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Major article

Comparative efficacy of commercially available alcohol-based hand rubs and World Health Organization-recommended hand rubs: Formulation matters

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Background: Use of alcohol-based hand rubs (ABHRs) effectively reduces transmission of pathogenic microorganisms. However, the impact of alcohol concentration and format on product efficacy is currently being debated.

Methods: Two novel ABHR formulations containing 70% ethanol were evaluated according to American Society for Testing and Materials E1174 (Health Care Personnel Handwash [HCPHW]) and European Norm (EN) 1500 global standards. Additionally, using E1174, the efficacy of these formulations was compared head-to-head against 7 representative commercially available ABHRs and 2 World Health Organization recommended formulations containing alcohol concentrations of 60% to 90%.

Results: The novel ABHR formulations met efficacy requirements for both HCPHW and EN 1500 when tested at application volumes typically used in these methods. Moreover, these formulations met HCPHW requirements when tested at a more realistic 2-mL product application. In contrast, the commercial ABHRs and World Health Organization formulations failed to meet HCPHW requirements using a 2-mL application. Importantly, product performance did not correlate with alcohol concentration.

Conclusion: Product formulation can greatly influence the overall antimicrobial efficacy of ABHRs and is a more important factor than alcohol concentration alone. Two novel ABHRs based on 70% ethanol have been formulated to meet global efficacy standards when tested at volumes more representative of normal product use in health care environments.

Hand hygiene is the most important intervention to prevent the transmission of pathogenic microorganisms and has been shown to reduce infection rates,[1-3] even among high-risk patient populations.[4-7] Alcohol-based hand rubs (ABHRs) reduce hand contamination during routine patient care more effectively than handwashing with soap and water.[8-11] In addition, using ABHRs is more convenient, less time-consuming, and less irritating than washing with soap and water.[12-14] The use of ABHRs in health care settings has been associated with reduced transmission of pathogens and reduced hospital-acquired infection rates,[15-17] including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[18-22]

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) promote the use of ABHRs containing 60% to 95% alcohol as the standard of care for hand hygiene practice in health care settings when hands are not visibly soiled.[23,24] To assist countries and health care facilities in the adoption of ABHRs, the WHO has created relatively simple formulation recipes for local preparation, particularly for developing countries, where suitable commercial products may be unavailable or unaffordable.[24] One formulation contains 80% ethanol volume per volume (vol/vol) and the other contains 75% isopropyl alcohol (vol/vol).

In the CDC guidelines, it is stated that antiseptic hand hygiene products intended for use by health care workers in the United States are regulated by the Food and Drug Administration (FDA), and requirements for testing of health care worker handwash products are outlined by the FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products.[23] Because of the magnitude of

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Table 1
Summary of test products used in this series of studies

Code	Test product name	Manufacturer	Active ingredient	Format
A	PURELL Advanced Instant Hand Sanitizer	GOJO Industries	70% Ethanol (vol/vol)	Gel
B	PURELL Advanced Instant Hand Sanitizer Foam	GOJO Industries	70% Ethanol (vol/vol)	Foam
C	PURELL Green Certified Instant Hand Sanitizer	GOJO Industries	70% Ethanol (vol/vol)	Gel
D	Sterillium Comfort Gel	Bode Chemie Hamburg	90% Ethanol (vol/vol) 85% ethanol (wt/wt)*	Gel
E	WHO-recommended hand rub formulation with ethanol	n/a	80% Ethanol (vol/vol)	Rinse
F	WHO-recommended hand rub formulation with isopropanol	n/a	75% Isopropanol (vol/vol)	Rinse
G	Endure 320 Advanced Care Waterless Antimicrobial Hand Rinse with Moisturizer	Ecolab	62% Ethanol (vol/vol)	Gel
H	Avagard Foam Instant Hand Antiseptic with Moisturizers	3M	70% Ethanol (vol/vol) 62% ethanol (wt/wt)*	Foam
I	Avagard D	3M	68% Ethanol (vol/vol) 61% ethanol (wt/wt)*	Gel
J	Alcare OR Foamed Antiseptic Hand Rub	Steris	62% Ethanol (vol/vol)	Foam
K	Rio Gel Antiseptico	Rioquímica	70% Ethanol (vol/vol)	Gel
L	Cutan Alcohol Foam Antiseptic Handrub	DEB	60% Ethanol (vol/vol)	Foam

