Chapter 20

Polymeric Nanoparticle-Based Insecticides: A Controlled Release Purpose for Agrochemicals

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Additional information is available at the end of the chapter

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1. Introduction

Insects are one of the biggest animal populations with a very successful evolutive history, once they can be found chiefly in all possible environments all over the world, and the number of species and individuals. Their success can be attributed to several important evolutionary aspects like wings, malleable exoskeleton, high reproductive potential, habits diversification, desiccation-resistant eggs and metamorphosis, just to name a few. Some species are especially valuable for humans due to their ability in providing several important goods, such as honey, dyes, lac and silk. On the other hand, many insects are vectors of many diseases, and many others damages crop plantations or wood structures, causing serious health and economic issues.

Among all identified insects, over 500,000 species feed on green leaves. About 75% of them have a restrict diet, eating only a limited range of species, sometimes being even specie specific [1]. This kind of insect brings major concern to the agriculture. Their high selectivity implies in a closer insect attack on crops. It is estimated that about 10,000 insect species are plagues and, compromising the food production, either in the field or after the harvest [2]. It was estimated that somewhere around 14-25% of total agriculture production is lost to pests yet [3].

Agriculture is one of the main pillars of human population increase over the last millenniums, providing mankind with several important commodities such as food, fuel, healthcare and wood. This huge production should feed 7 billion people, and also generate several inputs for many industrial processes and commercial applications. In order to combat the nu-

merous losses that are caused by insects on agriculture, several chemicals have been used to kill them or inhibit their reproduction and feeding habits. Those classes of compounds are collectivity known as insecticides. These molecules are able to interfere in the insect metabolism. They alter is in such a way that the plague cannot feeds on the crop or the harvest or even reproduce anymore. The use of insecticides is described since ancient times, with documents providing evidences as far as in the 16th century BC. The *Ebers Papyrus*, wrote by the Egyptians, reports several chemical and organic substances used against overcome fleas, gnats and biting flies among others [4]. Nowadays, the insecticides are widely employed around the world. Several known substances are extremely effective in controlling or even wiping out almost all important agricultural plagues. This multi-billion-dollar has an estimated production of 2 million metric tons of hundreds of chemical and biological different products, with a budget of a US$35 billion dollars worldwide [5].

Insecticides are used in different ways, based on the physical-chemical characteristics of the each chemical substance, the area that needs to be covered and the target. Typical application of insecticides in crops is made by spraying a solution, emulsion or colloidal suspension containing the active chemical compound, which is made by a vehicle which may be a hand pump, a tractor or even a plane. This mixture is prepared using a liquid as a carrier, usually water, to ensure a homogenous distribution. Other methods for applying insecticides are through foggers or granule baits embedded with the active compound, among others that are less used. However, due to several degradation processes, such as leaching or destruction by light, temperature, microorganism or even water (hydrolysis), only a small amount of these chemical products reaches the target site. In this case, the applied concentrations of these compounds have been much higher than the required. On the other hand, the concentration that reaches its target might be lower than the minimum effective one. In general, depending of the weather and method of application, the amount of applied agrochemicals, as much as 90%, may not reach the target and so do not produce the desired biological response. For this reason, repeated application of pesticides become hence necessary to efficient control of target plagues, which increase the cost and might cause undesirable and serious consequences to the ecosystems, affecting human health [6]. Due to the lack of selectivity, their unrestrained use can also lead to the elimination of the natural enemies, what implies in the fast growth of plague population. Moreover, it often makes the insects resistant to the pesticides.

Another important point that needs attention is the formulation for the application of the insecticide on the crops. There are several different classes of compounds, which sometimes do not match with a simple dilution in water and must be prepared by other means such as powders, emulsions or suspensions. Some kinds of formulations must be handled with more precaution, since it can severely contaminate workers on the field with small airborne solid particles that can be inhaled [7].

The advances in science and technology in the last decades were made in several areas of insecticide usage. It includes either the development of more effective and non-persistent pesticides and new ways of application, which includes controlled release formulations (CRFs). The endeavors are direct towards the successful application of those compounds on

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crops and their efficacy and availability improvement and reduction of environmental contamination and workers exposure [8]. In that line, new types of formulation were developed. One of the most promising is the use of micro and nanotechnology to promote a more efficient assembly of the active compound in a matrix.

2. Application of insecticides nanoformulations

2.1. Nanoemulsions

Casanova *et al*. [9] evaluated the production of a nicotine carboxylate nanoemulsion using a series of fatty acids (C10 – C18) and surfactant. The oil-in-water nanoemulsion showed a monomodal distribution of size, with mean particle sizes of 100nm. The bioactivity of the insecticide formulations was evaluated against adults of *Drosophila melanogaster* by assessing the lethal time 50 (LT_{50}). They observed that the encapsulation efficiency decreased with increasing size of the fatty acids tested. The bioactivity followed the same trend, with better bioactivity when the chain length decreased. This would be readily attributed to the higher amount of active compound inside the nanoemulsion. For the smallest fatty acid emulsion used, the capric acid (C10) one, the greatest encapsulation efficiency was observed, but it had the lowest bioactivity. The results were explained in terms of lesser bioavailability of the insecticide in its active form due to increased stability of the organic salt formed between the insecticide and the fatty acid. This experiment highlights the necessity of developing different kinds of possible assembles between the active compounds and matrix, and extensively studying the interactions in nanoscale formulations, where sometimes nontrivial effects might be unexpectedly observed.

Wang *et al.*[10] developed an assemble of oil-in-water nanoemulsion (O/W) with 30 nm droplets by careful control of experiment conditions, using the neutral surfactant poly(oxyethylene) lauryl ether and methyl decanoate to encapsulate highly insoluble β-cypermethrin. The dissolution of the insecticide was enhanced. The stability tests were performed by spraying nanoemulsion in a glass slide and observing under polarizing light microscopy. They showed no apparent precipitate in nanoemulsions samples. These results were different from the ones obtained using a commercial β-cypermethrin formulation, with apparent signs of solid residues after 24 hours. This enhanced stability may be used to decrease the concentration of insecticides in commercial spray applications, without losing efficiency.

