

## Specific DNA extraction through fluid channels with immobilization of layered double hydroxides on polycarbonate surface

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### ARTICLE INFO

#### Article history:

Received 23 September 2006  
Received in revised form 23 February 2008  
Accepted 25 February 2008  
Available online 4 March 2008

#### Keywords:

Layered double hydroxides  
Lab-on-a-chip  
Nano-extraction  
Fluidic system

### ABSTRACT

The purpose of this study was to immobilize inorganic layered double hydroxides (LDHs) on the polycarbonate (PC) substrate as the media to extract the specific DNA molecules through fluidic system and to enhance the extraction efficiency of specific DNA molecules from extreme low concentration in sample solution. LDH immobilized through solvent swelling and plasma treatment on the polymer surface captured the specific DNA molecules lysed from *Escherichia coli* (*E. coli*) cells as the target DNA molecules with  $2 \times 10^{-4}$  g/l of concentration in sample solution mixed biomacromolecules lysed from human blood. The encapsulated DNA molecules released through dissolve of LDHs by slight acid (pH 4–5) solution then amplified by polymerase chain reaction (PCR) process through the primers for *E. coli* cells. The DNA molecules amplified by PCR process were characterized by gel electrophoresis to recognize the existence of *E. coli* cells. The results show that immobilized LDHs could be regarded as the specific DNA detector in the sample solution mixed biomacromolecules for rapid disease diagnosis through fluidic system to approach the lab-on-a-chip (LOC).

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### 1. Introduction

“Lab-on-a-chip (LOC)” is named for devices that integrate multiple laboratory functions on a single chip within scale of several millimeters or centimeters. The LOC is utilized to analyze the less than microliters of liquid rapidly and precisely. The LOC for DNA detection included DNA extraction, polymerase chain reaction (PCR) and DNA hybridization is designed to integrate the three main steps in a microfluidic chip for automating DNA sample detection. Gene therapy is gaining growing attention for the treatment of genetic deficiencies and life-threatening diseases recently. Originated from microelectronics, it has spread into many other disciplines, such as biology, chemistry, medicine, and therapy for the application of new drugs, clinical disease diagnosis, food security and the chemical industry [1–8]. The DNA-detected chips containing thousands of microscopic DNA probes have been well investigated to analyze multiple genes simultaneously through bio-microelectronic mechanical system in a LOC

[9]. For the efficient introduction of foreign DNA into cells, a carrier system is required. Recently, it has been successfully demonstrated that novel layered double hydroxide (LDH) could form a nanohybrid by intercalating with biomolecular anion such as mononucleotides, DNA [10,11]. LDHs represented by the general formula  $[M_{1-x}^{II}M_x^{III}(\text{OH})_2][A_{x/m}^{m-}n\text{H}_2\text{O}]$  (abbreviated notation  $M_R^{II}M^{III}/A$  with  $R=(1-x)/x$ ), where  $M^{II}$  and  $M^{III}$  are di- and trivalent metal cations, respectively and  $A^{m-}$  is interlayer anion, are entirely degradable at acidic pH [12].

Such biomolecules can be incorporated between hydroxide layers by a simple ion-exchange reaction to form bio-LDH nanohybrids [10]. The negatively charged biomolecules intercalated in the gallery spaces would gain extra stabilization energy due to the electrostatic interaction between cationic brucite layers and anionic biomolecules. The hybridization between cationic layers and anionic biomolecules would greatly enhance the transfer efficiency of biomolecules into mammalian cells or organs. The charge neutralization through hybridization between LDH and DNA would facilitate the penetration of hybrids into cells through endocytosis [13,14], because it greatly reduces the electrostatic repulsive interaction between negatively charged cell membranes and anionic biomolecules during this process. Once bio-LDH hybrids are intro-

