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Alcohol-based Hand Sanitizers amid COVID-19: Chemical Formulation, Analysis, Safety

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Alcohol-based hand sanitizers (ABHSs) containing ethanol (EtOH) or isopropyl alcohol (IPA) to inactivate microorganisms help prevent the spread of respiratory diseases. These products have become very popular during the COVID-19 pandemic. Apart from vaccines or other preventative antiseptic measures, the majority of consumers have relied on different types of ABHSs to disinfect their hands. As a result, there has been a global rush in the demand for these ABHSs and other antiseptic hygiene products. This has resulted in the formation of many new commercial sanitizer producers. There are around fifty companies of varying sizes that have been marketing their ABHSs in Bangladesh, most of which have only been manufacturing their products for the first time since the COVID-19 pandemic. To monitor the quality and components of these products, the Bangladesh Council of Scientific and Industrial Research (BCSIR) analyzed approximately 200 different hand sanitizer samples using GC-FID method. All samples were alcohol-based except for 3 which were alcohol-free aqueous hand sanitizers. Of the supplied formulated ABHSs, 80 samples were found to contain only IPA and 54 contained only EtOH. However, 28 samples were found to be contaminated with methanol (MeOH), 7 samples contained only MeOH and 18 samples contained both EtOH and IPA. This is the first study to explore the analysis of alcohol content in formulated ABHSs and their marketing status in Bangladesh, but the findings could be of use in other jurisdictions as similar issues have been raised in many parts of the world.

Introduction

The highly infectious SARS-CoV-2 disease known simply as COVID-19 was first identified in December, 2019 in Wuhan, China and subsequently declared to be a pandemic by the WHO in March, 2020 led to an unprecedented and rapid global demand for sanitizing and disinfecting products, in particular, for alcohol-based hand sanitizers (ABHSs). However, as a result of many reports of incidents of deleterious effects due to either faulty use of, or of sub-standard commercially-available hand sanitizers and concerns about methanol contamination,[1] we wish to report on our own findings and studies in Bangladesh. In particular, we also report on the protocol which we developed and employed for the analyses of the alcohol contents of these hand sanitizer products.

Following the initial alarming spread of COVID-19, which has led to on-going widespread global health, socioeconomic and resulting political issues, several rapidly formed SARS-CoV-2, variants have been identified. These include B.1.1.7 ("Alpha"), B.1.351 ("Beta"), P.1 ("Gamma"), and B.1.617.2 ("Delta") and more recently the B.1.1.529 ("Omicron") variants.[2a–b] To date, B.1.1.529 and its genetically distinct subvariants BA.2, BA.4 and BA.5 quickly become the predominant variants globally. Although these Omicron variants and subvariants have been more contagious than previous variants of COVID-19 it is not yet clearly established whether or not they have caused more severe illness and death rates.[2a–b] Nevertheless, these emerging variants reflect progressively higher effective reproduction numbers which allow novel variants to outcompete previously dominant strains in the face of disease control interventions. This has led to concerns of potential future viral immune evasion and decreased vaccine effectiveness.

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A pathogenic virus can be transmitted by a variety of ways by infected persons even when they have no, or only mild symptoms.[3] The SARS-CoV-2 virus has proven to be remarkably stable in a variety of environments and surfaces[4] in which humans can come into contact with. Thus, pathogenic infection can occur when hands contaminated with pathogenic viruses or bacteria touch the mucosa of a person's mouth, nose, or eyes. Proper hand washing/sanitizing as recommended by the CDC therefore is one of the simplest, most important and cost-effective ways to minimize or prevent transmission and infection and to keep individuals healthy.