*Ethanol concentration on product label is reported as weight per weight (wt/wt); (vol/vol) concentration was determined analytically in the authors' laboratory.

effort and inherent challenges to conducting controlled clinical studies to demonstrate clinical effectiveness of ABHRs, in vivo laboratory studies using human subjects are used to determine their antimicrobial efficacy and serve as surrogates for clinical effectiveness.[12] In the United States, the Health Care Personnel Hand Wash (HCPHW) method, which is synonymous with American Society for Testing and Materials (ASTM) E1174, is used.[25] In the European Union, the hygienic hand rub method, European Norm (EN) 1500, is used.[26] Although both methods are intended to measure the reduction of transient challenge bacteria by ABHRs, the methodologic details differ significantly. ASTM E1174 utilizes *Serratia marcescens* as the challenge organism, and the test product is evaluated after both a single use and repeated use. The US FDA requires that products achieve at least a 2-$\log_{10}$ reduction of the marker organism after the first application and a 3-$\log_{10}$ reduction after the tenth and final application.[25] EN 1500 utilizes *Escherichia coli* as the challenge organism, and the test product is evaluated against a reference ABHR (60% isopropyl alcohol [vol/vol], applied in 2 applications of 3 mL for 30 seconds each) using a crossover design. To meet the requirements of the European norm, the $\log_{10}$ reduction for the test formulation must not be significantly inferior to those observed for the reference solution.[26] Given the differences between the ASTM E1174 and EN 1500 methodologies and requirements, ABHRs that meet one standard may not necessarily meet the other standard.

Despite the long-standing conclusion that ethanol concentrations ranging from 60% to 95% are safe and effective for routine hand antisepsis[24,25,27,28] and numerous reports demonstrating that ABHRs reduce infection rates in clinical settings,[15-18] recent studies have questioned the efficacy of gel and foam ABHRs, particularly those containing <75% alcohol.[29-32] These studies have concluded that both alcohol concentration and product format (ie, gel, foam, or rinse) are critical determinants of ABHR efficacy. However, because such studies have not separated these and other interdependent variables, and in some instances have modified the test methods, drawing valid conclusions by interpreting the results is difficult.[29-32]

To address the questions that have been raised regarding the influence of alcohol concentration and product format on ABHR efficacy, a series of studies was conducted to determine the ability of novel 70% ethanol gel and foam ABHR formulations to meet global in vivo efficacy standards. Furthermore, to understand better the relative influence of alcohol concentration, product format, and total product formulation on ABHR efficacy, these formulations were compared with several ABHR formulations containing alcohol concentrations ranging from 60% to 90%.

METHODS

Test products

Twelve ABHR formulations were evaluated (Table 1). Marketed products were acquired through normal sales and distribution channels. The WHO formulations were prepared based on the specifications provided in the WHO guidelines.[24] A 70% ethanol-in-water control and vehicle controls (all ingredients except the 70% ethanol) were prepared for products A and B.

In vitro time-kill experiment

In vitro time-kill suspension tests were performed as described in ASTM E2783-10.[33] The challenge bacteria were *S marcescens* (ATCC No. 14756) or MRSA (ATCC No. 33591). Test samples were evaluated at 99% concentration using a 10-mL total reaction volume and a 15-second contact time. Immediately following the 15-second contact time, the test samples were neutralized and diluted in Butterfield's buffered phosphate solution with lecithin and polysorbate-80 as product neutralizers (or BBP+). Colonies were enumerated on tryptic soy agar with product neutralizers (or TSA+).

