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Review

Hand sanitisers amid CoViD-19: A critical review of alcohol-based products on the market and formulation approaches to respond to increasing demand

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ABSTRACT

The world is facing a medical crisis amid the CoViD-19 pandemic and the role of adequate hygiene and hand sanitisers is inevitable in controlling the spread of infection in public places and healthcare institutions. There has been a great surge in demand for hand sanitisation products leading to shortages in their supply. A consequent increase of substandard products in the market has raised safety concerns. This article, therefore, presents a critical review of hand sanitation approaches and products available on the market in light of the scientific evidence available to date. This review also provides a range of hand sanitisation product formulations, and manufacturing instructions to allow for extemporaneous preparations at the community and hospital pharmacies during this urgent crisis. In addition, this emergent situation is expected to continue, hence hand sanitisers will be in demand for an extended time, and the availability and purchase of substandard products on the market create an ongoing safety concern. Therefore, this article shall also provide various commercial organisations, interested in stepping forward the production and marketing of hand sanitisers, with a guide on the development of products of standardised ingredients and formulations.

1. Introduction

A new infectious disease, namely CoViD-19, was first identified in December 2019 in Wuhan, China (CSSE, 2020) caused by a novel coronavirus (SARS-CoV-2) (Zhu et al., 2020). CoViD-19 has then rapidly spread around the world and was declared as a pandemic by the World Health Organization (WHO). As of 14th April 2020, around two million people have contracted the disease, and over 125 thousand deaths have been attributed to CoViD-19 globally (CSSE, 2020). The outbreak has triggered the so-called “pandemic pantries”, a term that well defines the spikes in stockpiling of emergency supplies all around the world. Among these supplies, stocks of hand sanitisers have rapidly vanished from some markets, as soon as the frequent handwashing and sanitisation was recommended by the public health agencies across the world. According to a market research from Nielsen, the sale of hand sanitisers skyrocketed by 300% and 470% in the last week of February and first week of March 2020, respectively, in comparison to the same time in the previous year (Huddleston, 2020). Similarly, in Italy – one of the most affected countries by CoViD-19 - sales of hand sanitisers in supermarkets augmented by 561% during the first three weeks of the pandemic (24th February-15th March 2020) compared to the previous year (Ufficio Studi Coop, 2020). There have been reports across the world that supermarkets and pharmacies, as well as hospitals and other healthcare facilities, have been running out of hand sanitisers.

A search in Google Trends enables to understand the magnitude of the emergent interest of the general public in hand sanitisers. Google Trends analyse and compare the search volume of given keywords on Google. Fig. 1A shows the trend of the search of the keyword “hand sanitizer” (American English spelling) within the United States. A fairly constant volume of Google searches on this topic was shown until February 2020, when a massive spike of 100-fold increase in interest in “hand sanitizer” appeared. This finding correlated with the increased search of the word “CoViD-19”, hinting the obvious relationship between the two terms. To put these numbers into context, comparison between the search on “hand sanitizer” to that of the words “pill”, “drug” and “medicine” was done in Fig. 1B. Results show that before the spread of the new coronavirus, these words were constantly googled 25–50 times more frequently than “hand sanitizers”, while during the

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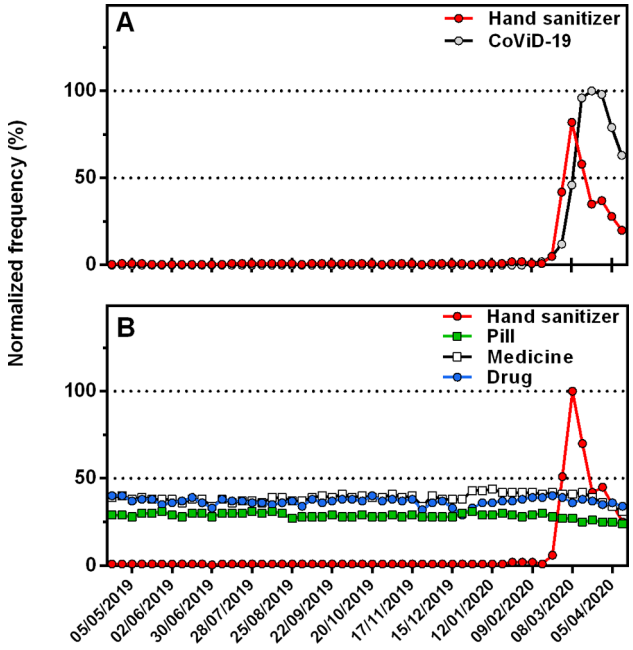