2.2. Classical micro and nanoparticles

Allan *et al.* [11] published the first report on a controlled release system of an insecticide through a polymeric encapsulation. Even so, at first the encapsulated systems were not so effective. Problems associated with controlled release and particle stability hindered their practical field application for some decades. In one of the first successful works in the field of pesticides encapsulation, Greene *et al.* [12] used poly (n-alkyl acrylates) (Intelimer®) to produce temperature-sensitive microcapsules of the organophosphate insecticide diazinon.. The active chemical was controlled release by increasing the ambient temperature above

30ºC, which is the melting temperature of the polymer,. Experiments were performed with Banded cucumber beetle *Diabrotica balteata* and Western corn rootworm *Diabrotica virgifera* as target insects at 20ºC and 32ºC, under and above the polymer melting point respectively. Mortality was compared to commercial granular formulation. At lower temperatures, the commercial formulation showed the best mortality. At higher temperatures the activity of the encapsulated formulation was better, showing about 90% of mortality for over 8 weeks. The commercial formulation had indeed lost some of its activity, presumably due to heat degradation.

Latheef *et al.* [13] tested several different polymers such as poly (methyl methacrylate) (PMMA), ethyl cellulose, poly(α-methylstyrene) and cellulose acetate butyrate to produce microcapsules of the insecticide sulprofos. Ethyl cellulose formulations were the only ones that had shown good results against eggs and larvae of the tobacco budworm *Heliothis virescens* in cotton plants. The results were comparable to the ones obtained with the use of an emulsifable-concentrate (EC) commercial formulation of sulprofos.

In other to develop commercial formulation containing microencapsulated cyfluthrin, Arthur[14] evaluated its use against the rice weevil *Sitophilus oryzae* in stored wheat, for a period of 8 months. Survival of beetles was statistically correlated with the concentration of the pyrethroid insecticide in the formulation. The average survival rate was only 12% when 4ppm was used, with constant activity throughout the entire experiment. This evidenced the controlled release of the substance over a long period of time.

In the work carried out by Quaglia *et al.* [15], a hydrophobic waxy prepared through a mixture of di- and triglycerides of PEG esters was used to construct microspheres containing the insecticide carbaryl. Microparticles was obtained with particle size ranging from 16 to 20μm. Controllable release dynamics depended on the amount of gelucire used, Studies of release profiles from the encapsulated formulation showed a lower vertical mobility of the insecticide when compared to a commercial nonencapsulated formation. This suggested that the controlled release profile of the microcapsules may be useful to avoid or minimize groundwater contamination.

Cao *et al.* [16] produced diffusion-controlled microcapsules with diameter ranging from 2 to 20μm with encapsulated acetamiprid, an alkaline and high temperature-sensitive insecticide, using tapioca starch as matrix with urea and sodium borate as additives. The particle showed increased degradation resistance by heat for 60 days, and UV radiation over 48h, with no more than 3% of degradation. This represents less than one tenth when compared to the UV degradation of commercial emulsifable concentrate. Even in those conditions, it was also able to promote controlled liberation of the active compound for up to 10 weeks depending on the formulation used.

In another work with acetamiprid, Takei *et al.* [17]produced microparticles with diameter of 30-150μm using poly-lactide (PLA) as the polymeric matrix. Initial results showed that microspheres containing only PLA did not have a good release kinetic of the active chemical compound from its interior. It is presumably due to their tight structure and high hydrophobicity, which hinders water diffusion and therefore limits the insecticide liberation. The in-

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clusion of poly(ε-caprolactone) (PCL) into the matrix in 50-80% weight were analyzed, with formation of microspheres of PLA/PCL blend with 20-120μm of the diameter, showing up to 88,5% of insecticide release in aqueous media over a 48h period.

In contrast to conventional desire to produce compounds with extended residual activity, quick-release microcapsules are demanded in certain areas of agriculture. However, sometimes it is also necessary a quick liberation of the active compound from the matrix after the application. The strong backbone might pose as a problem to effectively deliver. Studies performed by Tsuda *et al.* [18,19] have shown that is possible to assemble "self-bursting" microcapsules that retain its form in water suspension, but easily burst after solvent evaporation. They used the interfacial polymerization method to assemble spherical polyurethane microcapsules containing the insecticide pyriprofixen, obtaining particles with mean diameter of 23μm. The entrapment ratio was 99% for all formulations tested, greatly improving the solubility of the pesticide in water. According to the results, there is a correlation between the wall thickness of the microcapsules and the self-bursting phenomenon. Tuning this property a controlled released can be achieved.

The effectiveness of encapsulated formulations, it is not restricted to extend the residual activity of insecticides, but should also include the overcoming of problems associated with accumulation of recalcitrant organic pollutants that remains in ecosystems in amounts above the Maximum Residual Level (MRL). Therefore, it can be harmful to the environment and to people who might consume the treated crops. For instance, Guan *et al.* [20] encapsulated imidacloprid, a chloro-nicotinyl systemic and broad spectrum insecticide in a mixed sodium alginate/chitosan microparticle through self-assembly layer-by-layer (LbL) methodology. The capsules showed a mean diameter of 7μm. Particles were impregnated with a photocatalyst made of SDS/TiO2/Ag, and the photocatalytic property and the insecticidal activity of the microcapsule was evaluated. Prolonged residual activity of the encapsulated formulation was observed. The toxicity was higher in the *Martianus dermestoides* adult stage compared to the one of pure insecticide. In a field test with soybean [21], the nano-imidacloprid formulation prevented the accumulation of the pesticide on the soybean leaves and soil. The results showed pronounced degradation over 25 days of trials when compared to commercial concentrate formulations, even though the initial concentration of both formulations was equivalent. In this way, regardless the initial effectiveness of the insecticide, safer levels of agrochemicals can be obtained in less time, improving the safety of insecticide application.