As a result, there has been a great surge in demand for hand sanitization products, as frequent hand-washing and sanitization has been recommended by global public health agencies to prevent the spread and infections due to COVID-19 and in general, other pathogens. To meet the great demand, many pharmaceutical and chemical and other companies, eg. breweries and perfumeries, throughout the world started producing hand sanitizers via a variety of methods. However, appropriate formulation and manufacturing directions needed to ensure adequate quality of the formulated products have not always been employed. The most important factor in determining the efficacy of a hand sanitizer during the COVID-19 outbreak is its alcohol content. Alcohol-free hand rub products are not recommended by both the CDC and WHO to prevent COVID-19 infection although hand washing using soap can effectively remove all types of pathogens; hand-washing facilities are not always readily available in many work-place environments or public places. Hand sanitizers however can also effectively kill about 99.9% of germs[5] and are most effective and convenient during frequent contact with individuals or goods.[6] Therefore, the convenience and portability of ABHSs has led their widespread availability, and have been recommended by WHO as alternative hand hygiene products. Generally, ABHSs remain more versatile, convenient, quick and can also be less irritating than frequent hand washing with soap and water.[7]

The first case of COVID-19 was reported in Bangladesh on March 8, 2020. At the time of writing, according to WHO data globally more than 6.55 million cases and over 6.55 million confirmed deaths attributed to COVID-19 have been reported.[8] In Bangladesh, to date[8] more than 2.03 million cases and more than 29,400 confirmed deaths have been reported. Most recently, concerns have been expressed about the Omicron B.1.1.529 variant and the re-emergence of Covid-19 infections in Europe and its possible implications for Bangladesh.[9] In response to the COVID-19 pandemic public health concerns, many companies and organizations in Bangladesh started to produce ABHSs. In 2020 the Bangladesh Council of Scientific and Industrial Research (BCSIR) started to receive high numbers of samples daily for their alcohol content analysis and providing their analysis reports in a prescribed format. This report is of the findings from this BCSIR work which may help as a baseline data for further related studies and for the quality evaluation of ABHSs. The results from similar testing by other international organizations have been reported elsewhere.[10]

Dhama et al recently reviewed the roles of health care products including various disinfectants and sanitizers for which the COVID-19 pandemic has brought unprecedented demands and impacts.[11] Among health care products ABHS have long been the most common recommended means for maintaining good hand hygiene.[12] In general, hand hygiene is a mainstay of infection prevention by preventing the transfer of pathogens via the hands of an individual and is necessary to lessen the spreading of infection to the general public and healthcare workers. The most regularly used ABHS should have an alcohol concentration of 60 to 85%[12] to ensure destroying up to 99.99% of microorganisms on hands.

The SARS-CoV-2 virus is a member of the *Coronaviridae* family. The virus and contains highly glycosylated spikes on the protein membrane in a crown-like arrangement. These spikes can bind to the functional receptors of a host's respiratory cells, namely at the host angiotensin converting enzyme-2 (ACE-2) protein.[13] The possible mode of action of alcohol molecules against the virus is shown in Figure 1. Alcohols likely cause the disruption of microbial membrane and inhibits metabolism through the key mechanisms such as lipid membrane dissolution and protein denaturation.[13]

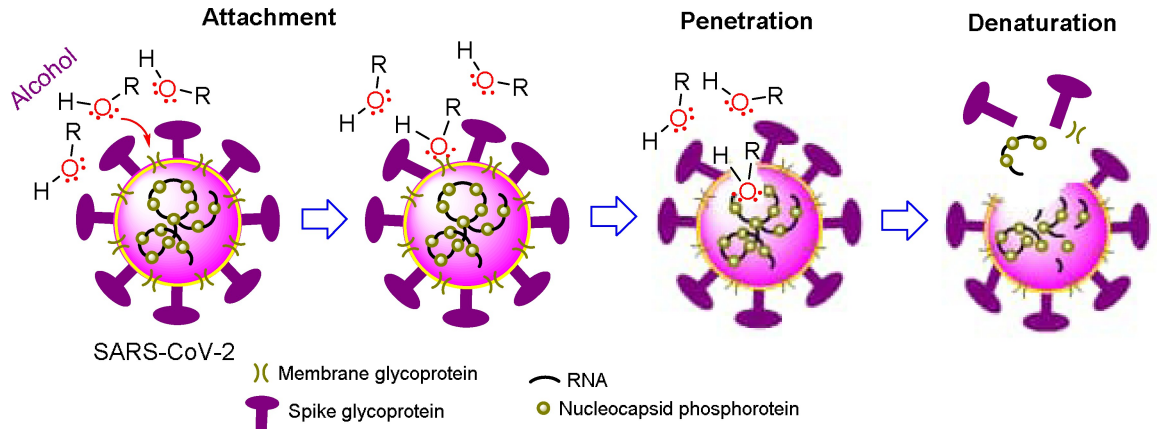

Figure 1. Plausible interaction to inhibit pathogens growth by ABHS.

