Special Topic: The Forum on Avermectins

Problems and Development Trend of Avermectins Pesticide Formulations

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Avermectin family has several members such as avermectin, emamectin, ivermectin and doramectin. Avermectin that Bla is the main activity compound with no less than 90% comes from the extraction of fermentation broth. Modifying Bla'structure leads to the discovery of other compounds which have special bioactivity. Emamectin and emamectin benizoate has insecticidal activity as more than ten times as avermectin. Ivermectin has low acute oral toxicity to nontarget pests. Eprinomectin can be used to animals in milk and lactation. Doramectin has high efficiency, long-lasting activity, safety and low dosage, which makes it the best medicine killing parasites such as arthropods and worms on and in animal bodies.

Avermectins antibiotics have been one of the most excellent bioinsecticides since 1980' and important insecticide in pesticide and medicine market due to their high effect, safety, broad spectrum and special action mechanism.

Avermectins activity compounds have some properties related to their formulations as followings:(1) high melt point, (155-157) ℃ for avermectin and (141-146) ℃ for emamectin benizoate;(2) low solubility in water, 7.8μg/L(21 ℃) for avermectin, 24 mg/L (pH=7.0) and 300 mg/L (pH=5.0) for emamectin benizoate and 10 mg/L for ivermectin;(3) easy to dissolve in organic solvents;(4)stability in water and under normal temperature;(5)insecticidal rate in field is 0.1～0.5 g.a.i./667m^2;(6) easy to oxidize, especially sensitive to ultraviolet light;(7) high toxicity to non-targets, such as hydrobios, bees and silkworms and low toxicity to birds. From those considerations, it's good to make avermectins avtivity components into solid formulation and water-based formulations with 1%~2% content, and emulsifiable concentrates (EC) should not be taken as the normal formulation.

1 Current problem of avermectins pesticide formulations

At present, EC is the main formulation of avermectins pesticides, and this situation must be changed because it contains large amount of organic solvents that has great influence on environment and food safety.

Generally, Yougao which contains 3%~9% abamectin B1 substituting avermectins technical in formulations makes the toxicity of formulations to nontargets increase greatly, which goes against the extension and use of avermectins pesticides.

2 Formulations suitable to avermectins pesticides

More than 80 species pests including nematodes, insects and mites have been reported to be killed by avermectins insecticides. Different pests, crops and application environment need respectively different pesticide formulation to give the best control on the targets. Several formulations can be developed according to physicochemical properties of avermectins pesticides. Their technical melt point are high compared to that of pyrethroid pesticides and spinosad,etc, which makes solid formulation the very adaptive one, while most of pyrethroid pesticides technical have low melt point and even are liquid.

They easily dissolve in all kinds of non-polar solvents and are conveniently made into emulsifiable concentrates of low concentration with high efficiency. They are stable in water and could be developed into water-based formulations more easily than pyrethroid pesticides and spinosyn.

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Appropriate formulations developed can drop down the toxicity of avermectins pesticides to nontargets and increase their stability to UV light, which do a favor to the extension and use. Avermectins have high toxicity to hydrobios that LC_{50} of avermectin to trouts (96 h) is 3.6 μg/L, LC_{50} to blue-gill sunfishes (96 h) is 9.6μg/L, LC_{50} by food intake to bee is 0.009 μg/L/bee and LC_{50} by contact method to bee is 0.002 μg/L/bee, the LT_{50} on leave is 4 h and the residual pesticide on leave after 4 h has low toxicity to bee, high toxicity to silkworm that the rest pesticide on mulberry leaves even 40 d later after spraying has obvious contact action , but low toxicity to birds. LD_{50} (48 h) of emamectin benizoate to bee by contact is 0.009064μg /bee, the stomach toxicity for bee LC_{50} (48 h) is 1.024 mg/L, LC_{50} (96 h) to Brachydanio rerio is 0.2390 mg/L and LD_{50}(96 h) to silkworm is 0.011 09 mg/kg mulberry leaves which is at extremely toxicity level. Avermectins pesticides can be oxidized easily, especially sensitive to ultraviolet light.

