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Paper Diagnostic for Instantaneous Blood Typing

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Agglutinated blood transports differently onto paper than stable blood with well dispersed red cells. This difference was investigated to develop instantaneous blood typing tests using specific antibody−antigen interactions to trigger blood agglutination. Two series of experiments were performed. The first related the level of agglutination and the fluidic properties of blood on its transport in paper. Blood samples were mixed at different ratios with specific and nonspecific antibodies; a droplet of each mixture was deposited onto a filter paper strip, and the kinetics of wicking and red cell separation were measured. Agglutinated blood phase separated, with the red blood cells (RBC) forming a distinct spot upon contact with paper while the plasma wicked; in contrast, stable blood suspensions wicked uniformly. The second study analyzed the wicking and the chromatographic separation of droplets of blood deposited onto paper strips pretreated with specific and nonspecific antibodies. Drastic differences in transport occurred. Blood agglutinated by interaction with one of its specific antibodies phase separated, causing a chromatographic separation. The red cells wicked very little while the plasma wicked at a faster rate than the original blood sample. Blood agglutination and wicking in paper followed the concepts of colloids chemistry. The immunoglobin M antibodies agglutinated the red blood cells by polymer bridging, upon selective adsorption on the specific antigen at their surface. The transport kinetics was viscosity controlled, with the viscosity of red cells drastically increasing upon blood agglutination. Three arm prototypes were investigated for single-step blood typing.

Detecting blood type (ABO) is critical for many medical procedures. Different blood typing techniques are available: gel column,[1−3] thin-layer chromatography (TLC)−immunostaining,[4] fiber optic-microfluidic device,[5] spin tube method,[2] etc. Among those, the identification and automation of red blood cell (RBC) agglutination by antigen−antibody interaction often requires optical or microfluidic analytical instruments not available in many parts of the world.[6−11] Cheap paper based diagnostics offer an attractive alternative. We have observed that the transport of blood in a porous media such as paper widely varies whether its red cells are agglutinated or not. This study explores this observation for developing low cost paper based tests for blood typing.

Blood is essential for sustaining living tissue by supplying oxygen and other soluble nutrients to provide immune protection and metabolic turnover.[12] Blood is a concentrated stable colloid suspension made of red blood cells (erythrocytes, 4−6 million cells/mL, 6−8 μm), white cells (leukocytes, 4000−6000 cells/mL, 10−21 μm), and platelets (150 000−400 000 cells/mL, 2−5 μm) dispersed in an aqueous solution (plasma) containing a host of biomolecules (albumins, fatty acids, hormones).[13−16] Some of these biomolecules, such as the glycoproteins and carbohydrates, responsible for blood type and tissue immunity (antigens), are directly adsorbed onto the surface of the blood cells.[17] Common portable testing methods for blood include analysis of glucose content, cholesterol, metabolic panel (sodium, potassium, bicarbonate, blood urea nitrogen, magnesium, creatine, calcium, triglycerides), microbial and disease markers, and protein molecular profile (liver, prostate).[14] Surprisingly, there are no robust and convenient low cost disposable tests available for "on the spot"

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analysis of blood type. Blood samples are typically outsourced to an analytical laboratory. Reliable tests to instantaneously provide critical blood analysis, without requiring sophisticated laboratory analytical instrumentation such as chromatographic and spectroscopic methods, would be invaluable for improving health in developing countries. Blood analysis is also important in veterinary medicine, also requiring low cost and versatile devices designed for field use.

This study investigates a blood testing platform based on the principle that red cell agglutination, triggered by specific antigen interaction, drastically decreases blood wicking and transport on paper or chromatographic media. The agglutination process also considerably enhances the chromatographic separation (elution) of the blood components, especially the red cells from the plasma.

EXPERIMENTAL SECTION

Materials. Antibody solutions of red cell antigens A, B, and D (Epiclone Anti-A, Anti-B, and Anti-D) were purchased from CSL, Australia. Anti-A and -B come as blue and yellow color reagents, respectively, and Anti-D is a clear solution. Anti-D can agglutinate any blood (A, B, O) with the rhesus factor (D). These antibodies are made of immunoglobin M (IgM).[18,19] Phosphate buffer saline (PBS) (Invitrogen, Australia) was used as diluent for all antibody solutions. Two millimeter wide paper strips (Whatman filter paper #4) were used as porous substrate for antibody. To measure the wicking distance, 2 mm units were laser printed with a HP LaserJet 4250n on each paper strip. Standard blotting papers (Drink Coster Blotting, 280 g/m^2) were used to remove the excess of antibody solution from the treated paper strips. Reflex paper (Australian Paper, Maryvale, Australia, 80 g/m^2, sized) served as a semihydrophobic surface. Blood samples (AB+, A+, B+, and O+) were collected from adult volunteers (3 males and 2 females) with the help of a professional nurse. Blood samples were kept in a standard plasma separating tube (PST) with lithium heparin as anticoagulant. Preliminary results suggested that the type of anticoagulant (e.g., ethylenediaminetetraacetic acid (EDTA)) has little impact on the paper based blood typing technique. All the antibody and blood samples were stored below 4 °C. Blood samples were used within 5 days. Plastic tubes (Microtubes, 1.7 mL; Axygen, USA) were used to mix the blood with the antibody (200 μL). A calibrated micropipet served to dispense standard (20 μL) droplets on the paper strips.

