Review Article

A Review on Hand Sanitizer

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ABSTRACT

Current outbreak of Covid 19 has made us mandatory of using hand sanitizers everywhere. The hand hygiene is now being very essential in the public. Compliance with hand hygiene recommendations is critical to reducing colonization and infection of the hands of all people. Hand hygiene is of utmost importance because it may be contaminated easily from direct contact with airborne microorganism droplets from coughs and sneezes. Particularly in situations like pandemic outbreak, it is crucial to interrupt and cut the transmission chain of the virus by the practice of proper hand sanitization. The use of hand sanitizers drastically reduce the transmission of microorganisms to patients, ultimately reducing morbidity, mortality, and costs associated with healthcare-associated infections (HCAI). It can be achieved with contact isolation and strict infection control tool like maintaining good hand hygiene in hospital settings and in public. The success of the hand sanitization solely depends on the use of effective hand disinfecting agents formulated in various types and forms such as bathl soaps, water-based or alcohol-based hand sanitizer, with the latter being widely used in hospital settings. To date, most of the effective hand sanitizer products are alcohol-based formulations containing 70%–95% of alcohol as it can denature the proteins of microbes and the ability to inactivate viruses. The present study correlated with the data available in Pubmed, and it will investigate the range of available hand sanitizers and their effectiveness as well as the formulation aspects, adverse effects, and recommendations to enhance the formulation efficiency and safety.

Keywords: hand sanitizer; hand disinfectants; infection control, SARS-CoV-2, COVID-19, hand hygiene.

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INTRODUCTION

Study about hygiene is a branch of science which is involved in knowledge and practices related to promotion of health.[1] Hygiene is defined as maintenance of cleanliness practices which carries utmost importance in maintenance of health. Keeping bodily hygiene and usage of cleansers are most requisites of healthy living. These concepts highlight the need of maintaining hygiene in prevention of diseases.[2]

The emergence of novel pathogens, bacterial or viral, has always posed serious challenges to public health around the globe. One of these dangerous pathogens is "severe acute respiratory syndrome coronavirus 2" or SARS-CoV-2, more commonly known for causing coronavirus disease 2019 or COVID-19, which has been declared a global pandemic by the World Health Organization in early 2020. Since its discovery in December 2019 in Wuhan, there have been over three million confirmed cases worldwide by April 2020.[3] One of many ways implemented to prevent the spread of this virus, as with previous contagious pathogens, is frequent and effective hand washing. In both healthcare and community settings, alcohol-based hand sanitizers have become a popular alternative to the traditional hand washing with soap and water. Alcohol based hand sanitizers have been utilized as an effective alternative to handwashing with soap to prevent the spread of bacterial and viral infections, making it one of the essential protocols in decreasing healthcare burden.[4, 5]

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can persist and remain infectious on surfaces for up to 9 days.[6, 7] Hence, it is crucial to interrupt the transmission chain of the virus through contact isolation and strict infection control tools.[8] Following face masks, appropriate hand hygiene is of utmost importance as hands may be contaminated from direct contact with patients' in direct contact via surfaces, which may then facilitate the transmission and spreading of the disease.[9-11] The 2003 severe acute respiratory syndrome (SARS) outbreak was caused by a novel human coronavirus (CoV) (SARS-CoV) that could survive on surfaces for 24-72 h.[10] The studies on SARS-CoV outbreak settings showed that providing efficient. CDC), the United States has promoted and encouraged hand hygiene through hand washing or use of hand sanitizer.[11] Different types of delivery systems are also formulated—for instance, rubs, foams, or wipes. The World Health Organisation (WHO) recommends alcohol-based hand sanitizer (ABHS) in line with the proven advantages of their rapid action and a broad spectrum of microbicidal activity offering protection against bacteria

and viruses. However, the effectiveness against non-enveloped viruses is still debatable and questionable.[12-17]

Ayurvedic Approach in Hand Hygiene

Ayurveda is the traditional medicinal system of India and believed to have originated over 6000 years ago. It describes the ways to remain healthy as well as methods to treat disease. The name itself means "Knowledge (Veda) of life (Ayu)" Ayurveda is not only a curative medical science but also is a comprehensive way of healthy living. Guidelines related to healthy or "swastha" individual are termed as "Swastha vritta".[18, 19]

Considering ayurvedic approach; an attempt has been made to screen classical literature for the herbs with cleansing properties and found that, *Pancha Valkala* (the barks of five plants) has activities like, *Vrana prakshalana, Vrana ropana, Shothahara, Upadan shahara, Visar pahara. Pancha Valkala* is tha combination of barks of five different plants (i.e.) **Vata**- *Ficus bengalensis* Linn.,; **Udambara**- *Ficus glomerata* Roxb.,; **Aswattha**- *Ficus religiosa* Linn.,; **Parisha**- *Thespesia populnea* Soland.Ex. Correa.; **Plaksha**- *Ficus lecor* Buch.Ham. [20-25]

Types of hand sanitizers

Hand sanitizer are generally classified into two groups as,

- Alcohol-based hand sanitizer (ABHS)
- Alcohol-free (NABHS).

