

New Generations of Pesticide Formulations for Organic Agriculture

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Abstract

Agricultural sustainability involves activities that have to fulfil environmental and public health requirements. Among the criteria for sustainable development, organic agriculture is a primary key to satisfy the above goals because it is different from conventional agriculture that avoids or reduces synthetic agrochemicals use, replacing them with natural based, less toxic, and environmentally friendly products. The current development trends in pesticide formulations from such a perspective view are applications of new generation types, with high biological activity and safer, low toxicity to mammals, and other beneficial organisms. In these formulations, the toxic, non-biodegradable additives/adjuvants ingredients are replaced by natural-derived environmental-friendly ones, the new technologies are also applied to increase biological efficiency, reduce environmental pollution such as reducing the size of particles (wettable powder to suspension concentrate); replacing toxic organic solvents with water or water-based formulations and increasing the coverage of applied surface area (Emulsion concentrate or Organic solution to Microemulsion/Nano-formulations); reducing wastage and dose rate (Dust to Controlled-release formulations); and applying combination/mixed formulations such as ZC, ZE and ZW to expand the spectrum of action and reduce consumption. Some new generation of pesticide formulations include Suspension concentrates (SC), Emulsion in water (EW), Micro-emulsion (ME), Combination/mixed formulations, Water dispersible granules (WG), Capsule suspension (CS), Nano-formulations, Seed treatment formulations, etc., were discussed in the aspects of textures, components, processing as well as applications in this review.

Keywords: Pesticide formulation, organic agriculture, sustainable development.

1. Introduction

According to the Food and Agriculture Organization (FAO) of the United Nations report in 2011, agriculture has always played an important role in the global economy because more than 40% of the world's population works in this field. Therefore, along with sustainable development, the concept of "sustainable agriculture" has been formed and become a crucial link to create a sustainable future.

Organic agriculture is one of the directions that is being interested in and applied to agricultural production because of its similarity to the development of sustainable agriculture. According to the definition of the International Federation of Organic Agriculture Movements (IFOAM), the 4 basic principles: "Health - Ecology - Fairness - Care" associated with organic agriculture are specifically:

- Sustains the health of people and planet.
- Nourishes living ecological systems and cycles.
- Builds relationships ensuring fairness among people and other living beings.
- Protects and cares for the health and wellbeing of current and future generations.

In the development of modern agriculture in general, it is impossible not to mention the role of agrochemicals such as fertilizers, pesticides, plant growth regulators, and soil improvers. In particular, the use of pesticides to prevent and control pests is an effective, powerful, and indispensable measure to protect crops, increase the quality of agricultural products, and reduce post-harvest losses. In fact, in many agricultural countries in the world, the demand for pesticides always increases with the development of agriculture.

However, pesticides are often highly toxic, easily harmful to animals in general and humans in particular and have a negative impact on the ecological environment. Therefore, today, with the aim of developing sustainable agriculture, the production and use of pesticides must go hand in hand with environmental protection and public health.

To minimize the harmful effects of pesticides, scientists are always looking for new directions of development to create products with high prevention efficiency but safer, in which it is recommended to limit the use of chemical synthesis and use raw materials and products of natural origin. In fact, the plant protection industry has had many changes in recent times: Many new active ingredients and additives have been invented;

new processing and packaging technologies have been applied leading to effective, safe and environmentally friendly products; the process of using pesticides has been improved to manage pests sustainably as well as supporting organic agricultural production. Among them, the technology of processing new forms of pesticides has had many remarkable developments.

Vietnam is an agricultural country with a large, cultivated area, favourable climate conditions, and a variety of crops, so pests develop diversely and year-round. Therefore, the need to use pesticides is very necessary and always requires innovation and development. However, in the context of sustainable agricultural development in our country, it is necessary to choose new and suitable processing forms to create environmentally friendly products for use, meeting the consumption needs of farmers while ensuring safety for the environment and public health

2. Development Trends of Plant Protection Products

Recent scientific and technological achievements applied to agriculture have helped increase crop productivity and quality, but there comes along the potential risks, causing serious consequences for the ecological environment and public health, making agricultural production unsafe. Therefore, development in agriculture must go hand in hand with safety and sustainability, with the goal of both increasing crop and livestock production to ensure food security, creating clean, safe products for current consumer needs without disrupting the ecological balance in the future.

To achieve the above principles, organic agriculture must avoid or eliminate most of the use of fertilizers, pesticides, and other agrochemicals of synthetic material or genetically modified origin in agricultural production. Along with that, it is necessary to pay attention to the ecosystem, including crops, livestock, and humans during the cultivation and use of pesticides. After the production process, pesticide residues must ensure that the quality of the land is maintained or even improved in fertility. The products obtained must meet the needs but be safe and user-friendly, avoiding the effects of pesticide residues on agricultural products.

Thus, the organic agricultural production process, ensuring increased agricultural output, guaranteed quality, environmental-friendly and maintained ecological balance, is an important link in sustainable agricultural development. In particular, in addition to improving plant varieties and developing farming methods, agricultural chemical products need to ensure selectivity in activity, safety for the ecosystem, and formulations that maximizes efficiency and does not leave residues in agricultural products as well as the environment [1].

2.1. Development of Natural-Derived Active Ingredients

Synthetic pesticides such as organic chloride compounds, organic phosphorus, carbamates, and old generation pyrethroids are highly toxic to humans and animals, persist for a long time, leave residues in agricultural products, and affect the environment and ecosystem. Thus, they are less suitable for clean agriculture. Moreover, products of chemical synthesis origin, especially from petroleum, are not renewable and easily cause pesticide resistance in pests, increasing the amount used in the fields, further increasing the risk of pollution.

In organic agricultural production, those Active Ingredients (A.I.s) need to be replaced by new compounds, with new modes of action and superior properties such as high biological activity and selectivity for harmful objects, low toxicity to humans and beneficial animals; low resistance; easy to decompose leading to no residue in agricultural products, soil, water; and convenient for formulating. With the above criteria, active compounds of biological or natural origin for plant protection products such as natural minerals; herbal (extracts, plant essential oils) or biological products from fungi, bacteria, etc., are interested in development and application. Natural derived protection products play a key and essential role in organic agriculture, but within the framework of this review, the group of authors will focus on new formulation with new technology and additives serving organic agricultural production.

