Nanoparticles based sensors for rapid detection of foodborne pathogens

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Abstract: Rapid detection of foodborne pathogens is a key step in the control of food related diseases. Conventional methods for the detection of food pathogens, although typically sensitive, often require multiple time-consuming steps such as extraction, isolation, enrichment, counting, etc., prior to measurement, resulting in testing times which can be days. There is a need to develop rapid and sensitive detection methods. This review is intended to provide food scientists and engineers an overview of current rapid detection methods, a close look at the nanoparticles especially magnetic nanoparticle-antibody conjugates based methods, and identification of knowledge gaps and future research needs.

Keywords: nano-sensor, magnetic nano-particle, food pathogens, nuclear magnetic resonance
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1 Introduction

According to the 2011 publication by the Foodborne Diseases Active Surveillance Network (FoodNet) of US Center for Disease Control and Prevention (CDC), foodborne diseases caused 1 in 6 Americans (or 48 million people) sick, 128 000 hospitalizations, and 3 000 deaths of foodborne diseases. Majority of the death was caused by *Salmonella*, *Listeria*, *E. coli* O157:H7 and *Toxoplasma*. The number of food product recalls by the USDA Food Safety and Inspection Service (FSIS) due to safety hazard reasons, mostly due to the presence of food-borne pathogens, were 70 and 96 in 2011 and 2012, respectively, accounting for thousands of tons of foods.

A key step in foodborne pathogen control is to effectively detect pathogens along food production and processing line in a timely manner. Portable, rapid and sensitive methods for real-time microbial detection and source identification would be welcome by or benefit

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producers, processors, distributors, regulators, and consumers. Food producers and processors can use rapid detection methods to screen raw materials, ingredients and finished products quickly for quality and safety control at the production and processing facility to insure fast release of product lots, short reaction time to necessary corrective actions, and saving money and labors. Distributors and regulators can use rapid detection methods to conduct on spot exams. Of course, this will help reduce and prevent foodborne diseases which claim thousands of lives and cost $6.5 to $34.9 billion annually, a benefit to the consumers and the industries.

There are strong needs for rapid and sensitive detection methods. Conventional methods for the detection of food pathogens, although typically sensitive, often require multiple time-consuming steps such as extraction, isolation, enrichment, counting, etc., prior to measurement, resulting in testing times which can be days. Therefore, the development of rapid and sensitive detection methods is gaining momentum. Many rapid detection methods, particularly those based on biosensors, have been developed and studied. However, there are a number of limitations of these methods: (1) low specificity and sensitivity, (2) high susceptibility to food components, (3) substantial sample preparation, and (4) difficulty with in-field, continuous and routine analysis of large numbers of samples. This review is intended to provide food scientists and engineers an overview of current rapid detection methods, a close look at the nano-particles based methods, and identification of knowledge gaps and future research needs.

2 Conventional fast detection methods

Conventional methods to detect foodborne pathogens rely on time-consuming and labor intensive procedures such as extraction, isolation, enrichment, counting, etc., which could take days. Many "rapid methods" have been developed in the last two decades. There is no commonly agreed definition of "rapid methods", They may include a vast array of methods such as miniaturized biochemical kits, antibody- and nuclear acid-based assays, and modified conventional tests[1-5]. Swaminathan and Feng provide an excellent review of rapid detection methods with tabulated lists of major categories[6,7].

2.1 Miniaturized biochemical kits

This method is similar to conventional methods in principles, i.e., they identify bacteria based on their biochemical characteristics. They used smaller physical devices and concentrated bacteria isolates and therefore significantly reduced the time. Their accuracy is about 90%-99% of that of conventional methods[1,8,9]. Most of the efforts were designed to identify a group or species of gram-negative enteric bacteria, but there are also kits for the identification of non-Enterobacteriaceae including Campylobacter, Listeria, anaerobes, non-fermenting gram-negative bacteria and for gram-positive bacteria. Miniaturized kits usually require 18-24 h incubation before reading, and pure culture isolates of bacteria.

2.2 Antibody based arrays

The antibody based arrays utilize the specificity of antigen-antibody reaction to identify targeted bacteria via immunoassays. These immunoassays target specific proteins or carbohydrate moieties unique to the pathogen. The antibody based immunoassays can be classified into immunofluorescent assays, enzyme-linked immunosorbent assays (ELISA) and Western blot analyses[10]. These methods use antibodies to "label" targeted bacteria and then use different instruments to measure the concentration of bacteria directly or indirectly with or without separation. Many of these methods are very successful in clinical diagnosis. However, these techniques require sophisticated instruments to prepare and to read the results, thus limiting its application in ordinary food company laboratories, not to say on field or on the spot tests. In addition, most of these methods require enrichment step to obtain reliable reading. Some methods are limited by the specificity, and interference from food components (e.g., autofluorescent compounds in foods). Further understanding of microorganisms' response to antibodies, food matrix, antigen expression and optimization with real-world samples to improve specificity and robustness of these methods[11].