Methods. *Blood Chromatographic Separation.* Paper strips were soaked into antibody solutions of different concentrations (Anti-A at 1.0×, 0.8×, 0.6×, 0.4×, 0.2×, and 0.0×); PBS was used as diluent (Figure A1 in Supporting Information). Excess antibody was removed from the paper strips with blotting papers. The antibody (Anti-A) active paper strips were then placed on Reflex Paper. Blood droplets of 20 μL were dispensed at the center of the paper strip using a calibrated micropipet. The wicking distance was measured from the center to either direction.

Agglutinated Blood on Paper. Blood samples and antibody solutions were mixed into plastic vials at different ratios (25:75, 50:50, and 75:25) to prepare 200 μL solutions. The plastic vials were manually shaken gently for 20 s and left to rest for 2 to 3 min. The paper strips were soaked into PBS, and the excess PBS was removed with blotting papers. The paper strips were then placed on Reflex Paper. For each different ratio of blood/antibody investigated, 20 μL of the premixed blood/antibody solution was dispensed at the center of a fresh paper strip.

Image Capture and Analysis. The wicking kinetics images were captured using a standard video camera (JVC Camcoder Everio GZ-MG530) and a digital SLR camera (SONY-DSLR-A100) with additional close-up lenses. The video clips were transferred to a computer and converted using Prism Video Converter v 1.27 and VirtualDub-1.8.8 software. The still and video images were analyzed using Image-Pro Plus 5.0 software.

RESULTS

We observed that the transport of blood droplets deposited on paper widely varies whether blood agglutinates or not. This difference was investigated to develop blood typing tests. Two complementary studies are presented. The first aims at quantifying the level of blood agglutination and fluidic properties on its transport in paper. Various blood samples were mixed at different ratios with specific and nonspecific antibodies. A droplet of the mixture was deposited onto a filter paper strip, and the kinetics of wicking and red cell separation were recorded using image analysis. In the second study, specific and nonspecific antibodies were adsorbed onto paper, and a droplet of blood was deposited; the transport by wicking and the chromatographic separation of the blood components on the treated paper were measured.

Transport of Blood/Antibody Solution on Paper. In the first study, B+ blood was mixed at different ratios with solutions of antibody-A and antibody-B. A 20 μL droplet of the mixture was gently deposited in the middle of a paper strip soaked in buffer (PBS), and the blood separation and wicking kinetics were quantified by image analysis. Pictures of the paper strips after 10 min of wicking are presented in Figure 1. A few observations are of interest. The blood B+/antibody-B mixtures undergo phase separation once deposited on paper (Figure 1a); the blood plasma readily wicks paper while the agglutinated red cells do not. The agglutinated red cells show no ability to wick paper; instead, they readily adsorb upon contact with the porous structure of paper, forming a very distinct red dot. The extent of red blood cell (RBC) separation decreases with the increases of blood/antibody ratio. Drastic separation of the RBCs occurs until a ratio of blood/antibody is up to around 50:50. The behavior of blood mixed with a nonspecific antibody on paper widely differs. For mixtures of blood B+/antibody-A deposited on paper (Figure 1b), no separation of red cells from the blood plasma occur and the extent of wicking is mostly independent of the ratio of blood/antibody.

Transport of Blood on Antibody Treated Paper. In the second study, paper strips were impregnated with solutions containing different concentrations of antibody-A. A 20 μL droplet of blood was deposited in the middle of a wet paper strip, and the blood transport and the separation dynamics were measured by image analysis. Two types of blood were investigated: AB+ and B+. The interaction of AB+ and B+ blood droplets with antibody-A treated paper is shown after 10 min in Figure 2a,b, respectively. There are three observations. First, for AB+ blood deposited on antibody-A treated paper, the red blood cells (RBCs) separate from the blood and adsorb on paper while the plasma

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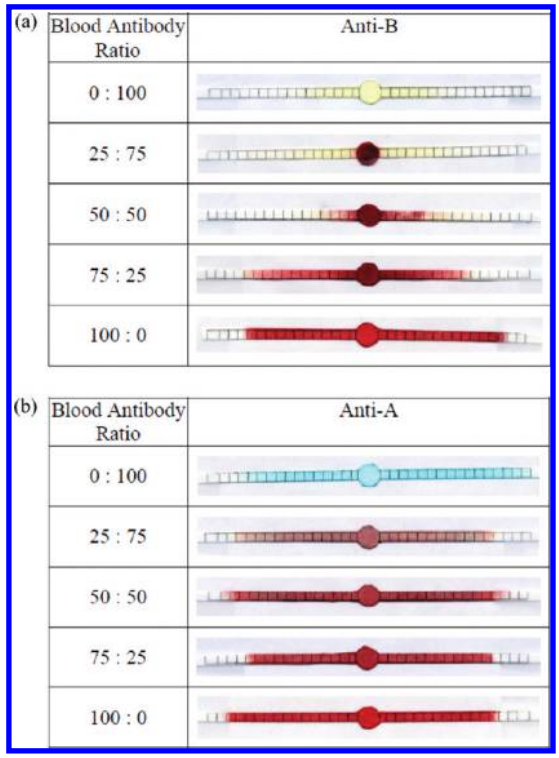