2.2. Development Trend in New Generation of Pesticide Formulations

Currently on the market, the pesticide formulations are quite diverse, including liquid, dry, gel or vapor form. In developing countries, popular pesticide products are often traditional forms such as water-soluble concentrated pesticides (SL), emulsifiable concentrate (EC), granules (GR), wettable powder (WP), etc. The technology for processing these products is easy to implement but has many limitations such as high toxicity to beneficial organisms, low dispersion, high risk of burning leaves and environment pollution, adversely affecting public health.

With the goals of organic agriculture and general requirements for new generation of formulations, current trends in developing pesticide formulations include following:

a) Limit the use of toxic, volatile, and flammable organic solvents and aim to completely replace them with water or water-based formulations. Make it easy to package, transport and use [2-7]:

- For liquid formulations, replace the oil emulsion like EC with new formulations such as suspension concentrate (SC); oil-in-water emulsion (EW); suspo-emulsion (SE) or micro-emulsion (ME).

- For dry processing, replace the WP, dust (D) with SC or water dispersible granule (WDG or WG).

- Increase the application of oil-dispersed (OD) form because it increases stability with water-sensitive A.I. (such as sulfonylurea herbicides) and the oil phase is also an adjuvant to increase effectiveness.

b) Increase the use of natural-derived, renewable additives. Several natural materials have been researched, developed and used as low-toxicity, biodegradable and reasonably priced additives [2-7]:

- Clay minerals such as bentonite, kaolinite and silicate materials.

- Biopolymers such as polysaccharides, lignin, cellulose, modified starch.

- Vegetable oils and biodiesel can also replace some solvents

- Use of natural surfactants, low toxicity, which have the effect of increasing the activity of the A.I. (bio-enhancing surfactant wetter)

c) Formulations with higher A.I. content (more concentrated) or a combination of several different A.I.s helps reduce labor, packaging and transportation costs. Although these types of formulation are more complicated and require careful research, they also have their own outstanding advantages [2-7]:

- Synergistic substances can increase biological effectiveness exponentially, widen the spectrum of action, which means reducing the dosage, leading to a reduction in the risk of harm.

- Mixing many types of drugs with different mechanisms of action helps diversify the target of attack to reduce the possibility of drug resistance.

- Fertilizers and plant nutrients can be mixed with pesticides or plant growth regulators.

d) Development of controlled release, targeting or seed treatments formulations that reduce drug use such as [2-7]:

- Encapsulation technology
- Nano-processing technology
- Effervescent tablet processing technology
- Gel formulation

- Processing technology for UAV/drone applications and precision agriculture [1, 2].

This brief review article will discuss the technology for processing new generations of pesticides formulations and their applications.

3. New Generation of Pesticide Formulations

3.1. Liquid Formulation

Liquid processing forms are considered a safe choice, replacing dry forms, dispersed granules in water. New liquid formulation must ensure properties such as less harmful to the skin, flexibility, limited use of toxic solvents, easy to use and clean. Recently new generations of liquid formulations included: Emulsion oil in water (EW), SE, ME or multiple emulsions including water in oil in water (W/O/W), and oil in water in oil (O/W/O) or formulation in oil. These are complex formulations, requiring careful selection of emulsifiers and stabilizers to ensure physical stability.

3.1.1. Suspension concentrate

SC are stable suspensions of one or more A.I.s in water. It is a concentrated dispersion of micro-sized solid A.I. in a liquid phase using wetting and dispersing agents. The liquid phase can be oil or water. This is a popular formulation in recent decades. It must be diluted with water before use.

SC formulation (% mass) includes [5]:

- Active ingredients: 20 - 50%;
- Wetting/dispersing agent: 2 - 7%;
- Antifreeze (propylene glycol): 5 - 10%;
- Anti-settling agent: 0.2 - 2% and enough water to 100%.

It should be noted for the processing of SC formulation as followings.

- The surfactant combination consists of a wetting agent and a dispersant.

- The mixture is ground in a wet mill to achieve a particle size of 0.1-5 μm .

- Anti-settling agents are added when processing SC to increase the viscosity of the product and create a 3-dimensional structure in the product mass to prevent the separation of active solid particles during storage. Commonly used anti-settling agents are bentonite (sodium montmorillonite) and a mixture with some water-soluble polymers (cellulose derivatives, natural gums, some polysaccharides such as xanthan gum) to increase efficiency.

- However, these substances are susceptible to bacterial attack, so it is necessary to add some preservatives to the processing formula [1].

The flow diagram of the processing of SC formulation and the graphical illustration of the texture of SC formulation was shown in Fig. 1

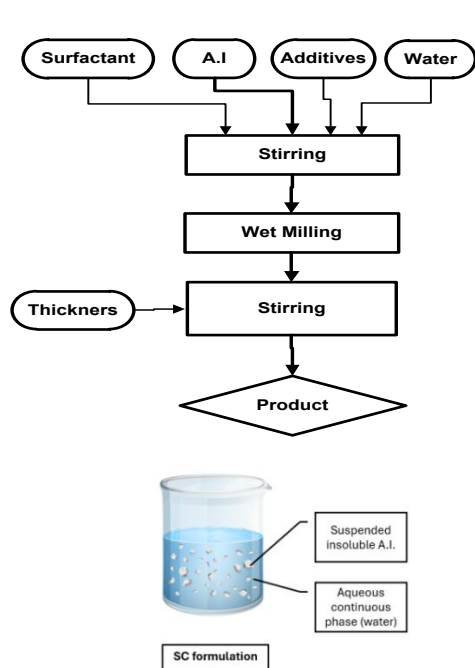


Fig. 1. Flow diagram of the processing and graphical illustration of texture of SC formulation

Examples: Azoxystrobin SC significantly reduced dust exposure eliminated, improved 90% suspensibility compared to WP formulation [8].

3.1.2. Oil-in-water emulsion

The final product of EW is in a heterogeneous liquid. The A.I. dissolves in organic solvents, forms a solution and disperses into small droplets in water. The EW formulation allows for a reduction in the use of volatile solvents. The oil droplets are small (less than $2\mu\text{m}$) so more A.I.s act on the leaf surface, improving biological effectiveness. Compared to EC (continuous phase is organic solvent), EW uses water instead, leading to better cost of production, transportation but safer for plants and environment. However, it is necessary to choose appropriate emulsifiers to ensure that the oil microparticles do not coagulation, creaming and flocculation.

