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Use of *in vitro* and haptic assessments in the characterisation of surface lubricity

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Abstract

Lubricity is a key property of hydrophilic-coated urinary catheter surfaces. *In vitro* tests are commonly employed for evaluation of surface properties in the development of novel catheter coating technologies, however, their value in predicting the more subjective feeling of lubricity requires validation. We herein perform a range of *in vitro* assessments and human organoleptic studies to characterise surface properties of

developmental hydrophilic coating formulations, including water wettability, coefficient of friction, dry-out kinetics and lubricity. Significant reductions of up to 40% in the contact angles and coefficient of friction values of the novel coating formulations in comparison to the control poly(vinyl pyrrolidone)-coated surfaces were demonstrated during quantitative laboratory assessments. In contrast, no significant differences in the more subjective feeling of lubricity between the novel formulations and the control-coated surfaces were observed when formulations were haptically assessed by the techniques described herein. This study, importantly, highlights the need for optimisation of *in vitro* and human haptic assessments to more reliably predict patient preferences.

Keywords

In vitro characterisation, human haptic assessment, hydrophilic coatings, lubricity, friction

Introduction

Intermittent self-catheterisation has become one of the most widely employed bladder drainage approaches for patients with poor control of their bladder function resulting from, for example, neurogenic bladder disorders, spinal injury or chronic disease.[1] In contrast to their indwelling counterparts which remain *in situ* for up to eight weeks

between scheduled changes, intermittent catheters are inserted and removed by patients, their carers or healthcare professionals up to eight times a day to void urine on an 'as required' basis.[2] These two types of catheters are shown in Figure 1.

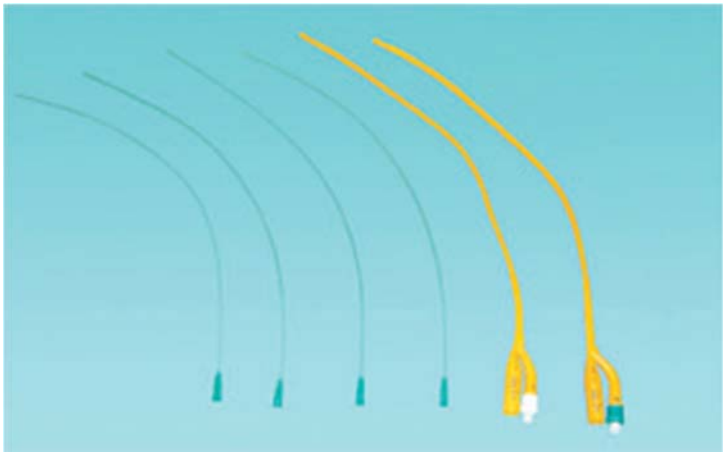

Figure 1. Urinary catheter types: four intermittent catheters are shown on the left and two indwelling catheters are displayed on the right. Reproduced from Lacroix *et al.* (2010).[3]

A number of factors make intermittent catheterisation the bladder drainage mechanism of choice: (i) the reduced risk of infection, catheter blockage and bladder spasm compared to indwelling catheters and (ii) the greater degree of personal independence resulting from the absence of the urine collection bag and the 'on demand' nature of catheter insertion.[4] There is also a significant financial drive for intermittent catheterisation given the Centers for Medicare and Medicaid's recent

decision to cease funding treatment of device-related infections, and revision of their catheter reimbursement policy from four to 200 intermittent catheters per patient per month.[5] Intermittent catheterisation is now recommended by the National Institute for Health and Care Excellence (NICE) as the preferred technique for catheterisation in their current guidelines to control healthcare-associated infections in primary and community care.[6]

Regular catheterisation can, however, lead to pain and urinary tract infections (UTIs) as a result of friction between the catheter surface and the urethral mucosa.[7] Other complications including urethritis, proctatitis and long-term urethral bleeding are reported to occur in up to 30% of intermittent catheter users.[7, 8] Hydrophilic polymer coatings have been applied to catheter surfaces to address the issues of mechanical irritation and tissue damage caused by the regular insertion and removal of poorly lubricated catheters, and the lubricating activity of these coatings has been widely investigated *in vitro* and *in vivo.*[9] Hydrophilic-coated catheters displayed lower coefficient of friction values in comparison to their uncoated counterparts in a recent *in vivo* animal model and, as expected, were shown to reduce urethral trauma, as determined by levels of haematuria, in a prospective, randomised clinical study with human volunteers.[10] Furthermore, in comparison to the alternative gel-lubricated uncoated catheters, the hydrophilic-coated counterparts were associated with a significantly higher degree of patient acceptability.[10, 11] The use of

