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The importance of the simulated wound fluid composition and properties in the determination of the fluid handling performance of wound dressings

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Abstract

Effective fluid handling by wound dressings is crucial in the management of exuding wounds through maintaining a clean, moist environment, facilitating healing by removing excess exudate and promoting tissue regeneration. In this context, the availability of reliable and clinically relevant standardised testing methods for wound dressings are critical for informed decision making by clinicians, healthcare administrators, regulatory/reimbursement bodies and product developers. The widely used standard EN 13726 specifies the use of Solution A, an aqueous protein-free salt solution, for determining fluid-handling capacity (FHC). However, a simulated wound fluid (SWF) with a more complex composition, resembling the protein, salt, and buffer concentrations found in real-world clinical exudate, would provide a more clinically relevant dressing performance assessment. This study compared selected physicochemical parameters of Solution A, an alternative, novel simulated wound fluid (SWF A), and a benchmark reference serum-containing solution (SCS) simulating chronic wound exudate. Additionally, FHC values for eight advanced bordered and non-bordered foam dressings were determined for all three test fluids, following EN 13726. Our findings demonstrate a close resemblance between SWF A and SCS. This study highlights the critical importance

Abbreviations: BSA, bovine serum albumin; FHC, fluid handling capacity; SCS, serum-containing solution; Sol A, Solution A; SWF A, simulated wound fluid A.

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of selecting a physiochemically appropriate test fluid for accurate FHC testing resulting in clinically meaningful evaluation of dressing performance.

KEYWORDS

EN 13726:2023, exudate composition, fluid handling capacity, simulated wound fluid, wound dressings

Key Messages

- Advocate for reliable and clinically relevant standardised testing methods, especially the selection and composition of the test fluid in the context of laboratory evaluation, for example, EN 13726:2023 fluid handling capacity testing.
- The widely used standard EN 13726 specifies the use of Solution A, an aqueous protein-free salt solution, for determining fluid handling capacity (FHC); however, it is argued that a simulated wound fluid (SWF) with a more complex composition, resembling the protein, salt, and buffer concentrations found in real-world clinical exudate, would provide a more clinically relevant assessment of dressing performance.
- This study has compared relevant physicochemical parameters of Solution A, an alternative, novel SWF A, and a benchmark reference serum-containing solution (SCS) simulating a chronic wound exudate, with additional FHC values for eight advanced bordered and non-bordered foam dressings determined for all three test fluids, following EN 13726.
- Our findings demonstrate a close resemblance between SWF A and SCS, both differing in results from Solution A, thus highlighting the critical importance of selecting a physiochemically appropriate test fluid for accurate FHC testing resulting in clinically meaningful evaluation of dressing performance.

1 | INTRODUCTION

1.1 | The need for a clinically relevant simulated wound fluid

When a wound does not follow the normal course of healing within a given timeframe the wound can be left stalled in a state of chronicity, often due to underlying wound pathology.[1] Chronic wounds represent a significant challenge, causing considerable clinical and economic burdens on both individual and societal levels for patients, caregivers, and healthcare systems alike.[2] The delayed healing of chronic wounds can partly be attributed to inadequate management of wound exudate, leading to increased risk of maceration, infection and higher pain levels.[3,4] In the development and assessment of wound dressings capable of handling exudate or discharge effectively, laboratory standardised testing of dressings should be clinically relevant and therefore, performed with clinically appropriate test solutions simulating real-world exudates.[5–7] Therefore, the availability of both robust and clinically relevant standard testing methods is crucial for informed decision making by clinicians, healthcare administrators, regulatory and reimbursement bodies.[6–8] Given the above, in the current work, a standardised formula for a new, robust simulated wound fluid (SWF) termed here 'SWF A' was developed, for use in standardised laboratory evaluations of the fluid handling performance of wound dressings.

1.2 | Simulated wound fluid formulations reported in the literature

It is well established in the literature that maintaining a moist wound environment, as opposed to either wet or dry, promotes the healing process.[6,9,10] Assessing wound dressings to determine whether they provide such balanced moisture conditions, while concomitantly preventing pooling or leakage of wound exudate and minimising

maceration of the peri-wound skin, poses a significant challenge.[6,8] Clinical measurement of the fluid handling performances of wound dressings is complicated and often deemed impractical due to the lack of standardised evaluation methods, and the variability introduced by differences in patients, wounds and care practices.[5] As a result, both industry and academia turn to controlled laboratory tests to assess dressing fluid-handling capabilities.[6,11–13] For these tests to be reliable sources of information for healthcare professionals, administrators, product designers, and regulatory bodies, they must be accessible, robust and reproducible.[5–8,13] Importantly, these laboratory tests should also closely mirror real-world clinical conditions associated with wounds, dressings and healing processes to ensure scientifically sound, clinically relevant, and accurate evaluations of dressing fluid-handling properties.[5,7,8] Consequently, the test fluid must realistically mimic wound exudate for the entire test method to be clinically relevant. Laboratory studies routinely employ the well-established EN 13726 test standard to evaluate dressing performance, including the fluid-handling capacity (FHC) method. The test fluid described in EN 13726 for FHC determination is Solution A, an aqueous salt solution with 142 mmol/L of sodium ions and 2.5 mmol/L of calcium ions as chloride salts.[12] However, as noted above, fluid handling test methods should include a test solution that mimics a biological composition and the resulting physicochemical characteristics of wound exudates.[5,7,14] Specifically, while the standard characterises Solution A as having an ionic concentration similar to that of human serum or wound exudate, it is acknowledged that there are significant differences in composition and physicochemical parameters compared to wound exudates.[5,7,13,15,16] Of note, Annex L of the latest revision of the standard EN 13726:2023 – Test methods for wound dressings – Aspects of absorption, moisture vapor transmission, waterproofness and extensibility, reads '*Laboratories may use other test fluids that simulate wound exudate. The laboratory shall note the alternative fluid as a deviation to the method, and shall include the rationale for selection of that particular fluid*', and also '*The committee encourages investigation and reporting of other potential test fluids to the committee so that these can be considered at the next revision*'.[12]