Recently, multiple emulsions have been developed, for example: Water in oil in water (W/O/W) or oil in water in oil (O/W/O) to reduce the toxicity of the A.I. by limiting it to the main emulsion droplet inside. However, this is a complex formulation of processing, requiring elaborate selection of emulsifiers and stabilizers to ensure physical stability of the product [2].

The flow diagram of the processing of EW formulation and the graphical illustration of the texture of EW formulation was shown in Fig. 2

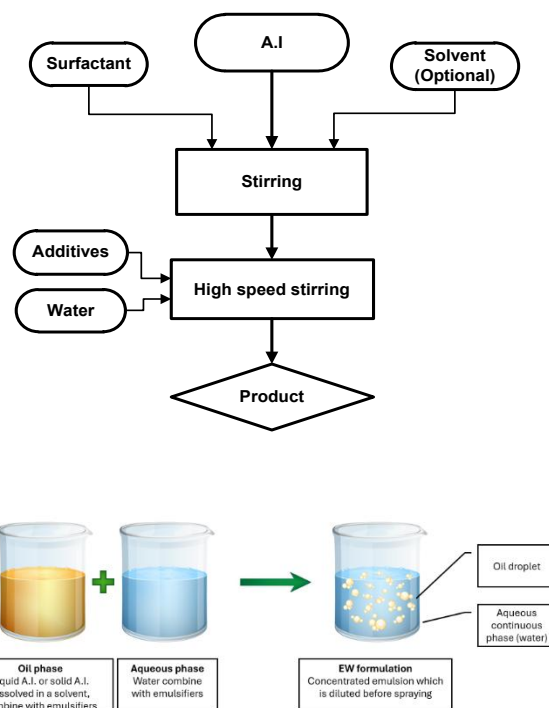


Fig. 2. Flow diagram of the processing and graphical illustration of texture of EW formulation

EW formulation ingredients include [5]:

- Active ingredients soluble in oil;
- Emulsifiers (polymeric and non-ionic surfactants with an average HLB of 11-16 to create a stable emulsion). Selected appropriate emulsifiers to prevent coagulation, creaming and flocculation of oil droplets.
- Thickeners: polysaccharides such as xanthan gum to prevent separation.
- Solvents and water.

It should be noted for the processing of EW formulation as following:

- Addition of lipophilic emulsifier with moderate HLB in the oil phase with APIs is optional. Hydrophilic emulsifiers with high HLB are required in water phase.
- Adding oil phase into water phase is preferred with moderate stirring first to homogenize. Then using high-shear or high-pressure homogenizer to reduce the size of droplets [9].
- Control the appearance of residue, cool temperature and pH to stabilize the emulsion.

Examples: Cypermethrin EW 10% significantly reduced 30–50% solvent content and the unpleasant odor compared to EC formulation [10].

3.1.3. Microemulsion

ME is a water-based formulation consisting of oil and water dispersed uniformly, with very small emulsified droplets that are easily mistaken for a transparent solution. The product is a transparent or milky white liquid, which can be used directly or diluted with water to form a microemulsion or normal emulsion.

The formulation consists of 3 components [5]: A.I. in liquid or solid soluble in oil; water, and surfactant system with high ratio (10–30%, while EW formulation requires only 5%). ME formulation has relatively low A.I. content but very high biological activity. Due to very small particle size (from 0.01 to 0.05 μm), they are thermodynamically stable in a wide temperature range and unlike conventional emulsion systems, phase separation is not the matter. ME is stabilized by anionic or non-ionic surfactant system with very high HLB value (Hydrophilic-Lipophilic Balance).

The flow diagram of the processing of ME formulation and the graphical illustration of the texture of ME formulation was shown in Fig. 3

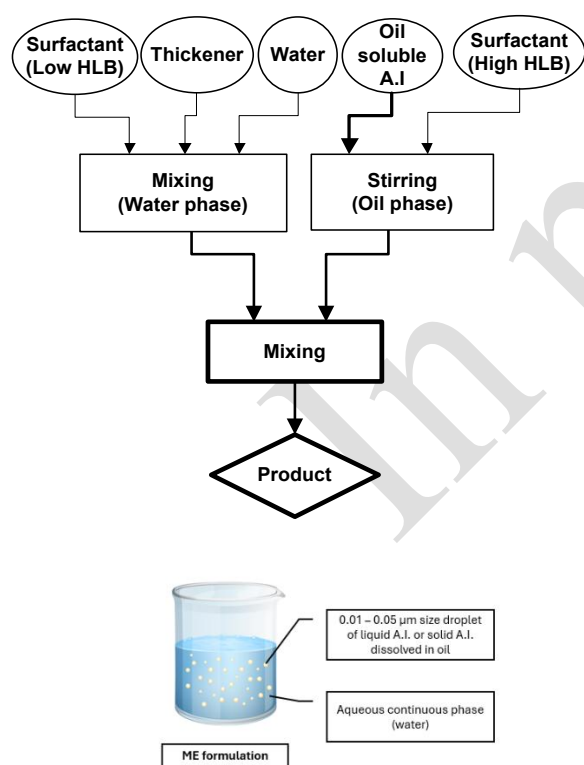


Fig. 3. Flow diagram of the processing and graphical illustration of texture of ME formulation

To be noted that, the building of pseudo-ternary phase diagram is necessary to determine the ME area. ME formulation does not require high-shear homogenizer, but can easily formed with proper ratio of oil-water-surfactant. On the other hand, the control of

the rate of addition water is crucial to avoid cloudy emulsion that can not return to ME formulation [11].

Anionic surfactants are required to form spontaneous emulsions, providing additional electrostatic stabilization, combined with non-ionic surfactants to provide steric stabilization at the emulsion interface. In addition, the A.I. must be completely soluble in the carrier solvent in oil phase [5].

Advantages: Increased biological efficiency due to the A.I. being dissolved in micro-droplets; thermodynamically stable, so it is durable in storage, with a longer shelf life; high flash point, low solvent usage, so it is safer; low viscosity, so it is easy to handle, transport and store.

Limitations: Low A.I. content; high surfactant content required and complex processing technology.