2.3. Entomopathogenic microorganisms encapsulated

Besides the chemical compounds, the micro- and nanotechnology have also been developed and applied to microorganisms that need special protection or to improve their solubility in aqueous phase. For instance, Ramírez-Lepe *et al.* [22] developed an aluminium-carboxymethylcellulose microcapsule with photoprotective agents for holding a *Bacillus thuringiensis* serovar *israelensis* (B.t.i.) spore-toxin complex named δ-endotoxin. The protein produced by this gram-positive bacterium during sporulation is extremely toxic to larval stage of some mosquitoes and flies which are vectors for important tropical diseases such as malaria and dengue. The encapsulated formulation was tested for its UV irradiation protective efficiency

in laboratory conditions. While the protein in its natural form had lost all of its activity after 24 hours of exposure, encapsulated formulations showed up to 88% of larvae mortality.

In their turn, Tamez-Guerra *et al.* [23] also tested the encapsulation of the spore-toxin of *Bacillus thuringiensis* Berliner, evaluating over 80 formulations of spray-dried microcapsules made of lignin and corn flour with and without photoprotective agents. The best formulations showed improved insecticidal activity in laboratory tests against neonates of European corn borer *Ostrinia nubilalis* when compared to nonencapsulated or commercial formulations of the same endotoxin. In a field test, the microcapsules showed increased residual insecticide activity in cabbage after 7 days against neonates of the cabbage looper *Trichoplusia ni* when compared to commercial formulations.

Very promising results have been obtained by the Agricultural Research Service of the USDA regarding the encapsulation of biopesticides made of species-specific nucleopolyhedroviruses (NPV) isolated from several insects, including celery looper *Anagrapha falcifera* (Tamez-Guerra *et al*., 2000 [24-26]), alfalfa looper *Autographa californica* [27], codling moth *Cydia pomonella* [28] and fall armyworm *Spodoptera frugiperda* [29]. In these works, formulations were developed using different mixtures of corn flour and lignin, through spray-drying technique to encapsulate the viruses. All results obtained in laboratory and field tests performed have shown improvements in insecticidal activity, resistance to environmental conditions, like rain and UV light exposure, and a prolonged residual activity against pests in field studies. Samples were kept in storage for up to 12 months and maintained their insecticidal activity.

2.4. Novel micro and nanoparticles for bioinseticides

Conventional protocols for encapsulation usually run under relatively high temperatures, which might be inadequate for preserving plant-derived essential oils integrity. Processes which use high pressure instead of temperature can be an alternative for encapsulating these sensible extracts. Varona *et al.* [30,31] developed new methods to produce stable particles of lavandin (*Lavandula hybrida*) essential oil, using polyethylene glycol 9000 (PEG9000) or n-octenyl succinic (OSA) modified starches as the shell material. The methods for preparing the microcapsules were based on PEG precipitation from a mixture of molten polymer and essential oil in supercritical CO_2, and PGSS-drying an oil-in-water emulsion of the essential oil with OSA starch. The difference between these processes is the presence of water on the latter, which needs to be removed by carefully tuning the equipment conditions to promote water evaporation. Microcapsules produced by these methods show a mean particle size of 10-500μm for PGSS, and 1-100μm for PGSS-drying. One important observation by scanning electron microscopy (SEM) images is that the experimental conditions can influence the shape of the microparticles. While PEG particles were only spherical (the best shape for controlled release mechanism), in PGSS-drying needle-like structures are formed,, depending on the pre-expansion temperatures of the mixtures, The last one, probably does not hold the active ingredient, presenting some limitations to this specific method without further improvements. Release kinetics were evaluated over a 20-day period. The amount of oil

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released was proportional to the initial oil concentration on particles, with less than 20% of liberation for low oil concentrations, and about 60% liberation for high oil concentration.

Yang *et al.* [32] assembled polyethylene glycol (PEG) nanoparticles loaded with garlic essential oil using a melt-dispersion method, reaching over 80% of encapsulation efficiency, with round shaped nanoparticles of lower 240nm of average diameter. The encapsulated formulations had their insecticidal activity evaluated against adult red flour beetle *Tribolium castaneum*. While the control experiment done with free garlic oil showed only 11% of efficiency over a five month period, the encapsulated formulation efficiency remained over 80% after five months. This was attributed to the slow and controlled release of the essential oil, and thus could be used as an effective pest control to stored products.

The basic structure of the polymer chitosan was used by Lao *et al*. [33] to build the amphiphilic-modified *N*-(octadecanol-1-glycidyl ether)-*O*-sulfate chitosan (NOSCS). Octadecanol glycidyl ether and sulfate were the hydrophobic and the hydrophilic groups sources respectively. They successfully entrap the herbal insecticide rotenone in the polymer. This chemical compound has been allowed for application in organic crop production due to its natural origin, short persistence in the environment, safety to non-target organisms and low resistance development. The encapsulation was necessary to defeat the problems of chemical stability of the substance to environmental effects and also to improve the solubility of this pesticide in water, which is usually quite low ($2.0 \times 10^{-6} g.L^{-1}$). Using the reverse micelle method, the authors have assembled nanometric micelles with 167.7-214.0 nm of diameter, with values of critical micellar concentration (CMC) of those chitosan derivatives ranging from 3.55×10^{-3} to 5.50×10^{-3} $g.L^{-1}$. Although the entrapment efficiency was not very high, they also improved the aqueous solubility of the chemical compound in 13,000 fold, up to $0.026 g.L^{-1}$, favoring a controlled release of the substance in aqueous media. The complete controlled release took more than 230 hours, almost 10 times more when compared to the chemical compound without nanoencapsulation.

