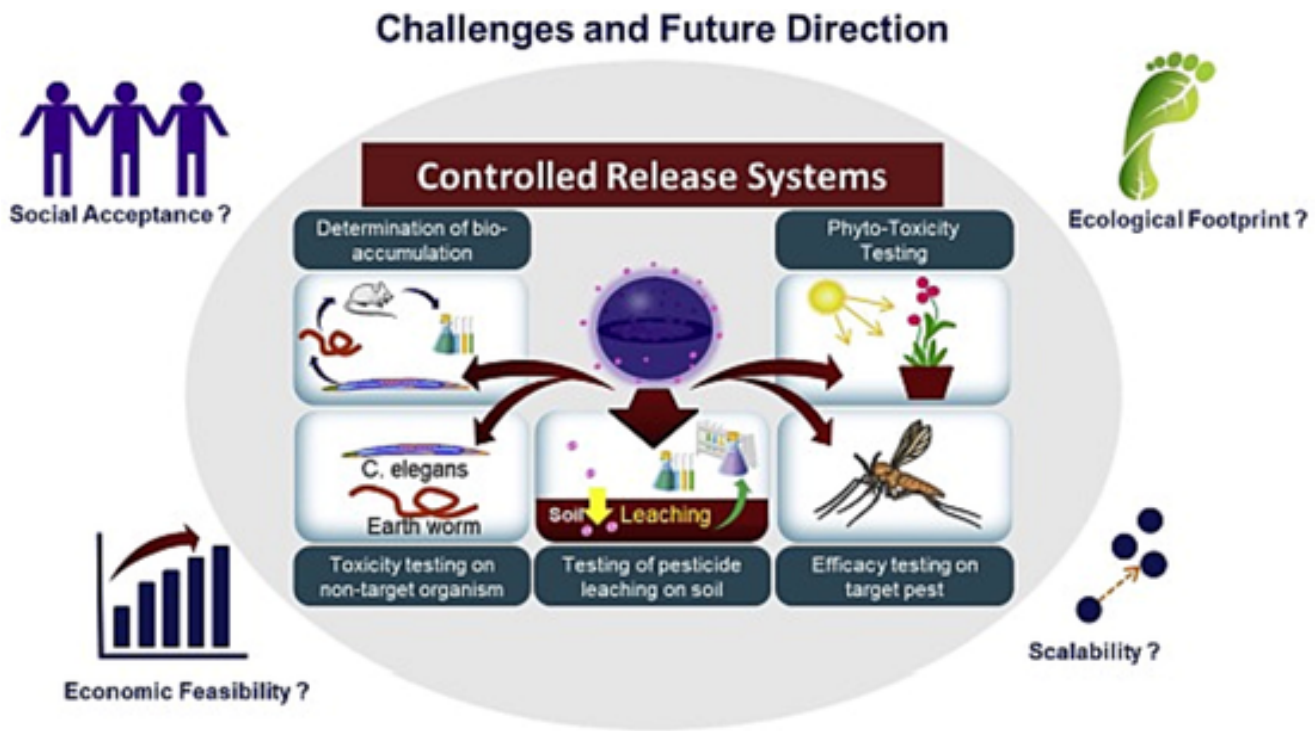

Fig. 10. Schematic illustration of design of study for future CRSs of pesticides. Reprinted with permission from Elsevier [3].

framework Safe-by-Design (SbD) approach can help the carriers to reach quickly the market. SdD is a general concept used in order to identify risks and uncertainties involved in human health and environmental safety during the initial stages of the material development. When designing polymeric materials the important part is that of tailoring their physicochemical properties according to the end usage. Materials used as delivery systems should be able to control the delivery of their cargo and remain stable throughout their shelf-life. Shifting to safety, it should not only be evaluated from the pesticide-polymer, but also from the polymer itself. Material toxicity can be screened through literature review (if such a material has been widely used) or using "non-testing tools". What is usually used for evaluating the toxicity and biological interface interactions of different techniques are used:

- (Quantitative) Structure-Activity-Relationship or (Q)SAR. It is a regression analysis often used for drug discovery, its aim is that of finding a relation between materials properties and the desired activity. The model will give a numerical prediction which will be able to asses if a certain material is safe for medical or agriculture applications.
- Grouping and Read-Across. The goal is that of filling in data gaps, initially by having groupings of materials properties and/or effects and then through interpolation for missing data. Here the idea is that similar materials show similar properties. Such an interpolation allows to predict a certain material endpoint if data are not available.
- Molecular modelling. These techniques are powerful tools for predicting the interactions between polymer surfaces and small or macro molecules. Molecular modelling is a complementary tool to laboratory activities, since it can be used to understanding some complex interactions. However, it cannot completely replace lab activities and it can not be used as a merely prediction tool.

Thus principal goals are to ensure safety, efficacy and quality in order to mitigate any potential risks associated to such pesticides. Another critical aspect, which has not received sufficient exploration, is the potential leaching of active ingredients from these controlled pesticide formulations. Extensive research has established that pesticide leaching is a major side effect that contributes to significant anthropogenic issues, including groundwater and soil pollution [127]. Hence, it is imperative to conduct thorough leaching analyses of CRSs containing pesticides in soil, some studies performed it, but it is a relatively small portion with respect to the available literature on the subject. The plausible study design for future requirements is illustrated in Fig. 10 [3]. In conclusion, CRSs show great potential as an innovative technology for mitigating the indiscriminate use of traditional pesticides and their associated negative effects.

The successful development of commercial CRS products has the potential to revolutionize the agricultural sector, ultimately contributing to global food security. However, it is crucial to emphasize that while CRSs offer numerous benefits, their use for controlled pesticide delivery must be approached with a deep understanding of potential environmental and human health consequences. Careful consideration and responsible implementation are essential to ensure that CRSs contribute positively to agriculture and do not inadvertently harm the environment or human well-being.

Uncited references

[19,20,25,26,27,28,29].

CRediT authorship contribution statement

Alessandro Zanino: . **Fabio Pizzetti:** Conceptualization, Investigation, Writing – original draft. **Maurizio Masi:** Investigation, Supervision, Writing – review & editing. **Filippo Rossi:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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