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REVIEW



Development of immunoassays for multi-residue detection of small molecule compounds

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ABSTRACT

The small molecule compounds like pesticide, veterinary drug, bio-toxin, and heavy metal are widely found in animals, plants, soil, etc. Excessive compounds residues will have a bad influence on human health and the environment. Thus, it is extremely urgent that can detect the small molecules simultaneously. At present, many researches of simultaneous detection for small molecules using the method of an immunoassays have been reported thanks to its advantages of fast speed, simple operation, and high specificity. The small molecules have only one antigenic determinant, so the competitive immunoassay is the main method for small molecule compounds detection. In this paper, our main job is to describe the development of immunoassay for multi-residue detection of small molecule compounds and introduce three ways to complete the analysis of multi-residue immunoassay of small molecule compounds. We also summarize deficiencies and make an expectation of the immunoassays.

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1. Introduction

Small molecule compounds include pesticides, veterinary drugs, bio-toxins, and environmental pollutants of small molecules (PCBs, dioxins), which represent a threat to human health and contaminate water, air, soil, and agricultural products (Malarkodi, Rajeshkumar, & Annadurai, 2017). Therefore, developing methods to detect small molecule compounds is of great value. A series of detection techniques for small molecule compounds have been developed, such as high-efficiency liquid chromatography (Beale, Kaserzon, Porter, Roddick, & Carpenter, 2010; Rejczak & Tuzimski, 2017; Xiong et al., 2016), gas chromatography detection (GC) (Farina, Abdullah, Bibi, & Khalik, 2017; Naksen et al., 2016; Qin, Qiao, Wang, & Zhao, 2010), gas chromatography-mass spectrophotometry detection (GC-MS) (Huo et al., 2016; Lee et al., 2017; Ozcan & Balkan, 2017), and liquid chromatography-mass spectrometry detection (LC-MS) (Grund, Marvin, & Rochat, 2016; Kmellár, Pareja, Ferrer, Fodor, & Fernández-Alba, 2011; Valse et al.,

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2017). However, these methods are limited by the expensive apparatuses required, long time needed for analysis, and requirement of professional staff, limiting the feasibility of their use in undeveloped areas. The immunoassay involving the specific binding of an antigen to an antibody has the advantages of simplicity, low cost, and high sensitivity (Shankaran, Gobi, & Miura, 2007; Yin, Yin, & Xu, 2008). An antigen contains immunogenicity and reactogenicity. However, small molecule compounds which only have reactogenicity are regarded as haptens (Kim, Cho, Lee, & Lee, 2003; Mitchell, 2010; Yu, Yu, Undersander, & Chu, 1999). Moreover, small molecules have low molecular weights and one antigenic determinant (Kobayashi & Oyama, 2011; Spinks, 2000). For this reason, small molecules can only combine with one antibody and cannot combine with two or more antibodies simultaneously. Therefore, competitive immunoassays are the main method for detecting small molecule compounds (Deng, Li, & He, 2016; Ha, Chung, & Bae, 2016; Zhang, Lai, & Yang, 2013). In addition, non-competitive immunoassays are also being used to detect small molecule compounds (Dong et al., 2014; Islam et al., 2011; Kobayashi et al., 2003; Li, Jeon, Suh, & Kim, 2011). Thus, there is great value in studying the detection of small molecules using immunoassays.