Since alcohols possess both hydrophilic and lipophilic (hydrophobic) properties, these facilitate their penetration through the viral envelope. Membrane fluidity in the virus is altered when an alcohol comes in contact with the virus.[14] The polar alcohol oxygen atoms destabilize and denaturate the protein structures of the virus moiety weakening the lipophilic interactions between the non-polar residues. As a consequence, the internal affinity of the membrane for water increases. Whereas the "alcohol" i.e ethanol (EtOH) and isopropyl alcohol (IPA) component is the main antiseptic in an ABHS, depending on the type of the formulation, the excipients can include viscosity enhancers, emollients, buffers, preservatives, colorants and fragrances.[12] It is however important to know that ABHSs are only effective when formulations are appropriate and are used correctly on hands.[6] The performance of ABHS products is most commonly defined as a function of their alcohol content and several factors are important in determining efficacy.

There are two major types of ABHS which are marketed: liquid hand rubs and hand gels. In Bangladesh, "hand sanitizers" are liquid formulated products (i.e. hand rub) and "gels" are semi-solid, or thick viscous products. Commercialized ABHS gel products available in the marketplace are thickened by using carbomer, while others contain cellulosic thickeners.[5] Typical cellulosic gelling agents are hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethyl cellulose (CMC) which are the viscosity enhancers recommended by the Italian Society of Compounding Pharmacists[15] for the formulation of ABHS gels against COVID-19. In Brazil, the Agência Nacional de Vigilância Sanitária (ANVISA) has recommended that ABHSs should contain water, EtOH, carbomer980 and triethanolamine; amines such as triethanolamine or aminomethyl propanol (AMP) or other bases have been used as a neutralizing agent to adjust the pH of the ABHS. ANVISA requires the EtOH content to be at least 70% and the product must have antibacterial activity.[16] Additionally, ABHSs may have other ingredients which perform a variety of functions, such as glycerol for example, which is added for skin care. The key considerations for ABHS manufacturers are the influence of these ingredients on product efficacy, safety and usage. Typically, biocidal products contain 60–80% EtOH[5] and the CDC recommended using an ABHS that contains at least 60% alcohol. The WHO recommended two hand rub formulations which have broad spectrum antimicrobial activity including efficacy against COVID-19 (Table 1). In many European countries, ABHS products have been established as a standard in hygienic hand disinfection.

Table 1. WHO-recommended hand rub formulations.

Formulation 1	Formulation 2
• Ethanol 80% (v/v), • Glycerol 1.45% (v/v), • Hydrogen peroxide 0.125% (v/v).	• IPA75% (v/v), • Glycerol 1.45% (v/v), • Hydrogen peroxide 0.125% (v/v).

In Bangladesh, several ad hoc factories emerged amid the COVID-19 pandemic to produce ABHS products. Most of these factories had no quality-control testing facilities for the compositions of their formulated hand sanitizers. As the primary research body of the Bangladesh government, the BCSIR has been providing analytical services to these industries and has been analyzing the ABHSs supplied by these factories by GC-FID (Figure 4) since the very beginning of the COVID-19 outbreak in April 2020. In this report, the data reported were obtained using GC-FID. Some other methods such as the use of specific gravity measurements using alcoholmeters, hydrometers or pycnometers, Raman spectroscopy and IR spectroscopy have been reported by others for the analysis of ethanol solutions.[17]

Mid-infrared (MIR) and near-infrared (NIR) spectroscopy associated with chemometrics are also useful to determine alcohol content in beverages, fuels and fermentation broths.[18] The problem with these methods however, is that the viscosity of gels hinders the use of alcoholmeters and the other methods require specific expensive equipment or require destructive and/or time-consuming sample treatments. Despite the fact that gas chromatographic (GC) equipment is also expensive, modern instruments have autosamplers that require only minute samples of the analyte and microprocessors which permit rapid automated analyses examples of which are provided in the Supporting Information.