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duced into cells, the hydroxide layer in the bio-LDH hybrids would then be removed slowly in the lysosome, where the pH is slightly acidic (pH 4–5), because the hydroxide layers of Mg and Al dissolve in an acidic environment. At the same time, interlayer biomolecules would be partially replaced by other anions in the cell electrolyte in such a way that the encapsulated biomolecules could be released inside a cell from a LDH hybrid. However, the major limiting factor in the development and application of these vectors has poor transfection efficiency due, primarily, to endosomal degradation in the solution. In previous studies, biodegradable organic groups such as pH- or redox-sensitive functions were introduced into cationic lipid/DNA complexes to obtain lipids that allowed eventual accelerated release of DNA from complexes [15]. However, it should be stressed that no particular biodegradable organic group emerges as consistently optimal in the reported studies, and the direct impact of the specific sensitivities of biodegradable groups on transfection efficiency remains generally unconfirmed to date. This observation prompted us to design and formulate LDHs as DNA extractor with immobilization in the polymeric tunnels to capture and release DNA molecules more efficiently from diseased blood through fluidic solution for applying in bio-chip. More precisely, our goal was to explore the possibility of formulating the polymeric tunnel with LDHs that were capable of complete extraction from the flowing solution mixed DNA molecules and macromolecules. Polycarbonate (PC) was utilized to be the substrate to fabricate the trenches on the surface by hot embossing process due to easy methods to manufacture and low price for commercialization [16,17]. In this work, our primary attention was focused on the immobilization of LDH on the surface of trenches fabricated from PC to nano-extract the DNA molecule from the mixed solution with human blood and diseased cells through fluidic system. The DNA molecules extracted from the mixed solution were amplified by PCR to analyze the efficiency of DNA nano-extraction through agarose gel electrophoresis.

## 2. Experimental

The amorphous PC was utilized as the substrate with 30,000 of molecular weight to fabricate the fluidic channels by hot embossing with the fluidic system structure, as shown in Fig. 1. Specimen with the target DNA molecules and the biomolecules lysed from human blood were driven into the channels marked the numbers 2 and 3 in Fig. 1 by air micropump, respectively. The DNA molecules and biomolecules mixed in the helix-like channel marked the number 1 were then driven into the channels marked number 6 for the DNA molecule extraction modulus. The LDHs were immobilized mainly on the channels marked numbers 5 and 6 to extract the specific DNA molecules. The schematic representation in Fig. 2 illustrates the process immobilized the LDHs on the PC substrate to capture and release the DNA molecule through surface treatment. The amorphous PC substrate was immersed in the ethyl acetate (EA), the good solvent to PC, for 1 min to swell PC chains on the surface [18]. The end of PC chains extended into the swell layer caused from the permeation of EA into the PC chains on the surface. After removing the EA from PC substrate, the sample was then subjected to oxygen plasma treatment with inlet mixed gas of 75%  $\text{NH}_3$  and 25%  $\text{O}_2$  for 3 min. The RF power of plasma with 300 W was carried out under the pressure of  $3 \times 10^{-2}$  torr with mixed gas of  $\text{NH}_3$  and  $\text{O}_2$  gas. The remaining ends of PC chains were chemically modified and rendered strongly hydrophilic. The substrate was then coated with various concentrations of LDHs by the spin-coated process of 700 rpm for 30 s, 1500 rpm for 10 s, 2500 rpm for 10 s, and 1000 rpm for 20 s on the channel surface marked number 5 in Fig. 1(b). Due to the hydrogen bonding and polymer entangle-