Figure 1. Wicking on paper of blood previously agglutinated from antigen−antibody interaction; (a) B+ blood with (a) specific antibody (Anti-B) and (b) nonspecific antibody (Anti-A).

wicks. The extent of RBC adsorption and, therefore, their reduction in wicking ability tends to increase with the concentration of antibody-A deposited on paper. Second, blood B+ transports differently on antibody-A treated paper; no red blood cell separation from the plasma is observed. However, the extent of blood wicking decreases as the concentration of antibody A on paper increases. This observation suggests that some type of weak nonspecific, nonagglutination related interaction between blood B and antibody A exists. A third observation is that some blood was observed to flow over the layer of blood agglutinated on the paper surface; this is especially prevalent at the center of the paper strip, where the blood is introduced (Figure 2). A fraction of the blood dispensed did not come into contact with the antibody in the first instance of contact and was allowed to flow over a layer of immobilized blood, therefore decreasing the sharpness of detection. A higher paper surface/blood volume ratio is required to minimize this side effect.

The effect of RBC agglutination through specific antibody−antigen interaction on paper wicking can be quantified. In the absence of agglutination, blood wicking on paper showed a faint gradient at the wicking threshold due to some component separated by paper chromatography. When RBC agglutination occurs by antigen−antibody interaction, two distinct layers are formed on paper: RBC and blood plasma. The blood plasma separated from RBC produced a white contrast on the blue paper surface. Figure 3 is a schematic representation of the phenomena with "z_1" defining the wicking length of blood (plasma with red blood cells) and "z_2" defining the wicking distance of plasma (no red cells) .The total wicking length is simply $z = z_1 + z_2$.

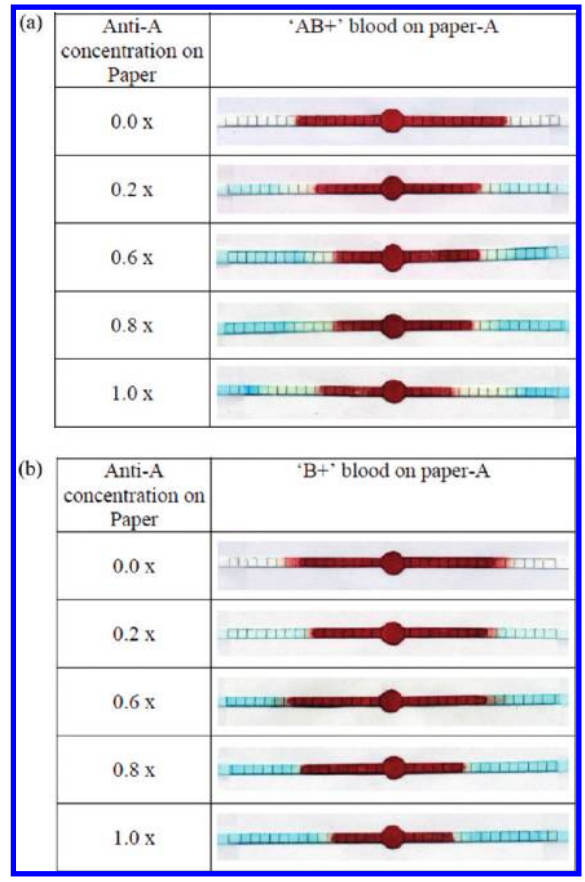

Figure 2. Blood wicking on Anti-A treated paper: 10 min after blood drop dispensing. Sample blood drops (a) AB+ and (b) B+ were dispensed on papers treated with different concentrations of antibody-A. "X" represents the dilution fraction.

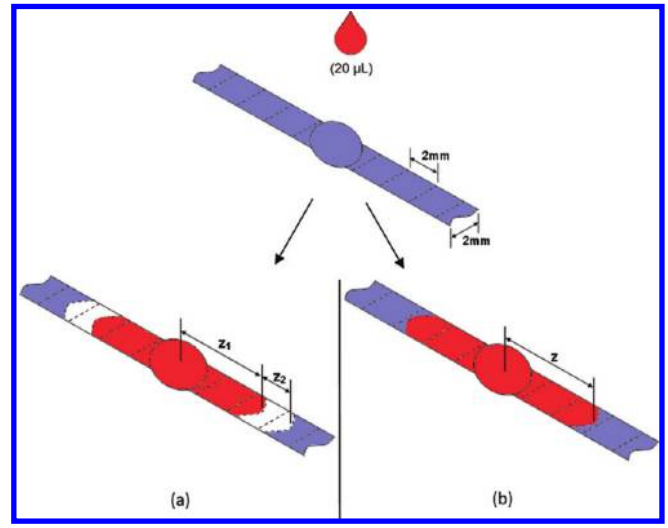

Figure 3. Schematic representation of the wicking of blood on paper treated with a specific and a nonspecific antibody (anti-A). (a) AB+ blood interacts with antibody-A on paper and creates a separate layer of RBC and plasma; (b) B+ blood wicks on paper without any distinctive separation.

