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Comparison of platelet suspension solutions for preserving platelet aggregatory function

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ABSTRACT

Background: Despite wide agreement on various aspects of platelet protocols, such as blood collection, anticoagulants, platelet isolation, and aggregometry, the optimal composition of platelet suspension solutions remains unestablished. Therefore, this study aims to compare five different suspension solutions to determine the most effective one for maintaining platelet function.

Methods: Washed platelets (WP) were prepared using five suspension solutions: two modified versions of Tyrode's buffer (Tyrode A and Tyrode B), Hank's balanced salt solution (HBSS), Hank's minimum essential medium (HMEM), and Leibovitz's L-15 medium (L-15). The solutions were evaluated by monitoring the decline in platelet aggregatory responses over time to assess their ability to preserve platelet function.

Results: Although all preparations showed a decline in thrombin- and collagen-induced aggregations over time, significant differences were observed among the solutions. The ability to preserve platelet function followed this order: Tyrode B > HBSS > Tyrode A ≈ HMEM > L-15. The pH remained stable for up to 8 h in WP prepared with Tyrode A, Tyrode B, and HBSS, while HMEM and L-15 exhibited a slight but significant decrease over time. Phosphatidylserine exposure increased across all WP, with the lowest increase observed in HMEM.

Conclusions: Tyrode B was the most effective for preserving platelet function. These findings offer valuable insights into optimizing platelet suspension solutions, with potential for further improvements.

Keywords: platelets, platelet aggregation, platelet suspension solutions, washed platelets

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INTRODUCTION

Platelets are circulating blood cells commonly used in suspension for in vitro experiments or clinical applications, such as transfusions [1-3]. Conventional media for platelet suspension are blood plasma and buffer solutions. Platelets suspended in plasma are termed platelet-rich plasma (PRP), while washed platelets (WP) are mainly suspended in buffer solutions [3]. Each medium possesses distinct characteristics with specific advantages and disadvantages. Blood plasma is often considered more physiological than inorganic salt solutions [4]. However, certain plasma proteins, such as proteases or glycosidases, along with undefined components, can damage platelet membranes, trigger activation, and cause aggregation [3]. Additionally, plasma used for suspension typically contains lower calcium levels than physiological levels owing to anticoagulants such as citrates and EGTA [4]. Therefore, plasma is not always superior to inorganic salt solutions as platelet media. In contrast, buffer solutions consist of much simpler constituents, including inorganic salts, glucose, and basic proteins such as albumin [3, 5, 6]. Consequently, they lack most of the plasma elements necessary for metabolism and do not support platelet activity for extended periods [3]. However, the simplicity of buffer solutions allows for easier modification and clearer interpretation of experimental results. Furthermore, buffer solutions are free from the potentially harmful effects on platelets that blood plasma might pose. Consequently, buffer solutions and blood plasma are widely used in platelet research, storage, and transfusion [3, 7].

Platelet aggregation testing is widely employed in clinical settings to diagnose congenital platelet function disorders and to evaluate the efficacy of antiplatelet therapies. However, these tests lack absolute diagnos-

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tic criteria and are subject to significant inter-laboratory variability. To address these limitations, clinical and scientific organizations, such as the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, have made ongoing efforts to standardize testing procedures [8]. The methodology for preparing platelet suspensions has been extensively studied and largely standardized. Key aspects, such as the choice of anticoagulants [8, 9], experimental conditions for platelet isolation [8], and platelet storage solutions, are generally agreed upon [10]. However, despite decades of research, no consensus exists on the optimal suspension solutions for platelet function studies. Currently, one of the most commonly used platelet resuspension solutions is Tyrode's buffer [6, 11, 12].