In vivo methodologies

EN 1500

Studies were conducted as described in the EN 1500 standard.[26] The subjects' hands were washed with soft soap, dried, and then immersed to the midmetacarpals in a broth culture of *E coli* (K12 NCTC 10538) for 5 seconds. Excess fluid was drained, and the hands air-dried for 3 minutes. The fingertips were rubbed for 60 seconds on the bottom of a Petri dish containing tryptic soy broth to obtain prevalues, and then dilutions were prepared and plated onto TSA. The hands were allowed to dry, and then either 3 mL of the test product was applied for 30 seconds or 2 applications comprising 3 mL (6 mL total) of the reference solution (60% isopropyl alcohol [vol/vol]) was applied for 30 seconds each (60 seconds total) using a crossover design. At the end of the prescribed contact time, the fingers were rinsed in tap water for 5 seconds to stop the reaction. Fingertips were again rubbed in a Petri dish containing tryptic soy broth with neutralizer to obtain postdisinfection values, and then dilutions were prepared and plated onto TSA. For each subject, the entire procedure was then repeated using the product not used during the first application procedure (ie, either the test product or reference solution). Colony counts were performed after 24 and 48

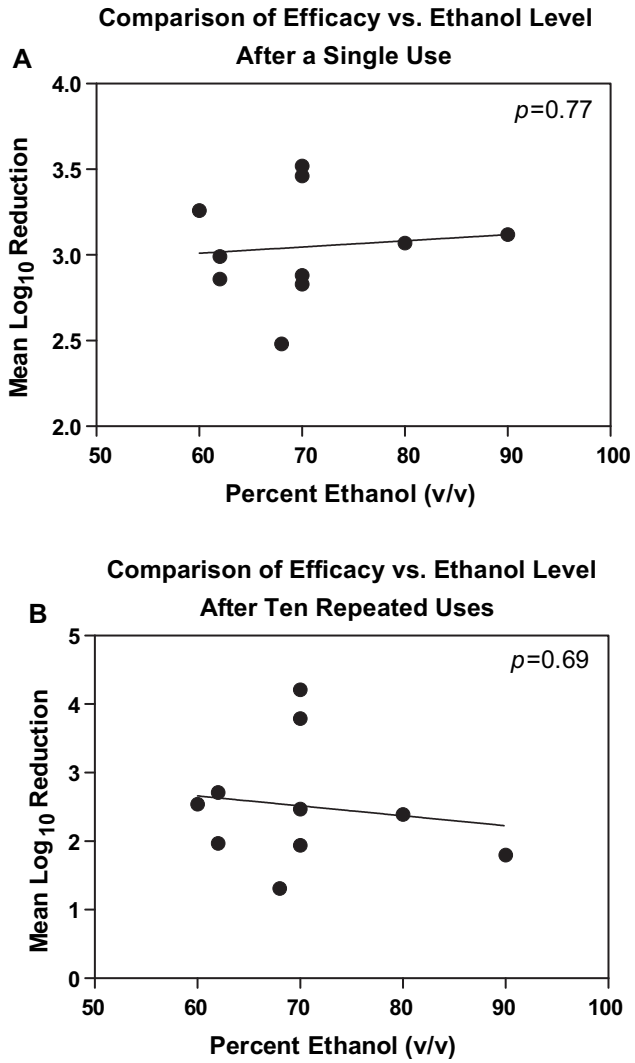

Fig 1. ABHR efficacy according to ASTM E1174 plotted against ethanol concentration after (A) a single product application and (B) 10 product applications for the 10 ethanol-based hand rub formulations shown in Table 3.

hours of incubation at 36°C. Log_{10} reductions were calculated, and test products were compared with the reference product using a Wilcoxon matched-pairs signed-ranks test. Test products that demonstrated log_{10} reductions significantly less than that observed with the reference solution were classified as not meeting the norm. Twenty subjects completed evaluations for products A and B, and 15 subjects completed evaluations for product C.