Chitosan derivatives were prepared [34]. They synthesized 6-*O*-carboxymethylated chitosan with anchorage of ricinoleic acid at the *N*-linkage, which further improve its solubility at neutral water (pH = 7.0), to encapsulate the herbal insecticide azadirachtin. Nanoparticles of 200-500nm were obtained by water dispersion with more than 50% of loading efficiency and tested for their stability in outdoor as controlled release systems. Results were compared against simple azadirachtin water dispersion and modified dispersion containing ricinoleic acid and azadirachtin. In 5 days of sun exposure, all content of control samples were lost, while the encapsulated formulation had a nearly constant residual concentration detected throughout the 12 days of the experiment, indicating that the nanoparticles produced were effective at controlling the degradation rate and the release mechanism of the botanical insecticide.

Extracts of Neem were prepared contend high concentration of azadirachtin being nanoencapsulated by Forim *et al.* [35]. Through the use of poly-(ε-caprolactone) polymer, they prepared nanocapsules and nanospheres with average diameter of 150.0 and 250.0nm, respectively. The morphological analysis revealed spherical nanoparticles (Figure 1). The azadirachtin was used as reference. The nanoformulations showed high entrapment efficien-

cy (> 95%) for this compound and a UV stability at least of 30 times more when compared with commercial products.

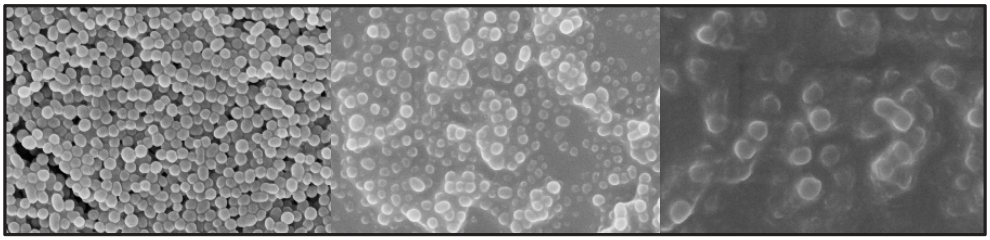

Figure 1. Scanning electron microscopy images of nanoparticles containing extracts of Neem.

2.5. Commercial products

The interesting results obtained in academic researches over the last few decades have been closely followed by several companies. Nevertheless, R&D in nano-based agrochemicals is led mainly by world's largest agroscience companies, further enhancing their market share and consolidating the market structure based on oligopoly that have been seen in late 20th century and early 21th century, when the 10 biggest companies hold around 80% of market [36].

Some companies over the last decade, such as Syngenta, Bayer, Monsanto, Sumitomo, BASF, and Dow Agrosciences have already deposited several different patents comprising a wide range of protocols for production and application of encapsulated formulations, which can be used to produce nanoinsecticides [37-46]. Despite the hard work and heavy investment, no commercial nano-insecticide formulation has been extensively commercialized up to 2012.

Along with those big industries, several other companies, as well as individual researches have been actively depositing patents in the area, thus promoting even more the research and investments in this new field of applied technology. However, as strongly reinforced throughout the world by dozens of organizations such as the ETC Group, the impact of nanotechnology is still unclear, and care should be taken to assure that its use will not bring more problems than solutions [47].

3. Developing new nanopesticides

Many attempts have been made to manage plague insects, for example, using biological control, which is very time consuming. Controlled release systems dawn in this scenario as a very attractive alternative in this battle field.

Controlled release formulations (CRFs) associate the active compound with inert materials. The last ones are responsible for protecting and managing the rate of compound release into the target site in a defined period of time. The main purpose of controlled release systems is

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ruling the (bio) availability of the active compound after the application [48]. They find the greatest applicabilities in two major agricultural fields: nutrition and protection. In the first one, CRFs are employed in the delivery of fertilizers [49-51]. In the second one, CRFs are mostly used to target plague insects in a sustainable way [52,53], but they can also be applied to block the growth of weeds [54]. Tomioka *et al.*, 2010. Controlled release formulations become especially interesting in cases of antagonist activity of biocides, what can naturally leads to a lower in effectiveness of one or both compounds. In this case the formulation should be "programmed" to release each one at different times [55,56]. Furthermore, still talking about protection, the application of CRFs in wood surfaces, like furniture or floor covering, helps to prevent the deterioration. Van Voris *et al.* [57] patented a formulation in which an insecticide is continually released in a minimum level for a long period of time and is absorbed by the wood. It thus creates a "chemical barrier", blocking the insect attacks.

Most of those controlled release biocides applications were and still are successfully made due to the advances in nanotechnology area.

Micro- and nanomaterials-based formulations are known for some decades. The first microcapsule-based formulation became commercially available in the 1970s [58]. Nanocapsules have been widely used in medicinal area as drug carrier in treatment of diverse diseases [59], from tropical ones [60] up to cancer [61].

Microencapsulation has been used as a versatile tool for hydrophobic pesticides, enhancing their dispersion in aqueous media and allowing a controlled release of the active compound. The use of nanotechnology is a recent approach, and has been a growing subject on several different areas of the science, with an overwhelming perspective. In general, materials that are assembled in nanometric scales (<1000nm) have distinct and almost always better characteristics when compared to the same material built in a conventional manner [62]. One nanometer is a billionth of a meter ($1nm = 10^{9}m$). In general, the chemical properties of materials in nanometric scale may be controlled to promote an efficient assemble of a structure which could present several advantages, such as the possibility to better interaction and mode of action at a target site of the plant or in a desired pest due to its tunable controlled release system and larger superficial area, acting as an artificial immune system for plants [34,63]. As smart delivery systems, they confer more selectivity, without hindering in the bioactive compounds towards the target pathogen [65]. Other advantages of the use of nanoparticle insecticides are the possibility of preparing formulations which contain insoluble compounds that can be more readily dispersed in solution. It reduces the problems associated with drifting and leaching, due to its solid nature, and leads to a more effective interaction with the target insect. These features enable the use of smaller amount of active compound per area, as long as the formulation may provide an optimal concentration delivery for the target insecticide for longer times. Since there is no need for re-applications, they also decrease the costs), reduce the irritation of the human mucous-membrane, the phytotoxicity, and the environmental damage to other untargeted organisms and even the crops themselves [65,66]. In a few words, nanotechnology can be applied in several ways in order to enhance efficacy of insecticides in crops.