Tyrode's solution was developed in the early 20th century as a modification of Ringer-Locke's solution [13]. Its application in platelet suspension can be traced back to the 1950s [14], and, as far as we are aware, its adoption for platelet function studies became more prominent in the late 1970s and early 1980s [15, 16]. As platelet research advances, modifications to Tyrode's buffer composition are introduced to varying extents. For example, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) was incorporated to stabilize the partial pressure of carbon dioxide and maintain pH [16]. In addition, proteins like albumin were supplemented to reduce cell damage during the preparation of WP by increasing solution viscosity and attenuating physical stress on platelets [17]. Despite this long-standing history, the reasons for the widespread acceptance of Tyrode's buffer have not been critically evaluated in the literature. Most studies refer to it simply as an "iso-osmotic phosphate buffer" [18], without providing a systematic comparison with other potential media. As such, the notion that Tyrode's buffer is optimal for platelet studies appears to be based more on convention and empirical experience than on robust scientific validation. This lack of critical assessment raised a fundamental question on the suitable platelet suspension solutions.

In this study, we evaluated five different suspension solutions to identify the optimal one and provide a basis for further improvement, including two variations of Tyrode's buffer (Tyrode A and Tyrode B) [3, 6], Hank's balanced salt solution (HBSS) [5], Hank's minimum essential medium (HMEM) [19], and Leibovitz's L-15 medium (L-15) [19] (Table 1). Their suitability was assessed based on their ability to preserve platelet aggregatory function, with a focus on mitigating platelet aging, the natural decline in function over time after preparation. Although the exact mechanisms underlying platelet aging still remain unclear, preventing this functional decline can be a key criterion for evaluating suspension solutions.

METHODS

Reagents

HMEM (catalog number 11575), L-15 (catalog number 11415), FITC-conjugated annexin V, and HEPES were obtained from Thermo Fisher Scientific (Waltham, MA, USA). Thrombin and collagen were purchased from Chrono-log (Havertown, PA, USA), and bovine serum albumin (BSA) was obtained from GenDEPOT (Altair, Texas, USA). Trisodium citrate and citric acid were sourced from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals used were of the highest available purity and were purchased from standard suppliers.

Animals

Male Sprague–Dawley rats at 5–6 weeks of age were purchased from Daehan Biolink (Eumseong, Korea). The animals were housed in a specific pathogen-free labora-

Table 1. Formula of suspension solutions[a]

	Tyrode A	Tyrode B	HBSS	HMEM[b]	L-15[c]
NaCl	136.5	134.0	138.0	138.0	138.0
KCl	2.70	2.90	5.33	5.33	5.33
$NaHCO_3$	12.00	12.00	4.17	4.17	–
NaH_2PO_4	0.43	–	–	–	–
Na_2HPO_4	–	0.34	0.34	0.34	1.34
KH_2PO_4	–	–	0.44	0.44	0.44
$MgCl_2$	1.00	1.00	0.49	–	0.99
$MgSO_4$	–	–	0.41	0.81	0.81
$CaCl_2$	2.00	1.00	1.26	1.26	1.26
HEPES	5	10	–	–	–
Glucose	5.55	5.55	5.55	5.55	–
BSA (%)	0.35	0.35	0.35	0.35	0.35
pH	7.40	7.40	7.40	7.26[d]	7.27[d]

[a] All concentrations are presented in mM, except for BSA, which is expressed as a percentage (%). [b] Additionally contains amino acids (L-arginine 0.6, L-cystine 0.1, L-glutamine 2, L-histidine 0.2, L-isoleucine 0.4, L-leucine 0.4, L-lysine 0.4, L-methionine 0.1, L-phenylalanine 0.19, L-threonine 0.4, L-tryptophan 0.05, L-tyrosine 0.2, L-valine 0.39) and vitamins (choline chloride 0.0071, D-calcium pantothenate 0.0021, folic acid 0.0023, i-inositol 0.0111, niacinamide 0.0082, pyridoxine hydrochloride 0.0049, riboflavin 0.0002, thiamine hydrochloride 0.0023). [c] Additionally contains amino acids (glycine 2.67, L-alanine 2.53, L-arginine 2.87, L-asparagine 1.89, L-cystine 1, L-glutamine 2.05, L-histidine 1.61, L-isoleucine 1.91, L-leucine 0.95, L-lysine 0.51, L-methionine 0.5, L-phenylalanine 0.76, L-serine 1.9, L-threonine 2.52, L-tryptophan 0.1, L-tyrosine 1.66, L-valine 0.39), vitamins (choline chloride 0.0071, D-calcium pantothenate 0.0021, folic acid 0.0023, i-inositol 0.0111, niacinamide 0.0082, pyridoxine hydrochloride 0.0049, riboflavin 0.0002, thiamine hydrochloride 0.0023), and other components (D-galactose 5, sodium pyruvate 5). [d] The pH value of media was measured at room temperature and without additional adjustment.