2.3 Nuclear acid-based assays

The nuclear acid-based assays or DNA-based assays

rely on Polymerase Chain Reaction (PCR) tests. The PCR tests are designed to identify DNA segments corresponding to an organism's genome. The nuclear acid-based assays are highly sensitive and selective. However, the technical limitations and costs of these methods are too large for them to be widely used even in the clinical diagnosis[12], not to say in the food industry at this point. Most of DNA hybridization assays have a detection threshold in the range of 104-105 bacteria cells and thus targeted bacteria must be selectively enriched before the assays could be applied. These methods may take one to two days. They also require undamaged microbial DNA and have to be performed in a laboratory setting by experienced personnel and expensive instrumentation and reagents.

In summary, despite the many advantages of the above discussed rapid detection methods, they are still faceing many challenges including low specificity and sensitivity, high susceptibility to food components, substantial sample preparation, high costs, and difficulty with on-field, continuous and routine analysis of large numbers of samples.

3 Magnetic nanoparticle sensors

Nanoparticles are very fine particles with sizes between 1 and 100 nanometers. Because nanoparticles are between bulk materials and atomic or molecular structures, they often exhibit size related properties of great scientific interests. Nanoparticles have found use in biology and medicine fields[13,14], including pathogen detections. Kaittainis et al.[12] provided an excellent review on the applications of nanoparticles in the clinical identification of microbial pathogenesis. As the nanotechnology-based systems are made more affordable, robust and reproducible, they are becoming practical tools for many non-clinical applications and suitable in rural areas of developing nations. Nanotechnology based assays can be conducted in opaque media, like blood and milk, without any sample preparation, providing fast and reliable results in simple and user-friendly formats[12].

Nanoparticles are usually used either as labels or separation aids or both in pathogen detection procedures because of the unique optical, electrical, or magnetic properties. When they are coupled with affinity ligands, they exhibit additional biological, biochemical, and physical properties which may be useful for pathogen binding and signal emitting. Detection methods range from color based[2,15] to fluorescence based[16], from immunology based to PCR based[17] tests. By varying the structural parameters (e.g., size, composition, self-assembly and binding) of nanoparticles, their electronic, spectroscopic (emissive, absorptive), light scattering and conductive properties can be modified[18] to produce different response patterns unique to particular type of interaction of the nanoparticle with the pathogen[12].

Magnetic nanoparticles (MNP) have been widely used in clinic and molecular biology laboratories[8,12,18]. For example, superparamagnetic nanoparticles have been utilized as contrast agents for magnetic resonance imaging (MRI)[19-23]. They are also used in enzyme immobilization, protein purification, and food analysis[24]. Magnetic nanoparticles conjugated to antibodies have been used for the immunomagnetic separation of nucleic acids, proteins, viruses, bacteria and cells[13,14,25-30]. Li and his co-workers[28] used magnetic nanoparticle-antibody conjugates to separate *E. coli* O157:H7 in ground beef samples. MNP-protein and MNP-microbe assemblies can also be used in other *in vivo* applications, such as tissue repair, immunoassay, detoxification of biological fluids, hyperthermia, drug delivery, and cell separation[27,28,31-35].

Recently, interactions between magnetic nanoparticles conjugates and bacteria are used for identification and quantification of mRNA, DNA, and pathogenic microorganisms. Detection of signals and signal changes caused by the addition of magnetic nanoparticles to the pathogen containing matrix may be achieved by using magnetometers or superconducting quantum interference device (SQUID), magnetic relaxometers and magnetic resonance imaging[36-41]. Li and his co-workers used magnetic nanoparticles conjugated with streptavidin or antibodies as "mass enhancers" to amplify frequency change in *E. coli* O157:H7 as detected by a quartz crystal microbalance (QCM) DNA sensor[42,43]. Figure 1 illustrates the

preparation of conjugates of magnetic nano-particles (MNP) and pathogen-specific antibodies and formation of pathogen-induced nano-assembly.