Examples: Chlorpyrifos ME left airborne residue 5–7 times lower than EC ones after treatment [12].

3.1.4. Oil dispersion

Oil dispersed (OD) is a stable suspension of one or more A.I. in a mixture of water and water-immiscible liquids. Dilute in water before spraying.

OD formulations contain one or more solid A.I.s dispersed in an oil phase. It is similar to the SC formulation, but the A.I.s are dispersed in oil instead of water (Fig. 4). SE formulation could be used in cases of multiple A.I.s in which one is insoluble, and the other is soluble in oil. Thus, the OD formulation will form an emulsion or suspension emulsion, contain emulsified oil droplets and dispersed particles when dilute in water. Medium for the oil phase can be different types of oils such as mineral oil, vegetable oil or methylated seed oil [7]. This is a non-aqueous formulation, so it is very suitable for A.I.s that are insoluble in water or are sensitive to moisture but required to be processed in liquid form, such as sulfonylurea herbicides.

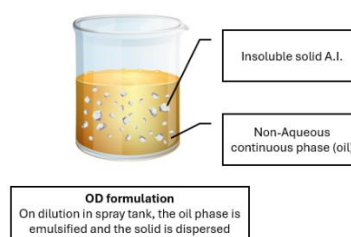


Fig. 4. Graphical illustration of texture of OD formulation

The OD formulation technology is similar to the SC formulation (Fig. 1), that using oil instead of water as the medium in the SC. The oil phase has better wetting, condensation when sprayed and better foliar absorption because of the natural permeability of oils. The surfactants in OD formulation must be compatible with

the selected oil to form a stable emulsion when diluted with water [4, 13].

Advantages: The OD formulation has better spreading and penetration than the SC form and is the most suitable processing method for hydrolyzed herbal pesticides. Moreover, research shows that oil has a synergistic effect with herbal pesticides and expands the spectrum of the bioactivity. The product does not require strict storing because it is not exposed to moisture.

Limitations: It is difficult to process and the A.I. can precipitate more than in water-based systems. Therefore, it needs to avoid storage at low temperatures and shake well before using [4, 8].

Examples: β -Cyfluthrin 8.49% + Imidacloprid 19.81% OD, Abamectin 1.8% OD [7].

3.1.5. Flowable concentrates for seed treatment

Most pesticides are applied by spraying crops or weeds, but a large number of fungicides and insecticides are also formulated for spraying directly on seeds before sowing. These are called seed treatments. It is estimated that the value of seed treatments currently accounts for about 3–3.5% of the total agricultural chemical market, of which fungicides account for about 70%.

Seed treatment chemicals are divided into four types: Powder for dry seed treatment (DS); Water dispersible powder for slurry seed treatment (WS); Solution for seed treatment (LS) and Flowable/suspension concentrates for seed treatment (FS). Among them, FS is the most popular form of seed treatment today because it is very safe to use due to its concentrated and water-based form [2, 4].

The FS formulation is a modification of the SC formulation (Fig. 1), which usually contains the same dispersant and the addition of an additive that adheres to the seed surface and a colorant to mark the treated seed. Seed treatment formulations often contain multiple A.I.s at high loading levels. Polymer dispersants are recommended because of their high molecular weight, multiple functional groups, and high repulsive barriers, allowing for stable seed treatment activities.

Wetting agents must be included during the grinding process to prevent agglomeration, which can increase viscosity and even cause grinding machine clogging, while allowing the dispersant to work. A rheology modifier must be added to prevent solid particles from settling (when the FS formulation is structurally unsuitable), which reduces the stability of the product over its shelf life and reduces its effectiveness. In addition, the A.I. must be distributed evenly and precisely on the seed surface and must remain there throughout the storage, sowing, and germination process. It is important that the product does not affect the germination process of the seeds.

Advantages: Water-based and water-dispersible. It is safe and convenient for users and preservation, little impact on seed germination; dust-free and easy to clean equipment.

Limitations: Extreme temperatures can affect storage stability; thick coating can make seeds sticky and less flexible.

Examples: Tebuconazole 6 g/L - Thiram 200 g/L FS

3.1.6. Combined/mixed formulation

a) SE formulation (Mixture of SC and EW)

The final product is a heterogeneous liquid, consisting of a stable dispersion of A.I.s in the form of solid particles and droplets in a continuous aqueous phase. The SE formulation is a mixture of a SC and an oil-in-water emulsion (EW) (Fig. 5). It can also incorporate several A.I.s into one product. There are three phases in the product: liquid oil droplets, dispersed solid particles and a water phase.

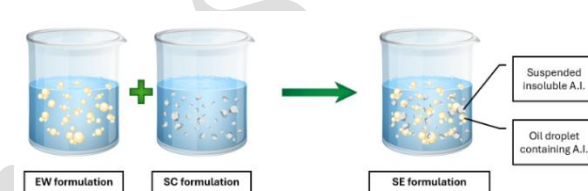


Fig. 5. Graphical illustration of texture of SE formulation

It is necessary to process SC and EW separately, then stir the semi-finished products together to obtain SE formulation. The most difficult technical problem when processing this formulation is the physical durability of the system. Therefore, it is necessary to choose suitable additives, add surfactants to avoid flocculation, and add thickeners to avoid separation of dispersed phases. The suitable surfactants used in SE processing are alkylglucoside groups. In addition, preservatives are necessary to prevent spoilage.

Advantages: Incorporates multiple A.I.s with different solubilities or melting points. A mixture of A.I.s is often used to provide a broader spectrum of pest control

Limitations: The surfactant system needs to support both an insoluble organic solid and a liquid. Partial solubility of the A.I.s in water or oil phases causes stability problems over time

Examples: Diafenthiuron + Pyriproxifen SE formulation

b) ZC formulation (mixture of SC and CS)

ZC is a hybrid formulation between the capsule suspension (CS) and SC (Fig. 6). The formulation is a stable suspension of polymer-coated microcapsules and fine solid particles, each containing one or more A.I.s

and diluted in water before spraying. Both CS and SC are mixed homogeneously by wet milling and gentle agitation.

The ZC formulation allows for controlled release of A.I.s, reducing product toxicity and reducing runoff. Like other liquid formulations, the ZC formulation is dust-free, non-flammable and has good miscibility with water. In addition, the combination of multiple A.I.s with complementary modes of action will broaden the spectrum of action on pests, facilitating the control of more pests with fewer sprays.