Study Design

The study design evaluated GC-FID methods to determine the alcohol contents of the submitted samples. FDA, Agilent, Phenomenex, ThermoFisher, and Shimadzu used GC-FID and GC-MS to develop chromatographic-based methods to analyze commercial hand sanitizers.[19] Several other scientific groups have published their own studies based on the analysis of different hand sanitizers.[20]

In this study, the optimum GC method employed compared the alcohol contents by comparison with the responses of the standards for which GC response calibration graphs were generated. The GC chromatograms (Figure S1–Figure S8) and retention times are listed in the Supporting Information (Table S1). The method was validated by measuring known samples prepared in our laboratory. To ensure whether or not any of the supplied samples contained MeOH, 0.50 μL of the liquid sample was injected directly into the GC. For the gels, samples were diluted with toluene in a 1:5 ratio and then 0.50 μL samples were analyzed under the same chromatographic conditions as all of the other samples tested. The names of the different hand sanitizer products, their corresponding chemical and commercial names provided by the manufacturer are listed in Table S2 (Supporting Information) by code. Each sample was measured in triplicate and the relative standard deviation (RSD) values were observed in the range of 0.4-4.0 for the supplied samples. For the standards for calibration, RSD values of < 2.0 were obtained.

Results

A total of 177 samples were analyzed in 2020 and 13 samples in 2021. Among the 190 samples analyzed, the majority (80) were found to be IPA-formulated products, 54 samples were ethanol-formulated and 7 samples were found to contain only MeOH. The mixed alcohols-containing samples (18) contained EtOH and IPA; 6 samples contained EtOH and MeOH; 13 samples had IPA and MeOH; 9 samples had ethanol, IPA and MeOH, and the rest (3 samples) contained no alcohol at all (Figure 2).

Among the samples, a total of 128 samples were hand rubs, 58 samples were in gel form, 3 samples were in spray form and 1 sample was from wipes (Figure 3). Among the 54 samples of EtOH-formulated ABHSs, 46 samples contained EtOH in the range of 60–90% and 6 samples contained more than 90% EtOH (Figure 4). Only 2 samples contained less than 60% EtOH. Among the 80 samples of IPA-formulated ABHSs, 70 samples contained IPA in the range of 60–90% and 7 samples contained more than 90% IPA (Figure 5).

During the May, 2020 to July, 2020 period, there was a great rush for hand sanitizers which was evident from the number of samples supplied by different companies for analysis. After that, the rush decreased a little bit and this trend continued till the August, 2020–October, 2020 period when once again the demand for ABHSs began to increase. A peak was reached during the November, 2020–January, 2021 period. After that, the volume of samples supplied from different companies decreased rapidly and surprisingly only 12 samples were analyzed in the period of February, 2021–December, 2021.

The huge demand of ABHS caused a few dishonest producers to emerge, disregarding proper manufacturing practices and often producing hand sanitizers that did not meet the specifications required for destruction of the pathogen, which gave the users a false sense of protection.

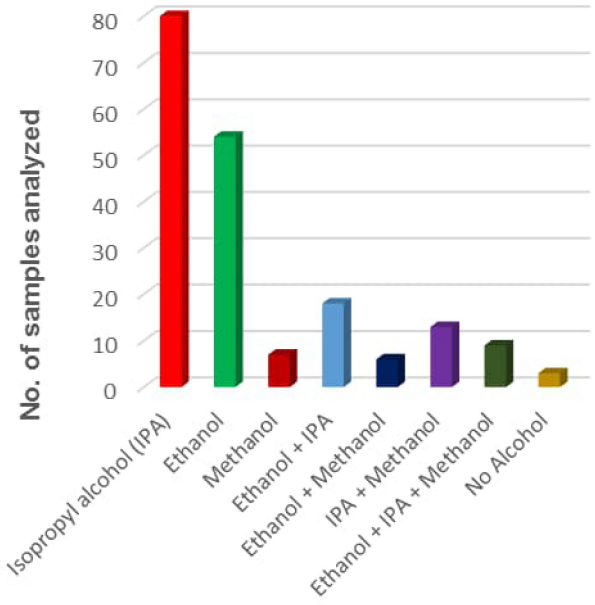

Figure 2. Comparative analysis of different alcohols found in the supplied ABSHs.