tory facility and acclimated for 1 week before the experiments. The facility was maintained under controlled environmental conditions, with a temperature of 22 ± 3°C, relative humidity of 50 ± 20%, and ambient noise levels < 60 dB. A 12-h light-dark cycle was enforced, with food and water provided ad libitum. All animal experiments were ethically performed following protocols approved by the Institutional Animal Care and Use Committee at Dongguk University (approval number: IACUC-2023-037-1).

Preparation of WP

WP were prepared as previously described [20]. Briefly, blood was collected from the abdominal aorta of rats anesthetized with diethyl ether, using acid–citrate–dextrose (ACD; 85 mM trisodium citrate, 66.6 mM citric acid, and 111 mM glucose) as an anticoagulant (ACD:blood = 1:6). The blood was centrifuged at 250 × g for 15 min to obtain PRP from the supernatant. The PRP was then centrifuged at 500 × g for 10 min, and the resulting platelet pellet was suspended in a washing buffer solution (140 mM NaCl, 10 mM $NaHCO_3$, 2.8 mM KCl, 1 mM $MgCl_2$, 0.5 mM Na_2HPO_4, 0.55 mM glucose, 22 mM trisodium citrate, and 0.35% BSA, pH 6.5). The suspension was aliquoted into tubes and centrifuged at 500 × g for another 10 min. The final platelet pellet was resuspended in suspension buffer solutions or media (Table 1). Platelet counts were measured using a Hemavet 950 hematology analyzer (Drew Scientific, Plantation, FL, USA), and the concentration was adjusted to 2×10^8 platelets/mL.

Analyses of platelet functions and conditions

Platelet aggregation was assessed using a four-channel aggregometer (Chrono-log). WP were left at room temperature for 0, 2, 4, 6, and 8 h. Aggregation was induced using 0.07 U/mL thrombin or 2.5 µg/mL collagen, the minimum concentration required to trigger submaximal aggregation in fresh WP. Agonists were added to WP under continuous stirring at 1,200 rpm and 37°C, following a 3-min pre-incubation on an aggregometer. Changes in light transmission were continuously recorded for up to 10 min, until maximal aggregation was reached. The extent of aggregation was expressed as a percentage of the light transmission relative to a blank containing the corresponding suspension buffer.

Phosphatidylserine (PS) exposure on the platelet surface was assessed using flow cytometry. WP were stained with FITC-conjugated annexin V at a ratio of 5 µL annexin V per 100 µL cell suspension, following the manufacturer's instructions. The incubation was performed at 37°C for 10 min in the dark. After staining, samples were diluted 1:1 with the corresponding suspension buffer and immediately analyzed using a FACSAria III flow cytometer (BD Biosciences, San Diego, CA, USA). Platelets were detected and gated based on forward and side scatter properties on a scatterplot, with FITC fluorescence intensity analyzed using a histogram. For each sample, a total of 10,000 events were acquired and analyzed using FlowJo software version 7.6 (FlowJo, Ashland, OR, USA).

The pH of the platelet suspension was measured using an Orion 3 Star series benchtop pH meter equipped with an Orion 8157BNUMD ROSS Ultra pH/ATC Triode electrode (Thermo Fisher Scientific). The platelet counts were measured at the indicated time points using a Hemavet 950 hematology analyzer.