3 Formulations can be developed for avermectins pesticides

3.1 Solid formulations

There are wettable powder (WP), water dispersible granule (WG),water dispersible tablet(WT),water soluble granule(SG),granule(GR),large granule(GG), fine granules(FG) and microcapsulated guanule belonging to solid formulations.

Solid formulation is one of the most adaptive formulations for avermectins pesticides with no solvents used, little spray draft and no water source pollution from lose in upland field application, low toxicity to silkworms, bees and fishes. It is convenient to add antioxidants, anti-uv light agents and wetting agents to solid formulations and to make their re preparations. All kinds of granules are mainly used to control underground insects and nematodes.

3.2 Liquid formulations

Suspension concentration(SC), suspension emulsion(SE), emulsifiable concentrates(EC), emulsion in water(EW), micro-emulsion(ME) and microcapsule suspension(CS) are main liquid formulations.

Suspension concentration should be put to the first position to develop which has similar advantages with solid formulations and is helpful to re preparation. Either emulsion in water or suspension concentration of avermectin can be made into re preparation of suspension emulsion with other pesticides. Meanwhile, avermectin technical can be developed into SC by a step with other pesticide technical fitting the requirements of SC. Micro-emulsion of avermectin can be used in some special areas such as golf turf, certain nematodes and animals fur, and is not recommended to vegetable and paddy land. Microcapsule suspension is a developing trend of avermectins pesticides which can decrease the toxicity to non-targets and sensitivity to UV light. It also has great action on underground pests.

3.3 Formulations for seed-treatment

There are water dispersible powder for seed treatment, flowable concentrate for seed coating and capsule suspension for seed treatment.

4 Developing trend

4.1 Develop formulations based on technicals

System research and development on the formulation of avermectins technicals should be ongoing, and Yougao should be out of those areas. Water dispersible granule and suspension concentration will be the main formulations of avermectins pesticides, and WP、GR、CS and FS will be developed greatly.

4.2 Develop formulations used in paddy land

Several technical difficulties must be overcome for developing high efficiency and safe formulations used in paddy field, which are

(1) decrease the photodegradation of avermectins pesticides in the maximal degree; (2)lower the toxicity of their formulations to hydrobios in the maximal degree;(3) improve wettability, permeability and spread ability of formulations greatly;(4)select the suitable re preparation components through optimized combination.

Photogegradation can be reduced by adding anti-uv light agents such as titanium dioxide and zinc oxide used successfully or anti-oxidants to formulations.

Yougao can not be used to make formulations and spray adjuvants especially spreader and penetrate should

be added into formulations which can decrease the toxicity of formulations to hydrobios. Avermectins pesticides are remixed with other component having low toxicity to fishes which is helpful to reduce the toxicity of formulations to fishes.

SE、SC、CS、CS+SC、CS+EW and WG,etc. can be selected for paddy land using.

5 Develop new application areas for avermectins pesticides

The application areas will extend to underground pests and nematodes from controlling insect pests and mites which will be one of the main markets. Formulations for seed treatment, granule and microcapsule should be developed and used in this new area.

(1) Avermectins pesticide granules have been marketed for controlling underground pests which replaced high toxicity insecticides such as carbofuran. But these formulations have very short persistent period due to that avermectins technicals are easily degraded in water and soil and adsorbed by soil. Microcapsules have no those problems and will be used for many crops.

(2) Avermectins pesticides have special activity on controlling plant nematodes especially for root-knot nematodes and are good nematicides while fumigant nematicides of bromomethane and metham-sodium being in eviction have heavy pollution to environment and non-fumigate nematicides of fenamiphos, aldicarb and ethoprophos,etc being used now have extremely toxicity. Formulations for this use are granules, microgranules, microcapsules and liquid formulations with good penetration ability.