Fig. 1. Trends in the search of the word "hand sanitizer" amid CoViD-19 in the Unites States, extracted from Google Trends on the 20th of April 2020. 1A shows the trend in the google search of the keyword "hand sanitizer" compared to that of "CoViD-19" over the past 12 months. 1B compares the google search for "hand sanitizer" to that of extremely popular medical keywords over the past 12 months. Note that the reported frequencies are not the raw data of the search volume, but are the normalised data against the maximum search interest (i.e. 100%) for that plot.

peak of the pandemic (March 2020), "hand sanitizers" was searched approximately twice as much as those keywords. Although, the astonishing peak of searches on "hand sanitizer" is moderately tapering down, it is expected that the interest in this topic will remain much higher than the pre-pandemic levels, because, until a vaccine against CoViD-19 will be made available, hand sanitisation will remain at the forefront of infection prevention measures. Moreover, it is reasonable to speculate that the current awareness of the general public of the importance of hand disinfection will remain assimilated and will become an integral part of people's hygiene practices, even post-CoViD-19 era.

To respond to the hand sanitiser's severe shortage, not only pharmaceutical companies, but chemical industries, breweries, and perfumeries have started, unconventionally, to produce hand sanitisers (Bomgardner et al., 2020). As academics and pharmacists working in pharmaceutical technology departments of schools of pharmacy, we have received a high number of requests related to hand sanitisers, spanning from other faculties and businesses requesting the production of hand sanitisers in our laboratories, to pharmacists asking for advice on the compounding of such products. Indeed, hand sanitisers can also be prepared extemporaneously in pharmacies; however, pharmacists need an appropriate formulation and manufacturing directions to ensure a consistent product with adequate quality. Consumer habits and patterns are rapidly reshaping under the CoViD-19 crisis (McKenzie, 2020) and the unprecedented demand of hand sanitisers is likely to remain as the "new normal" for an extended period of time. We, therefore, aim to provide in this article a technical perspective on the functionality and development of alcohol-based hand sanitiser formulations.

2. Alcohol-based hand sanitisers as a first-line measure for infection prevention

The general hand hygiene is deemed the cornerstone of infection prevention (Mehtar et al., 2018), and is essential to minimise the colonisation and the transmission of infection across public and healthcare workers. Hand hygiene includes: 1) handwashing, i.e. using simple soap and water; 2) antiseptic handwashing, i.e. using an antiseptic detergent and water; and 3) antiseptic hand sanitisation, i.e., using antiseptic hand rubs, generally alcohol-based hand sanitisers (Gold and Avva, 2020). In Europe, the terms "hand antiseptic" and "alcohol-based hand rub (ABHR)" are more commonly used than the term "hand sanitiser" (Todd et al., 2010).

According to the WHO, an ABHR is "*an alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants*" (Gold and Avva, 2020). Non-alcoholic products are also available, but they are less preferred by the health organisations (Kampf and Kramer, 2004; Todd et al., 2010) - including the Centers for Disease Control and Prevention (CDC) - for fighting CoViD-19 (Howes, 2020). This is due to their poorer efficacy and narrower spectrum compared to the alcohol-based sanitisation products (CDC, 2019a). The most important factor in determining the efficacy of a hand sanitiser is indeed the alcoholic content. Nevertheless, there have been worrying reports of alcohol-free hand rubs being constantly sold during the CoViD-19 outbreak (Allen, Marshall Song, 2020). Consumers must become aware that such alcohol-free products are not recommended by the health organisations and should therefore be avoided.

2.1. Handwash or hand rub?

Overall, the application of ABHRs remains more versatile, convenient, quick and less irritating than hand washing with soap and water (Edmonds et al., 2012). For the general public, the CDC suggests washing the hands with soap and water, rather than to use the ABHR, whenever possible. This is because hand washing can virtually remove all types of pathogens, while the hand sanitiser can effectively kill 99.9% of germs (e.g. less effective with *Cryptosporidium, norovirus, and Clostridium difficile*). Moreover, in case of extremely greasy or dirty hands, ABHR effectiveness is reduced due to poor penetration of the product through the layer of dirt in soiled hands. In contrast, the detergents in a hand wash enable deeper cleaning and higher removal of germs. Moreover, potentially harmful substances can only be washed by a soap and water rather than hand sanitisation using ABHRs. However, handwashing facilities are not readily available at work or public places. Moreover, in instances where hand sensitisation is needed more frequently, such as during frequent contact with individuals or products, the ABHRs are the most effective and convenient infection preventive measure (CDC, 2019a; Hadaway, 2020). It is however important to emphasise that ABHRs only work when used correctly. Thus, considering that not all ABHR formulations are the same, appropriate labelling is important in directing the correct dose/amount needed to achieve an adequate sanitisation (Hadaway, 2020). The choice of container, closure and dispenser is also vital in dispensing the correct amount of the sanitiser on each use.