hydrophilic-coated catheters has recently been endorsed by the European Association of Urology Nurses (EAUN).[8] Moreover, Clark *et al.* (2016) have recently analysed the cost effectiveness of hydrophilic-coated versus uncoated intermittent catheter use in adults with spinal cord injuries. Using a Markov decision model to incorporate the effects of different catheter designs on health-related quality of life, renal function and UTI's over the users' lifetime, the authors concluded that the use of hydrophilic-coated catheters is highly cost-effective in both hospital and community settings, with an estimated 16% reduction in the lifetime number of UTI's per user.[12]

Two major limitations of currently available hydrophilic coatings are (i) their sub-optimal water retentive properties and (ii) their limited durability to withstand the frictional forces typically experienced during the catheterisation process *in vivo*. In practice, this can result in loss of coating from the catheter surface with reversion back to the uncoated state or, alternatively, drying out of the coated surface before removal of the device from the body. As the coating dries out, the surface becomes 'sticky', leading to potential urethral irritation and bleeding.[9] There is therefore a major need to develop coatings with improved durability, water retention and lubricity properties.

In vitro test systems and human haptic, or finger, assessments are commonly employed for the initial pre-clinical assessment and comparison of developed hydrophilic coating formulations before the performance of more highly regulated and

costly *in vivo* studies. These models perform a valuable pre-clinical screening function facilitating the identification and optimisation of lead candidates. [13-17] We herein perform a range of *in vitro* studies to examine wettability, dehydration kinetics and friction properties of a range of developmental coating formulations, and subsequently investigate the more subjective feeling of lubricity by human haptic assessment.

Materials

Poly(vinyl pyrrolidone) (PVP) was provided by BASF Chemical Corporation (Ludwigshafen, Germany). Propan-2-ol (≥99.5%) was obtained from Sigma-Aldrich (Poole, Dorset, UK) and ethanol (absolute) was purchased from J.T. Baker, Deventer, Netherlands. Poly(vinyl chloride) (PVC) films (0.2 mm thickness) were obtained from Goodfellow Ltd. (Cambridge, UK).

Methods

Synthesis of novel coating formulations

Preparation of poly(vinyl pyrrolidone) (PVP) homopolymers. PVP (10 g) was added to a solution (100 mL) of propan-2-ol and deionised water (dH_2O) (1:1) slowly while stirring. The mixture was left stirring overnight to form a clear, colourless solution.

Preparation of semi-interpenetrating polymer networks (SIPNs). 1%, 5% and 10% w/w amphiphilic block copolymer (ABC)/PVP sIPNs were synthesised by addition of the respective mass of PVP (9.9 g, 9.5 g and 9.0 g) to a solution (100 mL) of propan-2-ol and dH_2O (1:1). After stirring overnight at ambient temperature, the resultant clear, colourless solution was cooled to 0°C before addition of ABC (0.1 g, 0.5 g and 1.0 g respectively) slowly while stirring.

Coating of poly(vinyl chloride) (PVC)

Surfaces of PVC samples were, firstly, etched by immersing in ethanol for 1 min. After solvent evaporation, the PVC samples were coated by dipping in the respective formulations for 30 sec, then dried in an oven at 40°C overnight before application of the second coating. Three coatings were applied in total.

Characterisation of novel SIPNs

Contact angle analysis. Sessile contact angles of the surfaces of PVC samples coated with the 100% PVP control and the 1%, 5% and 10% w/w ABC/PVP sIPNs were determined using a First Ten Ångströms (FTA) 200 video-based contact angle analyser (Portsmouth, Virginia, USA) in conjunction with FTA 32 video software for

image capture and analysis. The tangent associated with a single drop of dH_2O, used as the wetting medium, was measured in the equilibrium position on the sample surface. [18, 19] Measurements were performed in quintuplet.