An ABHS may contain one or more types of alcohol, with or without other excipients and humectants, to be applied on the hands to destroy microbes and temporarily reduces the spreading.[26] ABHS can effectively and quickly reduce microbes covering a broad germicidal spectrum without the need for water or drying with towels. Nevertheless, there are a few shortcomings with the effectiveness of ABHS, such as its short-lived antimicrobial effect and weak activity against protozoa, some non-enveloped (non-lipophilic) viruses and bacterial spores. On the other hand, the alcohol-free sanitizer makes use of chemicals with antiseptic properties to exert the antimicrobial effects. These chemicals have a different mode of action and function according to their chemical functional groups (Table 1). As they are non-flammable and often used at low concentrations, they are relatively safer to use among children as compared to ABHS. ABHS is available in different dosage forms, namely gel, liquid and aerosol. As each type has its own characteristics, a study was conducted to understand the impact on sensory attributes that may affect user's acceptance of the product and ultimately influence usage leading to hand hygiene compliance. [27–32]

Ingredients of Sanitizers

Table 1: List of alcohol, non-alcohol compounds, and commonly used excipients in hand sanitizers

Alcohol based sanitizer	Commonly used excipients	Alcohol free sanitizer
70-95% V/V alcohol	• Glycerin • Fragrance • Colorants	Antiseptic
Ethanol		Chlor hexidine
Isopropanaol		Chloro xylenol
n-propanol		Quaternary ammonium compounds
		Triclosan

Various Phases of sanitizers are[33]

Antimicrobial agent

- Emollients and moisturizers
- Emulsifier

Antimicrobial Agent

An Antimicrobial agent is an agent that kills microorganisms or stops their growth.

Emollient

Emollients are moisturizing treatments applied directly to the skin to soothe and hydrate it. They cover the skin with a protective film to trap in moisture.

Emulsifier

Emulsifiers are additive that help two liquids mix. For example, water and oil separate in a glass, but adding an emulsifier will help the liquid mix together.

Table 2: Chemical classification of commonly used disinfectants and their mechanism of action[27-29]

Chemical group	Example	Mechanism of action
Alcohol	• Ethanol • Isopropanol	Denaturation of proteins in the plasma membrane
Chlorine compounds	• Hypochlorites (ClO^-) (e.g., Sodium hypochlorite) • Chlorine dioxide (ClO_2) • Chloramine-t trihydrate ($C_7H_7ClNNaO_2S$)	Halogenation/ oxidation of cellular proteins
Iodine compounds	• Povidone-iodine (polyvinylpyrrolidone with iodine	Iodine can easily penetrate through the cell membranes of pathogens Followed by attacking vital proteins, nucleotides and fatty acids of cell

Quaternary ammonium compounds	Benzalkonium chlorides, including • Alkyl dimethyl benzyl ammonium chloride ($C_{22}H_{40}N+$), • Benzyl dimethyl octyl ammonium Chloride ($C_{17}H_{30}ClN$), • Didecyl dimethyl ammonium chloride ($C_{22}H_{48}ClN$).	Lower surface tension Inactivate enzymes Degrade cell-proteins
Peroxygens	Hydrogen peroxide (H_2O_2) • Peracetic acid (PAA) ($C_2H_4O_3$)	Free-radical oxidation of essential cell components
(Bis) phenols	• Triclosan	Penetrate cytoplasmic bilayer
Biguanide	• Chlorhexidine	Ionic interaction Disrupt cell membrane

Table 3: Mechanism of action of alcohols and non-alcohol compounds

Ingredient	Functions	Note
Alcohol based hand sanitizer (ABHS)		
Alcohol	Denatures protein and lipid membrane of Microorganisms	• Optimum concentration 60%–95%.
Hydrogen peroxide	Inactivates contaminating spores in the bulk solutions or excipients.	• Concentration is as low as 3%. • May fade the coloring agent • Corrosive in nature
Non-alcohol-based hand sanitizer (NABHS)		
Chlor hexidine gluconate		**Good activity** • Gram-positive bacteria • Enveloped viruses [a] **Weak activity** • Gram-negative bacteria • Fungi • Non-enveloped viruses [b]
Chloro xylenol		**Good activity** • Gram-positive bacteria • Gram-negative • Enveloped viruses **Weak activity** • Pseudomonas aeruginosa
Iodine/ Iodophors	Inhibits the growth of microorganisms on living tissues.	**Gram-positive bacteria** • Gram-negative bacteria • Fungi • Enveloped viruses • Spore-forming bacteria [c]
Quaternary ammonium compounds • **Benzalkonium chloride** • **Benzethonium chloride** • **Cetylpyridinium chloride**		**Good activity** • Gram-positive bacteria • Enveloped viruses **Weak activity** • Gram-negative bacteria • Mycobacteria • o Fungi
Triclosan		**Good activity** • Gram-positive bacteria • Mycobacteria • Candida spp. **Weak activity** • Filamentous fungi