(3) Seed coating agents of avermectins pesticides are good for controlling underground pests and nematodes at the same time which is an important formulation being worth researching and developing.

6 Research re preparations of avermectins pesticides with new concepts

Re preparation can give avermectins pesticides longer service life and broad controlling spectrum except for high activity.

Today, Research of re preparations is not only involved screening of components and efficiency but also formulations which is very important for the development of avermentins pesticides.

阿维菌素类农药制剂的存在问题和发展思路

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1 阿维菌素类农药制剂主要存在问题

1.1 从农药制剂角度看阿维菌素(类)

阿维菌素类农药主要有阿维菌素、埃玛菌素、埃珀利诺菌素和道拉菌素。

阿维菌素类抗生素以其超高的药效、安全、宽广的杀虫谱和独特的杀虫机理等优点成为上世纪 80 年代以来最优秀的生物源杀虫剂之一，并成为横跨医药(兽药)和农药领域的杀虫剂主要新品种。

从农药制剂的角度综观阿维菌素：(1) 原药熔点高，常温下为固体；(2) 在水中溶解度很小；(3) 易溶于有机溶剂；(4)在水中稳定，常温下不易分解；(5)田间杀虫生物活性；(6)易氧化，对紫外光尤为敏感；(7)对非标靶毒性高，对水生生物高毒，对蜜蜂和蚕高毒，对鸟类低毒。

阿维菌素类农药适宜的剂型框架主要有：(1)适宜制备固体剂型；(2)符合制备多种水基化剂型的条件；(3)制剂活性物质的含量在 1%~2%为宜，不宜大于 5%；(4)不适宜把乳油作为常用剂型；(5)确定制剂配方时要考虑降低相关的非标靶毒性和提高化学稳定性。

1.2 制剂存在的问题

(1) 不适宜以乳油为该药物的主要剂型，乳油既耗用大量有机溶剂又给环境和食品安全带来影响。

(2) 普遍使用“油膏”进行制剂，使阿维菌素的缺点被放大了，阿维菌素制剂的非标靶毒性被提高，严重影响了产品的使用和推广。

(3) 由于历史原因，对阿维菌素类农药的制剂开发缺乏系统的研究。

1.3 历史原因

(1) 发明者对产品应用开发的主攻领域是兽药。

(2) 产品开发的年代较早，在农药制剂技术上，带有鲜明的80年代初期的历史特征。

2 阿维菌素类农药可以被开发的主要剂型

2.1 农药剂型开发需要考虑的主要因素

农药剂型开发的总原则：(1) 原药物化性质，尤其是熔点、溶解度和稳定的条件等；(2)原药生物活性特征，尤其是药效、机理和发挥的条件；(3) 原药的非标靶毒性，包括对人、畜、作物、蜂、鸟、鱼和蚕等；(4) 施药对象；(5)施药环境：包括大、小环境；(6) 制剂成本和相关作物的价格；(7) 栽培方式和农民的用药方式和习惯；(8) 用药地国家和地方政府的法律、规定和政策导向。

2.2 阿维菌素类农药适合开发多种剂型

(1) 阿维菌素类农药杀虫谱广，对线虫、昆虫和螨均有驱杀活性。不同的防治对象、不同的保护作物、不同的用药环境，需要不同的制剂配套。

(2) 阿维菌素类农药的物化特性符合开发多种剂型的条件，与菊酯类、多杀菌素等多种农药相比，先天条件优越。

(3) 阿维菌素类农药的推广应用迫切需要制剂的开发来弥补对水生生物高毒等缺点。

2.3 阿维菌素类农药可以被制备成哪些主要剂型？

(1) 固体制剂：可湿性粉剂(WP)、水分散粒剂(WG)、可分散片剂(WT)等；水溶粒剂(SG)；颗粒剂(GR)、大粒剂(GG)、细粒剂(FG)、微囊粒剂(CG)等。固体剂型是阿维菌素类农药最适合的选择之一。