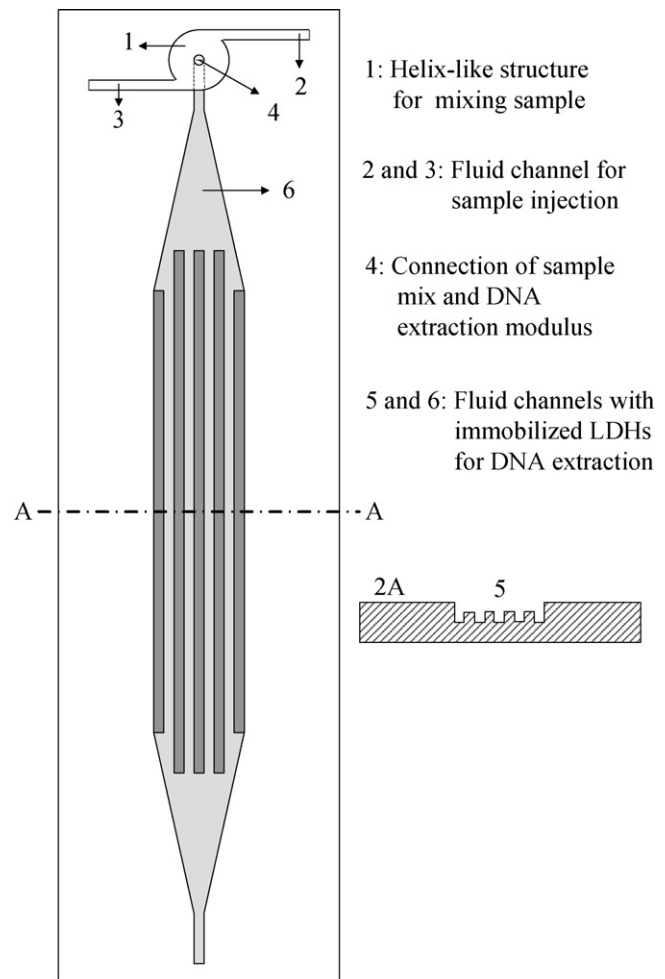
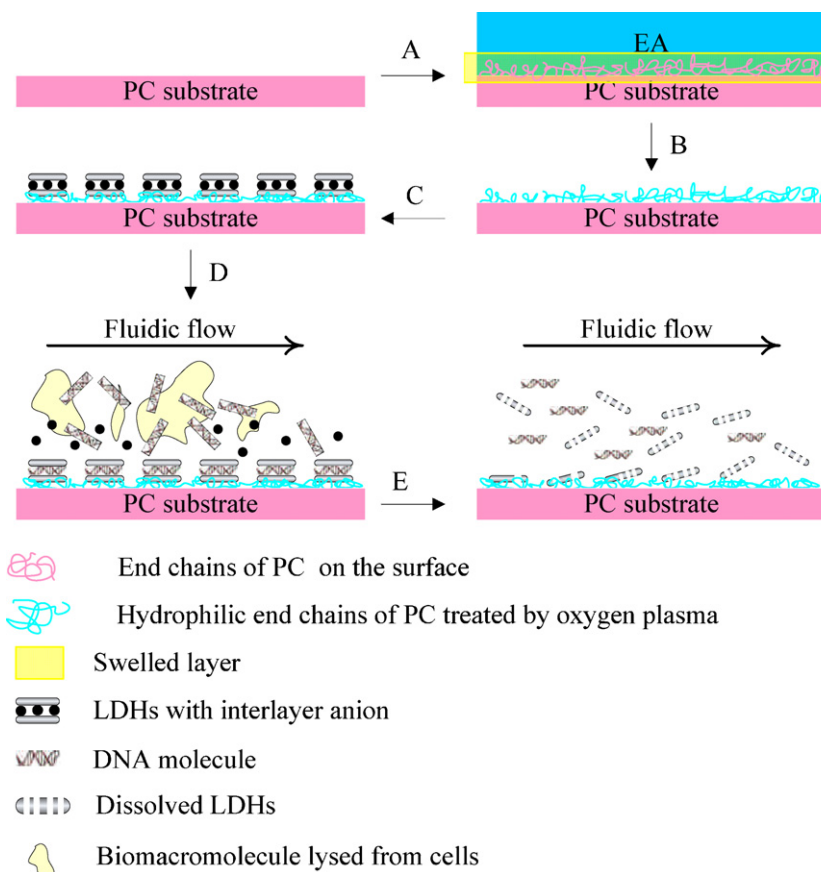


Fig. 1. The structure image of the fluidic system with (a) the helix-like and (b) straight channels immobilized LDHs for extraction of DNA molecules. The helix-like structure at left side was the injected inlet for sample solution.