Table 4: Excipients used in Hand sanitizer

Excipient	Nature	Action
Glycerol	Acts as humectants that maintain the skin moisture.	A lower concentration is considered to reduce the stickiness of the formulation.
Xanthum gum, polyacrylic acid, polyethylene glycol	Thickening agents	To enhance the viscosity of products
Fragrance and colorant	Aesthetic- Allows differentiation from other fluids.	May cause allergic reactions

[a]herpes simplex virus, influenza, HIV, cytomegalovirus; [b] enterovirus, rotavirus, adenovirus; [c] Clostridium spp., Bacillus spp,

H_2O_2

While alcohol is the active component in the formulations, certain aspects of other components should be respected. All raw materials used should be preferably free of viable bacterial spores. The low concentration of H_2O_2 is incorporated in the formulations to help eliminate contaminating spores in the bulk solutions and excipients[34, 35] and is *not* an active substance for hand antisepsis. While the use of H_2O_2 adds an important safety aspect, the use of 3–6% of H_2O_2 for the production might be complicated by its corrosive nature and by difficult procurement in some countries. Further investigation is needed to assess H_2O_2 availability in different countries as well as the possibility of using a stock solution with a lower concentration.

Glycerol

Glycerol is added to the formulation as a humectant to increase the acceptability of the product. Other humectants or emollients may be used for skin care, provided that they are affordable, available locally, miscible (mixable) in water and alcohol, nontoxic, and hypoallergenic. Glycerol has been chosen because it is safe and relatively inexpensive. Lowering the percentage of glycerol may be considered to further reduce stickiness of the handrub.

Alcohol mechanism of action against Bacteria

The compound, n-propanol, is the most commonly used alcohol compound in biocides. It is not known with much confidence the exact mechanism of alcohol's antimicrobial activity, however, it may be related membrane damage, and inhibition or uncoupling of mRNA and protein synthesis through effects on ribosomes and RNA polymerase, or associated with protein denaturation. For activity against bacteria, its optimal bactericidal efficacy is achieved at concentrations between 60% to 90%.[27, 36]

Alcohol mechanism of action against Viruses

The viral targets of alcohol-based hand sanitizers are predominantly the viral envelope, if present, which is derived from host lipid envelopes, the protein capsid, which contains and protects the genetic material. Given that all these components are essential for the viral life cycle (e.g., attachment, penetration, biosynthesis, maturation, lysis), and thus critical for its ability to transmit to another host, it can be presumed that altering the structure or function of any of the aforementioned components will typically render the virus ineffective. While less is known regarding the specific mechanism of action of alcohols agents against viruses compared to bacteria, it is understood that ethanols have a broader and stronger virucidal activity than propanols. In fact, high concentrations of ethanol have shown to be highly effective against enveloped viruses[34] and thus are effective against the majority of clinically relevant viruses. It is also interesting to note that adding acids to ethanol solutions can increase its efficacy against viruses that are more resistant to ethanol alone. [38]

Benzalkonium chloride

The cationic "headgroup" of BC is progressively adsorbed to the negatively charged phosphate heads of phospholipids in the lipid bilayer, and as a result, increase in concentration.[39] The consistent increase of BC concentration results in reduced fluidity of the membrane and thus the creation of hydrophilic gaps in the membrane. In addition, the alkyl chain "tail" component of BC further perturbs and disrupts the membrane bilayer by permeating the barrier and disrupting its physical and biochemical properties. Protein function is subsequently disturbed and the combination of the aforementioned effects results in the solubilization of the bilayer constituents into BC/phospholipid micelles. BC also interrupts intercellular targets and compromises the conformational behavior of DNA.[40, 41]

Chlorhexidine [42-45]

Similar to alcohol, chlorhexidine works by disrupting the arrangement of cytoplasmic membranes, thereby leading to precipitation of cell contents. It is most effective against Gram-positive bacteria and has modest activity against a Gram-negative bacteria, as well as enveloped viruses. As chlorhexidine is cationic, it is advisable to avoid using chlorhexidine-containing products with natural soaps and hand creams that contain anionic emulsifying agents as they may cause inactivation or precipitation of chlorhexidine, thus reducing its efficacy. Chlorhexidine gluconate 0.12% is likely to have antiviral activity against the coronavirus as it does against other enveloped viruses.