Detecting different types of small molecule compounds in the same sample requires a repeated operation, which is a time-consuming and energy-demanding process. However, a method that can detect multiple types of pesticides (veterinary drugs, bio-toxins, heavy metals, etc.) or different types of small molecules at the same time will result in an easy, fast, and inexpensive process (Chen et al., 2017; Jiang & Fan, 2012; Li et al., 2017). Hence, research on multi-residue detection methods is currently of great significance. Due to the long growth cycle of plants and to protect against various diseases and insects, farmers will spray a variety of pesticides (Tadevosyan, Tadevosyan, Kelly, Gibbs, & Rautiainen, 2013). Thus, the cultivation of plant-type agricultural products requires the detection of multiple pesticides simultaneously. There are three ways to analyse multi-residue immunoassays for small molecule compounds. The first is to design a universal hapten for the multi-residue analysis of small molecules (Liang, Liu, Liu, Yu, & Fan, 2008). The second is to form multiple antigenic determinants by connecting multiple haptens on the carrier protein or prepare multiple specific antibodies to perform the multi-residue analysis of small molecules (Mukunzi et al., 2016; Qiao et al., 2017). The third is to fluorescently label the antigen or antibody to achieve multiple residue detection (Chen, Wen, et al., 2014; Tang, Zhang, Cheng, & Lu, 2008). The similar structures are required in a first way among the analytes and individual targets cannot be distinguished, the second way can solve the problem but they are limited to detect a few kinds of analytes (Le et al., 2013; Liang, Xie, Wang, Gui, & Zhu, 2013; Yaneva, Ivanov, Todorov, & Godjevargova, 2017).

The immunoassay is an analytical method for detecting various substances using antigen-antibody specific binding reactions (Chen, Xu, et al., 2014; Hage, 1999). Immunoassays can be divided into unlabelled immunoassays and labelled immunoassays. Unlabelled immunoassays include immunodiffusion and immunoelectrophoresis. Labelled immunoassays include the radioimmunoassay (RIA), fluorescence immunoassay (FIA), chemiluminescence immunoassay (CLIA), enzyme-linked immunoassay (ELISA), and bio-barcode immunoassay. No matter the single or multiple detections for the small molecules, the most commonly used immunoassay method is ELISA (Briggs, Tapper, Sprosen, Mace, & Finch, 2017; Pavón, González, Martín, & García, 2012).

2. Immunoassays for the detection of small molecule compounds

Immunoassays are based on the specific antigen–antibody binding. The enzyme or luminescent substance is labelled with an antibody or antigen to detect the test compound in a sample. Immunoassays can be either non-competitive (Acharya & Dhar, 2008) or competitive (Hu et al., 2013). Competitive immunoassays are used to detect small molecule compounds with only one antigenic determinant, whereas non-competitive immunoassays are generally used to detect macromolecular compounds such as proteins and polysaccharides with multiple antigenic epitopes (Du et al., 2018; Rao et al., 2016).

2.1. Competitive immunoassays for the detection of small molecule compounds

Competitive immunoassay means the analyte and the hapten-carrier protein conjugations can react with the antibody simultaneous. Besides many reports on competitive immunoassay have been reported (Carter, Triplett, Striemer, & Miller, 2016; Yu et al., 2018). The RIA was first proposed by the American chemists Yalow and Berson in 1958 as the labelled immunoassay (Wang, 2008). The basic principle of the competitive immunoassay is to label the antigen with a radioisotope, and then, both the small molecule compound to be detected and the antigen will react with the antibody (Berson & Yalow, 2006). Thus, the amount of the small molecule to be tested is negatively correlated with the amount of the antigen. The disadvantages of the RIA include poor repeatability and a high rate of non-specific binding (Yan, 2013).

In the FIA, the antigen or antibody or hapten is labelled with a fluorescent substance, next the fluorescent molecules enter an excited state after irradiation with a light source. When the molecules in the excited state return to the ground state, the fluorescent substance emits light, making it possible to calculate the content of the analyte based on the fluorescence intensity. However, a disadvantage of the method is the large amount of background interference (Feng, Shan, Hammock, & Kennedy, 2003; van Genderen et al., 2010; Wu, 2008).

The basic principle of the CLIA is similar to that of the FIA. The antigen or antibody is labelled with a luminescent substance, and a luminescent substrate is added after the reaction ends (Zhao, Sun, & Chu, 2009). Thus, the content of the analyte can be calculated based on the fluorescence intensity (Wang, Wu, Zong, Xu, & Ju, 2012). The difference between the CLIA and FIA is that the CLIA does not require excitation with a light source, whereas the FIA does.

