PESTICIDE FORMULATIONS AND THEIR IMPORTANCE IN THE DEVELOPMENT OF PROMISING PROTECTANTS FOR CEREAL CROPS§

Cite this: *INEOS OPEN*, **2023**, *6 (2)*, 34–39
DOI: 10.32931/io2314r

Received 6 December 2023, Accepted 11 March 2024

http://ineosopen.org

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Abstract

The importance of the role of a formulation in realizing the potential of a new substance and promoting the preparation (medicinal or pesticide) on the market is undeniable. When developing a pesticide formulation, it is necessary to address the following issues: a convenient application form, drug fixation on the plant surface, penetration of an active substance into the plant, and high efficiency against weeds, plant diseases and pests. The modern formulations of nanoscale pesticides facilitate better realization of the biological potential of an active substance. This article gives a brief overview of the literature on pesticide formulations and their varieties, the preparation methods and effectiveness published in the last 10 years, with a particular focus on the authors' own work.

Key words: formulations, protectants, mechanical treatment, biological activity.

Abbreviations

– active substance (AS)
– wettable powder (WP)
– emulsion concentrate (EC)
– microemulsion (ME)
– suspension concentrate (SC)
– suspoemulsion (SE)
– colloidal solution concentrate (CSC)
– sodium carboxymethyl cellulose (NaCMC)
– tebuconazole (TBC)
– plant growth regulator (PGR)
– arabinogalactan (AG)
– hydroxyethyl starch (HES)
– glycyrrhizic acid (GA)
– disodium salt of glycyrrhizic acid (Na_2GA)
– licorice root extract (LE)
– mechanical treatment (m/t)
– solid dispersion (SD)
– flowable suspension (FS)
– flowable paste (FP)
– microencapsulated suspension (MES)
– oil emulsion (OE)

Introduction

Pesticides, the chemical plant protection agents, are indispensable in agricultural production, since only their use can ensure high crop yields which are necessary to support the growth of the world population. Without the use of pesticides, the loss in fruit production would be 78%, that in vegetable production—54%, and in grain crop production—32%. Therefore, pesticides play a crucial role in controlling weeds, reducing diseases, and increasing crop yields [1].

It is known that a biologically active molecule, for example, a drug substance, can realize its potential only with an appropriate dosage form. Analogously, an active substance (AS) of a pesticide can demonstrate its effectiveness only with a formulation that will allow this AS to unravel all its potential.

The search for a potentially active plant protection agent is performed based on the large-scale screening of a great variety of new synthesized compounds using, in particular, the computer prediction and modern analytical methods, such as structure–activity relationships, *etc*. The results of these studies are used to select potentially active substances of organic compounds as pesticide ASs. It should be noted that this approach to the search for new molecules has almost reached a saturation point [2]. It is also worth mentioning that such an active substance does not ensure the production of an effective pesticide, since the preparation future also depends on the correctly selected formulations for it. While at the first stage the role of formulations was reduced to the uniform distribution of a small amount of an active chemical substance over a large area, ensuring safety during handling and use of a pesticide, and stabilizing its composition during storage, subsequently the requirements to these forms became much more stringent in terms of safety requirements for the environment [3].

Modern formulations can be classified according to various parameters: by aggregation state, toxicity, *etc.* Below is a brief

† Deceased

description of pesticide formulations by their aggregation state [2, 4].

– The simplest form was dusts which included 3–5% of mineral oils to reduce the dusting properties and improve the particle retention on the processed surface.

– Dusts were replaced by wettable powders (WPs) which are still used today. They are easily suspended when mixed with water, forming stable working solutions for treating plants. In WPs, the AS content reaches 30–80%.

– The emulsion concentrate (EC) contains active substances, solvents, emulsifiers, and wetting agents, which ensure the stability of the emulsion obtained when mixed with water and good wetting of the processed objects. In true ECs, the dispersed phase consists of oil drops with a pesticide dissolved in it and the dispersed medium is water. Inverse emulsions are special formulations in which the dispersed phase is a pesticide dissolved in water and the dispersed medium is oil. When spraying them, the resulting drops, the top layer of which is protected by oil, do not evaporate and adhere well to the processed surface.