3.1. Biopolymers

When a commercial formulation for a practical field application is desired, it is very important to employ materials that are compatible with the proposed applications: environment-friendly, readily biodegradable, not generating toxic degradation by-products and low-cost. The use of several biopolymers, i.e., polymers that are produced by natural sources, which at the same time have good physical and chemical properties and still present mild biodegradation conditions, are an interesting approach to avoid the use of petrochemical derivatives that might be another source of environmental contamination. The common polymers (synthetic and natural ones) used in CRFs for insecticides application are listed in Table 1.

3.2. The nanoparticles used in biocides controlled release formulations

The most popular shape of nanomaterials (Figure 2) that have been using in CRFs for biocides delivery are:

a. Nanospheres: aggregate in which the active compound is homogeneously distributed into the polymeric matrix;

b. Nanocapsules: aggregate in which the active compound is concentrated near the center core, lined by the matrix polymer;

c. Nanogels: hydrophilic (generally cross-linked) polymers which can absorb high volumes of water

d. Micelles: aggregate formed in aqueous solutions by molecules containing hydrophilic and hydrophobic moieties.

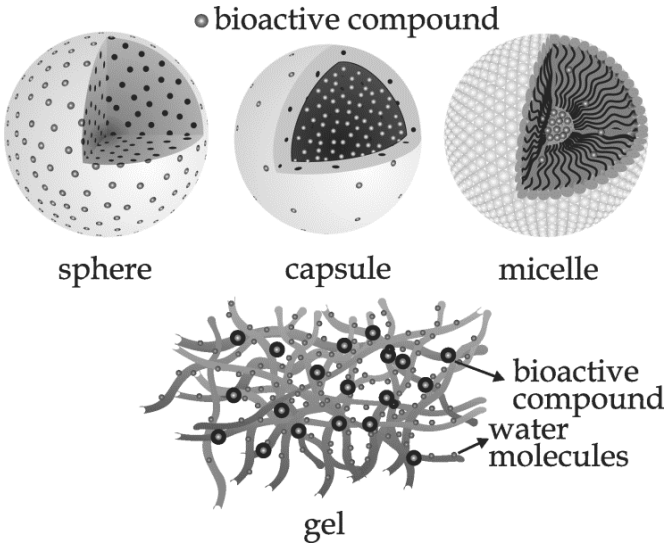

Figure 2. Morphological representation of different nanoparticles.

Polymer	Active compound	Nanomaterial	Ref.
Lignin-polyethylene glycol-ethylcellulose	Imidacloprid	Capsule	[67]
Polyethylene glycol	B-Cyfluthrin	Capsule	[68]
Chitosan	Etofenprox	Capsule	[69]
Polyethylene	Piperonyl Butoxide And Deltamethrin	Capsule	[70]
Polyethylene glycol	Garlic Essential Oil	Capsule	[32]
Poly(acrylic acid)-b-poly(butyl acrylate) Polyvinyl alcohol Polyvinylpyrrolidone	Bifenthrin	Capsule	[71]
Acrylic acid-Bu acrylate	Itraconazole	Capsule	[72]
Carboxymethylcellulose	Carbaryl	Capsule	[73]
Alginate-glutaraldehyde	Neen Seed Oil	Capsule	[74]
Alginate-bentonite	Imidacloprid or Cyromazine	Clay	[75]
Polyamide	Pheromones	Fiber	[76]
Starch-based polyethylene	Endosulfan	Film	[77]
Methyl methacrylate and methacrylic acid with and without 2-hydroxy ethyl methacrylate crosslinkage	Cypermethrin	Gel	[78]
Lignin	Aldicarb	Gel	[79]
Lignin	Imidacloprid Or Cyromazine	Granules	[75]
N-(octadecanol-1-glycidyl ether)-O-sulfate chitosan-octadecanol glycidyl ether	Rotenone	Micelle	[33]
Polyethyleneglycol-dimethyl esters	Carbofuran	Micelle	[80]
Carboxymethyl chitosan-ricinoleic acid	Azadirachtin	Particle[a]	[34]
Chitosan-poly(lactide)	Imidacloprid	Particle[a]	[81]
polyvinylchloride	Chlorpyrifos	Particle[a]	[82]
Cashew gum	*Moringa Oleifera* Extract	Particle[a]	[83]
Chitosan-angico gum	*Lippia Sidoides* Essentioan Oil	Particle[a]	[84]
Polyvinylpyrrolidone	Triclosan	Particle[a]	[85]
Anionic surfactants (sodium linear alkyl benzene sulfonate, naphthalene sulfonate condensate sodium salt and sodium dodecyl sulfate)	Novaluron	Powder	[86]
Vinylethylene and vinylacetate	Pheromones	Resin	[87]
Glyceryl ester of fatty acids	Carbaryl	Spheres	[15]
Poly(ε-caprolactone)	Active Ingredients[b]	Spheres	[88]
Poly(methyl methacrylate)-poly(ethylene glycol) Polyvinylpyrrolidone	Carbofuran	Suspension	[89]

[a] The authors do not mention which active compounds they encapsulated in the nanospheres; [b] The authors do not mention if the particles are spheres or capsules

Table 1. Several examples of polymers often used in the nanoparticle production.

Dendrimers, nanoclays, nanopowders and nanofibers are other possible formulations which might be used during nano or microparticle production[75, 76, 86, 90]. On the other hand, nanotubes are mostly applied in plants improvement. The polymeric nanoparticles and gels are by far the mostly used for insecticides application, because they have an extra advantage of being biodegradable.

3.3. Methods for preparation of nanomaterials based controlled-release formulations for biocides application

According to Wilkins [48], the methods for CRF preparation can be separated in chemical or physical ones (Figures 3 and 4, respectively).