The bio-barcode assay immunoassay was proposed in 2003 by Mirkin et al. (Nam, Thaxton, & Mirkin, 2003). In this method, a conjugate of hapten and a carrier protein is coated on the surface of magnetic nanoparticles or used to coat 96-well plates, and not only the conjugate but also the small molecule compound to be detected can react with the antibody. The method is simple to perform and can be easily popularized and applied (Du et al., 2016; Yang, Zhuang, Chen, Ping, & Bu, 2015).

2.2. Non-competitive immunoassays for the detection of small molecule compounds

The pattern of the non-competitive immunoassay for small molecule compounds is different from the conventional pattern of the “double antibody sandwich,” that is, “antibody–

antigen–antibody” (Barnard, Karsiliyan, & Kohen, 1991; Kobayashi & Goto, 2001). Compared with the competitive immunoassay, the non-competitive immunoassay has a higher sensitivity, wider linear range, and higher selectivity (Chen, He, & Xu, 2014; Hua et al., 2015). Because of continuous research efforts and the progress made in science and technology, non-competitive immunoassays can also be used for the detection of small molecule compounds. There have been many studies on non-competitive immunoassay for the detection of small molecules (Akter et al., 2016; Dalgleish & Kennedy, 1988; Liu, Anfossi, Shen, Li, & Wang, 2017). This type of assay has several modes: anti-idiotypic antibody (Hu et al., 2017), biotin-avidin-based sandwich immunoassay, anti-metatype antibody, and open sandwich immunoassay (OSIA) (Wang et al., 2017).

In the biotin-avidin-based sandwich immunoassay, the small molecule to be tested is acylated, and then, the small molecule to be tested can be combined with the labelled antibody and solid-phase avidin (Ishikawa, Tanaka, & Hashida, 1990). This mode has a high sensitivity, but it involves a complicated procedure.

The anti-metatype antibody can recognize the complex of the analyte and the antibody but cannot recognize the antibody or analyte alone. Therefore, a shortcoming of this mode is that it is difficult to identify antibodies that recognize antigen–antibody complexes. Hence, a new method called the phage anti-immune complex assay was established (González-Techera, Vanrell, Last, Hammock, & González-Sapientza, 2007), which has a high specificity, high sensitivity, and short screening cycle (González-Techera et al., 2015; Kim et al., 2010).

The reaction of the OSIA occurs in the variable regions; that is, the V_H and V_L regions can bind the small molecule to be detected (Hara, Dong, & Ueda, 2013; Ueda, 2002). Because only one antibody is used, there is increasingly more research on this method. Recently, the open sandwich based on the ELISA, immuno-field effect transistor (Sakata, Ihara, Makino, Miyahara, & Ueda, 2009), and FIA (Chung, Makino, Ohmuro-Matsuyama, & Ueda, 2017) have been reported. However, not all small molecules can bind the V_H and V_L regions; thus, some antibodies will not be able to combine with the analyte, so the OSIA has been limited in practical applications.

3. Approaches to multi-residue immunoassays for small molecule compounds

Specific antibodies are produced when the mice or rabbits or some other mammals were immunized with the corresponding specific small molecule substances-ovalbumin conjugates, which have the same structure with analytes (Tochi et al., 2016; Yaneva, Ivanov, & Godjevargova, 2017). To be specific, different individual conjugates as immunogens were injected into different mammals, which can produce the monoclonal antibodies. Therefore, the monoclonal antibody produced by a mouse can recognize the individual target which was injected into the mouse rather than recognizing other targets. In contrast, the polyclonal antibodies can recognize the family of the target compounds, as some structures among them are same (Bai et al., 2017; Ryan, Jones, Mitchell, & Mett, 2001; Wang, Zhang, Zhang, & Shen, 2011).