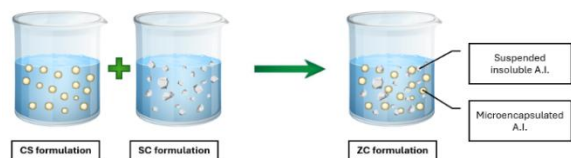


Fig. 6. Graphical illustration of texture of ZC formulation

However, commercial development of this formulation is limited, partly due to the complexity of the processing technology, especially the long-term stability of the product. In addition, different crops and pests require different rates of release of A.I.s [7].

Examples: Lambda-cyhalothrin 96 g/L – Thiamethoxam 126 g/L ZC, Acetochlor 290 g/L - Atrazine 145 g/L ZC; Bifenthrin, Pyriproxyfen, and Novaluron ZC.

c) ZE formulation (mixture of CS and SE)

ZE is a mixed formulation of CS and SE (Fig. 7). The finished product is a heterogeneous liquid, consisting of a stable dispersion of one or more A.I.s in capsules, solid particles, and droplets in a continuous aqueous phase, diluted with water before spraying. Processing the A.I.s together allows for control of a wider range of pests while avoiding mixing in the tank, which can lead to incompatibility.

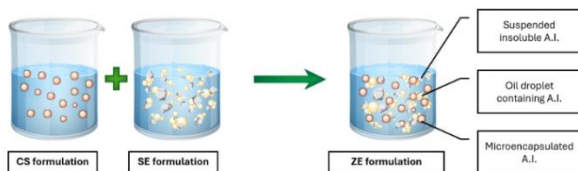


Fig. 7. Graphical illustration of texture of ZE formulation

Like other aqueous liquid formulations, ZE is dust-free, non-flammable and has good miscibility with water. The CS and SE formulations are first processed separately, and then mixed together. In this way, three A.I.s (one in capsule form, one in SC suspension concentrate, and one in emulsion form) can be used in a single formulation [7].

d) ZW formulation (mixture of CS and EW)

The finished product is in a heterogeneous liquid form, usually diluted with water before spraying. ZW is a blend of CS and oil-in-water emulsion (EW), which is a stable dispersion of microcapsules and emulsion droplets in a continuous aqueous phase (Fig. 8). Each microcapsule contains one or more A.I.s, enclosed in a polymer, which has the effect of slowly releasing the A.I.s, while the emulsion droplets contain other A.I.s, which can kill the target pests.

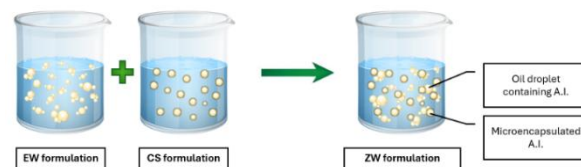


Fig. 8. Graphical illustration of texture of ZW formulation

Like ZE, the water-based ZW formulations are formulated with different A.I.s: one slow-release, the other with immediate biological effect, providing control of a wider range of pests with the same spraying rate and with the same advantages as the ZE formulations such as being dust-free, non-flammable, and miscible with water. Formulating the A.I.s together eliminates the need for tank mixing which can lead to incompatibility.

Examples: γ -Cyhalothrin 25CS + Chlorpyrifos 10EW [4,7]

3.2. Dry Formulation (Solid)

Dry formulations have two types: Some are ready-to-use (RTU). For example: Bait, Tablet, etc.; others are processed into a wettable form and must be mixed with water before spraying. For example: Dust (D); Granule (G); Soluble powder (SP); Wettable powder (WP); Water-dispersible granule (WDG); Water-soluble granule (SG), etc.

WDG and SG are produced in the same way as WP, then the powder is converted into granules. Compared to WP, these processing forms are almost harmless to the producer due to less dust, less harmful to the skin, and more environmentally friendly, so they are often chosen in sustainable agricultural development.

3.2.1. Water dispersed granule

WG or WDG is a solid particle form (different from the powder form of WP), which disperses quickly in water, creating a fine particle suspension. The shape, size, and activity of the particles depend on the processing technique. The dispersion time in water is a very important characteristic to ensure that there is no problem in the sprayer: the particles must be completely dispersed within 2 minutes at different temperatures and water hardness. To achieve these requirements, the

choice of surfactants and additives as well as the granulation method must be carefully considered.

The advantages of WG are dust-free so it is safer than WP. It can contain high A.I. content (up to 90%) but the particles are difficult to settle. Moreover, WG is easier to package and use compared to the conventional WP formulation.

However, the processing technology of WG is more complicated, so the cost is high and it is only suitable for A.I.s with high melting points.

The flow diagram of the processing of WG formulation and the graphical illustration of the texture of WG formulation was shown in Fig. 9.

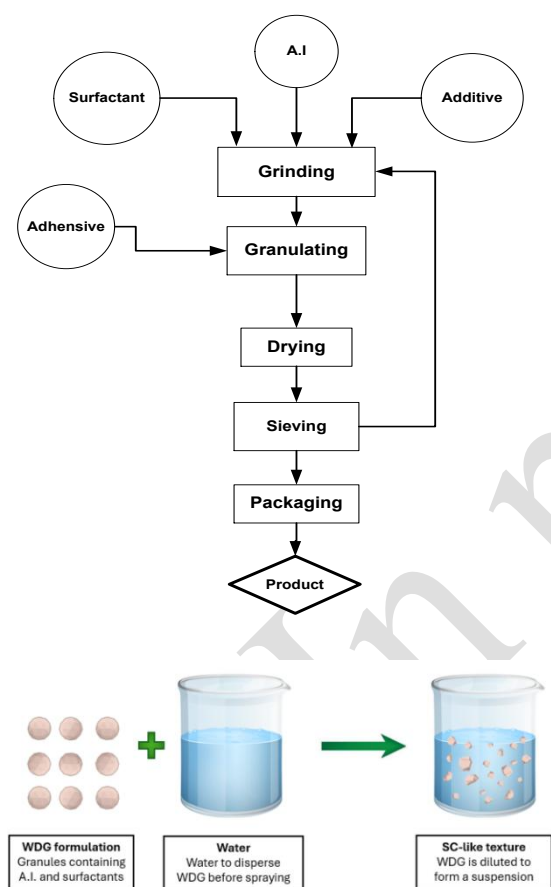


Fig. 9. Graphical illustration of texture of WG formulation

The composition of WG formulation includes [5]:

- Active ingredients: 50 – 90%;
- Wetting agent: 1 – 3 %;
- Dispersant: 5 – 10%);

If processed into SG, dispersant is not required.