Statistical analysis

The means ± standard errors of the data were calculated for all the experimental groups. One-way analysis of variance (ANOVA) followed by Dunnett's test was used to determine statistical significance in Figure 1, 3, and 4. For Figure 2, two-way ANOVA followed by Tukey's test was performed. All statistical analyses were conducted using SigmaPlot software version 13 (Systat Software, San Jose, CA, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Changes in pH were monitored in WP over time. In WP prepared with Tyrode's buffers or HBSS, the pH slightly increased or decreased, respectively, over the 8-h period, though these alterations were minimal (Figure 1). In contrast, WP prepared with HMEM or L-15 exhibited a statistically significant pH decrease, starting after 6 h or 4 h, respectively. The pH of suspension solutions without platelets remained stable for 8 h, suggesting that the pH decline is possibly due to platelet metabolic activity. The initial pH immediately after suspending the platelets differed from the pH of the suspension solutions.

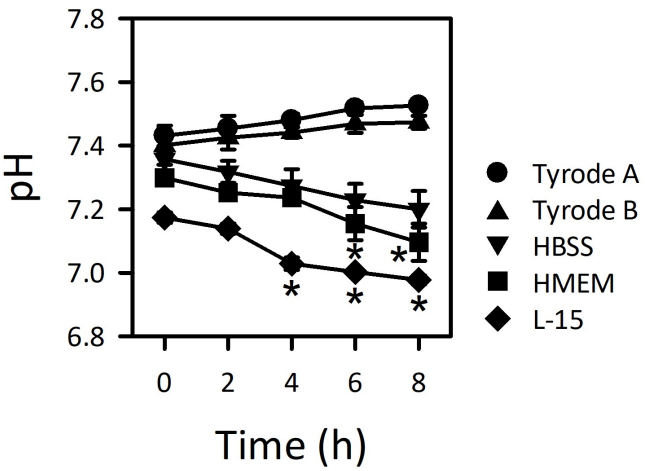

Figure 1. Changes over time in pH of WP

The pH values were measured using a pH meter at each time point. Values are presented as mean ± standard error (n=4). *p<0.05 vs. the initial pH at 0 h.

As is well known, the aggregatory response to thrombin decreased over time in all WP tested (Figure 2A and 2B). The aggregatory response was maintained for at least 4 h in WP prepared with Tyrode's buffer B and HBSS before it started to decline. In contrast, platelets suspended in L-15 medium showed a significant reduction in aggregation after 2 h, dropping from 74 ± 2% at 2 h to 15 ± 8% at 4 h. Platelets suspended in Tyrode's buffer A and HMEM exhibited an intermediate reduction in aggregatory function. Among the suspension buffers, the decrease in aggregation was least pronounced in WP suspended in Tyrode's buffer B at 6 h, while WP prepared with L-15 medium showed the greatest reduction at 4 h. Quite similar tendencies were observed in the responses to collagen (Figure 2C). Overall, the ability to preserve aggregatory function followed this order: Tyrode B > HBSS > Tyrode A ≈ HMEM > L-15.

The quality of platelets was evaluated by measuring PS exposure, a marker of platelet degradation, including senescence, apoptosis, and procoagulant activity. PS exposure gradually increased across all tested WP (Figure 3). This increase was minimal for up to 6 h and statistically significant only after 8 h in WP prepared with HMEM. In contrast, platelets suspended in Tyrode's buffer A and L-15 medium exhibited a significant rise in PS exposure from 4 h, earlier than the other solutions, while those in Tyrode's buffer B and HBSS showed intermediate levels of PS exposure. HMEM was more effective in preserving membrane integrity than others. Platelet counts in WP remained stable throughout (Figure 4), indicating that spontaneous aggregation did not occur or was negligible, with only the functional activity deteriorating during the test period.

DISCUSSION

Platelet suspensions have been widely used in platelet function studies, but standardized composition for suspension solutions remains unestablished. Although there is substantial consensus on protocols for platelet testing such as blood collection, anticoagulation, preparation of PRP, light transmission aggregometry, structural examination using transmission electron microscopy, and data analysis [3, 6, 21], there is little agreement on the optimal composition of platelet suspension solutions. This may be due to the widespread use of PRP in clinical tests, where standardization is critical for diagnostic purposes, whereas academic research allows for more flexibility. Additionally, differing opinions on the optimal suspension solution may hinder the development of universal guidelines. Nevertheless, the use of platelet suspensions in inorganic salt solutions remains essential for platelet storage, transfusion, and research [3, 10, 22], highlighting the need for standardized suspension solutions.