3.1. Preparation of a broad-specificity hapten or broad-specificity antibody

Analytes can be detected by preparing a broad-specificity hapten if these substances have the same molecular structure. Meng developed an assay for detecting organic phosphorus pesticides, including chlorpyrifos, triazophos, and phoxim, by preparing a broad-specificity hapten or broad-specificity antibody. These three pesticides all have a diethyl general structure. Thus, diethyl phosphonic acid as a broad-specificity hapten can detect these three pesticides simultaneously. Jiao developed an assay for detecting 10 analytes including 6 penicillins (amoxicillin, penicillin G, ampicillin, penicillin V, carbenicillin, and sulbenicillin) and four tetracyclines (tetracycline, oxytetracycline, doxycycline, and chlortetracycline) by preparing a broad-specificity antibody. The 10 analytes were coupled to bovine serum albumin in turn and were injected into the rabbit, which could produce the broad-specificity antibody. The broad-specificity antibodies can recognize the 10 analytes simultaneously (Jiao, Liu, Zhang, Zhao, & Wang, 2012). However, although this method can detect multiple residues of small molecules, they have to be the same type of small molecule. Moreover, the total content of the same types of small molecule can be detected rather than the concentration of each specific substance.

3.2. Preparation of multiple antigenic determinants or preparation of a variety of specific antibodies

If the compounds to be detected do not have the same molecular structure, then the method of preparing a universal hapten cannot be used. Instead, the substances are detected by preparing multiple antigenic determinants or preparing a variety of specific antibodies. Chen et al. developed a lateral flow immunoassay (LFIA) for detecting aflatoxin B₁, maize ketone, and ochratoxin A in maize, rice, and peanut. In this assay, specific antibodies for all three compounds were prepared, and then, the three antibodies reacted with their respective antigens (Chen, Chen, Han, Zhou, et al., 2016). Guo developed a multiplex bead-based competitive immunoassay based on suspension array technology for the simultaneous detection of the pesticides triazophos, carbofuran, and chlorpyrifos. In this paper, the three hapten–BSA conjugates were coupled with the beads. The three pesticide standards and beads with hapten–BSA conjugates can competitively react with monoclonal antibodies; goat anti-mouse IgG secondary antibodies labelled with horseradish peroxidase were added and were measured subsequently (Guo, Tian, Liang, Zhu, & Gui, 2013).

3.3. Multiple residue detection by fluorescently labelling the antigen or antibody

On the one hand, different fluorescent materials can be used, the different fluorescent materials are labelled with the corresponding antibodies or antigens, and the corresponding antibodies or antigens then undergo an antibody–antigen immune response with the antigens or antibodies. Qualitative and quantitative analyses are carried out using the characteristics and intensity of the fluorescence signals. This method is characterized by a fast speed and high specificity. On the other hand, the same fluorescent materials can be used, these same fluorescent materials are labelled with the corresponding antibodies or antigens, and the corresponding antibodies or antigens are used to coat the wells of

96-well plates. The fluorescence signal intensity in the wells is detected with a microplate reader. The fluorescent materials that can be used in this approach include organic dye molecules and quantum dots. Ye, Li, Zuo, and Li (2008) developed an assay for detecting sulfamerazine, streptomycin, and tylosin simultaneously using the organic dye molecule Cy5. The basic principle is that the antigen carrier protein and hapten were conjugated, the complex was then used to coat 96-well plates, and fluorescently labelled antibodies were added to the wells. Peng et al. (2009) developed an assay for detecting dexamethasone, gentamicin, clonazepam, medroxyprogesterone acetate, and ceftiofur simultaneously based on multicolour quantum dot probes. In this assay, the coating antigen carrier protein and hapten were conjugated and used to coat 96-well plates, and then, quantum dot-labelled antibodies were added to the wells. The maximum emission wavelengths of the five quantum dots used are 520, 545, 570, 590, and 635 nm. After the reaction is completed, the fluorescence intensity of each well is measured.