The chemical methods are based on a chemical bond (usually a covalent one) formed between the active compound and the coating matrix, such as a polymer. This bound can be placed in two different sites: in the main polymeric chain or in a side chain. In the first one, the new "macromolecule" is also called a pro-biocide, because the compound will get its properties in fact when it is released. In the second one, the insecticide molecule can bind initially to the side-chain of one monomer and then the polymerization reaction takes place or the polymerization occurs first and only after that, the biocide binds to the side chain. There is still a third way, based on the intermolecular interactions. In this case, the biocide is "immobilized" in the net produced by the cross-linkages in the polymer.

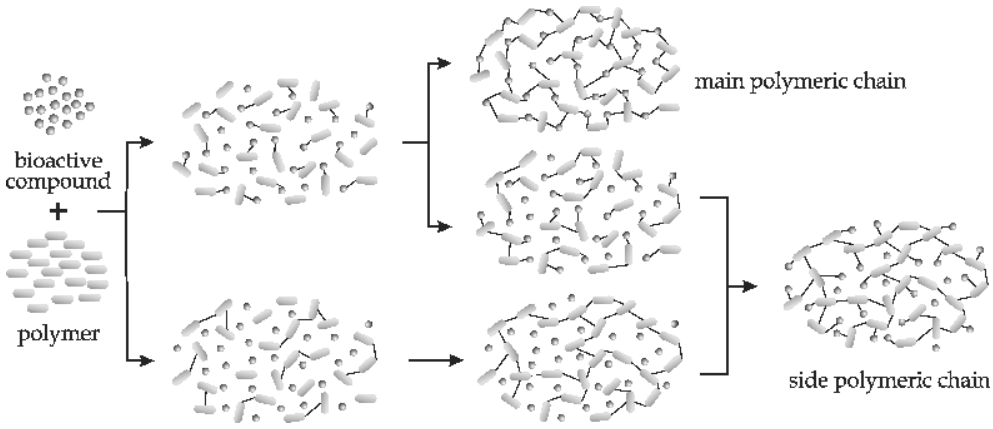

Figure 3. Chemical methods for CRF preparation

The physical methods can also be split in two distinct categories. In the first, a mixture of biocide and polymer is made. As the last has a higher energy density, it moves to a more external layer, forming a kind of monolithic structure. In the other one, the polymeric chain forms a "membrane" isolating the bioactive compound from the external environment. This is the method which will produce the nanocapsules themselves.

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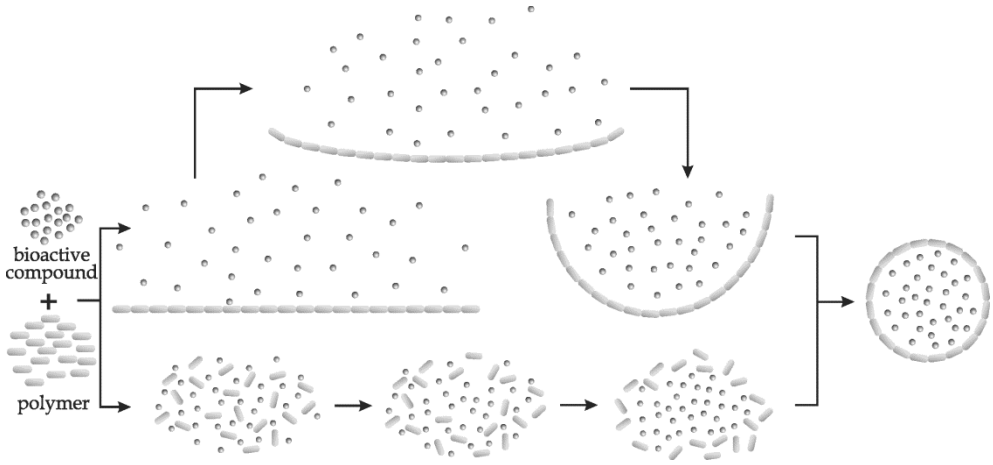

Figure 4. Physical methods for CRF preparation

Although there are some different kinds of nanomaterials that can be used in CR formulations, the micro- and nanocapsules are by far the most widely used for controlled release of biocides. For this reason, the techniques described here will be restricted to micro and nanoencapsulation process.

3.4. Micro and nanoencapsulation techniques

The first formulation containing polymeric-based nanocarriers for controlled release of biocides dates from the early 1970's [11,92]. Recently, John *et al*. [93] reviewed the most commonly techniques used to prepare micro- and nanocapsules containing microorganisms (for this kind of application, see section 2.3). However, the techniques they commented can be also utilized to prepare nanocapsules for insecticides application in general. Shahidi and Han [94] and Wilkins [48] classified them as physicochemical, chemical or physical process-based. Some are described below.

3.4.1. The physicochemical-based techniques

a. *Emulsion*: This technique is used to produce a system of two immiscible liquid phases (water and oil), where one (the dispersed phase) is dispersed into the other (continuous phase) in a controlled way (usually in a dropwise one). The bioactive compound (usually water-soluble) and the polymer are solubilized each one in a phase (water or oil). One of the solutions is gradually dripped into the other under vigorous stirring. After the homogenization, the emulsion is formed. If the oil is the dispersed phase, the emulsion is classified as O/W (oil/water). If it is water, the emulsion is called W/O (water/oil) [95].The emulsion itself also represents a crucial step for some other more complexes preparation ones.

b. *Coacervation*: This process is based on the reduction of polymer's solubility. According to Wilkins[48] the encapsulation goes through a separation of phases and can be simple

or complex. In a simple coacervation, the addition of an external agent, like a salt or water-miscible solvent, to an aqueous solution containing a hydrophilic polymer-insecticide complex causes its precipitation. Complex coacervation involves opposite charges and electrostatic attraction. A solution containing different ionizable polymers is submitted to a pH change. The polymers turn positively or negatively charged. The electrostatic attractive forces between the opposite charges become much stronger than the particle-solvent intermolecular ones, leading to the copolymer precipitation.

