HAND SANITIZERS: A REVIEW ON FORMULATION ASPECTS, ADVERSE EFFECTS, AND REGULATIONS

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Abstract:
It is very important to maintain good hand hygiene since it can become infected quickly from coming into contact with airborne microbe droplets from sneezes and coughs. It is very important to practice adequate hand sanitization in order to disrupt the virus's chain of transmission in cases such as pandemic outbreaks. Contact isolation and stringent infection control measures, such as practicing good hand hygiene in public and medical settings, can help achieve this. The success of the hand sanitization solely depends on the use of effective hand disinfecting agents formulated in various types and forms such as antimicrobial soaps, water-based or alcohol based hand sanitizer, with the latter being widely used in hospital settings. Further, this article highlights the efficacy of alcohol-based hand sanitizer against the corona-virus.

KEYWORDS: hand sanitizer, microbes.

INTRODUCTION:
Due to its contagious nature, the COVID-19 pandemic has become a major global public health problem, prompting widespread usage of hand disinfectants. As of May 7, 2020, there were 3.8 million documented cases globally, impacting more than 200 countries. The severe acute respiratory syndrome corona virus 2 is the infectious agent that causes COVID-19. It can linger and re-inflect surfaces for up to nine days. According to a recent study, SARS-CoV-2 can spread by fomite and aerosol, and depending on the amount of virus shed, it can live and spread for hours on surfaces and even for days in aerosols. Hence, it is crucial to interrupt the transmission chain of the virus through contact isolation and strict infection control tools.¹ Following face masks, appropriate hand hygiene is of utmost importance as hands may be contaminated from direct contact with patients’ respiratory droplets from coughs and sneezes or indirect contact via surfaces, which may then facilitate the transmission and spreading of the disease. Given the dangers imposed by this disease, the Centre for Disease Control and Prevention (CDC), the United States has promoted and encouraged hand hygiene through hand washing or use of hand sanitizer. Hand disinfectants are commercially available in various types and forms such as anti-microbial soaps, water-based or alcohol based hand sanitizers, most often used in hospital settings. The majority of hand sanitizer products
on the market today are alcohol-based formulations that include 62% to 95% alcohol because alcohol has the ability to denaturize microbial proteins and render viruses inactive. Due to the high alcohol level in this formulation, there are certain issues and worries about skintoxicity and fire dangers. The purpose of this comprehensive review is to examine the variety of hand sanitizers on the market, their efficacy against the human corona virus, the formulation of those sanitizers, any side effects, and suggestions for improving the formulation of those that are already on the market.²

**Types of hand sanitizers:**
The Centers for Disease Control and Prevention suggest using sanitizer instead of water and soap if they are not easily accessible. Alcohol-based and alcohol-free hand sanitizers are distinguished from one another by the use of alcohol as the primary antibacterial ingredient in the formulation.

While non-alcoholic sanitizers are composed of antimicrobials such as triclosan, povidone iodine, benzalkonium chloride, and chlorhexidine gluconate, alcohol-based sanitizers are mostly composed of alcohols such as isopropyl alcohol, ethanol, and n-propanol.³

Alcohol-based sanitizers apparently are efficacious against a wide array of pathogens such as viruses, bacteria, and fungi. They do, however, also come with a host of negative side effects, such as itching, redness, and contact dermatitis [13]. The development of alcohol-free sanitizers with antimicrobial- active ingredients and an economical manufacturing process overcame the drawbacks of alcohol-based sanitizers. This was also done in an effort to meet the market's rising need for sanitizers.⁴

**Mechanism of action of hand sanitizer:**
The different types of hand sanitizers have distinct modes of action for the elimination of pathogens. These are explained below:

Alcohol based hand sanitizer - The most popular hand sanitizers are alcohol-based ones, and the most often utilized alcohols in these products are isopropanol and ethanol. The most effective concentrations of alcohol are between 60 and 80 percent. Since proteins are difficult to denature without water, alcohol concentrations beyond 80% are less effective. Alcohol causes proteins to coagulate or denaturate, damaging the microorganisms' protective layer and ultimately eliminating them. Propanol, an alcohol, is very useful in biocides. Though its exact mode of action is unknown, it is thought to be connected to membrane damage or to the suppression of transcription and protein synthesis through the influence of RNA polymerase and ribosomes. The alcohol n-propanol is not accepted by FDA for hand sanitizer formulation as it can exhibit potentially toxic implications on human health. It is generally used to prepare industrial solvents (e.g., cleaner). Accidental or intended exposure by ingestion can result in symptoms like reduced breathing and heart rate, leading to death. Exposure to the skin or eyes can cause irritation and allergies.⁵

**Growing market of hand sanitizer during COVID-19:**
Hand sanitizers have become an essential part of our everyday lives, particularly in the wake of the COVID-19 outbreak. The demand for these products has been rising rapidly in recent years, and their popularity has soared.