HCPHW

Studies were conducted as described in ASTM E1174-94.[34] Institutional Review Board approval was obtained prior to enrolling study subjects who were at least 18 years of age, of mixed sex and race. All subjects' hands were free from disorders that could have compromised the subject and the study. Subjects refrained from use of antimicrobials for 7 days prior to the study. A 30-second handwash using nonmedicated soap and a 30-second rinse were performed to remove dirt and oil from the subjects' hands. Hands were contaminated with a total volume of 5 mL of a suspension of *S marcescens* (ATCC No. 14756), transferred into each subject's hands in 3 aliquots (1.5, 1.5, and 2 mL), and spread over all surfaces of the hands for 45 seconds following each aliquot. After a timed 2-minute air-dry, the glove juice sampling procedure was performed. It was followed with a 30-second handwash using nonmedicated soap and a 30-second rinse. This first contamination cycle provided the baseline population level. The hand contamination was repeated 10 times, each followed by product application with a randomly assigned test product. Test products were evaluated using an application volume of 2 mL (with the exception of the first study, in which products were evaluated using an application volume of 5 mL) and were rubbed on the hands until dry. Microbial samples were taken using the glove juice sampling procedure after product applications 1, 3, 7, and 10. Following the glove juice procedure, an aliquot was removed, diluted in BBP+, and plated onto TSA+. Plates were incubated at 25°C for approximately 48 hours, red colonies were counted, and log_{10} reductions were calculated. A neutralizer assay was conducted according to ASTM E1054-08 demonstrating the test products were effectively neutralized by the neutralization procedure (data not shown).[35]

The following number of subjects completed the studies: 8 subjects used products A and B, and 24 subjects used product C for the first study; 24 subjects used products A and B for the second study; and 12 subjects used products A through L for the final study. Statistical comparisons between products were made for the data shown in the first study using a 1-way analysis of variance and, for data in the final study, using a 2-way analysis of variance whereby $\alpha = .05$. For data shown in Figure 1, linear regression analysis was applied to determine the relationship between ethanol concentration and log_{10} reductions. If a significantly nonzero slope resulted ($P < .05$), then the relationship was considered significant.

Table 2
Efficacy of three 70% ethanol ABHRs evaluated according to EN 1500

Test product code	Mean log_{10} reduction (95% CI) product*	Mean log_{10} reduction (95% CI) reference†	Difference	*P* value
A	5.25 (4.78-5.72)	5.11 (4.79-5.43)	0.14	Not significant
B	5.06 (4.57-5.55)	5.11 (4.79-5.43)	−0.05	Not significant
C	5.17 (4.74-5.60)	4.80 (4.31-5.29)	0.37	Not significant

CI, Confidence interval.
*Three milliliters of test product applied for 30 seconds.
†Three milliliters of reference applied for 30 seconds followed by an additional 3 mL of reference applied for 30 seconds.

Table 3
Log_{10} reductions obtained using an in vitro time-kill method with a 15-second contact time against *S marcescens* and MRSA

		Log_{10} reductions in 15 seconds	
Test product code	Sample description	*S marcescens* (ATCC No. 14756)	MRSA (ATCC No. 33591)
A	As manufactured	≥5.8	≥5.8
	Vehicle (no ethanol)	0.6	0.6
B	As manufactured	≥4.7	≥4.2
	Vehicle (no ethanol)	0.1	0.0
Active control	70% ethanol in water	≥4.7	≥4.2

NOTE. The "≥" symbol indicates complete kill at the limit of detection.

RESULTS

Table 2 demonstrates that ABHR gel and foam formulations containing 70% ethanol are capable of meeting EN 1500 efficacy requirements. All test products were statistically noninferior to the isopropyl alcohol reference.