c. *Emulsion-solvent evaporation*: According to Iwata and McGinity [96] this technique comprises two or three steps. In the first one, an O/W (or W/O) emulsification must be initially formed. The polymer is usually solubilized in the dispersed phase. If the emulsion has only two components like this one, it is called a single emulsion. For this type, the whole process has only two steps and the first one ends here. However, there is also other type, called double emulsion, represented as W/O/W', where the emulsion already prepared in the first step is dispersed into an organic solvent, like acetonitrile. In this case, the aqueous solution containing the active compound is dripped in an oil phase (usually a vegetable oil), under stirring. This emulsion is then dispersed, under stirring, in an organic solvent solution containing the polymer. The last step, common for single and double emulsion, is the evaporation of the solvent, what can be performed at room temperature or under reduced pressure. After solvent removal, the particles are ready for use.

d. *Emulsion crystallization/ solidification*: According to the procedure published by Iqbal *et al*. [97], an emulsion is initially prepared as already described in this section. The only difference remains in the temperature in which it is made. The authors prepared the emulsion at 60ºC. The next step is crucial for technique success. The warm emulsion is pumped through a capillary partially immersed in a coolant liquid (temperature: 10ºC). At the capillary exit, the emulsion forms spherical drips which move to raise the cooling liquid's surface. The drop is cooled down during the course, solidifying and forming the particles which are collected at the top.

e. *Diffusion-controlled emulsion*: In this process, a monomer rich phase is laid over the aqueous solution containing the insecticide, under a smooth stir. The monomers then diffuse into the aqueous fase, "trapping" the bioactive molecules in a micellar structure [98].

f. *Liposome entrapment*: Some protocols to prepare liposomes are described by Mozafari *et al*. [99]. The standard one is resumed here.

In the first step, an organic solution (chloroform or methanol ones) containing hydrophobic molecules such phospholipids and cholesterol is prepared. The solvent then is evaporated forming a thin film. Next, an aqueous solution containing the bioactive compound is spread over this film. Some mechanical or thermal perturbation like ultrasound or heating is applied to the system to promote the formation of single or double layer sheet. The sheet will detach from the support, closing itself, forming the liposomes. During this closing process, the sheet traps the biocides molecules.

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3.4.2. The chemical techniques

a. *Interfacial polymerization*: As the name says, this technique is based in a polymerization reaction which occurs in an interface of two immiscible liquids. According to Wilkins [48], polymerization can occur through an addition or condensation reaction. In the mostly addition-governed process, the polymerization starts in the oil phase, where the monomers and insecticide are dispersed. However, the reaction only takes place when it is catalyzed by free radicals, which are dissolved in the aqueous phase. In condensation-governed process (the most suitable route for biocides nanoencapsulation), the reactive monomers are dissolved each one in a different phase. As the dispersed phase is dripped into the continuous phase, the reaction occurs in the droplet interface, producing the polymer. When a solvent with a low boiling temperature is used as the oil phase (either in dispersed or continuous one) and contains the monomers dissolved, the process is a little different. After the dripping, the system is heated. The solvent thus evaporates, leaving the particules that, due to the water insolubility, precipitates. This particular technique variation can also be called interfacial polymer deposition [100].

b. *Molecular inclusion*: This technique is used to increase the solubility of water-insoluble compounds in aqueous solution. Macromolecules like cyclodextrins [101] have an inner hydrophobic face and an outer hydrophilic face. An oil phase containing the biocide is dripped, under continuous stirring, into the aqueous macromolecule solution. During the dripping, the macromolecule "traps" the insecticide molecules via intermolecular interactions.

3.4.3. The physical techniques

a. *Extrusion:* The bioactive compound is mixed with hydrocolloids and then, the colloid is squeezed out under pressure. The pressure during the process should be adjusted according to the viscosity of colloids.

b. *Spray drying*: This technique is based in solvent evaporation at high temperatures. The spray drying process has already been described in details by Ré [102]. The following text is only a brief resume. Initially, the active compound and the polymeric matrix are solubilized in their respective solvents, which should not be miscible. Then, they are mixed under vigorous stirring to form an emulsion (or dispersion whether one of the components is in the solid state). The emulsion undergoes an atomization to produce droplets. In the next step, the droplets are submitted to a hot air flow that forces the solvent (generally water) evaporation, leaving only a dry powder. The greatest advantage of this technique is that it can be easily scaled up for a large scale nanocapsules production.

c. *Freeze drying*: This technique is also known as liophilization. It is the opposite of the spray drying, because it uses a low temperature system. A suspension or emulsion is prepared to enable the polymer-insecticide formation. For emulsions, an additional step is required before the execution of the technique: the removal of the oil or organic solvent under reduced pressure. For both (emulsion and suspension), the aqueous phase is

frozen and submitted to a low pressure system. When the pressure is drastically reduced, the water sublimes (goes from solid to vapor state), leaving only the particles.

3.5. Mechanism of biocide release

In the paper published by Kratz *et al.* [103] the text begins with the statement: "Nanoparticles only start working after they are placed in a desired location". In other words, an efficient CR formulation must remain inactive until the active compound is released.

The way how an inert material, such the nanopolymers, controlss the amount and rate a chemical is released is object of study since the late 1960's [104] and early 1970's [105].

How the release of the bioactive compound occurs depends basically on the chemical nature of the formulation. In various polymeric nanomaterials, the controlled release proceeds via diffusion. It does not matter if the bioactive compound is dissolved (micro- or nanospheres) or if it is encapsulated (micro or nanocapsules). The process does not depend on the chemical structure of the formulation constituents [11] neither on the intermolecular interactions. The rate control is made based on the interactions between the carrier and the biocide. The stronger the interaction will be slower the release rate. In the 1990's, the release dynamics was investigated via the use of ^{14}C-labelled molecules of herbicides [106,107]. Qi *et al.* [107] studied the dynamic of controlled release for herbicides. They used ^{14}C-labelled molecules of benthiocarb and butachlor and observed that the release is made by a diffusive process. Some years later and without any radiolabeled molecules, Fernandez-Perez et al. [108] found the same results. They prepared a granule-based CRF constituted by lignin and imidacloprid. They measured the amount of compound released in water under a dynamic flow condition during a defined period of time. The data fitted a diffusion curve based on the model proposed by Ritger and Papas [109,110]. Since then, other similar studies have been published [111-114].