Factors facilitating market growth –Increased Awareness of Hygiene
- Convenience
- Increased Demand from Healthcare Industry
- Improved Formulations
- Availability
- Affordability⁶
Challenges in Effective Sanitation Due to COVID-19:
Notwithstanding the World Health Organization's recommendations for frequent handwashing and social distance during the COVID-19 pandemic, a number of issues in certain areas hindered the virus's ability to be effectively stopped from spreading. The lack of facilities that are necessary for maintaining proper hygienic practices and the use of common areas like water sources or toilets was one of these (Pharmacoepidemiology 2023, 2 265). Consequently, several surfaces such as door knobs, faucets, and walls serve as fomites that allow the virus to spread indirectly. This is a prevalent problem in both urban and rural areas with high population densities.

During the epidemic, around 3 billion individuals were without access to basic hygienic supplies like soap and water. The use of masks and other personal protective equipment (PPE) was made mandatory in order to stop the coronavirus from spreading because it spreads through contact with surfaces and the air. Nevertheless, in spite of their significance in stopping the virus from spreading throughout the populace, these protective items were lacking (especially among patients and frontline personnel).

Keeping sizable reserves of such crucial materials on hand would be a crucial lesson to take away for the future.7

Various Phases of sanitizers are:
1. Emollients and moisturizers - Emollients are skin-soothing, skin-hydrating moisturizers that are placed directly onto the skin. To keep moisture in, they apply a barrier coating to the skin.
2. Emulsifiers - Emulsifiers are mixture enhancers for two liquids. In a glass, for instance, water and oil separate, but the addition of an emulsifier will aid in the liquid's mixing.8

Ingredients:
1. Alcohol based hand sanitizer – alcohol and hydrogen peroxide
2. Non alcohol based hand sanitizer – chlor hexidine gluconate, chloro xylene, iodine, benzethonium chloride and triclosan.9

Excipients used in Hand sanitizer:
- Glycerol - As a humectant, glycerol is added to the formulation to improve the product's acceptability. If an alternative humectant or emollient is reasonably priced, easily accessible, soluble in alcohol and water, non-toxic, and hypoallergenic, it can be utilized for skin care. The selection of glycerol is based on its safety and affordability. Reducing the handrub's glycerol content could perhaps lessen its stickiness even more.
  - Xanthum gum
  - Polycrylic acid
  - Fragrance
  - Colorant9

Benefits:
- Hand sanitizer has the advantages of being more time-effective, portable, easy to use, and handy.
- Families who use them are less likely to get respiratory and gastrointestinal infections.
- Hand sanitizers using readily available ingredients that are naturally derived and aid in preventing skin dryness
- If hand sanitizers are used correctly and I don't cause illness, the frequency of absenteeism in class can be reduced by 20%.10