The CDC recommends a frequent sanitisation of hands in healthcare settings, due to the potential frequent contact of hands with pathogens, while being not so heavily soiled and greased. The ABHRs are therefore the most effective measure of infection control during routine patient care. However, when hands are visibly dirty, such as before and after eating or after using restrooms, healthcare providers need to wash their hands properly with soap and water (CDC, 2019b; Edmonds et al., 2012; Gold and Avva, 2020).

3. Formulation

The ABHRs are healthcare products for topical use which contain active disinfectants and various excipients. Such products always contain a type of alcohol as the main antiseptic, and sometimes combined

with other non-alcoholic antiseptic agents. The excipients include viscosity enhancers, emollients, buffers, preservatives, colourants and fragrances, depending on the type of the formulation (Todd et al., 2010). The concentration of ingredients in this article is reported either in weight (w/w) or volume (v/v), as stated in the original studies. In the cases where it was not clear, data is presented without an indication of w/w or v/v.

3.1. Alcohol

Disinfectant effectiveness in the ABHRs depends on 1) type of alcohol; 2) concentration; 3) quantity applied on hands; 4) time of exposure (Todd et al., 2010). Isopropanol, ethanol, n-propanol, or combinations of these alcohols are most commonly used in hand rubs (Boyce and Pittet, 2002). Unlike other antiseptics, these alcohols do not have the potential for acquired bacterial resistance (Kampf and Kramer, 2004). None of these alcohols is effective against bacterial spores (Weber et al., 2003). When used at the same concentration, ethanol seems to have a lower bactericidal activity than propanols (Suchomel and Rotter, 2011). However, ethanol has superior viricidal activity than propanols against non-enveloped viruses (Kampf, 2018a). Also, skin tolerance is better with ethanol compared to n-propanol or isopropanol (Cartner et al., 2017; Houben et al., 2006), thus ethanol is often the alcohol of choice in the ABHR preparations (Suchomel and Rotter, 2011; Tarka et al., 2019).

Ethanol concentrations of 60% to 95% (v/v) are deemed safe and effective for disinfection by the United States Food and Drug Administration (US FDA), CDC and the WHO (Boyce et al., 2009; CDC, 2019a; FDA, 2020, 1994), including for use against SARS-CoV-2. Interestingly, Edmonds et al. suggested that the antimicrobial activity of the ABHRs is highly dependent on the choice of formulation (i.e., excipient) rather than on the concentration of alcohol. They also suggested that the liquid, gel and foam-based products can all be equally effective if the ethanol content used was within the 60–95% standard range (Edmonds et al., 2012). However, increasing ethanolic concentrations of hand rubs from 80% to 85% (v/v) can reduce the contact time necessary to achieve an efficient bactericidal activity (Suchomel et al., 2012; Eggerstedt, 2013; Wilkinson et al., 2017). Despite this, the WHO, US FDA and CDC still maintain their recommendations of 60–95% ethanol content in ABHRs. An analysis of some currently marketed products (discussed later in section 5) reveals indeed that ABHRs, sold in Italian pharmacies as biocides, contain percentages of ethanol between 62% and 74% (w/w)/(70% to 80% v/v). This goes in line with the standard WHO, US FDA and CDC guidelines (Boyce et al., 2009; CDC, 2019a; FDA, 2020, 1994). It is worth highlighting that ethanol, unlike water, has a density < 1 g/cm^3, which means that percentages of ethanol in water by weight (w/w) and by volume (v/v) can be significantly different and must be specified on the label. A useful comparison between percentages by weight and by volume of ethanol in ABHRs is reported in a recently published document (BDC, 2020). Although this concept might seem trivial, there are cases of published works, where the concentration expression (either w/w or v/v) was not specified, as indicated by Kampf (Kampf, 2018), ultimately presenting ambiguous information. In research work, compounding and manufacturing, it is recommended to clearly specify the concentration units of alcohol used in ABHRs.