To determine whether ABHR gel and foam formulations containing 70% ethanol are capable of meeting FDA HCPHW

Table 4
Comparative efficacy of ABHRs evaluated according to ASTM E1174

Test product code	Study No.*	Test product description	Application 1 $\log_{10}$ reduction (95% CI)	Application 10 $\log_{10}$ reduction (95% CI)	Meets US FDA requirements
A	1	70% Vol/vol ethanol gel	3.58 (3.34-3.82)	3.50 (3.26-3.74)	Yes
	2		3.35 (3.14-3.56)	4.09 (3.78-4.40)	Yes
B	1	70% Vol/vol ethanol foam	3.55 (3.32-3.74)	4.00 (3.26-4.24)	Yes
	2		3.48 (3.34-3.61)	4.41 (4.14-4.69)	Yes
D	1	90% Vol/vol ethanol gel	3.12 (2.89-3.35)	1.80 (1.57-2.63)	No
E	1	80% Vol/vol ethanol rinse	3.07 (2.84-3.29)	2.39 (2.17-2.61)	No
F	1	75% Vol/vol isopropanol rinse	3.12 (2.88-3.36)	2.03 (1.80-2.27)	No
G	2	62% Vol/vol ethanol gel	2.99 (2.77-3.21)	1.97 (1.75-2.19)	No
H	2	70% Vol/vol ethanol foam	2.83 (2.61-3.05)	1.94 (1.72-2.16)	No
I	2	68% Vol/vol ethanol gel	2.48 (2.26-2.70)	1.31 (1.09-1.53)	No
J	2	62% Vol/vol ethanol foam	2.86 (2.64-3.08)	2.71 (2.49-2.93)	No
K	2	70% Vol/vol ethanol gel	2.88 (2.66-3.10)	2.47 (2.25-2.69)	No
L	2	60% Vol/vol ethanol foam	3.26 (3.04-3.48)	2.54 (2.32-2.76)	No

CI, Confidence interval.
*Data are from 2 separate studies.

requirements, a study was conducted using ASTM E1174 with an application volume of 5 mL. Products A, B, and C achieved $\log_{10}$ reductions (95% confidence interval) of 3.94 (3.62-4.26), 4.14 (3.80-4.49), and 4.22 (3.93-4.50), respectively, after the first application and 5.47 (5.17-5.76), 5.45 (5.23-5.67), and 3.32 (2.97-3.66), respectively, after the tenth application. All test products met FDA HCPHW requirements for a 2-$\log_{10}$ reduction after the first application and a 3-$\log_{10}$ reduction after the tenth application. The $\log_{10}$ reductions for products A and B were significantly greater than the $\log_{10}$ reductions produced by product C after the tenth application ($P < .0001$).

A second E 1174 study was conducted to measure the efficacy of the novel 70% ethanol products, A and B, using an application volume of 2 mL, which is a more realistic volume used by health care workers. Products A and B achieved $\log_{10}$ reductions (95% confidence intervals) of 3.20 (3.04-3.37) and 3.62 (3.48-3.77), respectively, after the first application and 3.60 (3.37-3.82) and 4.06 (3.84-4.28), respectively, after 10 consecutive applications. Both products met FDA HCPHW requirements.

In vitro time-kill experiments were then performed to determine whether excipient ingredients in test products A and B contribute to their bactericidal activity. As illustrated in Table 3, products A and B and the ethanol-in-water control inactivated S marcescens and MRSA below the limit of detection in 15 seconds. In contrast, vehicle controls without ethanol did not exhibit significant bactericidal activity against the test organisms. These results demonstrate that ethanol is the active ingredient in products A and B.

Products A and B were then compared with representative ABHR formulations containing ethanol concentrations ranging from 60% to 90% tested according to ASTM E1174 (Table 4). Products A and B met FDA HCPHW requirements after both 1 application and 10 applications. Log_{10} reductions achieved by the comparative test products (D through L) declined from the first application to the tenth application, and all failed to achieve a 3-$\log_{10}$ reduction at the tenth application. Furthermore, product A produced statistically significant greater bacterial reduction than products G through K ($P < .05$), and product B had significantly greater bacterial reduction than products H through K ($P < .05$) at application 1. After 10 applications, products A and B were statistically superior to all other formulations tested ($P < .001$). To understand the relative contribution of alcohol concentration and product formulation on efficacy by ASTM E1174, $\log_{10}$ reductions were plotted against alcohol concentration for each test product (Fig 1). No significant relationship was found between ethanol concentration and ABHR efficacy after a single application ($P = .77$) or after 10 repeated applications ($P = .69$).