In the above context, it is important to recognise that Solution A originated in the 1970s,[17,18] well before the widespread adoption of modern spectroscopic techniques and proteomics. During that time, knowledge about wound exudate compositions was in its early stages, however, more recent investigations into the composition and characteristics of wound exudates have provided a more comprehensive insight into the intricate nature of these fluids.[9,15,16,19,20] Wound exudate, fundamentally derived from serum or plasma[1,3,9,21,22] exhibits variations in both appearance and composition based on the aetiology and specific conditions of the wound.[23] Typically, exudate appears pale, straw-coloured and possesses a watery consistency. In the presence of infection, it can undergo discoloration and become more viscous.[1,3,24] Additionally, the presence of bacterial enzymes that degrade biopolymers, such as those from *Staphylococcus aureus* and *Pseudomonas aeruginosa*, can contribute to a thin and watery exudate.[22]

In contrast to human serum, analyses of wound exudate samples have indicated an approximately 50% reduction in protein concentration,[15,16,19,20] with albumin identified as the predominant protein type in both serum and wound exudate.[1,19,25] Furthermore, the concentrations of inorganic electrolytes in wound exudate closely mirror those found in serum.[1,15,16] Cullen and Gefen[1] correspondingly proposed that physiological saline containing albumin should be considered the most basic version of wound fluid for physical fluid handling testing. The understanding that SWF representing the exudate of chronic wounds must not be a pure saline solution, but should exhibit properties of real-world exudates, for example, pH, viscosity, and overall visual appearance, has led to several investigations.[5,14,26–28] In order to create such a standardised test fluid for laboratory performance evaluation with relevant similarities to wound exudates, the biophysical interactions attributed to the biological elements themselves are of interest as included components. Such a formulation will impact the interaction of the test fluid with the tested dressing at all the dimensional scales, rather than phenomenologically representing only the physical and visual aspects.

1.3 | The physical interaction of a test fluid with a tested dressing

The absorbent component of numerous modern wound dressings commonly incorporates a fibrous layer, characterised by intricate fibrous networks. Capillary absorption of fluids within such networks primarily occurs along the open spaces between the fibres. Nevertheless, small quantities of fluid can also be absorbed into the fibre walls. The capillary absorption phenomenon in both the interstitial spaces and the internal regions of the fibres can be effectively represented by employing a simplified circular capillary absorption model.[29,30] Capillary absorption is not limited to fibrous materials but can also occur in hydrophilic foams, which represent an alternative class of materials extensively employed in contemporary wound dressings.[31,32] The capillary absorption model can be described by the Young-Laplace equation, which

indicates the relationship between the fluid and material properties, for example, how the capillary pressure is dependent on the surface tension of the test fluid as well as the contact angle of the test fluid and the capillary surface.[32,33] Yang and colleagues practically formulated this in their work on sorptivity,[34] a measure earlier described by Philip as the extent of a medium to absorb and desorb liquid, primarily by capillary action.[35] Yang showed that this sorptivity depends on the density, surface tension and viscosity of the fluid undergoing the capillary motion, the effective porosity of the dry absorbent material, the average tortuosity factor of the absorbent material, the average pore radius and the contact angle of the interface between the liquid and pore walls. This fundamental research implies that a fluid with a surface tension similar to protein-containing wound exudate is expected to influence absorption and overall fluid handling in a manner comparable to a real wound exudate itself. Conversely, using a protein-free test liquid with a surface tension different from that of native wound exudates, may yield contrasting results and inaccurately represent the wound dressing's ability to handle exudate. Therefore, to enhance the accuracy of wound dressing performance evaluations, it becomes essential to employ a test fluid that accurately mimics the biophysical properties of wound exudates as described in the work by Mennini et al.,[5] Lustig et al.[26] and Gefen et al.[7]

Empirical confirmations of the above theory to the practice of laboratory testing of wound dressings are abundant in the literature. As early as 1998, Sprung et al.[28] demonstrated in an immersion test that absorption characteristics for some wound dressings (hydrogels and hydrocolloids) can be influenced by the choice of test fluid (wound fluid, saline or water). This was also proposed by Mennini et al. (2016) who measured a significant difference in the FHC of a polyurethane-based dressing when using different test liquids (deionised water, Solution A, Gelofusine, whole milk and horse blood).[5] This was further validated by a recent study analysing the absorbency of various wound dressings in different test liquids (water, phosphate buffered saline and SWF based on 50 v/v% foetal bovine serum and 50 v/v% maximum recovery diluent). The investigators showed a significant difference in absorbency between the test liquids for five of the eleven wound dressings tested.[36]