- Colorant: 0 – 6%;
- Disintegrant, filler, binder and others: 100%;

Examples: α -cypermethrin 250 WG leads to 80% mortality of mosquitoes, that is much better than WP formulation applied with the same concentration [14].

3.2.2. Water soluble granule

The processing for WS formulation differs from WDG only in the granulating and drying stages: Extrusion, fluid bed, spray drying, and pan granulating technology.

Granulating and drying technology can cause differences in appearance and, more importantly, in their ability to disperse in water. Each method has its own advantages and limitations. The choice of technology depends on the physical properties of the material, the conditions of development and the specific product plan.

Extruded granules are slower to disperse in water because they are compressed during the processing. Spray-dried granules are usually the fastest to disperse due to their very small particle size and their hollow, fragile spherical shape. Fluidized bed agglomerates fall between these limits in terms of their ability to disperse in water.

In addition, the following technical issues should be noted in processing:

- Size: Solid A.I. with the required size of 1 – 10 μm ;
- Filler: Using fillers in WG and SG processing is not recommended. If necessary, the filler should be water-soluble salts;
- Wetting agents: Anionic surfactants are preferred for WG processing;
- Dispersants: Surfactants with high molecular weight often have good dispersion properties;
- Disintegrants: Substances that can swell in water, such as citric acid or sodium bicarbonate, often have good disintegration properties.

3.3. Controlled Release Formulations

Processing controlled release (CR) preparations is receiving much attention because they have many advantages over conventional preparations. CR is a form of processing in which the A.I. is adjusted to target the right concentration and duration of action to achieve the desired effect. The amount of drug used is sufficient to control pests during the application period.

The advantages of CR compared to conventional formulation is:

- Increased biological efficiency, prolonged effectiveness due to the controlled release of A.I.
- Increased selectivity, directing the drug activities to the destroying target;
- Reduced toxicity to humans, beneficial animals and crops and reduced environmental pollution by reducing drug evaporation and loss, reducing the amount of dose,

and reducing the use of solvents in the processing which also led to the reducing of (unpleasant) odor in the preparation.

- Improved the durability of A.I. while the product is more stable against the environment (rain, sun, etc.) or bacteria, light (UV) and;

However, the CR formulation has the disadvantage of complex processing technology, high production costs and is only suitable for non-aqueous A.I.s [2, 7, 15].

CR processing includes four main types:

- Encapsulated A.I.s;
- Polymer matrix systems containing physically bonded A.I.s;
- Polymer absorption systems covalently bonded to A.I.s;
- Polymer membrane systems containing A.I.s, for example micro-encapsules.

Among them, the use of polymer materials to create A.I.s coatings are the most favorable.

The release rate of A.I. can be controlled by adjusting the droplet size, polymer film thickness, cross-linking level, or polymer porosity [1, 2]. Currently, biological polymers such as polysaccharides, chitosan, starch, cellulose, or polylactic acid (PLA) are often used because they are environmentally friendly [6].

Micro-encapsulation is the process of encapsulating solid particles or small droplets of biologically active liquids with a coating or polymer film to form very small capsules to control the release rate, distribution of A.I. and prevent their decomposition. There are many methods of creating micro-encapsulation, such as physical, physicochemical, and chemical methods.

3.3.1. Encapsulation technology

a) Encapsulation by spray drying

This is the early encapsulation technique used to produce dry preparations. The processing included spray drying of an emulsion (or suspension) of A.I. with the capsule material dispersed in an aqueous solution. When the water evaporates, the shell material will cover the core material. This technique has a limitation on the capsulation size (10 – 150 µm) compared to new generation technology.

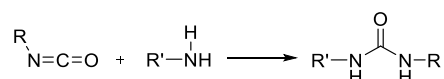
b) Interfacial polymerization (surface polymerization)

This is a polymerization reaction that only occurs at the interface between two immiscible phases. This is the most important technology for encapsulating pesticides. One of the processes of creating microcapsule suspensions using this method that is practically applied can be described as follows:

- A.I., usually liquids or waxy solids, dissolve in aromatic solvents C9 – C10 (often used for EC).

- An oil-soluble monomer (such as toluene diisocyanate) is further dissolved into the mixture, obtaining an oil/water emulsion by vigorously stirring an aqueous solution containing an emulsifier and an active amine (such as ethylenediamine).

- An emulsion containing microdroplets with a diameter of 10 – 30 µm is formed and polymerization between the isocyanate and the amine occurs at the oil-water interface to form a polymer film surrounding the microdroplets via this Encapsulating reaction between isocyanate and amine



c) *In situ* polymerization

This is a technology applied to create microcapsules *in situ* for water-insoluble A.I. They include two different methods:

- One is to apply the process of creating capsule shells by reacting polyamine with an aldehyde in an aqueous environment (urea formaldehyde or melamine formaldehyde).

- The second method is to create *in situ* capsules, in which the polymer shell is formed right in the oil phase containing the dispersed A.I. due to the hydrolysis of an isocyanate.

Although this processing technology is complicated and the cost is high, microcapsules are still a widely used in recent times. They are often processed in suspension forms such as CS (Capsule suspension) or CG (Encapsulated granule) capsules.

3.3.2. Capsule Suspensions formulation

CS is a water-based, slow-release formulation, also known as a microencapsulated suspension. This is one of the most advanced new generation pesticide formulations available today. When sprayed, the product is mixed with water, immediately forming a suspension with particles ranging in size from 0.1 to 20µm. The capsule wall is then broken, slowly releasing the exact amount of A.I. needed for effective pest control.

a) CS compositions:

When processing CS, the A.I. is covered by a polymer shell suspended in water by dispersants and wetting agents. Like SC and EC, CS formulations are stabilized by familiar surfactants and anti-settling agents. The composition of the CS includes (% w/w) [5]:

- Active ingredients: 10–30%;
- Surfactant (emulsifier, wetting agent, ...): 1–5%;
- Polymer: 10–15%;

- Solvent: 5–15%;
- Anti-settling agent: 1–3%;
- Some other additives (antifreeze, anti-foam, ...) and water to 100%.