– The flowable suspension (FS), flowable paste (FP), suspension concentrate (SC), and concentrated suspension (CS) contain up to 10 or more inert ingredients, including surfactants, stabilizers, and viscosity controlling substances that increase suspendability. These forms allow pesticide particles not to be washed off, to fix and settle on the surface of plants. They are easy in handling, do not generate dust, contain high AS concentration, but separate into layers during long-term storage. Their disadvantage is the need for storage at positive temperatures.

– The microencapsulated suspensions (MESs) contain AS particles encapsulated in a porous inert hard shell: a capsule consisting of polymers, gelatin or agar. MESs are similar to SCs, but they do not contain any additives, including surfactants. They are easily suspended in water. The rate and degree of release of active substances from capsules are controlled by the particle size, thickness of the capsule walls and their permeability. After entering the environment during spraying, the capsule loses its aqueous film and slowly releases the AS through a porous shell, which gradually decomposes. This form provides prolonged action, higher selectivity for crops, and lower toxicity for warm-blooded animals and reduces the AS volatility.

– The colloidal compositions, such as colloidal solution concentrates (CSCs) and oil emulsions (OEs), form non-separating working solutions, penetrate well into the processed objects, and have increased activity, which allows for reducing the consumption rates by 20–30%.

It should be noted that MEs and CSCs, compared to WPs, ECs, and CSs, have higher biological activity, since the particle dispersity reaches 0.005–0.1 µm, which is 50–1000 times lower than in the conventional forms. These innovative formulations, compared to the traditional ones, ensure higher biological effectiveness of the preparation with the same AS. In addition, they allow for reducing the rate of application of additives and the pesticide load [5].

Over recent years, the requirements to the production of pesticides have been significantly tightened. Nowadays, pesticides must ensure higher safety for both humans and the environment, higher biological effectiveness, lower price, *etc.* [6]. Formulation candidates cannot satisfy all these requirements simultaneously. Therefore, the improvement of formulations and application technologies to meet the above requirements for new and existing forms is an urgent problem.

The goal of this work was to review authors' own results on the development of pesticide formulations using mechanochemical tools and to show the role of formulations in the creation of effective protectants based on ASs from various classes of organic compounds with the analysis and evaluation of their biological activity.

Pesticide formulations and their role in promoting the preparations into agricultural practice

As is known, there are two main trends in the creation of new biologically active molecules, including chemical plant protection agents. The first one is the drug discovery: the search for new drug substances through large-scale chemical synthesis and biological screening. The second one is the modification of already known drugs (drug delivery) using various approaches that improve the solubility of substances and their biological properties (bioavailability, effectiveness, *etc.*) [7]. One of these approaches is the development of pesticide formulations, the improvement limits of which have not yet been reached and research in this field continues.

The variety of crops and methods for pesticide application (dressing, spraying, fumigation, *etc.*) dictates the need to create various formulations that can increase the pesticide effectiveness owing to its complete and better contact with protected plants and harmful objects. Most modern seed protectants are produced in the form of SCs, which contain adhesives that allow them to retain the AS particles on the seed (grain) surface. In recent years, the oil emulsions have proven to be more attractive as seed protectants, because they provide maximum penetration of the AS into seeds owing to their solubilization inside a microemulsion drop. The high permeability of the AS is also ensured by the addition of surfactants to the preparations [8].

Properties of pesticide ASs and methods for their modification to create effective formulations

The active substances of pesticides mostly belong to biologically active substances—the organic molecules poorly soluble or insoluble in water [9], which implies the use of excessive doses of ASs and thereby lead to higher prices for the preparation and increases its environmental toxicity. The following methods are used to increase the solubility of biologically active molecules [10]:

– physical (micronization, solid solutions, solid dispersions, *etc.*);

– chemical (production of metabolites, salt formation, complexation);

– other methods (production of cocrystals, solubilization, nanotechnology, *etc.*).

For our studies, we selected the following poorly soluble fungicide substances in order to improve their solubility:

– tebuconazole (TBC), (*RS*)-1-(4-chlorophenyl)-4,4-dimethyl-3-(1*H*,1,2,4-triazol-1-ylmethyl)pentan-3-ol, a systemic fungicide used for treatment of grain seeds. It belongs to the third generation triazoles, exhibits a systemic effect, and is active against phytopathogens transmitted by seeds. It dissolves well in organic solvents. Solubility in water is 32 mg/L [11].