Kinetics of dehydration studies. Kinetics of dehydration of the 1%, 5% and 10% w/w ABC/PVP sIPN coatings were examined in comparison to the 100% PVP control coatings by, firstly, immersing PVC samples (2 x 2 cm) coated with 100% PVP and the 1%, 5% and 10% w/w ABC/PVP sIPNs in dH_2O for 30 sec. Samples were blotted with filter paper to remove excess surface water, weighed and left to dry under ambient conditions of ~23°C and 35% relative humidity. At designated intervals, the coated PVC samples were reweighed until no further change in mass. The weight percentage of water within the hydrated coating was calculated at each time interval according to the following equation:

$$\text{Water Content (\%)} = (M_t - M_0)/M_t \times 100$$

where M_t and M_0 represent the sample mass at time t and the dried sample mass respectively. [20] Dehydration kinetic studies for five replicate samples were performed.

Lubricity assessment: coefficient of friction measurements. Coefficient of friction values were determined for the 100% PVP control and 1%, 5% and 10% w/w ABC/PVP sIPN coatings using a Stable Micro Systems TA-XT Plus Texture Analyser (Surrey, UK) fitted with an A/HFS horizontal friction system comprised of a aluminium platform for the friction sled to slide over. A schematic representation of the experimental set-up is shown in Figure 2. The substrate (5 cm x 5 cm) was fixed to the underside of an aluminium sled with double-sided tape before immersing in water for 30 sec. After gently wiping off excess water from the sides of the sled, the sled was attached to the load cell mount. Load was provided by a 1 kg weight placed centrally on the sled and a force acting in parallel to the surface was applied. Motion commenced when the applied force exceeded the opposing static force of friction (F_s), observed as a peak at the beginning of motion in the graph displaying frictional force versus distance travelled. The sled was moved along the test plate over a total distance of 150 mm at a constant speed of 5 mm/sec. The static coefficient of friction (μ_s) between each surface pressed together by a normal force (N) was calculated from the Amonton/Coulomb friction law:

$$\mu_s = F_s/N$$

As motion of the sled over the platform continued, a dynamic force of friction (F_d) acted in parallel to the surface to oppose the net applied force. The dynamic coefficient of friction (μ_d) was calculated as follows:

$$\mu_d = F_d/N$$

where N, again, represents the normal force acting perpendicular to the surface. Coefficient of friction values from at least five replicate samples were obtained.

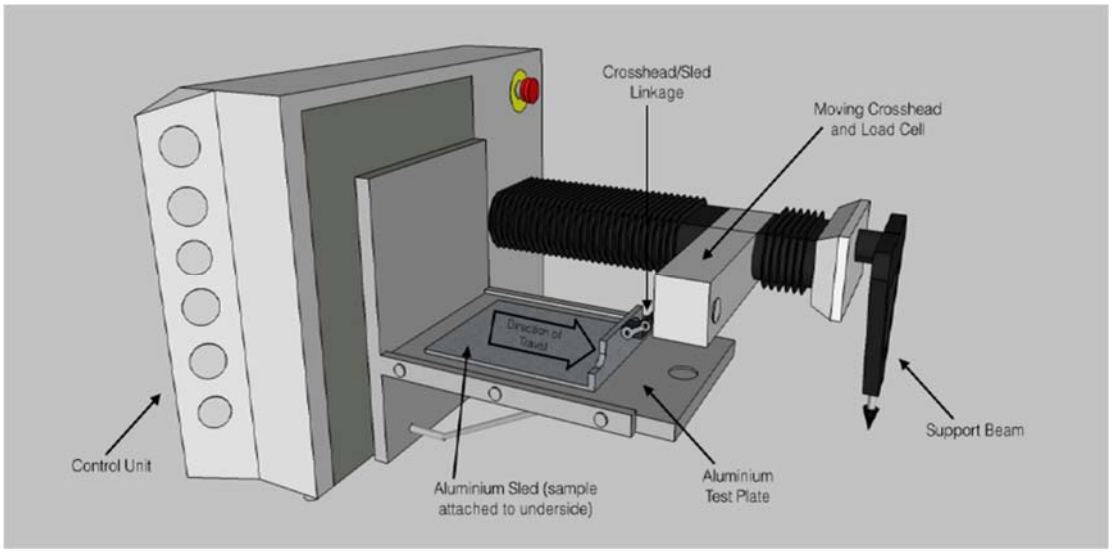

Figure 2. Horizontal friction rig set-up.