2 | CONSIDERATIONS IN THE DESIGN OF A NEW BIOLOGICALLY BASED SIMULATED WOUND FLUID

The addition of a protein source, such as albumin, to a test solution for fluid handling testing is in agreement with other research that relate to biological fluid–solid interactions and, in particular, protein-surface interactions.[37,38] In the realm of biomaterial and pharmaceutical research, investigations into solid–liquid interfaces extend beyond fluid handling testing. Studies addressing these interfaces also delve into understanding the dynamic behaviour of proteins under diverse environmental conditions. Thus, the role of each specific protein present at the interface between a wound exudate and a wound dressing, will depend on its environment, that is, the physicochemical properties of both the fluid and the absorbent material (e.g., the pH, temperature, ionic strength, surface tension and surface free energy). The environment will hence affect the protein adsorption onto a material and thus, also influence the fluid-material interactions.[37] Consequently, protein adsorption to an absorbent surface will essentially change the surface chemistry and hence influence the wetting, and accordingly, as explained by the Young-Laplace equation and related theoretical work specific to soft, absorbent biomaterials, the change in wetting is related to changes in capillary absorption of fluids.[32,33,37,38]

As noted above, it is not only the source and concentration of a certain protein included in the SWF which is important but also the interface conditions in which it is presented towards the interaction with the absorbent material. For example, the effect of pH on wound healing and indeed on the fluid handling ability of wound dressings is often underrated. However, it is well known that the pH of wound exudate plays a significant role in various biological processes, including wound healing. Both direct and indirect mechanisms have been identified for the role of pH in wound healing.[39,40] The pH of chronic wounds has been reported to range from 7.15 to 8.9.[41] These considerable changes in pH can affect the solubility, activity and physical properties of the proteins present in the exudate, potentially altering the appearance, viscosity and aggregation behaviour of the exudate.[1,7] Likewise, temperatures of chronic wounds also vary,[7,42] which may contribute to further conformational changes of the proteins.[43]

Therefore, in view of the importance of protein and environmental conditions on evaluating fluid handling performance of wound dressings, as well as the fact that wound exudates (patho)physiologically originate from serum, it would seem that the most clinically relevant test fluid would utilise serum. Despite some differences between human, bovine and horse serum, the similarities in biophysical properties outweigh the differences in this context.[44,45] These similarities have led to growing interest in the use of commercially available horse and bovine serum in experimental studies as a substitute for human serum. The use of animal serum in experimental studies

has the potential to increase availability and reduce both ethical and microbiological risks surrounding the use of human serum, as well as offer a more cost-effective and readily available alternative. Specifically, a SCS composed of 50% w/w horse serum and 50% w/w Solution A appears to be a reasonable choice for representing chronic wound exudates and can be considered a benchmark SWF, given that chronic wound exudates contain approximately half the total protein content of serum,[15,16,19,20] but an equivalent concentration of electrolytes.[15,16]

Indeed, biologically based SWF types containing 50% serum from an animal origin, similar to the aforementioned benchmark SCS, are commonly used and considered to be clinically relevant fluids for wound research and performance evaluations,[46–49] but serum extracted from animals may vary in composition, and a more defined composition of SWF is required for standardised testing.

Therefore, a more well-defined composition of SWF than SCS was developed here, to minimise the impact of biological variability across serum types and batches. A review of the literature for details on wound exudate composition[1,15,16,19,20] revealed that the composition and concentrations of proteins, salts, buffers and pH are the most important factors to consider. Since albumin is the most abundant protein in serum and bovine serum albumin (BSA) is used as a protein source in numerous, standardised laboratory and preclinical applications, BSA was selected as the sole protein in the new SWF A. Therefore, BSA is a rational choice, considering its widespread use, but also its availability from many different manufacturers, as well as its relatively low cost; especially in comparison with the cost of care associated with hard-to-heal wounds. A notable limitation related to the selection of the protein is the known, minor molecular and structural differences between mammalian albumin types.[45] Hence, there could be a slight difference between the hydrophobicity of bovine and human albumins, resulting in slight changes in protein material and test fluid interactions, but as human albumin is not a feasible option for routine, robust efficacy research in laboratories, BSA is still a solid choice. A final key consideration in the design of the new SWF A is, that the added BSA must be in its native form (as found in clinical wound exudates). Both protein aggregation behaviour and conformation of the protein is affected by pH levels and salt compositions and concentrations, via the processes known as 'salting in' or 'salting out' (Figure 1), which also is expressed in the Hofmeister series.[46–48] Accordingly, an important design goal for SWF A was to set its total ionic strength and composition to be similar to the total ionic composition of clinically relevant wound fluids, as described in the biochemical analyses reported by Trengove et al.[15] Aiba-Kojima et al. (2007) further support the findings of Trengove by confirming that the concentrations of Na, K, Cl, Ca, and Fe in wound drainage fluid were similar to those found in serum and remain relatively stable over time.[16]