ment, the LDHs were immobilized rapidly and rigidly by the end chains of PC with strong hydrophilic property after the dehydration of heating process at  $80^\circ\text{C}$  for 30 min. The surface immobilized with LDHs was then cleaned by surfactant solution for LDHs to remove the LDHs without immobilization on the PC surface. One nanogram of target DNA molecules lysed from *Escherichia coli* (*E. coli*) cells for extraction were mixed with  $200\ \mu\text{l}$  human blood and  $100\ \mu\text{l}$  buffer solution utilized to lyse the cells [19]. The sample solution diluted with 5 ml DI water as the sample solution then was driven into the channels marked number 5 in Fig. 1(b). The human blood in mixed solution was designed as the background biomacromolecules for real application of specific DNA molecule detection. The solution with biomacromolecules and DNA molecules from lysed cells was injected into the channel on PC substrate by air micropump for controlling the fluidic velocity and direction. The target DNA molecules from *E. coli* with concentration of  $2 \times 10^{-4}$  g/l were extracted at room temperature for 5 min with forward and backward cycles in the channels marked number 5 in Fig. 1(b). The DNA molecules suspended in the solution mixed biomacromolecules were captured rapidly by LDHs from the fluidic system through anion exchange with interlayer anion for 5 min. The buffer solution was then driven into the channels to wash the channel with LDHs at room temperature for 5 min to remove the unexpected biomacromolecules from the channels of PC to approach the nano-extraction by fluidic system. The LDHs then were removed slowly in the solution with slight



**Fig. 2.** Schematic representation of the process used to immobilize LDHs on the PC surface for extracting the specific DNA molecules from the sample solution mixed biomolecules from lysing cells. (A) The amorphous PC substrate was immersed in the THF to arise the end of PC chains from the surface as the pillar-like structure. (B) Oxygen plasma treatment was used to chemically modify the surface with arisen end of polymer chains to enhance the adhesion between PC surface and LDHs as the THF was removed from the surface. (C) LDHs dispersed in the surfactant solution were spun on the surface treated by oxygen plasma for immobilization by entanglement from the ends of polymer chains. (D) The sample solution mixed target DNA molecules and biomacromolecules lysed from the human blood was injected into the channels for extraction through a simple ion-exchange reaction to form bio-LDH nano-hybrids on the PC surface in fluidic system. (E) The slight acid solution (pH 4–5) was injected into the channels to dissolve LDHs for releasing the encapsulated DNA molecules after the biomacromolecules lysed from human blood were removed from the channels by fluidic system.

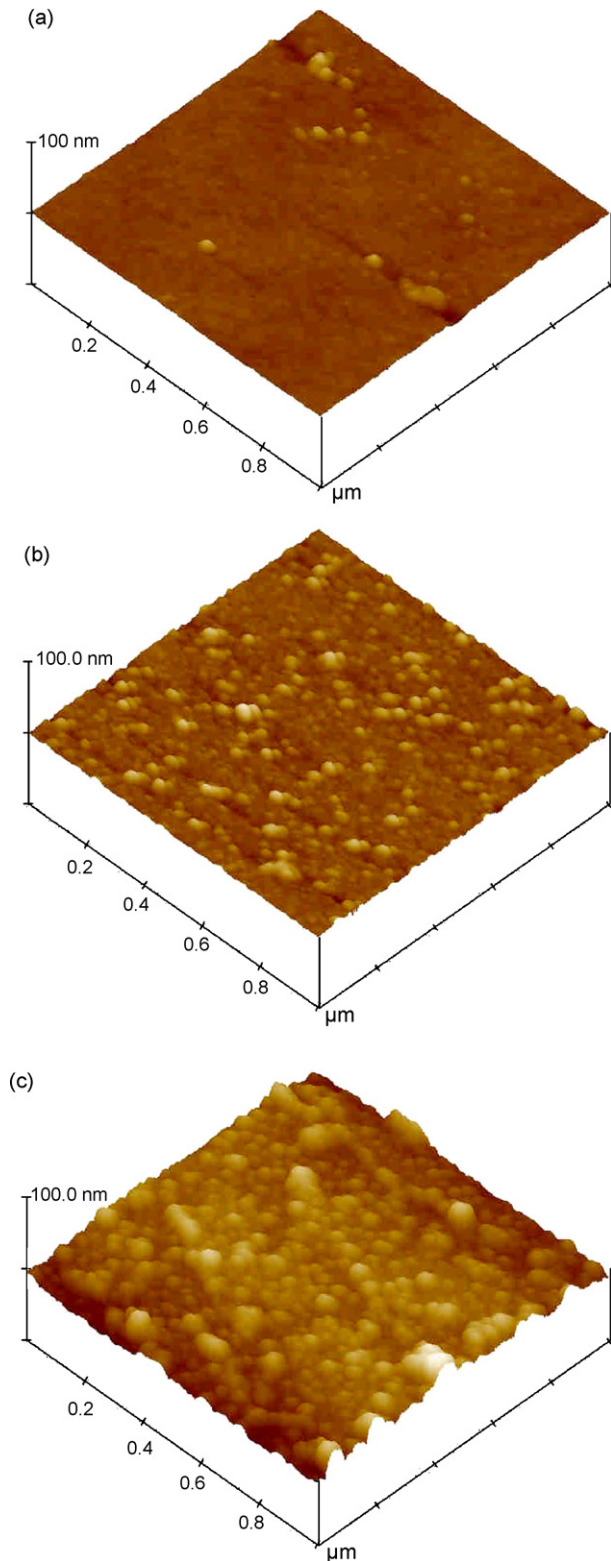
acidic (pH 4–5) because the hydroxide layers of Mg and Al dissolve in an acidic environment, then the encapsulated DNA molecules were released in the fluidic solution. The system was proceeded with the fluidic flow in the channel inside the PC substrate.