Platelets are highly sensitive to external stressors encountered during experiments, such as changes in pH, temperature, and physical shear stress, which can trigger unwanted activation and aggregation [23-25]. Suspension solutions are crucial in mediating these stresses. Tyrode's buffer, alongside its modified versions, is the most commonly used platelet suspension solution [6, 11, 12], though it may not be fully optimized. In this study, we focused on the ability of suspension solutions to preserve platelet aggregatory function during aging. Given that platelets begin to age once isolated from circulation and aggregation is a core platelet function, maintaining this ability could serve as a criterion for evaluating the suitability of suspension solutions.

Tyrode A and B are modified versions of the original Tyrode's buffer, containing bicarbonate, phosphate, and additional HEPES (Table 1). HBSS contains bicarbonate and phosphate but lacks HEPES, while cell culture media such as HMEM and L-15 include amino acids and vitamins in addition to inorganic salts. HMEM comprises Hanks' salts and uses bicarbonate and phosphate for buffering, while L-15 relies on phosphates and free-base amino acids [19]. The two media maintain pH without the need for CO_2 equilibration, making them suitable for platelet suspension. All of these solutions are viable for platelet suspension, but in this study, Tyrode B was found to be superior among the five media tested (Figure 2).

Tyrode A and B share similar compositions (Table 1), with the primary difference being that Tyrode B contains half the calcium concentration and twice the HEPES concentration of Tyrode A. Additionally, minor variations are seen in the concentrations of sodium chloride, potassium chloride, and phosphate. However, pinpointing the exact factors responsible for the observed differences is challenging, as the roles of calcium and HEPES in maintaining platelet function remain controversial [26-28]. Nonetheless, 1-2 mM calcium is typically used in platelet function studies without issues, and pH differences were not significant (Figure 1), which HEPES primarily regulates. Although considerable effort has been made to optimize each electrolyte concentration, definitive conclusions remain elusive. One challenge in optimization is the difficulty in conducting well-controlled experiments, as altering one component often requires adjustments to others to maintain osmolarity. Thus, optimizing the composition of suspension buffers frequently relies on empirical approaches.

Cell culture media, which contain nutrients including amino acids and vitamins alongside inorganic salts, are designed to mimic body fluids such as blood plasma and may offer a more favorable environment for platelets than inorganic salt solutions. In some studies, cell culture media was tested as platelet suspension solutions