Haptic assessment of coated polymer surfaces

Recruitment of volunteers. Staff and postgraduate students from the School of Pharmacy, Queen's University Belfast, with no prior knowledge of this area of research, were recruited by email invitation. A total of thirty-one volunteers (12 males and 19 females, aged 18-65 years) were recruited. The study was conducted in the School of Pharmacy, Queen's University Belfast, from March 2014 to May 2014. Ethical approval for the performance of human organoleptic assessments of the novel ABC/PVP sIPN coatings was obtained from the Ethics Committee at the School of Pharmacy, Queen's University Belfast. Written informed consent was obtained from all volunteers prior to the study and confidentiality assured.

Assessment method and data collection. Coated PVC samples (3 cm x 5 cm) were arranged in three pairs, each containing a 100% PVP control-coated sample and a sample coated with the 1%, 5% or 10% w/w ABC/PVP sIPN, denoted as "A" or "B". Participants were blinded to material assignment and ordering of the samples. The study was structured so that each participant would make a total of three two-way comparisons, each comparison being made between a test sample and control, labelled "A" or "B". In each case, the sample was immersed in the dH_2O wetting medium for 30 sec and then passed to the participant, who was asked to rub the coated surface for approximately 15 sec. These conditions were used to replicate standard

wetting conditions of most commercially available hydrophilic coated catheters in current practice. [21] After rinsing and drying their fingers, participants then touched the second material, following a similar 30 sec immersion period, before marking on a four-point Likert scale the extent to which they found material B to differ in terms of slipperiness to material A. Rank scores were generated for each formulation (a lot less slippery: 1; slightly less slippery: 2; slightly more slippery: 3; a lot more slippery: 4) and anonymised using a unique identifier code for each participant. This process was repeated for all three pairs of coated PVC samples.

Statistical analysis

Statistical differences between the surface contact angles, and static and dynamic coefficients of friction of the 1%, 5% and 10% w/w ABC/PVP sIPNs and the 100% PVP control were evaluated using GraphPad Prism software by a one-way analysis of variance, whereas the effect of interpenetration with ABC on the weight percentage water content of the formulations at selected time intervals (5, 10, 30, 60 and 90 min) was statistically evaluated by a two-way analysis of variance, followed by Tukey's honestly significant difference test for post-hoc comparisons between means of individual groups.

Rank scores from the Likert scale used in the human haptic assessments were statistically analysed using SPSS software. A Chi-squared test was performed to investigate significant differences between the slipperiness of the ABC/PVP sIPN and 100% PVP control coatings. In all cases, differences were considered significant when $p < 0.05$. [22]

Results and discussion

Surface contact angles, coefficient of friction values and kinetics of dehydration were herein measured during *in vitro* evaluations of the differences in surface wettability, lubricity and water retention ability of a range of novel candidate coating formulations. Human haptic assessments were subsequently performed to investigate the more subjective feeling of lubricity.

Contact angle analysis

The static contact angles measured for the 1%, 5% and 10% w/w ABC/PVP sIPN surfaces in comparison to the 100% PVP control are presented in Table 1.

Table 1. Static Contact Angles (°) of dH_2O on the ABC/PVP sIPN- and 100% PVP-Coated Surfaces.

Formulation	Contact Angle (°)*
100% PVP	54.1 ± 6.7
1% w/w ABC/99% w/w PVP	35.5 ± 3.3
5% w/w ABC/95% w/w PVP	25.3 ± 2.8
10% w/w ABC/90% w/w PVP	33.3 ± 1.2

*Values represent Mean ± SD of five sample measurements.

All surfaces were found to be water wettable, with contact angles less than 90°, due to hydrogen bonding of the surface-localised hydrophilic PVP moieties with water molecules.[23] Furthermore, all ABC-containing sIPN-coated surfaces exhibited significantly lower contact angles relative to the 100% PVP control (contact angle of 54.1°). While these findings signify an enhancement in water wettability of the surface upon interpenetration with ABC, the reductions in contact angle did not follow a linear relationship with the amount of ABC added. In this regard, the 5% w/w ABC/PVP sIPN surfaces exhibited significantly lower contact angles than the corresponding sIPNs containing 1% or 10% w/w ABC (contact angles of 25.3°, 35.5° and 33.3° respectively).