– propiconazole, 1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-1,2,4-triazole, a protective and curative systemic fungicide from the triazole class. It is used to combat diseases of grain crops. A colorless liquid which readily dissolves in most organic solvents, fully miscible with acetone, methanol and propanol. Solubility in water is 0.11 g/L [11].

– prothioconazole, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1*H*-1,2,4-triazole-3-thione, a systemic fungicide that has a protective, curative and eradicating effect. It is used for treating vegetative plants against pathogens of various diseases and for grain dressing. Solubility in water: 5.0 mg/L at pH = 4, 2.0 g/L at pH = 9 [11].

– prochloraz, *N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]-1*H*-imidazole-1-carboxamide, is a contact and systemic fungicide of the imidazole class with a protective and eradicating effect. It is used against a wide range of diseases. A golden-brown liquid that solidifies upon cooling. Soluble in toluene and xylene. Solubility in water is 5.0 mg/L [11].

To obtain solid dispersions of fungicide preparations (for example, based on tebuconazole), we used for the first time the method of solid-phase combined mechanical treatment (m/t) of TBC using polymer compounds [12, 13]. The resulting solid dispersions (SDs) showed not only increased solubility in water (see Table 1), but also high biological effectiveness in crops of spring wheat "Novosibirskaya-31" with a 2–5 times reduction in the TBC dosage [14].

Table 1. Solubility of tebuconazole and its solid dispersions with polysaccharides

Sample	Solubility	
	Absolute, mg/L	Increment
TBC (starting substance)	32	–
SD: TBC/AG (1:9)	480	15
SD: TBC/HES (1:9)	509	16
SD: TBC/GA (1:9)	995	31
SD: TBC/Na_2GA (1:9)	798	25
SD: TBC/LE (1:9)	610	19

Subsequently this method was extended to liquid systems in order to obtain suspension concentrates and suspoemulsions (SEs). Below are the examples of the use of mechanochemical tools in the production of protectant formulations.

Mechanical treatment of the formulation components as a promising technology for producing innovative pesticides

Mechanochemical tools allow one to combine joint grinding of fungicide substances, which differ in the aggregation state and solubility, and to obtain both powder (solid dispersions) [15] and liquid forms (suspensions, suspoemulsions) [16]. The comparative studies on the effectiveness of their use in different formulations outlines the preparative forms with the highest biological activity, increased solubility, adhesion, contact-systemic action, and the lowest toxic load. It was established [17] that seed treatment with the SD of the TBC/AG/surfactant composition afforded more effective control (compared to the reference—Raxil) over the infectious load of the main pathogen of common root rot *B. sorokiniana*.

Such high efficiency was explained by the formation of intermolecular complexes of TBC with polymer molecules, which was confirmed by dynamic ^{1}H NMR spectroscopy. It is known that the spin–spin relaxation time T_2 is very sensitive to intermolecular interactions and to the diffusion mobility of molecules [18]. This is due to a change in the time of rotational reorientation of molecules in the complex or, in the case of TBC molecules entering GA micelles, due to slower diffusion. The results of investigations on the spin–spin relaxation times for the TBC complex with GA (and its disodium salt) showed a decrease in these times by an average of 6.8 and 7.1 times, respectively [19].

Taking into account the positive results on the use of glycyrrhizic acid and its derivatives, in particular, a disodium salt (Na_2GA) to improve the membrane permeability of a number of pharmaceuticals [20], it seemed interesting to study the effect of GA and some of its derivatives on the properties of triazole protectants. Based on the results of preliminary investigations, the corresponding tebuconazole SDs were obtained that showed increased solubility and high efficiency. In the field conditions, when the TBC consumption rate was reduced by 3 times, the grain yield of spring wheat corresponded to that of the reference Raxil [21].

Search and development of multicomponent and multifunctional protectants as a current trend in the development of modern agriculture

Taking into account the wide range of diseases on cultivated plants as well as the need for comprehensive control of these diseases, research on the development of multicomponent protectants that reduce the number of treatments and leads to a decrease in the infectious load have been revived in recent years. To study the role of formulations on their biological activity, the oil emulsion and suspension forms were prepared based on TBC [22].