The flow diagram of the processing of CS formulation and the graphical illustration of the texture of CS formulation was shown in Fig. 10.

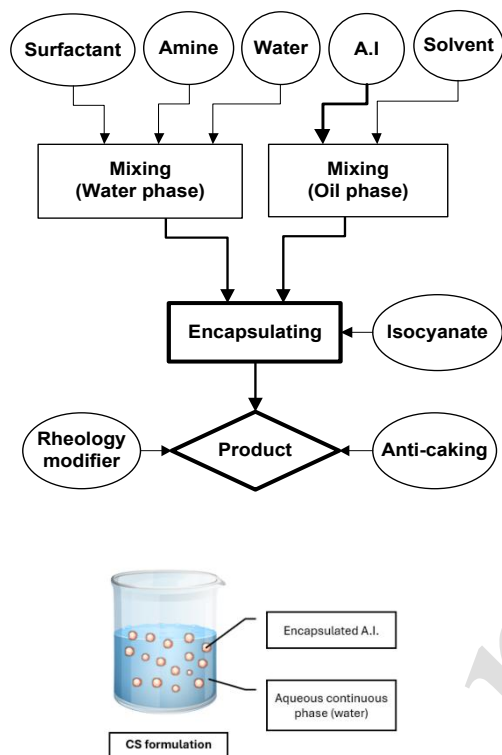


Fig. 10. Graphical illustration of texture of CS formulation

The A.I. suitable for CS form is a solid that is slightly soluble in water, easier to soluble in non-polar solvents or emulsifiable liquid in aqueous solution and is resistant to hydrolysis. Dispersants are needed to prevent flocculation and agglomeration of capsules during storage, because capsules are prone to flocculation, which increases particle size and is unstable [1, 15].

a) Processing procedure:

- In the container, about 90% of the determined volume of water was added, stirred with wetting agent, dispersant, antifoam agent and amine.
- A.I. in liquid or dissolved in solvent was added subsequently to form a concentrated emulsion. The A.I. needs to be emulsifiable with the amine. The particle size was checked as it determines the size of the capsule.
- While stirring vigorously, isocyanate was added to start forming the polyurea capsules.

- Continue stirring the mixture for about two hours at about 60 °C to ensure the correct capsule forming time.

- Antifreeze and rheology modifier was added. The ideal viscosity of the product is about 2000 – 4000 cp.

- Notably: when choosing the amine and isocyanate, their reactivity as well as the desired mechanical properties for the capsule should be considered. The higher the reactivity of amines and isocyanates, the faster the reaction occurs, resulting in more heat being released and making it more difficult to control. In general, aliphatic amines react faster than aromatic amines, which have lower alkalinity. Conversely, aliphatic isocyanates are less reactive than aromatics.

Advantages: Control/slow down the release of A.I.s, increase efficiency, prolong the effect; reduce A.I. decomposition by the environment; low dust, low solvent processing technology so it is safer, reduces toxicity to plants; reduces leaching and environmental pollution.

Limitation: Low A.I. content; complex and expensive technology and equipment leading to high cost while products are easily frozen. Therefore, up to now, CS processing technology has been mainly applied in the field of household disinfection.

Examples: γ -Cyhalothrin 4,9 CS, 10 CS, 25 CS, etc. [4, 7]. The CS formulation of γ -cyhalothrin significantly reduces the odor, 60–90% operator exposure, 50% re-spray frequency and phytotoxicity. [15]

Recently, it has been discovered that carboxy methyl cellulose (CMC) and diallyl, dimethyl, ammonium chloride (DMDAAC) in the form of monomers are effective encapsulating agents of the pesticide avermectin [3].

In addition to microcapsules, nano-processed forms also have the effect of controlling the release of A.I.s in pest control. The technology of processing pesticides with the ability to control the release of A.I.s in the world has been interested in research for over 20 years, but the commercialization of products and application still need more time to be practical.

3.4. Nano Formulation

Recently, nanotechnology has been applied to the production and processing of pesticides to increase the effectiveness of prevention and reduce negative impacts on the environment and humans. With outstanding features, nanomaterials are used as additives and carriers to process new forms such as nano-emulsion, nano-suspension, nano-dispersion, nano-encapsulation, nano-capsules, etc. [16].

The benefits of nano-processing are to improve the properties of pesticides such as solubility, dispersion, and penetration; control the release and distribution of A.I.s; protect them from decomposition by chemical and environmental factors; increase the stability and flexibility of the product. Thereby, it lengthened the

duration of action, increased the effectiveness of prevention, safety, and economic efficiency of drugs [16].

Compared with traditional processing, nano-processing has smaller particle size, larger surface area, increasing the coverage, adhesion and permeability of the A.I. to the pest. Moreover, by controlling the target distribution and release of the A.I., nano-processing also affects the mode of action of the drug, such as enhancing the function of ingestion and contact poisoning because it improves the dispersion, penetration and increases the amount of drug entering the body of the pest. In addition, the enhanced mobility, transmission and metabolism of nano-drug particles inside the pest will accelerate the poisoning process of the pest, increase the biological effect, and reduce the dose of the drug, thereby increasing the effectiveness of use [16].

3.4.1. Nano-emulsions

Nano-emulsions are thermodynamically stable systems in which two insoluble liquids (oil containing A.I./water) are mixed, forming a single phase thanks to an emulsifier. The main advantages of this form are that no toxic organic solvents are required to dissolve the hydrophobic A.I., which increases stability, improves absorption, and does not require stirring before spraying because of no precipitation or creaming. Unlike micro-emulsions, nano-emulsions require less surfactant (5 – 10% vs. 20%) although the particle size can be approximately the same (approximately 50 – 200 nm).

The biological activity and efficiency of nano-emulsions are also higher than that of micro-emulsions. Nano-emulsions are mostly used for A.I.s that are insoluble in water, such as pyrethroid insecticides (cypermethrin, cyhalothrin, etc.) [17].