The extent of blood wicking as a function of antibody concentration is shown in Figure 4 for paper strips treated with antibody-A. Two types of blood (AB+ and B+) and two wicking periods (4 and 10 min) were compared. Figure 4a,b quantifies the RBC/blood plasma separation for AB+ blood on treated paper

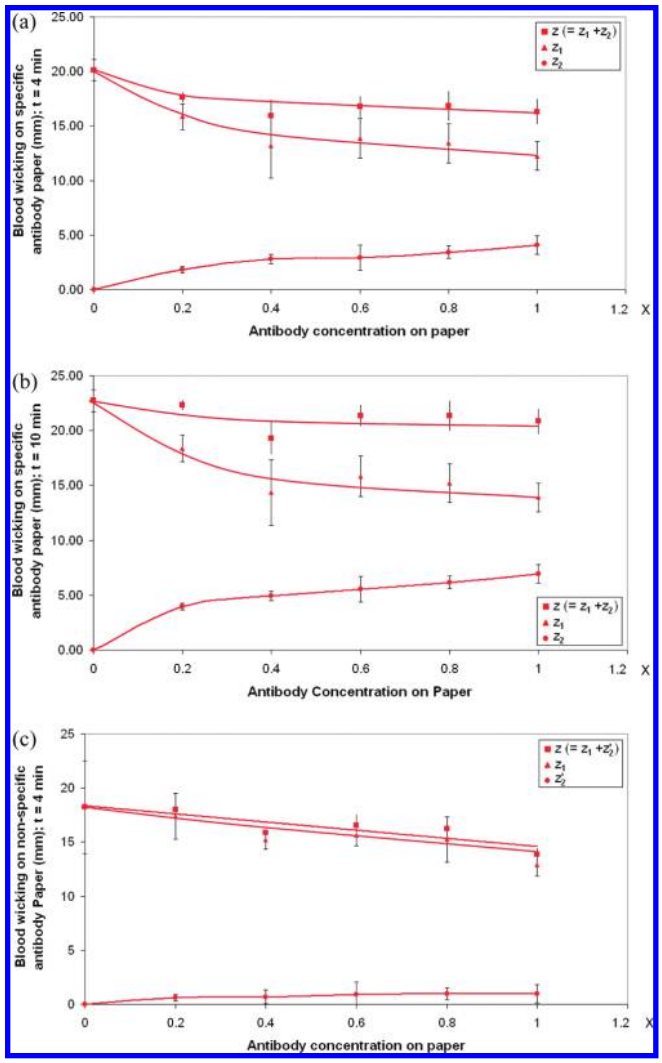

Figure 4. Evolution of blood wicking and separation on paper treated with different concentrations of antibody-A. AB+ blood wicking after (a) 4 min and (b) 10 min; (c) B+ blood wicking after 4 min; $n = 6$. "X" represents the dilution factor.

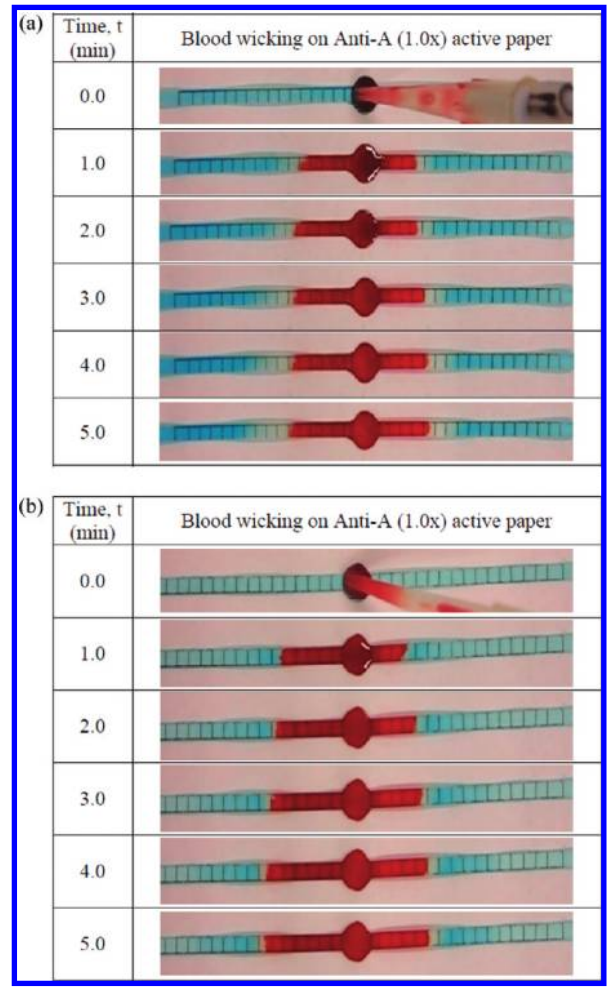

Figure 5. Evolution of blood wicking on antibody-A treated paper strips: (a) AB+ blood; (b) B+ blood.