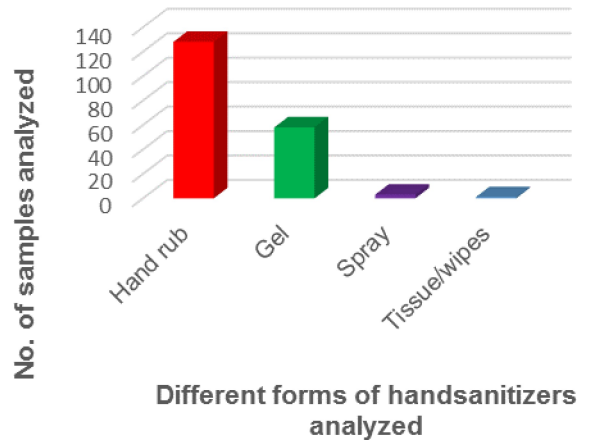

Figure 3. Different forms of ABHSs formulated products analyzed at BCSIR.

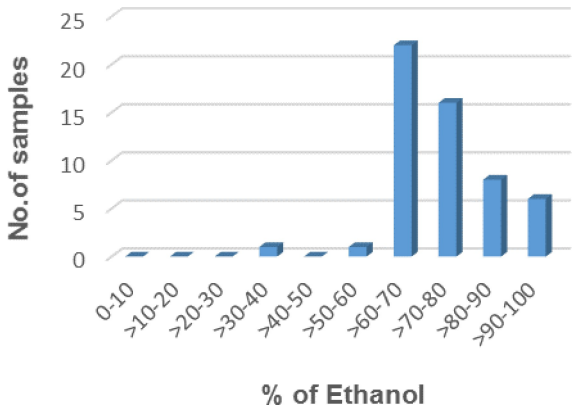

Figure 4. Percentage of ethanol in ethanol-containing hand sanitizers.

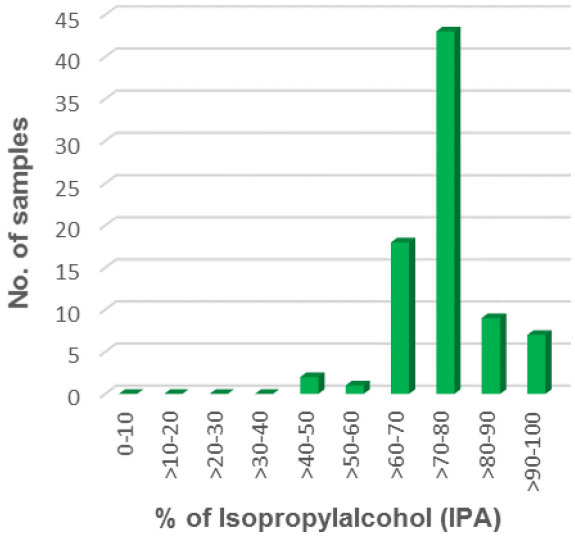

Figure 5. Percentage of IPA in IPA-containing hand sanitizers.

Again, since MeOH is cheaper than the EtOH or IPA, dishonest and new producers could have substituted MeOH for greater profit or without knowledge of ABHS formulation guidelines.