Some other polymeric nanomatrixes, especially those formed by a carboxylic acid and a metallic cation, can be disassembled when in contact with water, releasing the bioactive compound [92]. The release rates depend on the physicochemical characteristic of both molecules. The more hydrophobic the polymer slower will be the bioactive compound release. The same applies to the last one: the higher water-solubility, faster it will be released. The formulation itself also affects directly the release rate. In water-based one, the rate control tends to disappear, due to the matrix (or support) degradation. If the particles are solubilized in an organic solvent, like acetone, the formulation becomes sticky and the release rate slows down. A granule-based formulation sounds more efficient. It can be applied direct to the soil and the bioactive compound will be released according to the soil moisturize (water content), leading to a long lasting control.

In other formulations, the bioactive compound is covalently bound to the polymeric matrix [115]. To the release takes place, a chemical interaction must be broken. It usually occurs via a hydrolysis reaction, what affects many polymer-insecticide bounds in a chain reaction. The release control depends on the strength of those chemical bounds, the chemical properties of both molecules and on the size and structure of the macromolecule formed [11]. The higher the

biocompound solubility in water, faster the reaction occurs. Concerning the chemical properties of the polymer, Allan *et al.* [11] studied the differences in the release kinetics when 2-methyl-4-chlorophenoxy acetic is chemically bound to polyvinylalcohol (a water-soluble polymer) or when it is bound to cellulose or lignin (water-insoluble polymers). In the first situation, the level of the applied herbicide tends to go down, because the equilibrium

$$Polymer - insecticide \quad \rightleftharpoons \quad Polymer + Insecticide$$

will always exist. I the last situation, as the "free polymer" is water–insoluble, the equilibrium moves towards the right side and the level of the applied herbicide tends to go up (Figure 5).

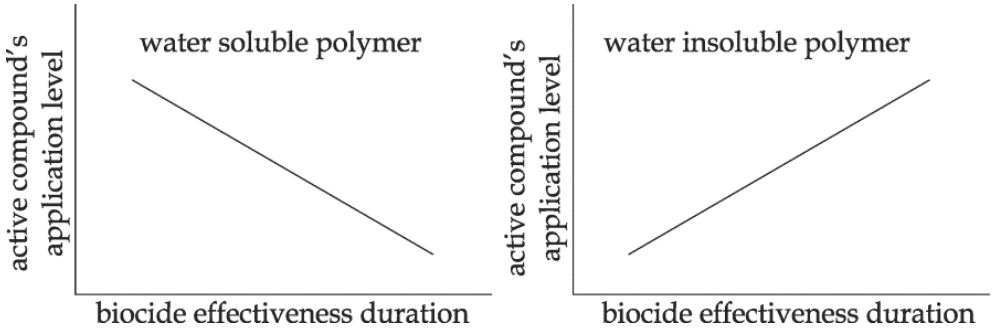

Figure 5. Trend in active compound's application rate (*Adapted* from [11]).

Whatever the mode of liberation, it should be kept in mind that controlled release formulations have a limited maximum amount for the release of the biocide[116]. This means that the total amount of released product may not be necessarily equal to the amount of chemicals incorporated to the formulation neither to the amount of free applied product[117]. This is the reason why the concentration of the active compound in a CRF is usually higher than in a conventional one. However it does not contradict what was said earlier about advantageous reduced amount if biocide applied, since the number of applications should be smaller.

Studies recently published suggested that the encapsulation of biocides reduces their toxicity [117,118]. However, many issues regarding the toxicity of the nanomaterial themselves towards the environmental and even the worker's health remains unclear [119].

4. Conclusion

The increasing worldwide demand for foods requires modern techniques of agricultural production minimizing losses in the crops, transportation and storage. Among the main causes of agricultural losses there are the plague insects. Insecticides are an important control tool. However, some collateral effects may be credited to their indiscriminate use such

as environmental contamination, human poisoning, reduction in the number of natural enemies, insecticide resistance by plague insects, etc.

In this scenario, nano- and microparticles have been reaching a prominent position. Formulations containing insecticides have been prepared in colloidal suspensions or powder, in nano or micro scale, where they present several advantages such as increasing stability of the active organic compound (UV, thermal, hydrolysis, etc.), foliar settling, reduction in foliar leaching, systemic action, synergism, specificity, etc. As consequence, the amount of insecticide necessary (dosage), the number of applications, human exposure to insecticides and environmental impact are reduced. The nano- and microformulations have been employed not only for synthetic insecticides but also in alternative products to control plague insects such as natural products (herbal extracts) and entomopathogenic microorganisms.

In order to prepare nano- and microformulations, several chemical and physical techniques have been developed. In general, they should be prepared by using polymeric materials which are biocompatible and biodegradable. This practice has the aim to avoid the emergence of new environmental and toxicological problems. The biopolymers are produced by microorganisms, synthesis or even petroleum derivate products. In common, when exposed to the environment they are easily destroyed by UV radiation and/or microorganism enzymes generating CO_2 and H_2O as final product. The degradation processes of biopolymers may lead, or not, to the release mechanisms of active organic compounds of a nano- or microparticles. Processes such as swelling, hydrolysis, diffusion, erosion, etc., must be manipulated in a controlled way in order to obtain the desired characteristics of application and biological activity for the formulated products.

As a result of the application of these new nano- and micro- technologies, which have been quickly developed due to new sensitive analytical technologies of characterization, new ways to control plague insects are emerging, thinking not only in lethal action on the target insect, but also in all ecosystems, which include fishes, natural enemies, vegetation, microorganisms, animals, the man himself, etc.

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