strips (antibody-A) after 4 and 10 min of wicking, respectively. Six replicates were used, and the average and standard deviations were reported. For AB+ blood on antibody-A treated paper, the total wicking distance (z) after 10 min was found to be a weak function of the antibody concentration. The wicking length of blood with RBC (z_1) gradually decreased as the concentration of antibody on paper increased. Blood plasma, with the red blood cells agglutinated/separated by specific antibody−antigen interaction, traveled longer distances (z_2); this tendency was further accentuated by increasing the antibody concentration on paper (Figure 4a,b). There was not much difference in the blood separation and transport after 4 or 10 min of wicking. Figure 4c quantifies the effect of antibody-A concentration on blood (B+) wicking after 4 min for a nonspecific system. There was virtually no separation of the red blood cells from the plasma ($z = z_1$, $z_2 \approx 0$). The separated layer of blood (z_1) at the wicking threshold was much smaller than that of the specific system (AB+ blood). The total wicking distance (z) for the nonspecific system (B+ blood) was also shorter than for the specific system. Interestingly, the wicking distance decreased as the concentration of nonspecific antibody on paper increased; this may be caused either by some interaction between nonspecific systems or by the antibody adsorption blocking or collapsing some of the pores of the paper structure.

Wicking Kinetics of Blood on Antibody Treated Paper. The transport dynamics of blood droplets deposited on paper strips treated with an antibody was quantified by image analysis. Droplets of two types of blood, AB+ and B+, were deposited on paper strips treated with antibody A (Figure 5). Figure 5a illustrates the evolution of wicking for the AB+ blood, capable of specific antibody−antigen interactions with the treated paper. Two phenomena are observed: wicking and separation of the blood components. The RBC and the blood plasma separated as a function of time or of the extent of wicking. The RBCs rapidly wicked in the first minute to level-off after around 4 min. The blood plasma separated from RBCs wicked for longer periods. Figure 5b illustrates the evolution of B+ blood wicking on the antibody-A treated paper; this system is unable of specific antibody−antigen interactions. Basically, no separation of the RBC from the plasma was observed. The blood wicking was rapid in the first minute and reached saturation after 4 min.

The wicking dynamics of two blood types (AB+ and B+) on antibody-A treated paper was quantified (Figure 6); the average and standard deviations are presented. For the specific antibody−antigen system (blood AB+), the wicking rate of the red blood cells (z_1) on treated paper (antibody-A) drastically slowed down

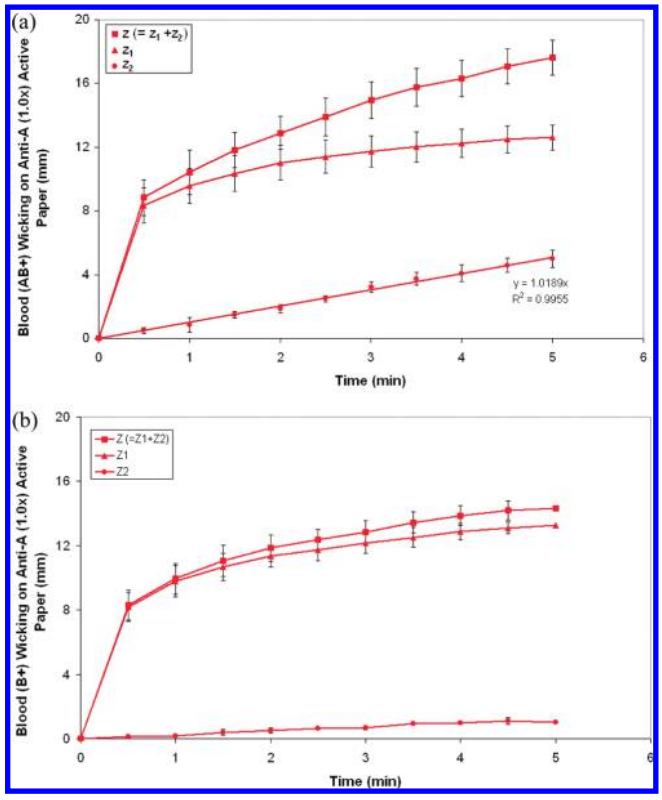

Figure 6. Evolution of the blood wicking and separation as a function of time on paper treated with antibody-A. Two types of blood were treated: (a) AB+ blood and (b) B+ blood; $n = 6$.

after about 2 min and leveled-off thereafter. However, wicking by the plasma fraction (z_2) proceeded at a constant rate of 1.0 mm/min (Figure 6a). Blood wicking (z) on paper for nonspecific antibody−antigen systems was slower (Figure 6b), and basically, no blood phase separation occurred ($z = z_1$, $z_2 \approx 0$).