Chloroxylenol [46, 47]

Chloroxylenol is a common agent as a preservative in cosmetics or as an antimicrobial agent in soap. The

antimicrobial effect of chloroxylenol is attributable to its ability to deactivate enzyme systems and alter cell wall synthesis in microbes. It is good at killing bacteria and enveloped viruses but less active against *Pseudomonas aeruginosa*.

Iodine/Iodophors [48-53]

Iodine was once an effective antiseptic used for skin disinfection. It can penetrate the microbial cell wall and form complexes with amino acids or unsaturated fatty acids to impair the synthesis of cellular components. Nonetheless, due to its potential to cause skin irritation and discoloration, iodophors have come into play to replace iodine as the active ingredient in antiseptics. The FDA has not cleared any liquid chemical sterilant or high-level disinfectants with iodophors as the main active ingredient.

Iodophors are a combination of iodine, iodide or triiodide, and a high molecular weight polymer carrier such as polyvinyl pyrrolidone. This carrier is responsible for improving the solubility of iodine, enhancing the sustained release of iodine, and minimizing skin irritation. The degree of antimicrobial activity determined based on the amount of free iodine present in the structure. Having said so, formulations with lower iodophor concentration may have significant antimicrobial activity as well because the amount of free iodine tends to increase after dilution.

Both iodine and iodophors exhibit germicidal activity against a Gram-positive, Gram-negative, and spore-forming bacteria, as well as various fungi and viruses. However, the concentration of iodophors used in antiseptics (e.g., povidone-iodine 5%–10%) is usually insufficient to achieve sporicidal action. Furthermore, the nasal povidone-iodine formulation has shown acceptable tolerability and favorable risk/benefit profile to help mitigate the perioperative spread of COVID-19 in patient decolonization.

Quaternary Ammonium Compounds [54]

Quaternary ammonium compounds are composed of four alkyl groups connected to nitrogen atom in the centre. The typical examples include benzalkonium chloride, benzethonium chloride, and cetyl peridium chloride. They act by adsorbing to the cytoplasmic membrane, thus causing leakage of the constituents. They are more active against Gram-positive bacteria and lipophilic viruses. The activity against fungi, mycobacteria, and Gram-negative bacilli is comparatively weak.

Triclosan [55- 57]

At low concentration, triclosan is bacteriostatic due to its harmful effects to bacterial enzymes responsible for the composition of fatty acid from cells wall and membranes. At high concentrations, triclosan disrupts the bacteria membrane, leading it to death. It has good activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, *Candida spp.* and *Mycobacteria*. The efficacy of triclosan may be affected by pH, use of emollients, and the ionic nature of certain skin formulations.

Other additives to the formulations

It is strongly recommended that no ingredients other than those specified here be added to the formulations. In the case of any additions, full justification must be provided together with documented safety use of the additive, its compatibility with the other ingredients, and all relevant details should be given on the product label. In general, it is not recommended to add any bittering agents to reduce the risk of ingestion of the handrubs. Nevertheless, in exceptional cases where the risk of ingestion might be very high (paediatric or confused patients), substances such as methylethyl ketone and denatonium benzoate may be added to some household products to make them less palatable and thus reduce the risk of accidental or deliberate ingestion. However, there is no published information on the compatibility and deterrent potential of such chemicals when used in alcohol based handrubs to discourage their abuse. It is important to note that such additives may make the products toxic and add to production costs. In addition, the bitter taste may be transferred from hands to food being handled by individuals using handrubs containing such agents. Therefore, compatibility and suitability, as well as cost, must be carefully considered before deciding on the use of such bittering agents.

A colorant may be incorporated to differentiate the handrub from other fluids as long as such an additive is safe and compatible with the essential components of the handrubs However, the H_2O_2 in the handrubs may tend to fade any coloring agent used and prior testing is recommended.

CONCLUSION

With the current study in the literature, it is difficult to confidently suggest one mode of hand sanitizing delivery over the other. A sufficient volume of sanitizer is important to ensure complete hand coverage, and compliance is critical for appropriate hand hygiene. The use of ABHS is becoming more common because of their rapid action and efficiency in killing microorganisms, mainly when hand washing using soap and water is always not practical and convenient. There are, however, some situations in which hand washing is preferred as ABHS are less effective when the hands are visibly dirty or stained and cannot cover certain kinds of pathogens. It is vital to select ABHS with the appropriate amount of alcohol and practice the correct hand hygiene technique when cleaning hands to ensure all the microorganisms are effectively killed. And finally, with extrapolating the virucidal data on viruses of similar structure to SARS-CoV-2, this virus can be effectively inactivated with current hand hygiene products, though future research should attempt to determine this directly.

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