3.4.2. Nano-suspensions and nano-dispersions

Nano-suspensions or nano-dispersions are solid drug particles with a size of 200 to 600 nm, insoluble in water, dispersed very finely in aqueous solutions or organic liquids. Nano-suspensions do not require any suspended substrate, are stabilized by surfactants, and are used to process A.I.s that are difficult to dissolve in both water and organic solvents, and some that are soluble in oil but cannot be processed into emulsions or liposomes.

Due to the small particle size and large surface area, this type of processing improves the dispersion of the A.I.s in water, covers the leaves evenly, and increases biological effectiveness.

Nano-suspension of chlorantraniliprole at 56 nm lead to the reduction of about 40% compared to that of the SC [18].

3.4.3. Nano-encapsulations

Nano-encapsulation of pesticides is to create nanoparticles containing A.I.s (nanocarriers) or to encapsulate the drug with nano-sized materials (called nano-shells or nano-coatings). Different nanomaterials

used to encapsulate pesticides are polymers, lipids, clays, or inorganic nanoporous materials. They create different nano-products that can disperse in water such as nano-capsules, nano-spheres, nano-gels, micelles, etc.

Nano-encapsulation capable to control the release rate and transmission to the target pest of the A.I. even better than micro-encapsulation ones, thus becoming much more effectiveness [19].

Nano-carriers include nano-sized hollow particles to contain A.I.; nanoparticles can bind to A.I. through ligands; polymer nanomaterials encapsulate A.I. or form a matrix, intertwined with A.I.. They are often organic and inorganic materials with nano-size such as clay minerals, silica materials, and polymer-structured substances. Among them, silicon-containing nanomaterials and naturally derived biopolymers are of most interest [16, 19]. Water-based mPEG-PLGA nanoparticle formulation of metolachlor showed excellent solubility despite its lipophilicity even though the formulation contains no organic solvent and surfactant [20].

Although nanoparticles have many potential advantages, so far there have not been many products commercialized and applied in agriculture. The reason is that the results of applied research are still limited, the cost of products can be high because of the difficulty in processing of nanoparticles or complex combinations.

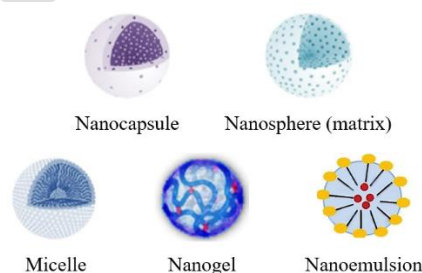


Fig. 11. Graphical illustration of texture of several nano-formulations

3.5. Seed Treatment Formulation

Seed treatment (ST) is a method of applying pesticides locally to seeds, reducing the doses of pesticides used per unit area and is considered the safest, cheapest, and most ecological method to protect seeds and young plants from pests in the early stages of the development [2]. Therefore, seed treatment products account for about 3 – 3.5% of the total market value of agricultural chemicals, of which fungicides for seed treatment account for 70%. The average growth rate in the period 2014 – 2020 is 10.8% per year [21].

ST are required not to reduce the quality of the seed or to be detrimental to germination. Rather, they should enhance germination and/or the formation of better, stronger seedlings, thereby improving crop quality and yield. Some ST products are sprayed directly onto the

seed; others are diluted with water but are more concentrated than field sprays. ST formulations are often modified to improve seed adhesion and accommodate different application scenarios. ST typically contain A.I.s and various adjuvants such as nutrients, germination, and seedling growth stimulants. They are divided into the following four main categories.

3.5.1. Powder for dry seed treatment

Dusting of powder forms can be overcome by converting them into water-dispersible granules (WG). The current trend in seed treatment is to develop concentrated suspensions (FS) and emulsion (ES) for seed treatment to reduce dust, improve product stability and increase adhesion to seeds. FS is the most popular formulation of seed treatment because of its high concentration and water-based nature, making it very safe [21].

3.5.2. Flowable concentrate for seed treatment

The FS formulation is very similar to the SC formulation because the continuous phase is water and similar additives are used. The A.I. (from 40% to 70% w/w) is insoluble in water, ground to micron size, and dispersed into a suspension.

The A.I. is often mixed with polymers, fillers such as talc, Al or Ca salts, and colorants to distinguish treated and untreated seeds. Liquid polymers can also be used alone as a final protective coating for seeds [2]. The formulation must have low viscosity and good fluidity for easy transfer to the sprayer. Therefore, it is necessary to choose effective wetting and dispersing agents to ensure good dispersion of the A.I. in water and a stable suspension without settling. Bentonite and xanthan gum mixtures are often used as additives for the FS form because they have synergistic properties, good suspension formation, and long-term stability at low viscosity, and low cost.

Examples: Thiram 40 FS, Tebuconazole 5.36 FS, Thiomethoxam 30 FS, Imidacloprid 48 FS, etc.

3.5.3. Emulsion for seed treatment

ES emulsion (milk) is a formulation of oil-in-water emulsion, similar to EW. The product is a stable emulsion system, used directly or diluted for seed treatment.

3.5.4. Other formulation for seed treatment

Besides the formulations mentioned above, there are also some other ones, less specific and less commonly used forms:

- Water dispersible powder for slurry seed treatment (WS).
- Solution for seed treatment (LS).
- Microcapsule suspension for seed treatment (CF) is also commonly used. In some special cases, gel for seed treatment (GF) can be applied [19].

- In addition, the application of nanomaterials in seed treatment has also received attention recently. Note that before seed treatment, it is necessary to survey and evaluate the conditions of use, such as size, concentration of nanoparticles, soaking time because they can cause side effects such as germination inhibition, adverse changes in metabolism, and effects on interactions of microorganisms at the base of the plant.

4. Conclusion

Formulation processing is an important step in the technology of producing pesticides. The main goal of pesticide formulation is to optimize the biological activity and bioavailability of the drug, creating safe and convenient products for use.

Currently, due to the large number of available A.I.s, many different types of formulation have been developed, depending mainly on the physical and chemical properties of the A.I.s.

Technological developments and new processing methods as well as new additives can provide competitive advantages for products, increase value or extend the life cycle of A.I.s and get rid of the disadvantages of tradition formulations.

The processing of new generation of pesticide formulations might be costly but the environment-friendly consideration is of important to save a lot of money to deal with the consequences. Moreover, the use of sustainable A.I., additives and solvents are also a matter of concern to serve the organic agricultural development.

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