PCR was utilized to amplify the target DNA molecules to enhance the quality of the DNA molecules. The forward and reverse primers of the PCR for target DNA molecules were 5'-A-CAGGATTAGATACCCTGGTAG-3'A and 5'-A-TTCCCTACGGTT-ACCTTGTT-3'A, respectively, and the length of the PCR product was 620 bp; PCR (PCR system MJ PTC-100) process conditions were 1 cycle of 5 min at 95 °C, 40 cycles of 30 s at 95 °C, 40 s at 58 °C and 40 s at 72 °C, and 1 cycle of 10 min at 72 °C through specific primer. PCR products with the length of 620 bp corresponded to the amplified 16S rRNA in the DNA fragments of *E. coli* genomic DNA. DNA ladders (SM0633, Taiwan Flow, Taiwan; DM100-2, Bioman, Taiwan) were utilized as the markers in the gel electrophoresis to separate DNA strands by size for qualitative analysis. Finally, quantitative experiments were investigated by an Agilent 2100 bioanalyzer (Agilent Technologies, USA).

### 3. Results and discussion

The morphology of the PC surface treatment by EA swelling was investigated by atom force microscopy as shown in Fig. 3. The amorphous surface of PC substrate without surface treatment

showed the smooth structure with 2.317 nm of the roughness as shown in Fig. 3(a). EA permeated into the amorphous surface to arise the ends of PC chains as the PC substrate immersed in the EA, which increased the roughness from 2.317 nm to 4.1366 nm of the PC surface as shown in Fig. 3(b). The PC surface swelled by EA was chemically modified and rendered strongly hydrophilic or polar by oxygen plasma treatment, causing the increase of roughness with 7.029 as shown in Fig. 3(c). The values of contact angle for the PC surface increased from  $54 \pm 5^\circ$  to  $82 \pm 5^\circ$  after the amorphous surface immersed in EA due to the formation of pillar-like structure. [20,21] The PC surface with pillar-like structure rendered strongly hydrophilic property, causing the value of the contact angle for water was closed to  $0^\circ$ . The morphology of the immobilized LDHs on the channels was shown in Fig. 4 with various concentrations of the LDHs in the mixed surfactant solution, in which the LDHs were dispersed on the straight channel surface. The 5 wt.%, 10 wt.%, 15 wt.% and 20 wt.% of concentration for LDHs coated on the PC substrate aggregated in the range of 20–60  $\mu\text{m}$  feature size due to the aggregation of LDHs in surfactant solution. The feature size of aggregated LDHs was approached 60  $\mu\text{m}$  as the 20 wt.% concentration of LDHs dispersed in the coating solution. The sample solution mixed with specific DNA molecules and biomolecules was flowed into the channels with the immobilized LDHs for specific DNA molecule extraction. The solution sample was driven forward and backward for four