Kinetics of dehydration

Dry-out properties are of primary importance for candidate intermittent catheter coatings expected to remain lubricious throughout the course of catheterisation. To compare the kinetics of the dry-out process between the 1%, 5% and 10% w/w ABC/PVP sIPN- and 100% PVP control-coated surfaces, values for the time-dependent relative dehydration (%) of the formulations were plotted after initially hydrating samples in dH_2O for 30 sec and are displayed in Figure 3.

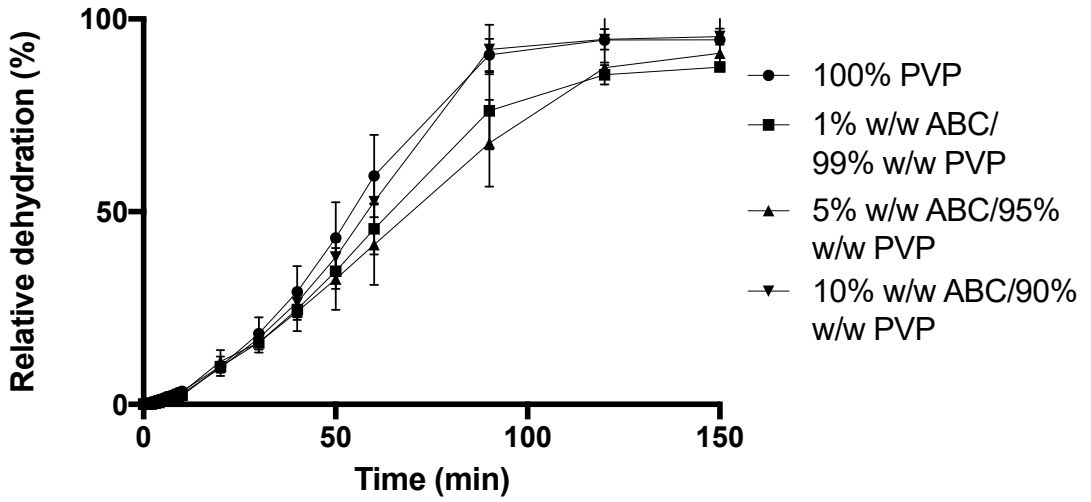

Figure 3. Time-dependent dehydration kinetics of the ABC/PVP sIPN and 100% PVP formulations. Error bars represent standard deviations of the mean values from dehydration studies of five replicate samples.

No statistical differences in the weight percentage water contents between the ABC/PVP sIPNs and the 100% PVP control were observed during the initial 50 min of drying. After 50 min, however, the water contents of both the 1% w/w ABC/99% w/w PVP sIPN and the 5% w/w ABC/95% w/w PVP sIPN were significantly higher than the 100% PVP control (65.4%, 67.5% and 56.8% respectively). Furthermore, these differences became more pronounced upon prolonged drying. For example, after 90 min drying, respective water contents of the 1% w/w ABC/99% w/w PVP, 5% w/w ABC/95% w/w PVP and 100% PVP coatings were 24.8%, 32.2% and 9.3%, thereby demonstrating the capacity of the novel sIPNs to retain water for longer than the 100% PVP control coating. A previous study has attributed differences in water retention ability of hydrophilic coatings, and subsequent ease of catheter removal, to differences in the osmolality of the outer layer of the coating. [24] The significant difference in dehydration kinetics between the formulations observed herein, namely the longer retention of water by the 5% w/w ABC/95% w/w PVP sIPN, was again expected on account of its significantly more hydrophilic surface and consequently enhanced ability to bind and retain water molecules. [24]

Coefficient of friction measurements

Frictional forces between two surfaces sliding past each other are dependent on chemical, topographical and mechanical properties of the surfaces, and may be

modified by application of lubricating gels or hydrophilic coatings.[23] The frictional forces as the coated surfaces slide over a control surface were herein measured as an *in vitro* assessment of the ease of catheter insertion and withdrawal. Testing was conducted using a horizontal friction system attached to a Texture Analyser. Samples were attached to the sled using double-sided tape and hydrated in dH_2O for 30 sec. Static and dynamic coefficient of friction values (μ_s and μ_d respectively) are displayed in Table 2.

Table 2. Static and Dynamic Coefficient of Friction Values for the ABC/PVP sIPN- and 100% PVP-Coated Surfaces.