Given the high efficiency of suspension forms of protectants, the preparations were produced based on tebuconazole, metalaxyl, and imazalil with the addition of a plant growth regulator (PGR) (preparation no. 1—crezacin, no. 2—floroxan) and without it (preparation no. 3), which effectively reduced fungal and bacterial infections. PGRs were used to reduce the retardant effects of TBC and their use exerted a positive effect on root length. This approach made it possible not only to carry out comprehensive protection of seed material from diseases, but also to effectively stimulate root formation. Hence, we confirmed the improved efficiency of seed treatment with complex preparations, the use of which prevents the formation of resistance to fungicides in pathogens [23].

The results obtained confirm that the introduction of PGRs into the fungicide formulations can improve their effectiveness [24]. The use of the latter in the technological process of growing grain crops in economically developed countries affords additionally about 20–30% of agricultural products [25]. The growth stimulants have a complex effect on the physiological and biochemical processes that occur in a plant. The manifestation of their activity at extremely low concentrations opens the way to wider use of PGRs in agricultural production and at present their use is of particular importance.

Our investigations also revealed some limitations of the solid-phase preparation of formulations. So, for example, in the case of low-melting substances (for example, the fungicide prochloraz), this method is unacceptable due to the melting of prochloraz on the grinding elements and its partial decomposition. Therefore, we proposed the technology of mechanochemical suspending in an aqueous environment [26], which allowed us to remove local temperature changes and obtain the fungicidal compositions for seed treatment in the following forms:

– suspoemulsions based on prochloraz, imazalil, TBC, and floroxan;

– suspoemulsions based on prochloraz, imazalil, TBC, and crezacin;

– suspension concentrate based on prochloraz, imazalil, and TBC.

The suspoemulsions bearing the PGRs stimulated growth of the root system under field conditions, which, as expected, reduced the incidence of root rot in plants. A more balanced development of plants in combination with fungicidal protection of the crop increased their resistance to stress, which is a positive aspect when growing spring wheat in order to obtain high yields and high-quality grain.

A peculiarity of the current level of research in the field of plant protection is the development of new nanoscale forms of plant protection agents with a convenient and technological form of application for farmers, improved penetration of active substances into plant tissues, with reduced consumption of application rates, as well as the use of complexes with biological additives and chemical inducers. We produced nanopesticides based on tebuconazole and natural metabolites (in particular, glycyrrhizic acid) in the form of alternative formulations such as microcapsules, nanosuspensions, and microemulsions. They were used to treat wheat seeds and showed high effectiveness against pathogenic microorganisms. The greatest healing effect in spring wheat seedlings was observed when seeds were treated with the TBC nanosuspension at a consumption rate of 0.5 L/t (100%) and a slightly lower effect (94.9–95.2%) was achieved with the microemulsion [27].

Such high efficiency was reached owing to the nanoscale sizes the resulting formulations, which were confirmed by dynamic light scattering. The narrowest size distribution (225 ± 40 nm) was observed for the nanosuspension based on LE. This preparation completely suppressed infections with *B. sorokiniana*, *Fusarium spp*., and *Penicillum spp.* possibly due to the presence of the natural saponin glycyrrhizic acid which interacts with plant hulls and promotes better penetration of TBC into the grain [28].

Our earlier studies using NMR spectroscopy revealed the dependence of the effectiveness of the TBC nanosuspension on its penetration into the grain. It was shown that the suggested formulation provides higher penetration of TBC into the grain than its aqueous suspension without auxiliary components. The most effective penetration occurred at the stage of grain germination. Initial TBC practically did not penetrate into the grain even at the germination stage in a humid atmosphere, while TBC from the nanosuspension showed significantly more effective penetration (25–55% of that used during treatment). This fact of increasing the bioavailability of TBC in the nanosuspension was explained by the use of mechanochemical treatment that enables the formation of nanodispersed preparations with multifunctional properties [29].