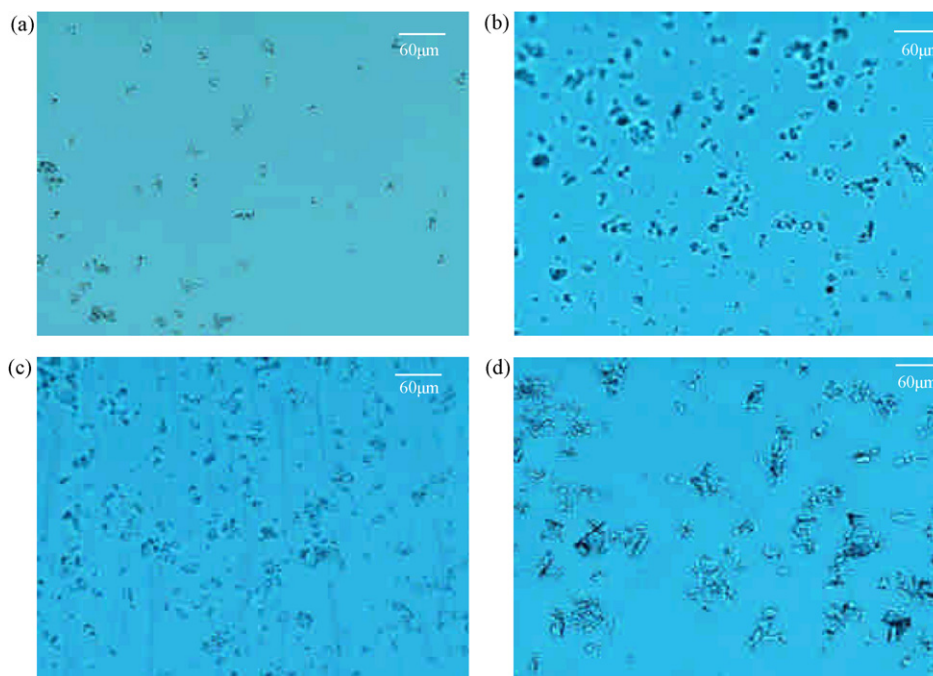


**Fig. 3.** Atom force microscopy images for the amorphous PC surface. (a) Original surface of PC substrate; (b) pillar-like structure arose by solvent (EA); (c) pillar-like structure surface treated by oxygen plasma for 60 s.

cycles in the straight channels to enhance the extracted efficiency due to the extreme low concentration ( $2 \times 10^{-4}$  g/l) of specific DNA molecules in sample solution. LDHs without immobilization aggregately flowed with the biomacromolecules from lysing the cells due to the adhesion caused the reduction of the efficiency for DNA molecule extraction as the LDHs mixed in the sample solution directly. The observation suggests that the immobilized LDHs on the channel surface increased the collision probability between LDHs and specific DNA molecules in the fluidic solution.