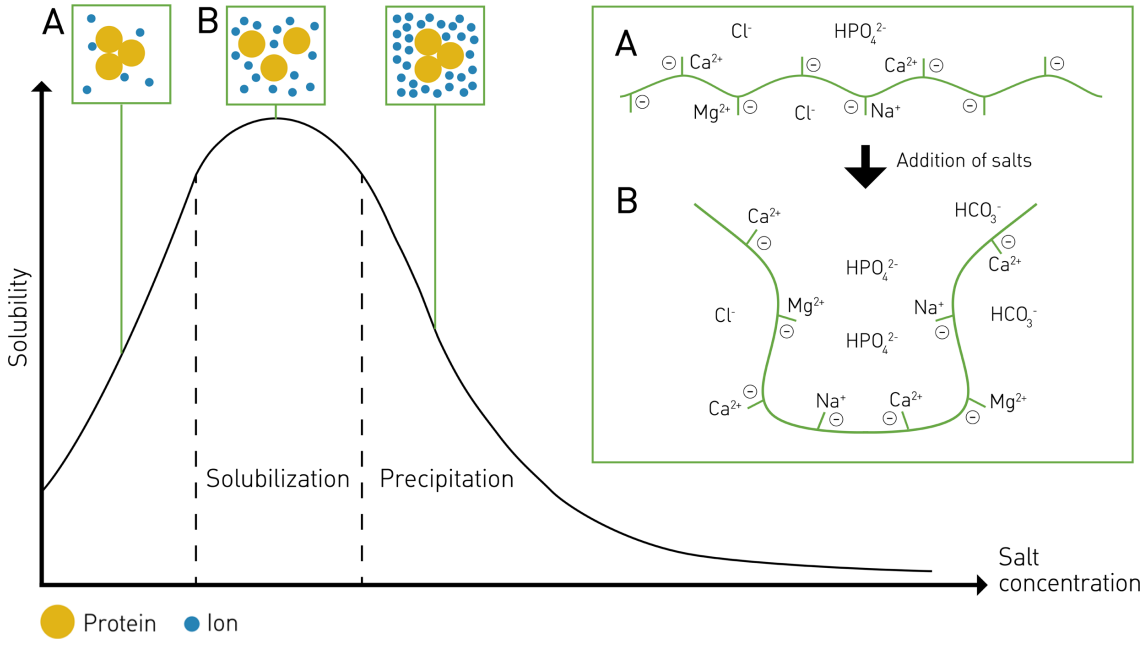

FIGURE 1 Schematic description of the solubilisation ('salting in') and precipitation ('salting out') of a protein; the frame on the right-hand side depicts the ion screening effect on a protein fragment.

3 | SIGNIFICANCE, OBJECTIVE AND SPECIFIC AIMS OF THE CURRENT STUDY

In this study, we present the scientific arguments for the necessity of developing and experimentally validating a more clinically relevant SWF as an alternative to Solution A. Our objective was to demonstrate the feasibility of formulating this novel SWF, referred to as 'SWF A', and to establish its utility in the robust assessment of the fluid handling performance of wound dressings in a laboratory setting.

The overarching aim was to create 'SWF A' as a reproducible, readily available and suitable test fluid for conducting comprehensive laboratory evaluations that closely mimic physiological conditions. This entails replicating key physicochemical parameters of native wound fluids, including pH, conductivity, viscosity (linked to protein content), contact angle, and surface tension.

Furthermore, our secondary aim involved investigating the impact of 'SWF A' on the fluid handling metrics of commercially available foam dressings. By methodically addressing the objectives and aims, our study contributes to the refinement of wound dressing research by introducing a tailored and reproducible SWF. This advancement enhances the reliability of laboratory assessments and deepens our understanding of the intricate interactions between materials and fluids in the context of wound healing.

4 | MATERIALS AND METHODS

4.1 | Preparation of the test fluids for comparative evaluations

Solution A was prepared by dissolving NaCl and $CaCl_2$ in deionised water as specified in EN 13726.[12]

The benchmark reference SCS was prepared by mixing 50% w/w horse serum (Håtunalab AB, Hästserum, Art no. 150, Sweden) and 50% w/w Solution A.

The newly designed SWF A was prepared by sequentially adding the salts listed in Table 1 excluding the calcium chloride to approximately 800 mL of deionised water under continuous stirring using a magnetic stirrer. Once all the components were fully dissolved, the freeze-dried powder of the (only) protein component, BSA (protease-free, lyophilised fraction V, purity ≥98.5%, Roche, Code: 10735086001, Germany) was added to the solution while maintaining a gentle stirring speed to prevent foaming of the BSA. The stirring process was continued for 2–3 h to ensure complete solvation of the BSA, following which calcium chloride was dissolved in approximately 100 mL of deionised water and subsequently added to the solution. The volume of the test fluid was then adjusted to 1 L by adding deionised water. Lastly, the final solution was sterile-filtered using a 0.2 μm pore-size polyethersulfone membrane (Pall®: Acropak®Filter, AcroPak 200 with Supor membrane 0.2 μm, Art nr 12 941, UK) to filter out potential aggregates.

TABLE 1 Composition of the newly designed simulated wound fluid (SWF A).

	Component	SWF A
Salts	Sodium chloride, NaCl	110 mM
	Calcium chloride, $CaCl_2$	2.2 mM
	Potassium chloride, KCl	2.7 mM
	Magnesium chloride, $MgCl_2$	0.5 mM
Protein	Bovine serum albumin (BSA), protease-free, lyophilised fraction V, purity ≥98.5%	34 g/L
Buffers	Potassium phosphate, KH_2PO_4	1.3 mM
	Sodium bicarbonate, $NaHCO_3$	20 mM

4.2 | Measurements of properties of the prepared test fluids

The following properties were measured for freshly prepared solutions of all the three test fluid types at consistent solution temperatures of 23°C.