DISCUSSION

In contrast to conclusions from previous reports, our data demonstrate that, when properly formulated, ABHRs containing 70% alcohol are capable of meeting global efficacy standards. Moreover, simply including alcohol at a concentration >75% will not guarantee that an ABHR formulation will meet global efficacy standards. These results highlight the importance of the total ABHR formulation in determining in vivo efficacy, particularly under high-frequency use. Excipient ingredients may either negatively or positively influence the antimicrobial properties of the alcohol. The importance of total product formulation is clearly demonstrated by the data in Table 4. The novel 70% ethanol gel and foam ABHR (products A and B) met FDA requirements when tested using a realistic application volume, whereas test products containing the identical level of ethanol (H and K) did not meet efficacy requirements and were statistically inferior to A and B in reducing bacterial contamination. Furthermore, products D through F were statistically inferior to products A and B and failed to meet FDA efficacy requirements after 10 applications despite containing higher levels of alcohol.

Varying the alcohol concentration within the range considered safe and effective by the FDA (60%-95%) had very little influence on product efficacy (Fig 1). In fact, product D, which is based on 90% ethanol (vol/vol), achieved the second lowest $\log_{10}$ reduction at the tenth application. This result is not surprising because others have reported that solutions containing concentrations of alcohol >90% are, in fact, less potent because proteins are not denatured easily in the absence of water.[36] In addition, others have reported that the activity of alcoholic solutions begins to decline when concentrations are >80%.[24]

Contrary to previous reports concluding that the efficacy of gel and foam ABHRs is inferior to that of ABHR rinses, the current studies demonstrate that product format does not have a major impact on efficacy. Test products A (gel) and B (foam) were statistically equivalent to each other and to the WHO recommended rinses (E and F) after a single use and statistically superior to products E and F after multiple uses. The efficacy of test products D through L, ranging in alcohol content from 60% to 90%, and representing rinse, foam, and gel formats were all similar after a single application (Table 4). Therefore, making broad assumptions about efficacy based on the format of a product is ill-advised.

Although the mechanism by which products A and B are able to significantly outperform other ABHRs is unclear, preliminary data suggest that excipient ingredients in the formulations enable alcohol to more efficiently disrupt bacterial membrane integrity

(unpublished data). However, as illustrated in Table 3, these excipient ingredients do not possess significant antimicrobial activity, and ethanol serves as the sole active ingredient in these formulations.

The primary limitation of these studies is that they utilize standard ASTM and EN test methods, both of which serve as surrogates for clinical effectiveness. The success criteria have been set somewhat arbitrarily and have not been demonstrated to correlate with clinical effectiveness.[22,37-39] Both the CDC and WHO have noted the shortcomings of the current methods and have emphasized a need to develop better in vivo test methods.[23,24] Future studies should be conducted to document and quantify the clinical effectiveness of various ABHRs taking into account product formulation, application volumes, and health care worker compliance. Such studies should include formulations that perform differently in standardized in vivo efficacy methods. The best ABHRs will be those that achieve at least a threshold of antimicrobial efficacy while optimizing product acceptance to ensure maximum usage (ie, hand hygiene compliance).

In conclusion, these studies collectively demonstrate that gel and foam are reliable formats for a novel 70% ethanol formulation that meets global efficacy standards when used at volumes that more accurately reflect use in clinical settings. Our results demonstrate the importance of careful ingredient selection and proper formulation when developing ABHRs to maximize antimicrobial efficacy. Finally, product format and alcohol content (within the range of 60%-95% [vol/vol]) are not the key drivers of product efficacy.

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