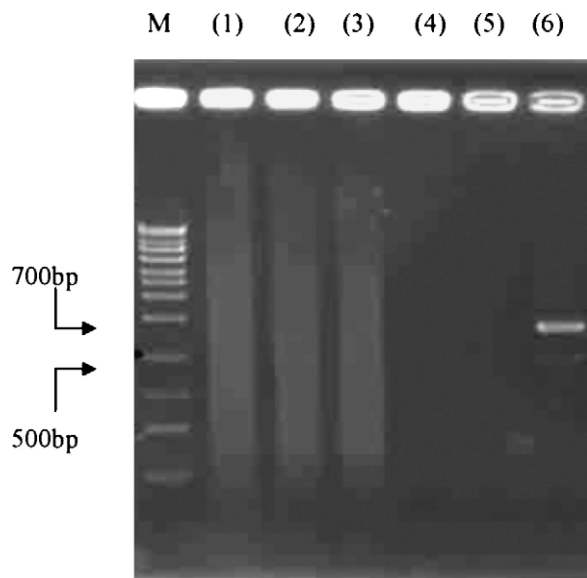
The encapsulated DNA molecules lysed from human blood cells and *E. coli* cells as the target were obtained from the solution by the amplification of PCR process to enhance the quality of target DNA molecule for identification. To investigate the function of immobilized LDHs, LDHs without immobilization on the surface were directly dispersed in the sample solution by mixing surfactant solution as a control experiment as shown in Fig. 5. The marker, lane (M), demonstrated the all well-known DNA molecule data base to compare with the results from other specimens through the agarose gel electrophoresis [22]. The lanes (1)–(3) in Fig. 5 represented the agarose gel electrophoresis diagrams of extracted DNA molecules by the process of LDHs directly dispersing in sample solution mixed with 10 wt.%, 15 wt.% and 20 wt.% of LDHs concentration in the sample solution. The results suggested that the DNA molecules extracted from LDHs without immobilization demonstrated the irregular length of DNA base pair after amplification by PCR process due to the low quality of extraction. Lanes (4) and (5) in Fig. 5 demonstrated the results of amplified DNA molecules extracted by LDHs without immobilization through PCR from the sample solution without target DNA molecules. Lane (6) in Fig. 5 was the standard agarose gel electrophoresis diagram of *E. coli* genomic DNA. The results of specific extracted DNA molecule amplified through PCR process by immobilized LDHs from the sample solution were demonstrated in Fig. 6. The marker, lane (M) in Fig. 5(b), demonstrated the all well-known DNA molecule data base to compare with the results from other specimens through the agarose gel electrophoresis. The lanes (1), (2), (5) and (6) in Fig. 6 represented the agarose gel electrophoresis diagram of specific amplified DNA molecules extracted by 5.0 wt.%, 10.0 wt.%, 15.0 wt.% and 20.0 wt.% of LDHs concentration in surfactant solution to immobilize on the PC surface, respectively. Lanes (3) and (4) in Fig. 6 demonstrated the results of amplified DNA molecules extracted by 10 wt.% and 20 wt.% of LDH concentration from the sample solution without target DNA molecules, respectively. LDHs with immobilization captured DNA molecules lysed from human blood cells and *E. coli* cells, in which the mixed DNA molecules were obtained after LDHs were dissolved by slight acid. The existence for DNA molecules of *E. coli* cells was confirmed by the singularity through amplification by PCR process by the specific primer. The specific DNA molecules released from LDHs with various concentrations in coating solution demonstrated the same result of 620 bp amplified by PCR but different brightness utilized to investigate the efficiency of the extraction. The lanes (5) and (6) in Fig. 6 demonstrated the higher brightness than that of lanes (1) and (2). The observation suggested that the efficiency of extraction increased with the concentration of LDHs from 10 wt.% to 15 wt.% due to the quantity of the specific DNA molecules captured by LDHs. Enlarged aggregation of the LDHs impeded the exchange of interlayer anions with DNA molecules for 20 wt.% of LDHs concentration caused the similar brightness between lane (5) and lane (6) as shown in Fig. 6. The DNA molecules longer than 620 bp obtained from PCR process were the primer or incomplete reacted DNA molecules for PCR process as shown in the end of the lanes in Fig. 6. The DNA molecules captured by immobilized LDHs on the channel surface, which included human and target DNA molecules, were separated previously by the PCR process through primer. Therefore, the exist-