The pH levels were measured using a pH meter (Mettler Toledo MP225, Switzerland) and a compatible electrode (InLab Semi-Micro, Mettler Toledo, Part No 51343165, Switzerland). This electrode was calibrated prior to all measurements by means of standard calibration solutions (of pH 4.01, 7 and 9.21) provided by the manufacturer of the pH meter.

The electrical conductivity of the fluids, a measure of the mobility of electrolytes in a solution,[50] was acquired using a conductivity meter (Mettler Toledo MC226, UK) with a conductivity sensor (PN 51302119, 0–200 mS/cm) for which the electrode was again calibrated prior to all measurements in a standard calibration solution (12.88 mS/cm), provided by the manufacturer of the conductivity meter.

The static contact angle, indicative of surface wettability, was determined using a Krüss Scientific

Easydrop FM40 contact angle meter. To ensure precision, contact angle data were verified against CP23 drop-shaped standards (Krüss Scientific, Germany) prior to measurements. Measurements were conducted on a flat, non-absorbing polyurethane film surface, a common material in wound dressings, mitigating potential influences from surface roughness and absorption. A lower static contact angle denotes improved wetting, indicating stronger attraction of the liquid to the solid surface.

The surface tension was measured for all the three test fluids according to the ring method as specified in the standard ISO 304:1985.

4.3 | Fluid handling capacity studies of dressings tested using the prepared test fluids

The FHC test for waterproof wound dressings was conducted and reported as described in the revised version of EN 13726 standard, with minor deviations.[12] Specifically, as detailed in Annex E of EN 13726:2023, FHC is the sum of the fluid absorbed and the fluid transpired through a tested dressing specimen (with an exposed surface area of 10 cm^2).[13] In contrast to clinical use, the FHC test method is performed on circular dressing samples (with a diameter of 50 mm) which are punched out from the wound pad area. A notable methodological modification considered in Annex E, compared to the FHC test protocol detailed in the previous version of this standard EN 13726-1:2002 is the introduction of a vented lid (with a 0.25 mm-diameter hole) in the test equipment (i.e., test cylinder) as detailed in Annex M of EN 13726:2023, to prevent negative pressure build-up in the test cylinder causing concave doming of the dressing specimens during testing. Additionally, in this study the amount of the test solutions used to determine the FHC was increased from 30 to 50 mL, based on prior knowledge that several of the dressing types being tested here have FHC values close to or greater than 3 g/L cm^2/24 h when tested using Solution A. The sample sizes for the FHC tests were $N = 5$, 10 and 5, for the Solution A, SCS and SWF A fluids, respectively; the SCS group had twice the sample size with respect to the other test fluids to minimise the inherent biological variability associated with using native horse serum in this solution.

4.4 | Statistical analyses

Descriptive statistics including means, standard deviations and confidence intervals were calculated for the measured properties as detailed above, and a Pearson correlation analysis was further conducted where relevant. The statistical analyses and plotting of data were performed using the Minitab Statistical Software version 17.2.1 for Windows (Minitab, LLC, USA) and GraphPad Prism version 9.5.0 for Windows (GraphPad Software, Boston, MA, USA). Multiple comparison analysis was carried out through the application of one-way or two-way analysis of variance as needed, followed by Tukey–Kramer pairwise comparisons. The statistical significance level was set at a conservative p-value equal or lower than 0.01.

5 | RESULTS

5.1 | Properties of the prepared test fluids

The pH values of both the SWF A and SCS test fluids were observed to be near-neutral and statistically indistinguishable, with readings of 7.7 ± 0.4 and 7.5 ± 0.4, respectively (mean $\pm$ 99% confidence interval),[41] whereas Solution A exhibited a significantly lower, sub-acidic pH of 5.6 ± 0.4 ($p < 0.01$ in a Tukey–Kramer pairwise test, $N = 3$). The electrical conductivities of SWF A and SCS were likewise statistically similar, with values of 13.4 ± 0.4 and 13.6 ± 0.4 mS/cm, respectively, whereas in contrast, Solution A had a significantly greater conductivity of 14.9 ± 0.4 mS/cm ($p < 0.01$, $N = 3$). The contact angles of the SWF A and SCS test fluids, $50 \pm 8°$ and $52 \pm 8°$, respectively, were statistically similar and both were significantly lower than those of Solution A, being $79 \pm 8°$ ($p < 0.01$, $N = 5$). Correspondingly (given the physical relation between the contact angle and surface tension: A greater surface tension of the liquid contributes to a higher contact angle and thus to decreased wetting of the solid.),[7,51,52] Solution A also exhibited the greatest surface tension; surface tension values were 68 ± 0.4 mN/m, 56 ± 0.4 mN/m and 51 ± 0.4 for Solution A, SWF A and the SCS (all were statistically significantly different, $p < 0.01$, $N = 4$). That is, considering the current contact angle and surface tension measurement results together, the wettability of Solution A on polyurethane, a major material component of foam dressings, is shown to be statistically significantly lower than those of the biologically based fluids SWF A and SCS.