(2) 液体制型：悬浮剂(SC)、悬乳剂(SE)、乳油(EC)、水乳剂(EW)、微乳剂(ME)、微囊悬浮剂(CS)。悬浮剂应作为开发的重点，它具有阿维菌素固体制剂相似的优点。悬乳剂为阿维菌素类制复配制剂提供了极大空间。

应该减少乳油的使用。但改用植物油配制的乳油会起到增效作用并显著提高展着性能。ME 会有一些特殊用途，但建议不要用于蔬菜和水田。

微囊剂是阿维菌素发展的一个方向。通过制剂技术，能有效的降低非标靶毒性和减轻光敏感等问题，同时在防治地下害虫方面会很有作为。

(3) 种子处理制剂：种子处理可分散粉剂（WS）、悬浮种衣剂（FS）和种子处理微囊悬浮剂（CF）。

3. 科技创新、扩大应用、开拓市场

3.1 把制剂科技创新的起始点放到阿维菌素类的原药上来

WG、SC 将会逐步成为阿维菌素类农药的主要剂型，WP、GR、CS、FS 等也会得到较多发展。

3.2 开发阿维菌素制剂的水田应用

开发阿维菌素安全高效用于水稻田的制剂，需突破多道技术障碍。

(1) 最大程度的减缓光照氧化降解现象。一是选择适当的抗紫外光材料进入制剂，成功的经验有用粒径在 0.5 μm 以下的二氧化钛和氧化锌作为组分进入制剂。二是制剂中添加合适的抗氧化剂。

(2) 最大限度降低制剂的水生动物毒性和毒力。首先，毒性被严重放大的“油膏”绝对不能进入制剂，第二，添加经过筛选的喷雾助剂尤其是展着剂和渗透剂进入制剂，这对减少农药流失和提高药效是非常必要的。第三，选择鱼毒较低的第二复配组分有助于降低制剂的鱼毒。

(3) 大力提高药剂的润湿、渗透和展着性能。

(4) 优化组合，筛选合适的农药复配组分。

要尽量把上述功能统一到一个产品中去，农药剂型的选择是关键。SE、SC、CS、CS＋SC、CS+EW、WG 等属于有条件进入被筛选的剂型。

3.3 开发阿维菌素防治对象的新领域

把应用面由防治昆虫、螨类害虫扩展到防治地下害虫和线虫等，应成为阿维菌素类农药进一步推广应用开拓市场的主要方向之一。对此要重点研究开发种子处理剂、粒剂、微囊剂等农药剂型。

(1) 把阿维菌素类制成粒剂用于防治地下害虫，以代替克百威等剧毒农药，现已进入市场。由于阿维菌素在土壤和水中易降解，并易被土壤吸附 ，故粒剂的持效很短。而微囊剂则不受环境的影响，缓释期限大大加长，将在许多作物中得到应用。

(2) 阿维菌素类对防治植物线虫有特效，特别对根结线虫杀虫效果显著。施药的主要方式有土壤处理、种子处理、灌根、对植物直接注射(对林木)、喷施等。其剂型主要用粒剂、微粒剂、微囊剂、各种渗透性优秀的液剂等。

(3) 种衣剂是把阿维菌素类农药杀灭地下害虫和植物线虫两个功能统一起来的最适用的剂型。

3.4 以新的概念开展复配制剂的研发

与阿维菌素相关的复配制剂的研发，除以兼治和增加药效为目的外，更主要的任务是：(1) 延长产品的使用寿命；(2) 扬长避短，扩大使用面。

现代复配制剂的研究不单纯是组分和药效双因素的筛选，而要结合剂型的开发，甚至包括适合的复合剂型研究。这对阿维菌素类农药的经营和开发者们是十分重要的。