Formulation	Static coefficient of friction (μ_s)*	Dynamic coefficient of friction (μ_d)*
100% PVP	0.215 ± 0.035	0.202 ± 0.053
1% w/w ABC/99% w/w PVP	0.162 ± 0.050	0.160 ± 0.038
5% w/w ABC/95% w/w PVP	0.131 ± 0.051	0.122 ± 0.044
10% w/w ABC/90% w/w PVP	0.149 ± 0.033	0.168 ± 0.051

*Values represent Mean ± SD from at least five replicate sample measurements.

All ABC-containing sIPNs exhibited statistically lower static coefficient of friction values than the corresponding 100% PVP control (μ_s of 0.215). The extent of this reduction was up to 40% for sIPNs with a 5% w/w content of ABC (μ_s of 0.131). The 5% w/w ABC/PVP sIPN also demonstrated a significantly lower dynamic coefficient of friction value than the 100% PVP control (μ_d values of 0.122 and 0.202 respectively), with the magnitude of this reduction again 40%.

Hydrogel coatings such as poly(vinyl alcohol) or PVP have previously been applied to reduce frictional resistance between two sliding surfaces, for example to minimise trauma to vasculature upon insertion of polyurethane central venous catheters.[23] Water absorbed by the polymer acts as a lubricant, increasing chain mobility and leading to swelling of the polymer network.

Importantly, sIPNs with a 5% weight fraction of ABC were also reported to possess the highest degree of water wettability and retention, as determined by water contact angle measurements and assessment of dehydration kinetics, respectively, of the coated surfaces. The agreement between all three *in vitro* analyses was expected based on the assumption that the higher water contents of more hydrophilic surfaces would lead to lower frictional forces.[9, 24] This relationship has not always been found, however. Jones *et al.* (2004) have previously reported no correlation between lubricity (defined as the work required for withdrawal of catheter segments from a model biological medium (1% w/w agar)) and receding contact angle.[25] Furthermore,

Marmieri *et al.* have previously found polyurethane tubing to have lower lubricity following surface hydrophilisation by oxygen plasma than their untreated counterparts, despite the more wettable surfaces of the former. [15] The authors attributed this finding primarily to surface irregularities on the plasma-treated surfaces which increased the degree of friction and resulted in mechanical interlocking between the sliding surfaces. Limited penetration of the plasma treatment through the surface and the corresponding low levels of lubricating water, in addition to plasma-induced differences in surface chemistry resulting in stronger forces of attraction between the sliding surfaces, were also proposed to contribute to the higher frictional values obtained for the plasma-treated surfaces.

Haptic assessment of coated polymer surfaces

Thirty-one volunteers (12 males and 19 females, aged 18-65 years), who were blinded to assignment of the 100% PVP control- and 1%, 5% and 10% w/w ABC/PVP sIPN-coated samples, completed the haptic assessment. Rank scores ranged from 1 to 4 for all three formulations. The percentage of participants who ranked the ABC-containing sIPN formulations, 1% w/w ABC/99% w/w PVP, 5% w/w ABC /95% w/w PVP and 10% w/w ABC /90% w/w PVP in coating pairs one, two and three

respectively, as a lot less, slightly less, slightly more or a lot more slippery than the 100% PVP control coating are displayed graphically in Figure 4.