5.2 | Fluid handling capacity studies

To study the influence of the test fluid composition and properties (for the three different test fluid types) on the

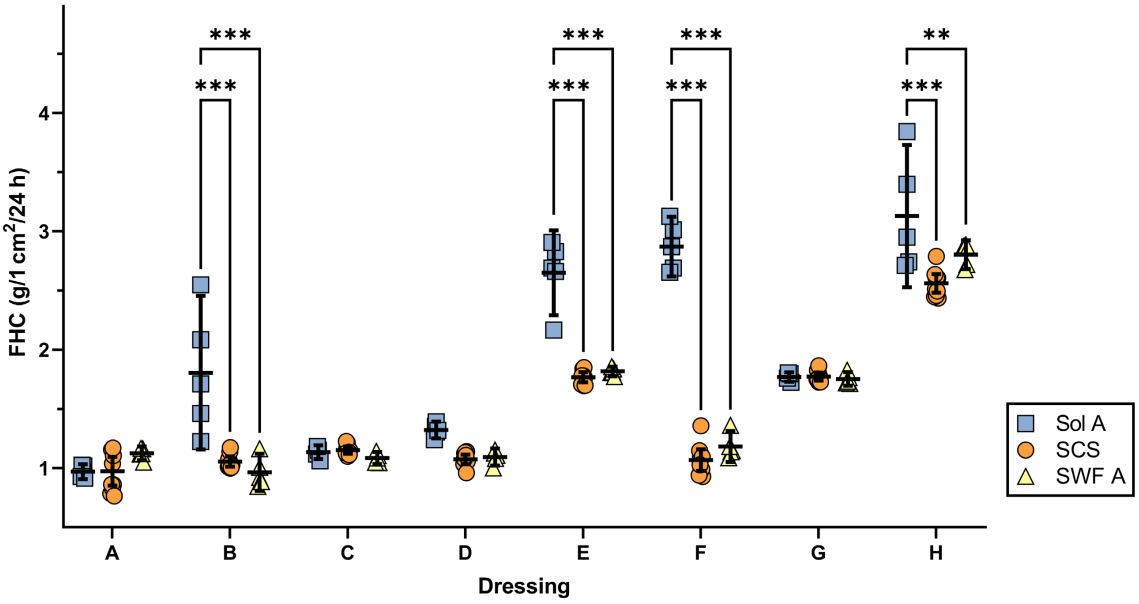

FIGURE 2 Fluid handling capacity (FHC) data (showing the mean and 95% confidence intervals) for the eight tested wound dressings (A–H) evaluated using Solution A (Sol A, blue squares), the serum-containing solution (SCS, orange circles) and the newly designed simulated wound fluid (SWF A, yellow triangles). Sample sizes were $N = 5$, 10 and 5, for Sol A, SCS and SWF A, respectively (the SCS group had twice the sample size with respect to the other test fluids to minimise the inherent biological variability associated with using native horse serum in this solution). **p-values between 0.01 and 0.001, ***p-values <0.001.

FHC performance of wound dressings as per the EN 13726:2023 standard,[12,13] eight advanced, commercial, and commonly used foam dressings, including four bordered (products A, C, E, G) and four non-bordered (products B, D, F, H) foam dressings were selected. The FHC performance of these anonymised dressing products are plotted in Figure 2 and the associated numerical data are provided in the Table S1.

Consistent with the significant differences in the physicochemical properties of the test fluids as reported above, the FHC performance measures of the dressings under investigation were considerably impacted by the choice of the test fluid type. Specifically, the FHC values were statistically significantly lower for half of the evaluated dressings (B, E, F, and H) when tested using the SCS and SWF A fluids compared with their testing using Solution A (SCS vs. Sol A: $p < 0.001$ for dressings B, E, F, and H; and SWF A vs. Sol A: $p < 0.001$ for dressings B, E, F, and $p < 0.01$ for dressing H). Importantly, no statistically significant differences in the mean FHC outcomes were observed for any of the dressings when comparing the SCS to the SWF A test data. Considering SCS and SWF A as being more biologically representative of real-world exudates (as these two test fluids contain protein but Solution A does not) and using their pooled FHC data (detailed in Table S1) as reference results, yields that use of Solution A overestimated the FHC capacity of dressings B, E, F, and H by 79%, 48%, 155%, and 17%, respectively, which are all large errors in a clinical context. Moreover, these errors caused by use of Solution A in the testing of dressings compared to biologically based test fluids are nonuniform and therefore unpredictable, which is another argument against using Solution A in efficacy research of wound dressings. Of note, the observed differences in FHC outcomes for Solution A versus the SCS and SWF A (biologically representative) test fluids were independent of whether the dressings were bordered or non-bordered, that is, were evident for both dressing classes.

Another important perspective to the clinical relevance of SWF A is provided by the Pearson correlation analysis of mean FHC values (Figure 2 and Table S1), which demonstrated that the FHC data obtained for using SWF A and SCS correlated significantly ($p < 0.0001$, $R^2 = 0.98$), whereas the results obtained using Solution A versus SCS or versus SWF A did not (with $p = 0.078$, $R^2 = 0.43$; and $p = 0.063$; $R^2 = 0.46$, respectively). In addition, the use of Solution A resulted in substantially greater variabilities of FHC data points around the means (in particular for dressing products B, E, F, and H for which the FHC ranges were 1.33, 0.74, 0.48, and 1.13 g/1 cm^2/24 h, respectively), whereas contrarily, the variabilities of the FHC data obtained with SWF A were always lower than 0.32 g/1 cm^2/24 h.