DISCUSSION

Mechanism of Blood Agglutination. The red blood cells were agglutinated by one of their specific antibodies. From a colloidal perspective, this can proceed by two main mechanisms. The first is polymer bridging, in which a macromolecule of radius of gyration larger than the electrical double layer thickness binds the colloid particles (RBC) into aggregates.[20,21] The second is charge reversal; this involves the surface electrical neutralization by adsorption of oppositely charged small molecules.[22,23] It is of interest to analyze the ability of blood antibody to agglutinate the red blood cells by bridging and charge reversal mechanism.

Blood can simplistically be viewed as a concentrated colloid suspension with its negatively charged red cells electrostatically stabilized in the plasma, a weak aqueous electrolyte continuous phase. The RBCs have an average diameter of 7 μm and bear a moderate negative charge characterized by a zeta potential (ζ) of −15 mV.[24] The concentration of the main electrolytes in blood, sodium (Na), potassium (K), and calcium (Ca), are respectively 140, 5, and 2.5 mmol/L.[25] These electrolytes compress the double electrical layer of the red blood cells, therefore diminishing their stability.

The double layer thickness of the red blood cell in the electrolyte continuous phase can be approximated with the Debye length ($1/\kappa$) where κ is calculated from the diffuse layer thickness using the classical Gouy−Chapman model:[26,27]

$$\kappa = \frac{(2e^2 N_A c z^2)^{1/2}}{\varepsilon k T} \quad (1)$$

where e is the electron charge (1.6×10^{-19}C), N_A is the Avogadro number (6.02×10^{23} 1/mol), c is the electrolyte concentration (mol/m^3) of valency z, ε is the media permittivity (c^2/Jm), k is the Boltzmann constant (1.38×10^{-23} J/K), and T is the temperature (K). Assuming an additive effect of the salts, we calculate at room temperature (25 °C) a double layer thickness of 0.8 nm; for blood samples diluted by a factor of 10 and 100, the double layer thickness is 2.5 and 8 nm, respectively. A bridging molecule usually needs to be at least twice a big as the double electrical layer thickness for efficient coagulation between two colloids.[26]

On the surface of the red blood cells lie antigen molecules able to selectively bind only with their counter antibody. Antibodies are made of five different immunoglobins (Ig), denoted as IgM, IgG, IgA, IgD, and IgE, varying in molecular weight and concentration in the blood[25,28,29] (Table A1 in Supporting Information). Two of these immunoglobins can assemble into bigger units: IgM into a star shape pentamer carrying 10 antigen binding sites and IgA able to dimerize into a linear structure. IgM and IgA can both self-assemble by the base of their heavy chains, leaving their antigen binding sites at the extremities. The diameters of an IgM molecule and a pentamer assembly are 11 and 40 nm, respectively.[30−32] This means that the IgM molecules can easily agglutinate the red cell blood by bridging.

Mechanism of Blood Transport on Paper. The transport of agglutinated blood on paper was found to drastically vary from that of nonagglutinated blood (stable blood). When a droplet of stable blood is deposited onto paper, it wicks as a uniform phase with the red cells well dispersed in the plasma. However, when agglutinated blood is deposited or has been agglutinated on paper, separation of the red cells from the plasma and chromatographic separation occur; wicking of the plasma fraction proceeds at a faster rate than that of the original blood sample.

Blood transports in paper mostly by wicking through the interfiber spaces. The driving force is capillarity driven by the

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difference in surface energy between the fluid and the solid. The resistances are friction and viscous dissipation. In its simplest form, wicking can be described by the liquid flow in a capillary. The Lucas-Washburn equation states that a liquid of viscosity η and surface tension γ will flow in a capillary of radius r and length l at a velocity V defined by:[15]

$$V = \frac{\gamma r \cos \theta_E}{8\eta l} \quad (2)$$

where θ_E is the equilibrium contact angle formed by the fluid on the capillary.

Red blood cell agglutination has two direct effects: a drastic increase in local red cell blood viscosity (η) and the reduction of paper capillary (r); both effects decrease the wicking of the red blood cells according to eq 2. Another effect of RBC agglutination is the separation of the plasma from the blood; this reduces the viscosity of the liquid phase, which contributes to an increase in wicking velocity. Agglutination can affect the surface tension of blood solutions; agglutination of tension active molecules, such as lipids, would increase the surface tension of the solution.

Mixing the antibody solutions at increasing ratios with blood has two main effects. A first effect is to decrease the solution viscosity which increases the wicking velocity (η antibody < η blood). A second effect is to increase the concentration of antibody in solution and also the ratio of antibody/antigen molecules. This affects the kinetics and the extent of blood agglutination. Optimal colloid coagulation by polymer bridging occurs at half surface coverage, when there are as many polymer patches as empty surface patches (homo polymers typically adsorb as monolayers: a polymer patch deposits on a bare surface patch).[26,33] The question of interest regards the concentrations of antibody and antigen. The antibody solutions were used as received, and their concentrations were not measured. However, our observations, by comparing the transport behavior of the same type of blood but from different subjects, suggest that antigen concentration on red blood cells and RBC concentration can both vary from subject to subject. Likewise, similar laboratory observations advocate a variation in concentration among the different types of antibody solution used (A, B, and D). A strategy relying on dilutions was, therefore, adopted in this study to alleviate these issues.