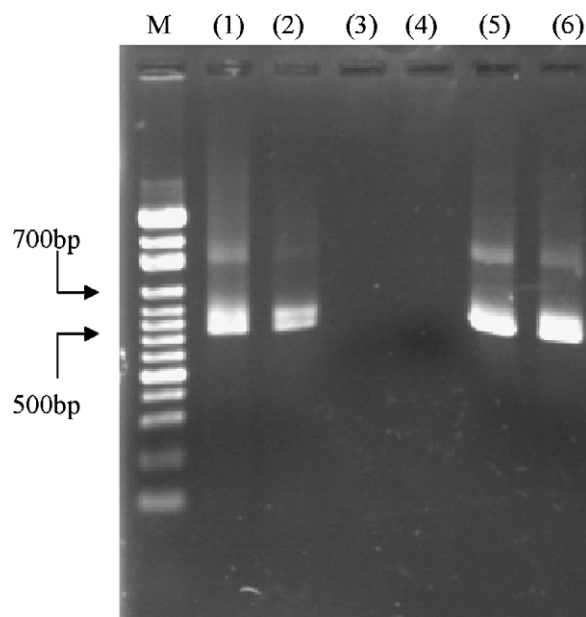


**Fig. 4.** Optical microscope images of the channels immobilized LDHs with (a) 5.0 wt.%, (b) 10.0 wt.%, (c) 15.0 wt.% and (d) 20.0 wt.% of concentration in the surfactant solution on the channel surface of PC surface.

tence of *E. coli* cells could be detected exactly by the fluidic system with the immobilized LDH channels. The LOC system could be approached through the integration of extraction modulus, PCR modulus and DNA probe micro-array modulus in the fluidic system to detect the disease with specific DNA molecules in the blood rapidly.



**Fig. 5.** Agarose gel electrophoresis diagram of the specific DNA molecules of *E. coli*. Cells obtained from the fluid system without immobilized LDHs, which were amplified by PCR process. Lanes (1), (2) and (3) were the agarose gel electrophoresis results obtained from LDHs, which directly mixed with the sample solution with 10 wt.%, 15 wt.% and 20 wt.% of LDHs concentration in the sample solution. Lanes (4) and (5) were the agarose gel electrophoresis results obtained from LDHs, which directly mixed with the sample solution with 15 wt.% and 20 wt.% of LDHs concentration in the sample solution without the specific DNA molecules of *E. coli* cells. Lane (6) was the standard agarose gel electrophoresis diagram of *E. coli* genomic DNA molecules.



**Fig. 6.** Agarose gel electrophoresis diagram of the specific DNA molecules of *E. coli*. Cells obtained from the fluid system with immobilized LDHs, which were amplified by PCR process. Lanes (1), (2), (5) and (6) were the agarose gel electrophoresis results obtained from LDHs with 5 wt.%, 10 wt.%, 15 wt.% and 20 wt.% of LDHs concentration on the channel surface, which extracted the specific DNA molecules from the sample solution with the DNA molecules of *E. coli* cells. Lanes (3) and (4) were the agarose gel electrophoresis results obtained from LDHs with 10 wt.% and 20 wt.% of LDHs concentration on the channel surface, which extracted the specific DNA molecules from the sample solution without the DNA molecules of *E. coli* cells.

#### 4. Conclusion

In conclusion, we have demonstrated a novel strategy for the preparation of immobilized LDHs on the PC substrate for the extraction of specific DNA molecules. The key feature of this approach is

the use of polymer entanglement enhanced by the solvent swelling and plasma treatment to immobilize LDHs on the PC surface but buried LDHs in the PC. The efficiency of encapsulation of DNA molecules reduced as the LDHs buried in PC substrate due to polymer entanglement surrounding. This approach provides an attractive intermolecular force between DNA and the substrate surface for the DNA extraction method based on results from PCR amplification and agarose gel electrophoresis analysis. The LDHs with hydrophilic property adhered with biomacromolecules as the LDHs suspended in the solution caused the increase of difficulty of separation between LDHs and biomacromolecules for the extraction of DNA molecules. The efficiency was enhanced by immobilized LDHs on the PC substrate to extract the specific DNA molecules from the biomolecule solution. The immobilized LDHs on the surface of channels captured the specific DNA molecules from  $2 \times 10^{-4}$  g/l of concentration in sample solution through fluidic system and release the DNA molecules in slight acidic. The results obtained from agarose gel electrophoresis suggest that the immobilized LDHs on the surface could be regarded as the rapid detector for specific DNA molecule in the human blood by one droplet human blood to approach the LOC system. The brightness in the gel electrophoresis test indicates that the concentration of LDHs above 15 wt.% demonstrated the higher efficiency to amplify the specific DNA molecules for detecting previously. This study provides a practical and an efficient method for LOC to be more realistic.

### Acknowledgement

The authors would like to thank the National Science Council of the Republic of China for financially supporting this research.

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