Miniaturized detection devices powered by various heaters: A quick review under the background of water-borne disease epidemics

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Abstract. With the progress of society and the development of productivity, the problem of water pollution and water shortage caused by water pollution is becoming more and more serious. Water-borne diseases caused by pathogenic microorganisms also bring great harm to human beings and other life forms. These microorganisms include bacteria, viruses, protozoa, and parasitic pathogens. Traditional detection methods are time-consuming and costly, and can't meet the needs of water resource detection. Therefore, there is an urgent need for accurate, rapid, specific, and portable detection equipment for detecting pathogenic microorganisms in water. We analyzed and sorted out the detection methods and detection equipment for detecting pathogenic microorganisms that cause water-borne diseases, summarized these detection methods and detection equipment, and analyzed the advantages and disadvantages of these detection methods. We reasonably concluded that a good detection method for pathogenic microorganisms in water should have the advantages of low cost, low energy consumption, simple operation, strong specificity, and high portability, which can more easily meet the needs of the water quality detection field. Multifunctional small nucleic acid detection devices have been reported for decades, which reduce the reaction time of nucleic acid amplification from hours to minutes, and these miniaturized devices based on nucleic acid amplification are not only highly specific but also low cost, which is very suitable for resource-limited environments.

Keywords: Water-borne disease; Nucleic acid amplification technique; Portable equipment; heater.

1. Introduction

Water is an essential component of all life on Earth and an important natural resource that people depend on for survival. Clean water is of great significance to human life, industrial production, agricultural irrigation, and economic development. The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) estimated that 2.2 billion people did not have access to safe drinking water, 3 billion people had no proper handwashing supplies at home, and 4.2 billion people did not have access to a toilet with proper waste disposal methods[1]. However, due to the progress of society and the accelerated process of industrialization, water resources are polluted. Pathogenic microorganisms in these pollutants are the main cause of water-borne diseases. According to the World Health Organization, global mortality attributable to waterborne diseases is estimated to be > 2.2 million per year, among which about 1.4 million are children, resulting in nearly $12 billion per year of economic loss worldwide[2]. In 2014, an estimated 3–5 million cases of cholera occurred globally with more than 100,000 deaths, mainly in developing countries without safe drinking water treatment and sanitation[3]. Waterborne diseases are caused by ingestion, airborne transmission, or contact with contaminated water by a variety of pathogenic microorganisms (bacteria, viruses, protozoa, and worms)[4] and pose significant health risks to people. In recent years, Escherichia coli (E. coli) O157 and other coliform bacteria are the major causes of water-borne infections[5]. E. coli is a conditional pathogen. Under certain conditions, it can cause gastrointestinal tract infection, urethra infection, and other local tissues and organs in humans and animals[6]. Not only can E. coli cause harm to water, but other microorganisms (Salmonella, Campylobacter, Shigella, cryptosporidium, Giardia, and norovirus, among others) can contaminate water supplies and cause a

variety of waterborne diseases[7]. The traditional method for detecting pathogens in water is mainly plate culture[8], but this method is time-consuming, costly, complex, professional, and power-consuming, and can not meet the needs of water quality detection. For decades, nucleic acid amplification testing has revolutionized the field of biological detection, offering greater possibilities for new diagnostics that are highly specific, efficient, and cost-effective. Nucleic acid detection technology (NAAT) is the main method used to analyze and detect pathogens, such as polymerase chain reaction (PCR), rolling ring amplification (RCA), loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), CRISPR-related amplification, etc. NAAT is widely used in clinical settings to detect a variety of infectious agents, including viruses, bacteria, and parasites. Nucleic acid amplification techniques (NAATs) are essential molecular tools in achieving high sensitivity and specificity in bio-detection[9]. NAAT amplifies nucleic acids through a variety of advanced amplification techniques to detect specific sequences of DNA or RNA[10]. Real-time reverse transcription polymerase chain reaction (RT-qPCR) is one of the most commonly used NAATs, with high sensitivity and specificity. However, traditional PCR takes a long time from sampling to detection completion. If the sampling site is far from the detection site, it will take even longer to obtain results. In addition, the qPCR instrument has high power consumption, high price, poor portability, complex structure, and the need for professional operation. Not suitable for remote areas and areas with limited resources. Isothermal amplification is an alternative method for nucleic acid detection. Unlike PCR, LAMP only requires a constant temperature, which reduces the skill and complexity of the instrument. Although the isothermal amplification method is faster than general PCR, has strong specificity, and high sensitivity, and is easier to adapt to the needs of POC testing than PCR, the detection instruments used now cannot adapt to various sudden situations due to its shortcomings of large volume, high cost and poor portability, and cannot achieve instant water detection and temporary detection. To improve the efficiency of detection, analysis, and detection of pathogenic microorganisms in water, and reduce water-borne diseases that seriously endanger human beings and other life in the world today, fast, low-cost, portable, and specific detection equipment is urgently needed. Nucleic acid amplification assay technology is very suitable. In general, equipment using nucleic acid amplification detection technology will use some heat cycling devices as a heating source. The miniaturization of these thermal cycling devices offers the possibility of using a wider variety of options and is key to the miniaturization of testing equipment. Previous work on miniaturized nucleic acid detection equipment has used a variety of heating devices, which are divided into contact heaters (Peltier elements, thin film resistors, cartridge heaters) and non-contact heaters (light-assisted heating (infrared, laser, LED, and solar thermal), microwave heating, induction heating) depending on whether the heating source is in contact with the sample. Based on the heaters used in the miniaturized nucleic acid detection equipment mentioned above, we have organized the small nucleic acid detection equipment used for molecular diagnosis and pathogen testing in recent years. The types of heaters used in miniaturized nucleic acid detection equipment are introduced in detail. The development of these small heaters raises the possibility of miniaturization of pathogen detection equipment. These miniaturized devices are highly portable and of great significance to the water quality testing industry and have great potential for the prevention and diagnosis of water-borne diseases in the future.