The specific interaction between the antibody solution and the red cell antigen proved very efficient in agglutinating blood, which controls the blood wicking and separation onto paper. All systems (A, B, and D) had different (uncontrolled) ratio antibody/antigen and red cell concentrations, but they all behaved similarly. This suggests a remarkable resiliency for controlled wicking through red cell agglutination. We believe this concept can be generalized for the transport of any stable/coagulated colloids onto porous media.

Small reductions in paper wicking rate were also observed between blood in contact with one of their nonspecific antigens, especially at high antibody concentrations. It is unclear whether the phenomena is attributed to a nonspecific interaction antibody–antigen causing some agglutination, if the antibody solution might have been impure and indeed contain traces of a specific antibody, or if the antibody solution might simply have caused a reduction in the paper capillarity (r).

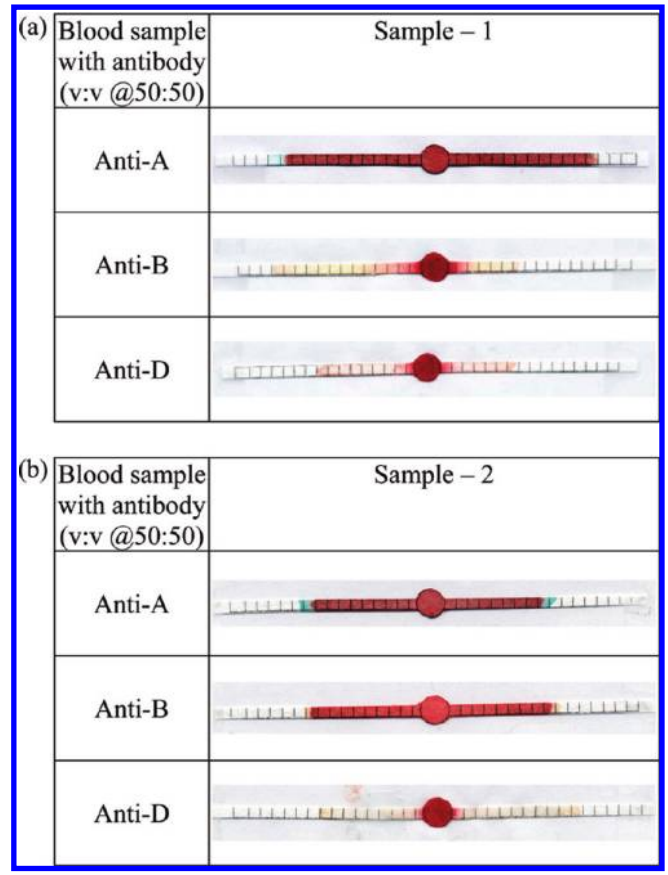

Figure 7. Blood group detection using wicking of agglutinated colloids from specific antigen/antibody interaction on dry paper strips. Blood typing: (a) B+ and (b) O+.

Paper Diagnostic for Blood Typing. Instantaneous paper based blood diagnostics can be engineered from the difference in wicking between a stable and an agglutinated blood sample. Blood agglutination can be triggered by the specific interaction between the antigen naturally present on the surface of the red blood cells and the corresponding antibody immobilized on the paper test.

Figure 7 presents blood typing of unknown blood samples using the wicking behavior of a blood/antibody mixture on paper. In the first example, two blood samples were separately mixed with the three antibody solutions, A, B, and D, in 50:50 volumetric ratios. A 20 μL droplet of each blood/antibody mixture was deposited on a buffer soaked filter paper strip. Clear phase separation resulted for the mixtures of blood sample 1 with antibody-B and -D (Figure 7a), and no separation occurred for the blood sample 1/antibody-A mixture. For blood sample 2, phase separation only happened for the blood/antibody-D mixture (Figure 7b). These observations identify blood samples 1 and 2 to be of type B+ and O+, respectively. The accuracy of the results was confirmed from the volunteers' health records.

An antibody treated paper diagnostic was designed for blood typing. Figure 8 illustrates blood group detection from RBC/plasma separation on the antibody treated paper. Blood wicking was guided through three fluidic channels (2 mm wide and 20

(33) Fleer, G. J.; Stuart, M. A. C.; Scheutjens, J. M. H. M.; Cosgrove, T.; Vincent, B. *Polymers at Interfaces*, 1st ed.; Chapman & Hall: London, 1998. (Reprint).