A working hypothesis mentioned in Section 4 which guided the design of the current study was that use of the SCS test fluid would inherently involve more variability

than that occurring for Solution A, due to the intrinsic biological variability associated with using native horse serum in the SCS. However, surprisingly, the FHC values obtained in the two test runs with SCS (Table S1) were highly correlated (Pearson analysis: $p < 0.0001$, $R^2 = 0.95$) for the eight different dressing products. Additionally, no statistically significant differences were observed in the FHC data between the two test runs using SCS for seven of the eight dressing types (results were different only for product A, $p < 0.001$, which notably had the lowest mean FHC results among all products; Figure 2 and Table S1).

6 | DISCUSSION

The variability in biological fluid composition and properties of wound exudates presents a major challenge for laboratory performance evaluations of wound care products.[3,9,15,53] Exudates observed in clinical settings range from being clear and watery to opaque and highly viscous with varying levels of wound debris, proteins, bacteria, and sometimes pus.[1,7,9,22] Standardised quality and efficacy performance testing of wound dressings requires a specified, highly reproducible test liquid to simulate the clinical exudates with minimal specimen-to-specimen variations, to obtain robust and reliable results. To address this challenge, a novel simulated wound fluid (SWF A) has been developed. SWF A approximates a typical wound exudate based on the median concentrations of key components found in chronic wound exudates of non-healing wounds (Table 1). This new formulation balances the need for standardisation in industry and academic testing, while also incorporating the main biological components. This is primarily done to achieve biochemical realism and a more complex, yet still watery viscosity, which is pivotal for studying the solid–fluid interactions with tested dressings[7,9,14,54]

The current work focuses on taking the first steps in developing and characterising SWF A, a well-defined test fluid to simulate a watery chronic wound exudate type for fluid handling testing of wound dressings, for example, according to EN 13726:2023. This SWF A is seen as a platform for potentially adding other components for even more enhanced realism or specific clinical contexts in the future, such as further addition of, for example, nutrients, residual exudate debris, thickener, suspended particles of relevant size, as previously suggested by the Gefen group[26,55] and by Mennini et al.[5] in their SWF-related work. In the context of fluid handling testing, glucose is, however, unlikely to critically change the performance outcomes of the tested dressings[1]; although this needs to be confirmed experimentally.

Initially, in this study, the benchmark reference SCS for chronic wound exudate was established as a baseline for comparison. Subsequently, to meet the requirements of standard laboratory testing, reproducibility, minimal variation and global availability, the SWF A was defined, developed, and its physicochemical properties were characterised, primarily to avoid the batch-to-batch variations that are inherent to native (horse) serum products.[15,56] Importantly, the design of the SWF A targeted a physiochemically similar test fluid without the aforementioned drawbacks of natural variation. Indeed, the results and their statistical analyses demonstrated that the SWF A is associated with low variability in FHC measurements of wound dressings and is, therefore, not only a viable alternative to SCS, but also facilitates a robust and more clinically relevant alternative to Solution A when testing according to EN 13726:2023. In addition, while our findings also suggest the applicability of SCS in FHC testing, the cost-effectiveness of SWF A makes it an even more appealing and practical alternative from an economic standpoint.

The physiochemical properties of the biologically based test fluids, SWF A and the SCS were similar but both differed significantly from those of Solution A. Specifically, the pH of SWF A and the SCS were statistically indistinguishable and both aligned with the typical, neutral to alkaline pH range reported for chronic wounds, 7.1 to 8.9,[41] whereas in contrast, the pH of Solution A was, as expected, acidic. Likewise, the electrical conductivities of SWF A and SCS were statistically similar, whereas Solution A had a significantly greater conductivity. Conductivity is a measure of the mobility of electrolytes in solution,[50] and it is assumed that similar interactions occur in a clinical situation because similar amounts of electrolytes and proteins are present in SWF A, SCS, and wound exudate.[15,16,25] Wetting describes the ability of liquids to form interfaces with solid surfaces. The more hydrophilic the material, the lower the contact angle; however, a lower surface tension of the liquid also contributes to a lower angle and thus better wetting of the solid.[51,52] Lastly, the wetting capacity of polyurethane, which also is the main material component in foam dressings, for both SWF A and SCS was significantly greater than that of Solution A. The combined measurement results clearly indicate that the physicochemical properties of SWF A resemble those of the SCS and both differ substantially with respect to Solution A. This imperative finding must be attributed mostly to the inclusion of proteins in a relevantly composed salt solution in both the SWF A and SCS test fluids,[49,57] but simplicity, repeatability, reproducibility, and cost considerations all point to the SWF A as the superior choice for laboratory studies.

The protein content in the biologically based test fluids also significantly impacts the most critical performance outcome measure of FHC, as demonstrated in Figure 2 and Table S1. Upon contact between a protein-containing fluid and a wound dressing surface, interactions involving adherence of the protein molecules to the solid surface occurs. This interaction, or adsorption, is influenced by the material properties, as well as the chemistry of the proteins (polarity, or lack thereof, and ionic charges of the proteins). Eventually, an equilibrium state is reached, at which the proteins coat a large extent of the surface.[38] The forming protein coating layer, its density, uniformity, and thickness, influence the continued absorbency of the fluid into the tested dressing, and ultimately, the measured FHC metrics. Consequently, if a test fluid in contact with a soft, absorbent biomaterial lacks proteins, the subsequent data analysis should take into consideration the variations in results between non-protein versus protein-containing fluids in regard to fluid-material interactions.