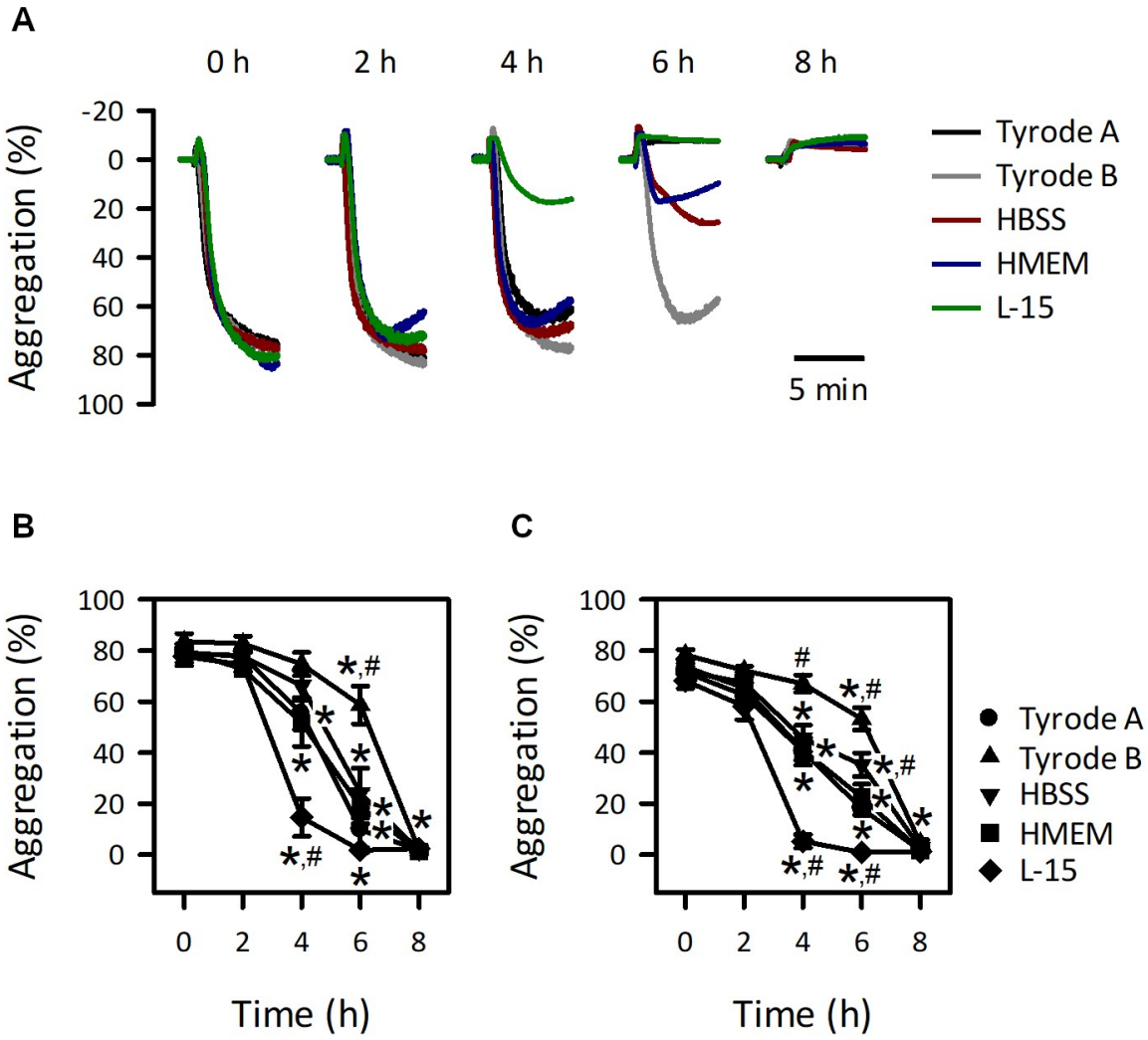

Figure 2. Decrease in platelet aggregatory responses over time in different solutions

Panel A shows representative tracings of thrombin-induced platelet aggregation. Panels B and C present the averaged percentages of aggregation induced by 0.07 U/mL thrombin and 2.5 µg/mL collagen, respectively. Values are expressed as mean ± standard error (n=4). **p*<0.05 vs. the initial aggregation at 0 h, #*p*<0.05 vs. other groups at the same time points.

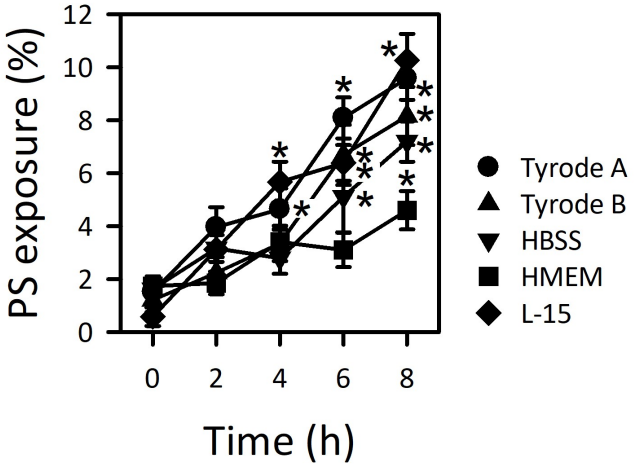

Figure 3. Increase in PS exposure on platelet surface

Values are expressed as mean ± standard error (n=9). **p*<0.05 vs. the initial PS exposure at 0 h.