Discussion

As in many countries around the world, Bangladesh faced emergency preventative and curative health rules amid the COVID-19 pandemic. Along with proper mask-wearing, social distancing and vaccinations needed to control the spread of infection in the population, the role of hand sanitizers was/is one of the least costly and most convenient essential. Presently, different ABHSs are to be found throughout Bangladesh and other countries in the world whereas before the sudden outbreak of this pandemic, the hand sanitizer market was relatively dormant. After the appearance of the first COVID-19 cases and following public health experts' recommendations, overwhelming demands ensued for hand sanitizers. In Bangladesh the quest for hand sanitizers was particularly intense in the capital city, Dhaka. This was evidenced by the rush in formulated ABHS samples manufactured by different known and unknown producers which were submitted for quality testing in our laboratory at the BCSIR. Prior to 2020 no ABHS samples had been analyzed in our laboratory. The rush in ABHS products for submitted for quality testing obliged the analysis to be conducted during the country lockdown. Based on the public demands, the hand sanitizer producers in Bangladesh concentrated significantly on the packaging of the sanitizers to make them cheaply available to everyone, often with inadequate information. About 50 manufacturers in Bangladesh are currently engaged in the production of ABHSs. Drug manufacturers and small-scale chemicals and cosmetics producers are the main sources of hand sanitizers for the city as well as for the country at large. Most of them are now currently manufacturing hand sanitizers based on WHO guidelines, in which EtOH or IPA is the main active ingredient(s). According to market research from Nielsen, the sale of hand sanitizers skyrocketed by 300% and 470% in the last week of February and in the first week of March 2020, respectively, in comparison to the same time in the previous year in the USA.[21] Similarly, in Italy, one of the most COVID-19 affected countries sales of hand sanitizers in supermarkets were augmented by 561% during the first three weeks of the pandemic (24th February-15th March 2020) compared to the previous year.[5]

Safety Concerns

Although the focus of most concern regarding ABHS performance has been their alcohol concentration, added ingredients and auxiliary factors also play a role in their efficacy, safety and long-term utility. The main safety concerns with commercialized ABHS products at the consumer level are their flammability, ingestion (accidental or intentional) and dermatological. A case of an individual who suffered burns from exposing his hands which were wet with sanitizer to a flame illustrates this potential risk.[12] It is therefore obligatory to provide appropriate cautions concerning flammability on product labels. ABHSs, packaged in liquid or gel containers have some ingestion risks.[22] As well, ABHS products adulterated with MeOH are especially concerning due to methanol's toxicity. MeOH is metabolized to formic acid,[23] and has long been known to cause blindness, renal damage, coma, seizures and death and yet daily reports still appear implicating methanol (and also IPS) toxic episodes. Thus, it is imperative that ABHS manufacturers avoid using MeOH, or methylated spirits containing MeOH.[23] The intentional misuse of MeOH-containing ABHS as a substitute for ethanolic beverages has led to serious adverse health consequences and deaths.[24] This highlights the importance of manufacturers to ensure that they have adequate quality controls to prevent such adulterated products from reaching the marketplace. Tragically, hundreds of deaths and numerous cases of loss of sight was reported in Iran in 2020 when individuals unknowingly consumed ABHS contaminated with MeOH.[25] Deaths attributed to the use of MeOH-contaminated ABHS were also reported in the Southwest USA in the summer of 2020.[26]

Regular application of ABHS may cause skin irritation and allergy problems.[12] With irritated or damaged skin, alcohols may cause a burning sensation. Recently, a 12 year-old child felt severe irritation in his hands following the over-application of a 70% isopropanol-based hand sanitizer.[27] EtOH is also capable of causing contact dermatitis, although the causative chemical may be either the alcohol or associated impurities or an aldehyde metabolite.[10] Many ABHSs are colored and had specific fragrances whose nature and concentrations are not known. Such incorporations of coloring and fragrance agents may not be suitable for some consumers due to their possible allergic sensitivities. Emollients such as myristyl alcohol, glycerol, dexpanthenol, levomenol, hydrogen peroxide and lanolin alcohol etc. used in some ABHS may also have adverse skin effects. For example, tocopherol, various fragrances, propylene glycol, benzoates, and cetylstearyl alcohol are common potential allergens in ABHS.[28] Fragrances can sometimes cause contact allergies.[29] While some fragrance compounds may weaken the sensitizers, metabolism or oxidation of the parent compounds may produce potent allergens.[30] Packaging of ABHSs for marketing and storing are also of safety concerns. High EtOH concentrations alone are sufficient to degrade container liners and trigger corrosion of aluminum, eventually leading to failure of the can wall and leakage of liquid to the exterior environment.[31] A CDC survey showed nearly half of adult respondents were unaware hand sanitizers should be kept out of children's reach.[32] Since ABHSs are considered as non-prescribed drugs, appropriate regulatory control should be in place over the distribution of these products.