Yang *et al.* [30] performed the microencapsulation of TBC and determined the effect of the resulting formulation on corn emergence and bioeffectiveness against corn smut (*Sphacelotheca reiliana*). An increase in seedlings, fresh shoot weight, fresh root weight, carotenoid and chlorophyll content was observed. Phytohormone analysis showed that the beneficial effects of microencapsulated TBC are caused by prolonged release of TBC, which is likely to affect the balance of phytohormones in corn sprouts. This formulation also resulted in a slight increase in the gibberellin level, elimination of abscisic acid accumulation in corn, and better protection against corn smut compared to the commercial formulation.

Taking into account the fact that the basis of the modern range of chemical plant protection agents in grain production in the Russian Federation is formed by the azole-containing systemic fungicides (TBC, prothioconazole, cyproconazole, difenoconazole, *etc*.), we studied the possibility of expanding the method of mechanochemical suspending to these active substances [22]. The oil emulsions obtained using this technology and suspension concentrates of the protectants based on prothioconazole and tebuconazole were used for complex protection of seed material from pathogens of root rot (*Bipolaris sorokiniana Sacc. Shoemaker*, *Fusarium spp.*) and mold fungi (*Alternaria spp*. and *Penicillium spp.*). It was shown that the oil emulsion stimulated root formation more effectively and suppressed seed diseases, while the emulsion form with prothioconazole had a positive effect on the germination process, seed survival, and stimulation of sprout growth. These studies revealed the prospects of using oil emulsions of a two-component protectant.

Continuing research in the field of creation of multicomponent seed protectants for grain crops, we developed the formulations based on TBC and propiconazole in the form of solid dispersions and studied their biological activity on spring wheat plants in the conditions of the Trans-Urals [31]. The use of the resulting compositions enabled a reduction in crop damage by root rot by 85–87%, an increase in productive tillering by 6–11% compared to the control, and an increase in the crop yield of 2.2 c/ha or 14%. The introduction of the PGR floroxan into the dressing mixture reduced the retardant effect of TBC and stimulated the growth and development of wheat seedlings.

Recommendations for the use of the developed protectants

Nowadays, nanotechnologies are actively entering our lives. Special progress in this field is observed in industry and medicine. The use of nanotechnologies in the agricultural sector is lagging far behind, despite the growth of scientific reports on the topic. In the field of plant protection, the advantages of nanopesticides include a significant reduction in the consumption rates of protectants and their harmful effects on the environment [4–6].

In recent years, we tested several formulations of plant protection agents based on triazole derivatives with delivery systems such as polysaccharides, prepared using mechanochemical tools. These investigations revealed that polysaccharides provide high efficiency in increasing the solubility and permeability of the protectant plant protection agent AS. An important problem in developing an effective seed treatment preparation is to increase the efficiency of adhesion and penetration. However, which factor is more important for plant protection or which factor plays the key role in the protectant activity, namely, the amount of the protectant on the seed surface or the amount that penetrates into the grain, remains an open question.

To address this issue, the solid dispersions of TBC with plant metabolites arabinogalactan, glycyrrhizic acid and its derivatives were prepared [32]. The resulting SDs formed stable working solutions in water, convenient for treating grain seeds, which showed high penetration ability of TBC into the grain. The comparison of the biological effectiveness of the treated grain with its processed and washed counterpart did not reveal differences in their effect on the pathogens of common root rot. Almost the same results were observed when comparing the growth processes of spring wheat seedlings. These studies show the possibility of increasing the yield of grain crops by increasing the coefficient of preparation penetration into wheat grain.

An integrated approach with participation of chemists, technologists, agronomists, and biologists allowed for proposing the protectants for grain crops, potatoes, vegetables, cotton, *etc*. [33–37].

Conclusions

Summarizing the results presented, it should be noted that currently nanotechnologies are entering into agriculture, in particular, in the field of creation of new effective plant protection agents. This is achieved through the development of nanoscale systems with controlled release, such as polymer nanoparticles, micelles, *etc*., using a wide variety of materials. Our research group has developed an original approach based on mechanochemical tools for the production of nanopreparations (suspoemulsions, nanosuspensions) based on the triazole derivatives, fungicidal substances, and PGRs.

Acknowledgements

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (agreement no. 075-00277-24-00).

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References and notes

§ This article is devoted to the memory of the member of the Russian Academy of Sciences N. G. Vlasenko.

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