Efficacy of hand sanitizer:
- Bacteria and fungi - Hand bacteria are often divided into resident and transitory floras. Staphylococcus aureus, Staphylococcus epidermidis, and Enterococci faecalis are common resident floras that colonize deep layers of the skin and are resistant to mechanical removal. Conversely, the skin's outermost layers are colonized by transitory floras such S. aureus, Escherichia coli, and Pseudomonas aeruginosa. Numerous bacterial strains that can possibly cause a range of
bacterial infections are also capable of being transferred to the host from external sources. Without water or towel drying, ABHS are particularly effective in rapidly eliminating a variety of germs through the action of the aqueous alcohol solution. According to the Centers for Disease Control and Prevention (CDC), ABHS have excellent in vitro antimicrobial activity, including multidrug-resistant pathogens, such as methicillin-resistant S. aureus, vancomycin-resistant Enterococcus. According to specific in vitro experiments, hand sanitizers with 60%–80% ethanol produced a 6–log reduction against a variety of bacterial and fungal species in 15–30 seconds. Moreover, in vivo antibacterial activity from contaminated hands has been shown in numerous research. Propanol-based hand sanitizers were more effective than ethanol with the largest zone of inhibition, even though different alcohol-based hand sanitizers all showed antimicrobial effects against various gram- positive and gram-negative bacteria using the Kirby-Bauer method, which uses antibiotic-impregnated disks to test the susceptibility of strains. Given the growing prevalence of hand sanitizers as an infection control strategy, it’s critical to be aware of any potential bacterial tolerance mechanisms. Recent isolates of E. faecium were found to be more alcohol-tolerant than older isolates in an in vitro test employing a lower dose of isopropanol. Similar research on different infections has also shown that exposure to lower alcohol-holiday doses increases tolerance. Alcohol is not the only substance for which tolerance arises; BC. The presence of any selective pressure in environments encourage microbes to adapt and evolve resistance to such pressures, and in the case of BC, researchers have observed resistant strains that were able to survive certain concentrations of BC (0.1%–0.4%) since the 1960s. Because of this, tolerance to drugs containing quaternary ammonium is not a new finding. It is inevitable that tolerance will only grow as time passes and both alcohol and BC are used in hand sanitizers and disinfectants. As more research is done to identify new mechanisms of tolerance, it is crucial to stress the need of adhering to hand hygiene protocols, which call for the right exposure, volume, and concentrations of hand sanitizers in order to minimize selective pressures and, consequently, tolerance.

- Viruses - Numerous investigations have attempted to authenticate the efficiency of hand sanitizers on viruses, despite the fact that viruses are more challenging to investigate in vivo than bacteria. The World Health Organization advises using alcohol-based hand sanitizer formulations that effectively inactivate viruses such as coronaviruses, hepatitis C virus, Zika virus, and murine norovirus, as demonstrated by quantitative suspension tests. Other formulations from Sterillium that contain isopropanol as the main ingredient also completely inactivated enveloped enteric and respiratory viruses, such as H1N1 influenza A virus, but failed to inactivate nonenveloped viruses, except rotavirus. Numerous in vivo investigations have also been carried out in which the virus is applied to the fingertips and the effectiveness of hand sanitizers in lowering the quantity of viral particles that can be extracted from the hands is assessed. Since most nonenveloped viral strains are known to be more resistant to disinfectants than enveloped viruses, a large number of these finger pad tests exhibit only moderate efficiency against them. Because large concentrations of ethanol have been demonstrated to be very efficient against enveloped viruses, which makes them effective against the bulk of clinically relevant viruses, it is imperative to maintain track of the specific strains of viruses. That being said, Sattar et al. suggest that 60% ethanol was sufficient to reduce the titers of rotavirus, adenovirus, and rhinovirus by >3 log10 within a 10-second contact period. This is despite the fact that nonenveloped viruses, such as Hepatitis A and enteroviruses, require 70%–80% alcohol to be reliably inactivated. It is possible to achieve adequate activity even with nonenveloped viruses by using higher alcohol concentrations and longer contact durations.

Data from earlier coronaviruses can be extrapolated in the context of the effectiveness of hand disinfection given their structural similarities, especially as evidence on the novel SARS-CoV-2 continues to emerge quickly. Nine out of ten small case-control studies suggesting that hand washing were included in a systematic review that looked at the 2002–04 SARS outbreak. Albeit only three demonstrated statistical significance, which may be partially attributed to the small sample sizes of the trials, lowers the risk of nosocomial and community transmission. Some research used hand sanitizers, while others did not mention whether hand washing was accomplished using soap and water or sanitizers. This means that the methods used for hand cleaning varied among the studies. While it is not possible to obtain a standardized approach for direct in vivo confirmation of virus inactivation following hand sanitizer usage, research conducted in vitro have verified the efficacy of alcohol-based hand sanitizers in reducing the viral load. In vitro experiments with SARS-CoV-infected patient sputum cultures and four distinct alcohol-based hand sanitizer formulations were all successful in inactivating the virus below the detection limit.
Conclusion:

It is challenging to recommend one method of hand sanitizing delivery over another with confidence given the state of the studies in the literature. We can say, however, that sanitizer is not as effective as soap and water. In situations where hand washing is not possible or practical, a sufficient volume of sanitizer is necessary to provide total hand coverage. Adherence to recommended hand hygiene is also crucial. Finally, extrapolating the virucidal results on viruses with a structure similar to SARS-CoV-2, it can be concluded that current hand hygiene solutions can successfully inactivate this virus; nevertheless, direct determination of this should be the goal of future research.

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