2. Testing equipment that uses a heater as a heating source when in contact

Today, most commercial PCR systems rely on Peltier elements for heating. Although their power is high and their efficiency is low, Peltier-based devices offer design simplicity for heating and cooling under the right heat sink. Khandurina et al. proposed a PCR system using double Peltier thermoelectric elements as heat sources to achieve efficient amplification[11].

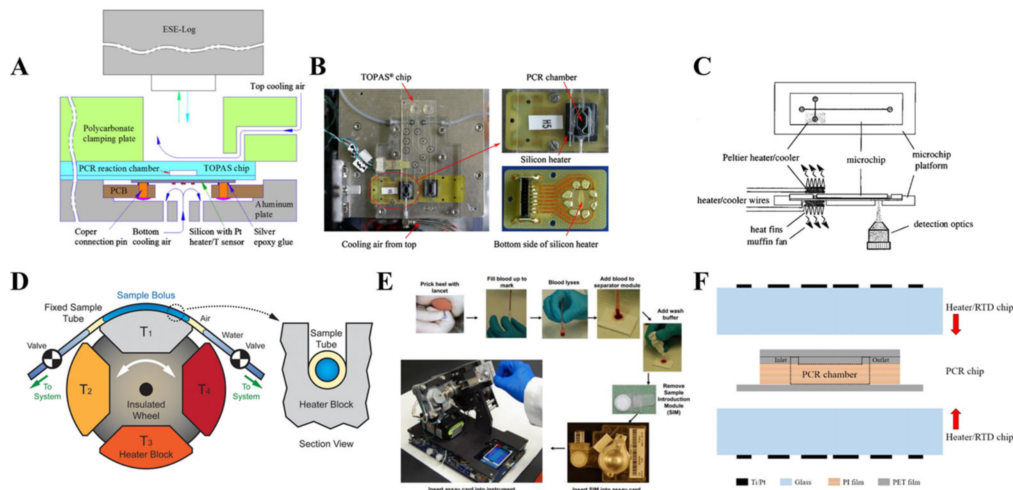

Fig. 1. (A) Illustration of a thermal cycler based on a silicon heater. (B) Physical diagram of thermal circulator based on silicon heater. (C) Schematic of the dual Peltier assembly for rapid thermal cycling followed by electrophoretic analysis on-chip. (D) Functional schematic of the RZTC wheel. (E) Schematic of the workflow of the card-box-based portable PCR. (F) Double film sandwich structure.

Bartsch proposed a rotating zone thermal cycler (RZTC) that uses four different temperature thermal conductances to heat micro-upgraded samples in a capillary tube. The capillary tube can be stopped in four different temperature ranges by driving the motor to achieve fast temperature cycling[12]. Jangam et al. propose a card-box-based portable PCR that uses two thermoelectric modules as heaters and a centrifugal blower for heat dissipation. The system achieved 6.3 °C/s heating and 315 °C/s cooling for a 9 μL reaction[13]. Jeong et al. developed a portable thermal cycler using two small thermal mass diamond-shaped film Pt heaters placed on the top and bottom of a PCR chip. Double-row low-power blowers are introduced to dissipate heat. The device completes 50 cycles in 30 min and can quickly detect pathogens in the field[14]. Bu et al. developed a silicon heater that integrates a platinum film resistance heater and a temperature sensor, capable of completing 20 cycles in 30 min[15].

3. Testing equipment that uses a heater as a heating source when in non-contact

The non-contact heater does not come into direct contact with the sample when providing reaction conditions as a heating source, thus reducing the risk of cross-infection of the sample. In addition, the non-contact heater increases the rate of temperature change, shortens the reaction time, and improves efficiency.