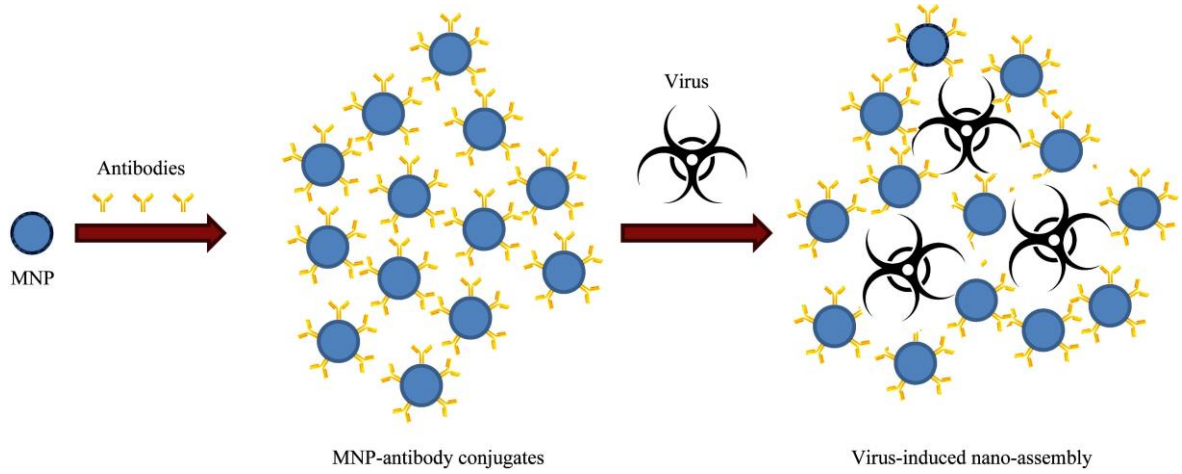

Figure 1 Preparation of conjugates of magnetic nano-particles (MNP) and pathogen-specific antibodies and formation of pathogen-induced nano-assembly. The formation of the nano-assembly causes changes in certain properties such as electronic, spectroscopic (emissive, absorptive), light scattering and conductive properties which can be detected with corresponding instruments

In nuclear magnetic resonance (NMR) technical term, the aggregated paramagnetic nanopartilces can dephase the spins of surrounding water protons more efficiently than MNPs present as the dispersed state and thus decrease the spin-spin relaxation time T_2[44]. The changes in T_2, i.e., ΔT_2, can be correlated to the concentration of the pathogens bond to the antibodies of the MNPs. Figure 2 shows an example of detection of herpes simplex virus (HSV) using a nano-sensor composed of superparamagnetic iron oxide core caged with a dextran coating onto anti-HSV-1 antibodies.

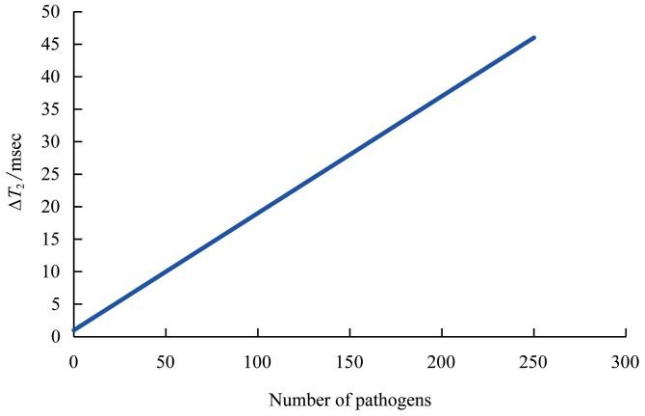

Figure 2 Linearity between number of pathogens (herpes simplex virus, HSV) and ΔT_2[41]

Several researchers studied the relaxation properties of biological samples as affected by magnetic nanoparticles[34-35,45]. The interactions between bacteria and magnetic nanoparticle-antibody conjugates make magnetic nanoparticle a very sensitive bacterial probe. Bacteria's size is in the range of 0.2-10 microns. Addition of even a few bacteria will induce the assembly of the nanoparticles on the bacterial surface, resulting in significant changes in the T_2. Thus, a very low concentration of bacteria can be quantified[37].

Perez et al.[35] reported that magnetic nanoparticles can be used as magnetic relaxation switches for sensing molecular interactions detectable with nuclear magnetic resonance techniques such as NMR spectroscopy and magnetic resonance imaging (MRI). This provides a principle to relate T_2 changes to the concentration of MNPs and hence the number of microbes attached to the MNPs. This principle was demonstrated for detection of a number biological agents including biomolecules, bacteria and virus[34,35,39-41,45-47].

It should be noted that low field NMR spectrometers are relatively cheap compared with most of the instruments for immunoassays. Many small to large food companies can afford to buy low field NMR instruments. Therefore, nano-sensors using NMR relaxometry as the detection method have the potential to be practically implemented by food manufacturers of any sizes.