4. The application of immunoassays in multi-residue detection

4.1. Multi-residue detection of pesticides

Limited amounts of pesticide residues are permitted in agricultural products, but pesticide residues frequently exceeded the maximum residue limit. The problem affects the quality and safety of agricultural products and has captured wide public attention.

Niusha (2016) presented an ELISA and a CLIA for the determination of three pesticide (fenpropathrin, decamethrin, λ -cyhalothrin) residues and compared the results of the two methods. Pesticide residues were detected by preparing a broad-specificity hapten in this assay. The three pesticides have an α -cyano pyrethroid structure, so the common moiety of α -cyano pyrethroids without one side chain of the cyclopropane ring was used as the broad-specificity hapten. The conjugation of the broad-specificity hapten and coating carrier protein was regarded as the immunogen, and it could produce specific antibodies. The IC_{50} values of fenpropathrin, decamethrin, and λ -cyhalothrin using this ELISA were 2.6, 8.2, and 31.1 ng/mL, respectively.

4.2. Multi-residue detection of veterinary drugs

Chen developed an assay for detecting β -lactams, tetracyclines, quinolones, and sulphonamides in milk using a near-infrared fluorescence-based multiplex LFIA. Multi-residues of the four veterinary drugs were detected by preparing four specific antibodies in this assay. The limits of detection of the four veterinary drugs were 8, 2, 4, and 8 ng/mL. The detection ranges of the four veterinary drugs were 0.26–3.56, 0.04–0.98, 0.08–2.0, and 0.1–3.98 ng/mL, and the linear correlation coefficients were greater than 0.97. The recovery rate of spiked samples ranged from 93.7% to 108.2%, and the coefficient of variation was less than 16.3% (Chen, Chen, Han, Liu, et al., 2016). Wang (2013) developed an assay for detecting streptomycin, tetracycline, and penicillin G in milk simultaneously using an FIA with quantum dots. Multi-residues of the three veterinary drugs were detected by preparing three specific antibodies in this assay. The linear ranges of the

three veterinary drugs were 0.01–25, 0.01–25, and 0.01–10 ng/mL. The limit of detection (LOD) of the three veterinary drugs was less than 0.005 ng/mL.

4.3. Multi-residue detection of bio-toxins

Zhu (2016) presented a time-resolved FIA for measuring zearalenone, aflatoxin B₁, and chlorothalonil in corn. Multi-residues of the three bio-toxins were detected by preparing three specific antibodies, and the detection limits were 0.043 µg/kg for zearalenone, 0.011 µg/kg for aflatoxin B₁, and 0.084 µg/kg for chlorothalonil. Guo et al. (2014) presented an ELISA for the determination of deoxynivalenol (DON), 3-acetyl-DON, and 15-acetyl-DON. The IC₅₀ values of the three bio-toxins were 22, 15, and 34 ng/mL, respectively.

4.4. Multi-residue detection of persistent organic pollutants

Yang (2014) developed an assay for the detection of polychlorinated biphenyls, including PCB12, PCB37, PCB77, and Aroclor1248, using a bio-barcode direct competitive immunoassay and bio-barcode indirect competitive immunoassay. Multi-residues of the four environmental pollutants were detected by preparing four specific antibodies in this assay. The LOD values of the four compounds by the bio-barcode direct competitive immunoassay were 2.63, 4.35, 1.72, and 10.20 pg/L. However, the limit detection values of the four compounds by the bio-barcode indirect competitive immunoassay were 4.36, 4.64, 9.12, and 2.55 pg/L.