3.1 Portable inspection equipment using light-assisted heating

In recent years, many innovative designs have adopted light-assisted heating methods[16]. Infrared (IR) is the most common and widely used method in photo-assisted heating[17]. The wavelengths used in infrared can be activated and reach the operating temperature in a matter of seconds, without the need to heat an intermediate medium, such as air, to quickly reach the sample surface. In addition, infrared heating can overcome the influence of irregular surface shape on heat transfer, so that the sample is heated evenly. In 1998, Oda et al. used a tungsten lamp as an IR radiation source to take effective thermocycling, which allowed for rapid temperature to get an average cycle time of 17.0 ± 0.4 s[18]. The device can perform PCR amplification of genomic DNA in microliter samples, which can be easily controlled with precision due to the easy adjustment of power consumption. In 2004, Ke et al. used a halogen tungsten lamp as a heating source to rapidly heat the DNA of Mycobacterium tuberculosis in a silicon microreactor. The device uses the LabVIEW control program to adjust the

voltage applied to the lamp for precise temperature control[19]. Terazono et al. reported for the first time a real-time fluorescent quantitative PCR system using an infrared laser beam as a heating device. The infrared laser can act directly on the sample without transferring heat to the surrounding environment. The system uses an infrared laser at 1480 nm and can achieve a variable temperature speed of 32 K/s[20]. Hettiarachchi et al. created an oil petri dish platform that uses a low-power (20-40 mW) infrared (IR) laser to illuminate nanoliter droplets at 1,460 nm for rapid heating and cooling. The simplicity of the platform provides a simple and efficient tool for DNA analysis of living cells and can be integrated with other microfluidic techniques for complex and large-scale detection[21]. The Erickson group at Cornell University describes a portable device for the quantification of isothermal nucleic acids heated by multiple energy sources. It can be heated by sunlight, flame, or electricity, as a phase change material (PCM) is inserted between the device's two insulated cylinders to absorb and release the latent heat generated by sunlight, ensuring a constant temperature after the LAMP's melting stage of 68 °C. TINY makes use of readily available and inexpensive consumables to facilitate field use. By testing KSHV DNA in human skin samples from Uganda, the TINY-qPCR agreement was 67/71 (94%) across all patients, demonstrating that the device is suitable for use in resource-limited Settings[22].

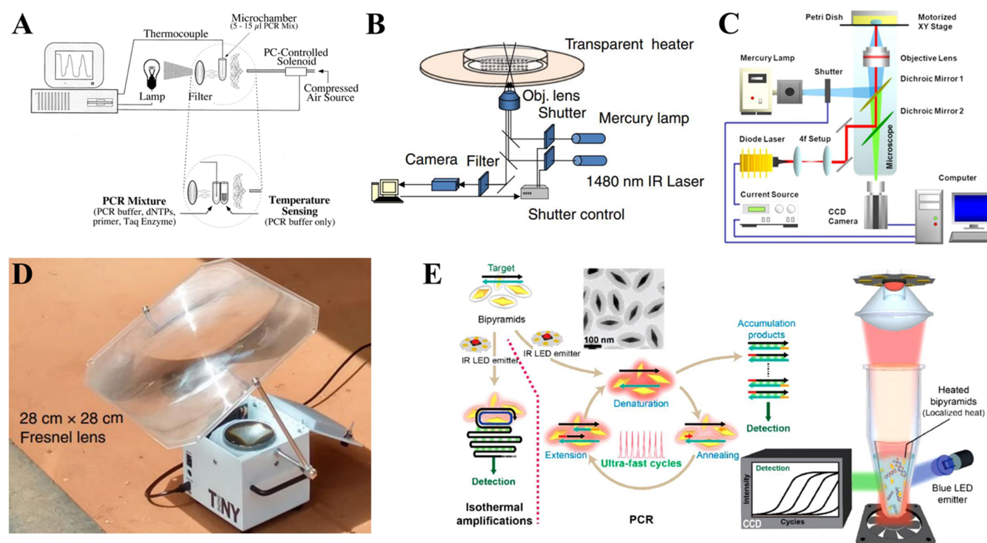

Fig. 2. (A) Infrared tungsten lamp mediated thermal cycling instrument. (B) 1480nm infrared laser-mediated detection device. (C) LabVIEW computer-controlled optical PCR instrument. (D) A portable nucleic acid quantification device driven by sunlight, flame, or electricity. (E) PPT-based NAAs schemes and Scheme of LED-assisted PPT device using PEG-Si-AuBPs.