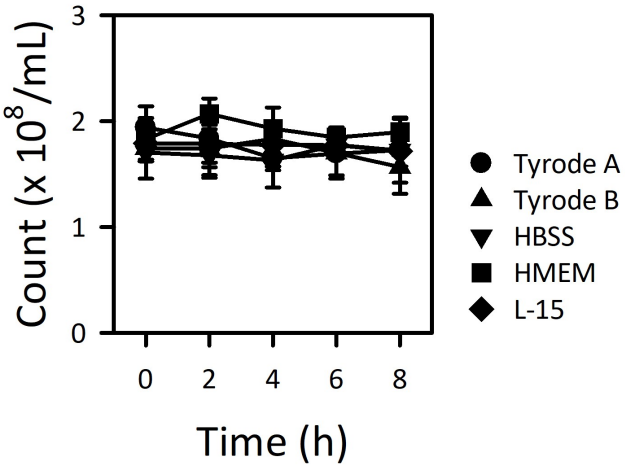

Figure 4. Alteration of platelet concentration in WP

Values are expressed as mean ± standard error (n=3). No statistically significant changes were recorded.

and were effective in preserving platelet aggregation in response to ADP [15]. Accordingly, HMEM and L-15 were selected for testing in this study because they can be used in ambient environments without a CO_2 incubator [19]. HMEM, in particular, was efficient at limiting PS exposure over time, suggesting a favorable environment for platelets. However, cell culture media are not generally used for platelet suspensions, possibly because their primary function is to support cell growth rather than accurately simulate physiological conditions [29]. Considering that platelets are anucleate and do not proliferate [1], many components in cell culture media may be unnecessary or even harmful to platelets. The presence of nutrients could enhance metabolism, resulting in the accumulation of metabolic byproducts and pH changes that impair platelet function [6]. Indeed, we observed significant pH decreases over time with HMEM and L-15, whereas other balanced salt solutions were more resistant to pH alterations (Figure 1). Furthermore, certain components in cell culture media may directly influence platelet function. For example, arginine serves as a substrate for nitric oxide synthesis [30], which plays a vital role in regulating platelet function [31]. Additionally, vitamin E reduces platelet procoagulant activity by inhibiting PS exposure and prothrombinase activity [32]. Despite the potential benefits of adding nutrients in cell culture media, simple inorganic salt solutions have been used to suspend platelets, possibly owing to their low cost, ease of preparation, and convenient pH adjustment. These simpler solutions were sufficient for our purposes in this study. The potential to prevent PS exposure did not directly correlate with the ability to preserve platelet aggregation (Figure 2 and 4), indicating that these two properties reflect different aspects of platelet functionality.

CONCLUSIONS

Tyrode B is the optimal choice for maintaining platelet aggregability among the tested media, though the specific components contributing to its superior performance remain unclear. Our findings suggest that more refined compositions for platelet suspension solutions may exist, with Tyrode's buffer serving as a promising starting solution for further optimization. Additionally, we recommend conducting platelet aggregation studies within 4 h of preparation to minimize artifacts caused by the suspension solutions [33].

ABBREVIATIONS

ACD – acid-citrate-dextrose

ANOVA – analysis of variance

BSA – bovine serum albumin

HBSS – Hank's balanced salt solution

HEPES – 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

HMEM – Hank's minimum essential medium

L-15 – Leibovitz's L-15 medium

PRP – platelet-rich plasma

PS – phosphatidylserine

Tyrode – Tyrode's buffer

WP – washed platelets

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AUTHORS' CONTRIBUTION

WJ: conceptualization, methodology, investigation, formal analysis, visualization, writing- original draft preparation, writing- review and editing

JHK: conceptualization, methodology, investigation, formal analysis, visualization, writing- original draft preparation, writing- review and editing

JMP: methodology, investigation

YSS: methodology, investigation

HJH: methodology, investigation

MYL: conceptualization, writing- original draft preparation, writing- review and editing, supervision, funding acquisition

CONFLICT OF INTEREST

None to declare.

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