We found that the FHC values were statistically and significantly lower for half of the evaluated dressings (both the non-bordered and bordered) when using the biologically based test fluids compared to Solution A. Considering that the extent of the FHC measurement bias caused by Solution A was affected by the specific dressing type being examined (Figure 2 and Table S1), that is, the bias associated with the use of Solution A was not uniform and unpredictable, it is impossible to consistently correct the variations in the measured FHC caused by the lack of protein in Solution A. Furthermore, while the FHC data obtained using the SWF A and SCS test fluids showed intercorrelation, the FHC data from Solution A did not correlate with either SWF A or SCS. It is therefore plausible to infer that Solution A does not offer reliable evaluations of the fluid handling performance of wound dressings in a clinical context. This may help to identify why dressings from different manufacturers have similar FHC values when tested according to the EN 13726 standard using Solution A, but have been seen to perform differently in clinical practice.[6,8,58–60]

Our empirical observations on the impact of the selection of the test fluid on the fluid handling properties of wound dressings align with several prior research publications in this domain,[5,28,36] but for the first time, this study offers a practical and inexpensive approach of using the new SWF A to resolve this issue.

In future work, as noted by Cullen and Gefen (2022),[1] it would be beneficial to study the biochemical and biophysical changes in wound exudate compositions of different wound aetiologies throughout the course of healing and how such potential changes may affect the exudate-related properties relevant to interactions with dressings (such as the composition, pH and viscosity). This knowledge would provide a more complete understanding of the complexity of wound exudate behaviour when absorbed into dressings, and how SWF A can be further enhanced in order to better simulate the clinical realism of wound exudates. Such future developments originating from SWF A will facilitate laboratory testing of wound dressings designed for specific wound aetiologies, exudation levels and types, ultimately providing clinicians with enhanced guidance in the selection and utilisation of wound dressings adapted to the specific status of a given wound. Noteworthy, for complete clinical relevance, use of SWF A (or improved fluids building upon the SWF A platform) in any test apparatus must be made while considering other important factors that influence the test fluid-dressing interactions, such as the flow rate and volume, directionality of the flow in the context of clinical use of the tested dressing, orientation of the dressing with respect to gravity, representative simulated wound temperature and controlled surrounding conditions in the laboratory.[7] Only such a holistic approach to the efficacy research of dressings can allow for high-quality predictions of the fluid handling performance to be made, in particular, regarding identification of the susceptibility of certain dressings to failure in clinical settings, manifested, for example, as pooling and/or leakage of exudate, that may result in wound deterioration and skin maceration.

This study underscores the profound importance of incorporating clinically relevant protein-containing test fluids in the assessment of wound dressing performance. Further, this paper advocates SWF A as a valuable tool for assessing the performance of wound dressings using EN 13726:2023. However, it is essential to acknowledge certain limitations and outline avenues for future research to enhance the acceptance and applicability of SWF A in wound dressing performance evaluations. Specifically, the authors recognise that additional evaluation and validation of SWF A is required, utilising multiple operators, laboratories and a broader range of dressing materials and test methods, if this SWF is to be universally accepted. In this study, a serum containing fluid was used as the benchmark reference as it most closely represented human exudate based on published, well-recognised research data, however, it is anticipated that future research involving physicochemical testing may also have to be conducted using human exudate samples in comparison to SWF A and SCS. With that said, we foresee no barriers to the generalisability of the current findings and to the adoption of SWF A by the wound care industry in the FHC EN 13726:2023 testing.

Currently, SWF A is being offered in a single formula (Table 1). While contributing to the standardisation of

testing and considerably improving the quality of laboratory tests (compared to testing on the basis of Solution A), the current composition of SWF A still does not represent the variability in human exudates.[9,21,54] For further improving its clinical relevance, the development of an exudate property database, encompassing properties specific to various wound aetiologies and healing stages, as well as for non-healing and deteriorating wounds, is an essential next step. Such a database would provide valuable guidance for formulating future variants of SWF A, leveraging it as a robust starting point, that can accurately represent the diverse scenarios encountered in clinical settings. This approach ensures coverage of a wide range of exudate compositions in the formulation of clinically relevant test media.[7,9,21,22,54]

7 | CONCLUSIONS

Introduction of SWF A is crucial for advancing the field of wound dressing fluid handling testing. So far, Solution A is recognised as the standard SWF for quantifying the fluid handling metrics of wound dressings, in accordance with the EN 13726 test standard. However, as shown here, in terms of its physicochemical properties, Solution A is far from being representative of biological wound fluids, which is indeed manifested in partially biased fluid handling results obtained for dressings tested using Solution A. This study aimed to improve wound dressing fluid handling testing conditions and making them more clinically relevant through the introduction and characterisation of a novel test fluid, SWF A. SWF A has been demonstrated to behave more realistically in a clinical context, primarily due to its protein content. In addition, this study revealed the impact that the test fluid composition has on measured wound dressing fluid handling performance outcomes, which underpins that a test fluid must be representative of the clinical situation. Industry and academic teams focusing on the science of wound healing and specifically, on efficacy research of existing and new dressing products, are encouraged to shift away from Solution A and use SWF A instead, to enhance the clinical relevance of the performance tests. Conducting laboratory tests on wound care products under clinically relevant conditions, including application of a representative simulated wound fluid, could lead to better evidence-based decisions, improved clinical and healthcare cost outcomes, and enhanced quality of life for patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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