In recent years, people have been trying to take advantage of the advantages of gold nanoparticles, using pulsed or continuous wave laser excitation for rapid PCR. In 2015, Son et al. developed a novel ultrafine photon PCR for light-emitting diodes (LED) as heating devices, using a thin gold (Au) film to improve the efficiency of photothermal conversion. Through the gold plasma-assisted absorption of light energy, 30 thermal cycles were achieved in 55 min, and the heating rate and nuclear cooling rate were 12.79 ± 0.93 °C/s and 6.6 ± 0.29 °C/s. The device uses LED as an inexpensive heating source that uses lens focusing to excite light, an ideal PCR heat source for POC testing[23]. Lee et al. developed a real-time quantitative device for light-driven photothermal heating of gold double-cone nanoparticles (AuBPs), called PPT-NAA. Using infrared light-emitting diodes (IR-LED) as heat sources, AuBPs can allow specific light excitation and heat release and ensure precise and uniform heating[24]. Kang et al. designed and developed a vacuum-driven PF-PCR chip that utilizes an LED as a heating source, assisted by an array of glass nanocolumns from the Gold Nanoisland, for efficient thermal cycling. The chip has a small size, few samples, and high specific surface area, and achieves rapid temperature change. The chip takes lambda-DNA as a sample and can be rapidly amplified within 264s, which can provide rapid, point-of-care molecular diagnostics[25].

3.2 Portable inspection equipment using microwave heating

Microwave energy has been used for decades to rapidly heat food and drinks. However, it is only recently that microwave energy has been applied to microfluidic systems to heat solutions in reaction chambers[26]. microwave heating can directly heat the PCR solution with a high transmission efficiency (up to 95 %) and a uniform heating profile[27]. Fermér et al. used microwave-assisted PCR for the first time, and the time used for microwave heating was only about the same as that used by conventional PCR machines. Microwave direct irradiation reaction liquid, without heating blocks and tubes, improves the heating rate[28]. In contrast, RCA does not require complex temperature control compared with conventional PCR methods, and isothermal conditions are appropriate for controlling microwave heating. In 2006, Yoshimura et al. first reported microwave-assisted RCA using a multimode microwave generator, but with low repeatability[29]. After that, the group developed a novel single-mode resonant cavity microwave generator with a fiber-optic probe to improve accurate temperature measurement and reproducibility[30]. The microwave reaction temperature is strictly controlled using a microwave coater optimized for enzyme-grade reactions.

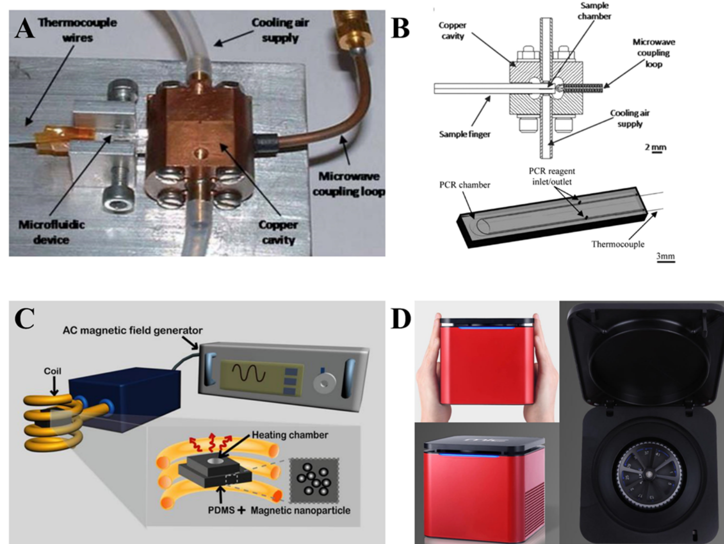

Fig. 3. (A) Schematic diagram of a cylindrical microwave cavity. (B) Cross-section diagram of microwave cavity and schematic diagram of microfluidic device design. (C) Schematic drawing of induction heating based on the magnetic nanoparticle-embedded PDMS (MNP-PDMS) chip. (D) The world's first commercial magnetic induction Cycler.

3.3 Portable inspection equipment using induction heating

Kim et al. embedded magnetic nanoparticles into PDMS (polydimethylsiloxane) as a heating source, and the magnetic nanoparticles generated heat under an alternating magnetic field[31]. The World's First Magnetic Induction Cycler MIC was developed. The Mic real-time PCR cycler uses patented magnetic induction technology to heat and fan-forced air for cooling, it can do 35 cycles in 25 min. The Mic is bundled into a small 2kg cube and can be carried with you[32].

4. Conclusion

In conclusion, this paper reviews recent miniaturized nucleic acid testing devices or methods that can be used for the diagnosis of waterborne diseases. Classified by contact heater and non-contact heater, many small size, low cost, low power consumption, and high portability testing equipment are introduced. In the future, with the development of science and technology and the process of industrialization, there may be more water pollution, to meet the water quality testing

market, it is necessary to develop faster, lower cost, lower power consumption, simple operation and detection equipment that can be used to detect pathogenic microorganisms in water.

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