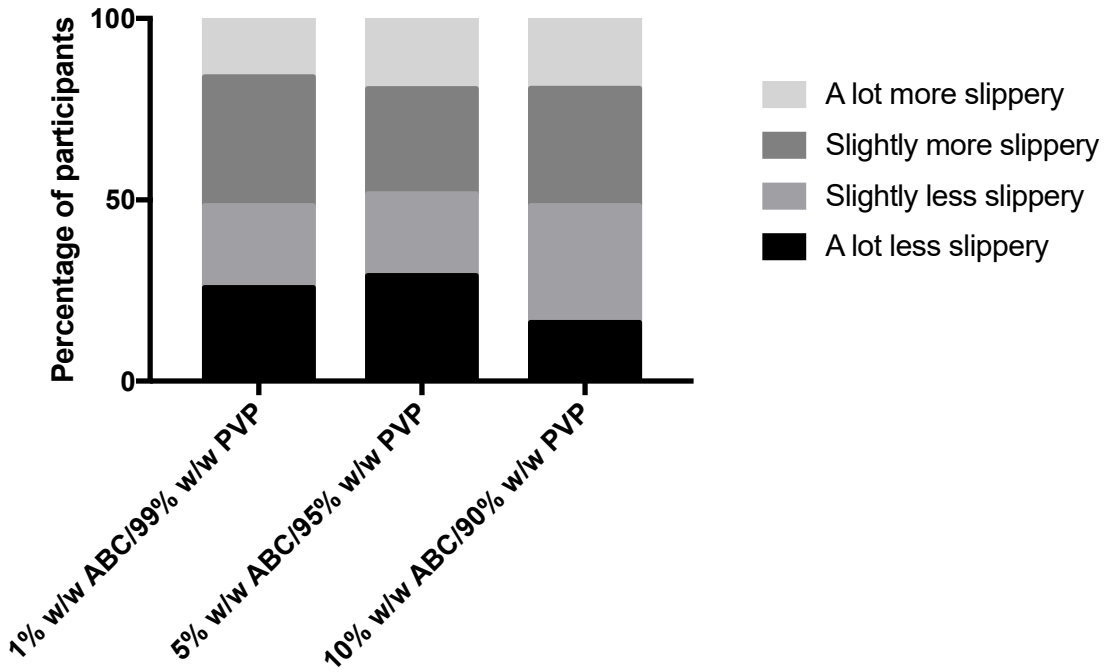

Figure 4. The percentage of participants rating the 1% w/w, 5% w/w and 10% w/w ABC-containing sIPN coatings as a lot less, slightly less, slightly more or a lot more slippery than the 100% PVP control during the human haptic assessment.

No significant differences were observed between the percentage of participants within any of the four categories of the Likert scale when the 1% w/w, 5% w/w or 10% w/w ABC-containing sIPN coatings were haptically assessed in comparison to

the 100% PVP control. The four categories: a lot less slippery; slightly less slippery; slightly more slippery and a lot more slippery, were then recoded into two categories: less or more slippery, to reduce the spread of data from the thirty-one participants. Despite a higher proportion of participants (52%) rating 1% w/w ABC/99% w/w PVP and 10% w/w ABC/90% w/w PVP as more slippery than the 100% PVP control, these differences were not statistically significant.

The results of this haptic assessment contrast with the significant formulation-dependent differences in surface properties observed during *in vitro* laboratory assessments. For example, while sIPNs containing 5% w/w ABC displayed significantly lower μ_s and μ_d values than the 100% PVP control (p = 0.0009 and 0.0013 respectively), no statistically significant difference in the subjective parameter of surface slipperiness between these two formulations was reported during haptic assessment (p = 0.857).

Differences between the findings of the organoleptic study and the *in vitro* laboratory tests may be related to the high variability of human tissue, which acts as the countersurface in haptic assessments. For example, the effect of surface moisture levels on coefficient of friction values between human fingers and contacting surfaces has previously been examined by Tomlinson *et al.* (2011).[26] Their study found that friction initially increased to a threshold value upon application of low levels of moisture to the finger, and then decreased at higher levels. The authors attributed the

increase in friction primarily to the increased contact area and subsequent adhesion between the more supple finger following water absorption and plasticisation of the stratum corneum. At higher levels of surface moisture, a more stable lubricating film of water formed between the finger and the material surface, thus reducing friction. In a related study, the lower coefficient of friction values demonstrated upon pulling spherically-tipped glass probes across skin on the forearm in comparison to more hydrophobic polypropylene counterpart probes were attributed to the more stable interfacial layer of water formed on the hydrophilic glass.[27] Additional factors, such as variations in finger rinsing and drying times between comparisons, may account for some of the variability in the lubricity of the coatings perceived by the participants herein. Limitations of our haptic study, including the use of a small sample size of non-catheter users and unvalidated Likert scale, may also account for differences in findings between the *in vitro* and organoleptic assessments and should be addressed in further studies to validate the use of these approaches in predicting patient preference and performance of urinary catheters *in vivo*.

Conclusions

Despite the significant differences in surface contact angles and coefficient of friction values observed between the ABC-containing sIPNs and the 100% PVP control, these

differences were not reflected during human haptic assessments of the subjective and multifactorial feeling of surface lubricity, as performed herein. This study therefore highlights the need for optimisation of *in vitro* testing models and validation of haptic assessments considering their importance and utility as pre-clinical screening tools in the development of novel device coatings.

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Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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