4 Knowledge gaps and further research needs

The development of MNP based detection methods is still in its early stage and the factors affecting the sensitivity, specificity, and operation of MNP based detection methods for food safety assurance have not been carefully examined and optimized. The complex food matrices present significant challenges[48].

4.1 Selection and preparation of MNPs

The sensitivity of the method relies on the magnitude of T_2 change (ΔT_2) as a result of the interactions between the targeted bacteria and MNP conjugates. First the magnetic anisotropy and moment is a function of type of magnetic metal, size, and shape. Magnetic anisotropy and moment may be enhanced by a decreasing particle size, probably attributed to an increasing surface to volume ratio[49,50]. Selection and preparation of MNPs will therefore affect their magnetic properties. Second, the magnetic anisotropy and moment is also affected by the surface modifications often necessary to enhance stability of and add surface functionality to MNPs. For example, the iron oxide core can be coated with polymers, such as dextran, polyacrylic acid and silica. Such surface modifications will affect the magnetic properties of the MNPs[51]. Preparation conditions such as the time of addition of the polymer, temperature and the use of particular capping agents also affect the magnetic properties[36]. Therefore, attentions must be paid to selection of MNPs and coatings and optimization of preparation procedures.

4.2 Selection of antibodies and methods to prepare NMP-antibody conjugates

Selection of antibodies and methods to conjugate antibodies to MNPs should also be examined because the properties of the MNP-antibody conjugates will certainly have a profound impact on the affinity between the conjugates and targeted bacteria. Another related issue is that when the number of bacteria is relatively high and the organic ligands (antibodies) conjugated on MNPs are limited, the low valency nanoparticles would switch to a quasi-dispersed state due to their limited interaction with targeted bacteria, resulting in smaller changes in the ΔT_2 at high cell concentrations[52]. Although the number of bacteria in fresh and processed foods without enrichment is not expected to be very high, a careful study must be conducted to determine some sort of critical ratios of bacteria to MNP conjugates for given conditions (bacteria type, food matrix, MNP conjugates, etc.).

4.3 NMR and MRI methodologies

Finally, very little has been done to optimize the NMR and MRI methodologies for such immunoassay based detection method. Relaxometry is method dependent. The representativeness of the data is dependent on the data acquisition techniques including pulse sequences and instrument parameters[53]. A 90 degree pulse will allow us to acquire relatively short T_2 while a CPMP pulse sequence can detect longer T_2. An inversion recovery pulse sequence will allow us to acquire spin-lattice relaxation time T_1, which provides information on the interactions between the magnetic moments and the environment. No study has used T_1 to quantify the interactions between MNPCs and targeted bacteria. More work is needed to understand the significance of T_1 as well as the interactions between T_1 and T_2. Recently, a new NMR technique "2D NMR relaxometry" has been developed, which enables researchers to acquire T_1 and T_2 simultaneously and delineate the interactions between T_1 and T_2 and their relationship to certain physiochemical properties[54,55]. Application of 2D NMR relaxometry in the study of MNP based bacteria detection method is expected to improve data acquisition, analysis, and interpretation.

Furthermore, the analysis of the data is even more method dependent and experience driven[53]. Several models, including single component model, discrete multi-component model, and continuous distribution model have been used to analyze relaxation data[56-61]. The choice of data analysis model will govern the interpretation of the relaxation data.

NMR test requires minimal preparation and usually takes a few seconds. There is possibility to automate the analysis process, and further to design handheld chip driven device. Therefore the speed of the entire detection procedure will not be limited by the NMR test. MRI is a technique with potential for greatly increasing test throughput. Multiple samples may be placed the

wells of a multi-well microtiter plate and imaged simultaneously[62]. The throughput will be multiplied by the number of cells compared with NMR spectrometer test.

5 Conclusions

Conventional detection methods involve multiple time-consuming and labor-intensive steps due to the difficulties in isolating pathogens from food matrix and the fact that pathogens are usually present in extremely low numbers. A rapid, sensitive, and selective detection method certainly works to the advantages of food industries in terms of fast release of product lots, short reaction time for necessary corrective actions, and saving of money and labors. Innovative rapid foodborne pathogen detection methods embracing nanotechnology, immunology, microbiology, and advanced NMR techniques can play a significant role in identifying foodborne pathogen sources during processing and distribution, and hence enabling food processors and distributors to control foods safety and reducing the potential risk of unintentional and deliberating contaminations of food products. The benefits of timely detection and corrective actions to producers, processors, distributors, regulators, and consumers are enormous: thousands of lives and $6.5 to $34.9 billion will be saved annually.

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