4.5. Multi-residue detection of illegal additives

Shan, Xi, Sun, Zhang, and Wang (2012) developed an ELISA for the detection of Sudan red-1, Sudan red-2, Sudan red-3, Sudan red-4, para red, and Sudan red-G in eggs. Multi-residues of these six environmental pollutants were detected by a preparing broad-specificity hapten. The broad-specificity hapten had a structure in which 4-amino-3-methylbenzoic acid was attached to o-toluidine and then bound to beta-naphthol, which detected the six small molecule compounds simultaneously. The detection limits of the six small molecule compounds ranged from 0.08 to 0.2 ng/g. Some immunoassay methods for detecting pesticides, veterinary drugs, bio-toxins, environmental pollutants, and illegal additives are listed in [Table 1](#).

5. Conclusions

The main methods for the detection of multiple residues of small molecule compounds include RIA, FIA, CLIA, ELISA, and bio-barcode assay immunoassay. These immunological techniques have their own advantages and disadvantages. Immunoassay methods are used to detect a specific substance instead of an unknown substance. However, commercial monoclonal antibodies are expensive, and some small molecule antibodies are difficult to prepare.

Compared with GC-MS and LC-MS methods, immunoassay methods feature simpler sample processing steps, faster processing speeds, and lower costs. With the development

Table 1. Examples of multi-residue immunoassays for the detection of small molecules.

Group	Compounds	Method	Sensitivity ($\mu\text{g}/\text{kg}$)	References
Pesticide	Parathion, methyl parathion, fenitrothion	CLIA	1.24–5.57 ^a	Zou et al. (2017)
	Organothiophosphate pesticides, organophosphate pesticides	ELISA	13–135 ^b	Li, Zhao, Zhao, and Yang (2015)
Veterinary drug	Chlorpyrifos fenthion	ELISA	0.20–0.50 ^b	Navarro et al. (2013)
	Clindamycin, lincomycin	ELISA	1.8, 6.8 ^b	He et al. (2017)
	Penicillin G, amoxicillin, ampicillin, penicillin V, cloxacillin, oxacillin, cloxacillin, carbenicillin, dicloxacillin, methicillin, nafcillin	ELISA	0.7–9.3 ^b	Jiao (2013)
Bio-toxin	Streptomycin, tetracycline, penicillin G	FIA	5 \times 10 ^{-3b}	Song et al. (2015)
	Deoxynivalenol, zearalenone, T2/HT2	LFIA	80–1000 ^b	Foubert, Beloglazova, and De Saeger (2017)
Persistent organic pollutants	Fumonisin B ₁ , fumonisin B ₂	FIA	157.4, 290.6 ^b	Li, Mi, et al. (2015)
	Permethrin, Aroclor1248, Aroclor1254	ELISA	1.5–14.3 ^c	Bronshtein, Chuang, Van Emon, and Altstein (2012)
Illegal additive	Malachite green, brilliant green, crystal violet	ELISA	1.34–1.98 ^a	Shen et al. (2011)
	Sudan red-1, Sudan red-2, Sudan red-3, Sudan red-4, Sudan red-G	ELISA	0.2–0.6 ^b	Chang et al. (2011)

^aIC₅₀;^bLOD;^cI₂₀.

of immunological techniques, the sensitivity and application range of these assays continue to increase.

6. Prospects

Immunoassays have attracted attention because they allow fast analysis in the field. There are three methods for multiple residue detection of small molecule compounds: preparation of a broad-specificity hapten or broad-specificity antibody, preparation of multiple antigenic determinants or preparation of a variety of specific antibodies, and multiple residue detection by fluorescently labelling the antigen or antibody. Two of these methods can be combined to expand the detection range. Because of the hazards associated with these compounds, researching and developing methods to detect a variety of small molecule compounds simultaneously and quickly has become a popular area of study.

With the development of science and technology, there have been several new immunoassays, such as aptamer technology. Aptamer technology replaced the traditional pattern in which an antibody binds specifically to the target substance. Furthermore, with the development of nanotechnology, nano-materials such as nano-gold, quantum dots, and carbon materials are being used in immune technologies to amplify signals and improve sensitivity. The multiple detection of small molecules using immunoassays has good development prospects with the development of gene engineering and cell engineering techniques.

Disclosure statement

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