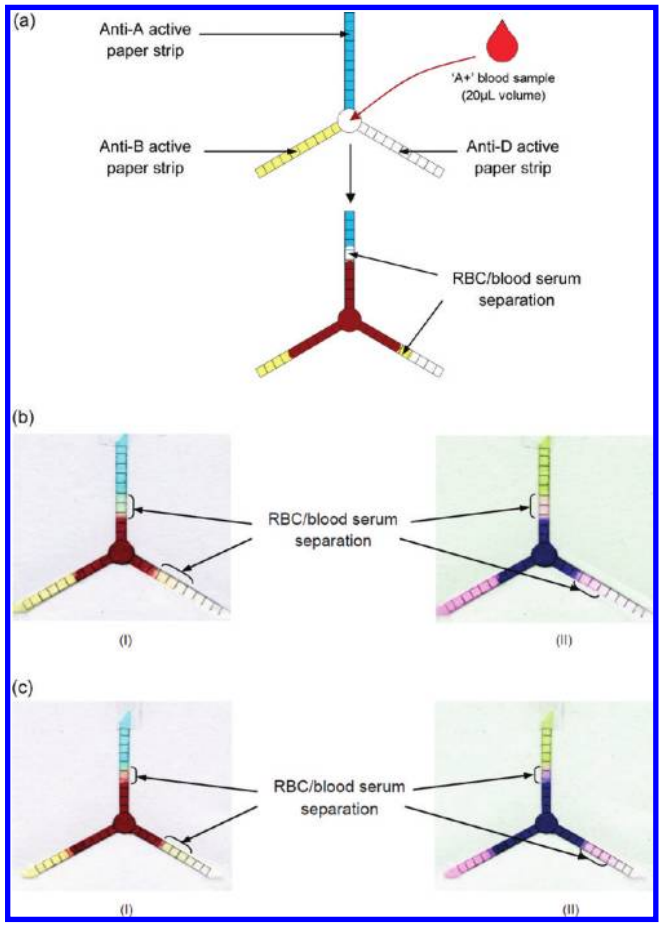

Figure 8. Blood typing relying on RBC/blood plasma separation on antibody treated paper. (a) Schematic of colorimetric indication of phase separation on the paper channels; (b) and (c) are two replicates of same blood sample confirming A+ blood typing. For better resolution, RGB images of b(I) and c(I) are converted into BRG images b(II) and c(II), respectively.

mm long) fabricated from Whatman#4 paper, each treated with a different antibody solution (A, B, D). The diagnostic is used as follows. Upon depositing a 20 μL droplet of the blood sample on the paper strip, clear RBC/blood plasma separation is observed at the wicking front on the fluidic channel(s) treated with one of the antibodies specific to the blood sample. In contrast, no distinct separation occurs on the fluidic channel(s) treated with a nonspecific antibody. Figure 8b,c presents two replicates of the same blood sample. For both trials, RBC/blood plasma separation was observed on the antibody-A and D treated fluidic channels, which confirms A+ blood. To improve resolution, the original RBG (red-blue-green) images (Figure 8b(I),c(I)) were converted to BRG (blue-red-green) images (Figure 8b(II),c(II)).

CONCLUSION

Agglutinated and agglutinating blood transports vary differently onto a porous media, such as paper, than stable blood with well dispersed cells. This concept was explored to engineer paper diagnostics for instantaneous blood typing.

Two series of experiments were performed. In the first, blood samples (A+, B+, AB+, O+) were mixed with different amounts of antibody solutions (A, B, and D), and a droplet of each mixture was deposited onto a filter paper strip. As expected, blood mixed with its corresponding antibody and agglutinated but transported differently in paper than the stable blood solutions (blood mixed with a nonspecific antibody). The agglutinated blood phase separated, with the red blood cells (RBC) forming a distinct spot upon contact with paper, while the plasma wicked; in contrast, the stable blood solutions wicked uniformly. In the second series of experiments, the filter paper strips were pretreated with an antibody solution (A, B, or D) varying in concentration. Droplets of blood were deposited on the antibody-treated paper, and their wicking/transport kinetics was quantified by image analysis. Drastic differences in transport were observed. Blood agglutinated by interaction with one of their specific antibodies phase separated, causing a chromatographic separation. The red blood cells wicked very little while the plasma wicked at a rate of 1 mm/min, faster than the original (stable) blood sample which wicked as a uniform solution. The concept of blood typing using a paper diagnostic was demonstrated with a three arms prototype, each arm treated with a different solution of antibody (A, B, and D).

Blood agglutination and blood wicking in paper follow the concepts of colloids and surface chemistry. The antibodies (IgM) selectively agglutinated the red blood cells (RBC) by polymer bridging upon adsorption on the corresponding RBC antigens. Transport kinetics also follows expectations and is viscosity controlled, with the red cell viscosity increasing by orders of magnitude upon RBC agglutination.

Blood typing paper diagnostics are cheap, biocompatible, and biodegradable. The paper diagnostics manufacturing cost is a few cents/test and can promote health in developing countries. The concept of diagnostics based on differences in wicking and chromatography upon colloids stability/agglutination can be generalized to other blood testing and bioassays. All is needed is the ability to control the stability of a colloid system by selective adsorption or by another mechanism.

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SUPPORTING INFORMATION AVAILABLE

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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