Although the WHO-recommended vaccines and preventive measures against COVID-19 have advanced considerably, the spread of COVID-19 due to new variants is still increasing. Nevertheless, in developing countries especially, keeping hand hygiene using soap and water or ABHSs plays an essential role. The alcohols present in the ABHS formulations triggers bactericidal action through denaturation of microbial proteins however, rising concerns about the prevalence of inappropriate and excessive use of ABHSs and substandard products in the

marketplace creates an ongoing additional concern. These can cause frequent microbial exposure to low doses or substandard concentrations of alcohol which can lead to making the pathogens ineffective and lead to the development of further mutations.[5,33] Prolonged exposure of susceptible resident bacteria on human hands can also generate a progressive stepwise accumulation of natural mutations and emergence of alcoholic tolerance in microbes. In the near future, these developments can become a serious challenge to the further on-going use of ABHSs.

Study limitations

There are limitations in our study; the alcohol content of only the formulated ABHSs provided by producers or others such as interested people, law enforcers, journalists etc for quality test were measured in this study and the antimicrobial activity of these samples were not determined. Only codes for each sample instead of the producers or brand name (SI, Table S3) are reported.

Conclusion and Recommendation

The novel COVID-19 pandemic is unlike anything the modern world has ever experienced and is affecting daily life. ABHSs are very inexpensive and effective in limiting microbial transmission during routine work, travel, journeys or in the workplace. The fear of the pandemic resulted in a huge demand for hand sanitizers, producing severe shortages and the use of ABHSs increased exponentially 2020. In the rush to meet the demand, instances of products lacking adequate quality control appeared in the marketplace. Quality control and quality assurance is very important for commercially-available sanitizers to ensure consumers' health care. In this work, a simple GC-FID technique was used to determine the alcohol content in formulated ABHSs appearing in Bangladesh. Some of the formulated ABHS products supplied by the producers for quality test were adulterated by MeOH or contained only MeOH as the main alcohol, or contained varying mixtures of EtOH and IPA. Even though ABHSs are easy to formulate, they must only be used after proper testing of their contents have been conducted and their producers should follow strict standard operational procedures to produce standardized products. Inappropriate use and prevalence of imperfect ABHSs can also lead to the potential for stepwise accumulation of alcohol-resistant mutations and consumers should be aware of the quality and storage of ABHS products. This study reinforces the need for constant vigilance by responsible authorities to ensure that the marketed products have the required quality. Furthermore, the quality concern of ABHSs pointed out in this study may attract attention of regulatory agencies as well as producers to take appropriate measures to safeguard the public health. The GC technique described herein can be employed by regulators and industries to ensure product quality controls.

Authorship contribution

Md. Monarul Islam: Conceptualization, Investigation, Data curation, Formal analysis, Writing-original draft. Khondoker Shahin Ahmed, Md. Rezaul Karim, Bikash Dev Nath, Shyama Prosad Moulick, Rashedul Islam, Sharkar Md. Mahmudul Hassan: Investigation, Data curation, Formal analysis. Md. Hemayet Hossain, Mohammad Moniruzzaman: Methodology, Supervision. Md. Sarwar Jahan, Md. Aftab Ali Shaikh: Supervision, Funding acquisition, Review & editing. Paris E. Georghiou: Review & editing.

Supporting Information Summary

Supplementary materials associated with this article such as experiments, GC condition and chromatograms can be found in supporting information.

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Conflict of Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

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

Keywords: Alcohol · COVID-19 · GC-FID · Hand sanitizer · Hand rub · WHO guideline

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