According to the US FDA's Tentative Final Monograph (TFM) for health care antiseptics, isopropanol should be used as an antiseptic alcohol at concentrations between 70 and 91.3% (v/v) (FDA, 1994). This range of concentration has also been re-endorsed by the US FDA for the preparation of ABHR during the CoViD-19 health emergency (FDA, 2020).

Although biocidal agents other than alcohol have been incorporated in hand sanitisers (Kampf and Kramer, 2004; Todd et al., 2010), their efficacy is considered inferior to alcohol. Also, their addition to alcohol-based sanitisers did not seem to have superior bactericidal efficacy (Kampf et al., 2017). Moreover, unlike alcohol, certain biocidal agents may also cause antibiotic resistance, hence they are no longer preferred for use in ABHRs (Kampf, 2018b).

3.1.1. Do alcohol-based hand rubs kill the CoViD-19 coronavirus?

There are some reports of novel formulations emerging on the market claiming to be effective against all viruses, including SARS-CoV-2 (Dei Pharmaceuticals, 2020); however, there is no evidence yet published to support the label claims. In a recent article, Jansen has examined the evidence on disinfectants efficacy against SARS-CoV-2 (Jansen, 2020). It was noted that definitive claims on the effectivity of various disinfectants against SARS-CoV-2 cannot be made, simply because this is a new virus and the range of off-the-shelf ABHRs has never been tested for SARS-CoV-2. Like other respiratory viruses, the new coronavirus is known to spread mainly from person-to-person through airborne droplets (CDC, 2020). Moreover, the information about the virus survival on surfaces and the environment is still limited (Jansen, 2020). It has, however, been indicated that SARS-CoV-2 can also be transmitted through surfaces, as it can survive for a long period of time on various materials; for instance, the virus remains stable on plastic and stainless steel for 2–3 days (van Doremalen et al., 2020). This implies that anyone touching infected surfaces can potentially contact and spread the virus (Jansen, 2020). It is in this context that hand disinfection becomes highly crucial.

SARS-CoV-2 is an enveloped virus hinting the presence of a lipid layer protecting the viral core. Typically, enveloped viruses can be effectively inactivated by most antiseptic agents (Jansen, 2020). A study in 2017 reported that Zika (ZIKV), Ebola (EBOV), severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) and other enveloped viruses were all efficiently killed by two alcohol-based formulations, one containing ethanol 80% (v/v) and the second containing isopropyl alcohol 75% (v/v), recommended by the WHO (Siddharta et al., 2017). These data confirm that ABHRs can be successfully used as an effective infection preventive measure during viral outbreaks.

A recent unpublished study reveals that both commercial alcohols and the WHO-recommended alcohol-based hand rubs can effectively inactivate SARS-CoV-2, the virus responsible to cause CoViD-19 (Kratzel et al., 2020). Remarkably, both ethanol and 2-propanol, individually, could kill the virus within 30 s at a minimal final concentration of $\geq$ 30% (authors did not specify the concentration units). This provides a strong evidence to support the use of ABHR amid the CoViD-19 outbreak. Efficacy of alcohols in hand sanitisation is also dependent on various other factors, such as the quantity applied to the hands (the dose), the exposure time, and the application/rubbing technique.

How long hands need to be rubbed together when using an ABHR is an important question, but the recommended time by various public health organisations varies from as low as 10s to 60s (Boyce et al., 2009). It has been argued that rubbing time is significantly affected by various other factors such as the dose of the sanitiser, the hand size (application surface area), and the formulation itself. Wilkinson et al. (2017) reported that drying time was strongly associated with the dose and hand surface area. The evaporation rates of alcoholic ingredients may vary in gel and liquid-based sanitisers and may directly correlate to the time when hands start to feel dry after application. This can, therefore, directly influence healthcare professionals' perception of the sufficient rubbing time (Kenters et al., 2020).

The sanitisation dose may be controlled by using specialised containers and closure systems, such as pump containers, that may dispense a pre-calibrated amount on each dispensing. This can guarantee that a minimum effective dose is always dispensed to assure efficacy. However, the dose is subject to sanitisation surface area and may be subject to users' perception on how much is sufficient. An adequate training on hand hygiene and sanitisation amid infection control within health care facilities, is, therefore, a key to ensure that a correct dose

and technique are always used. However, this is complicated by the range of formulations and products available on the market with varying viscosity and alcoholic evaporation rates. A standardised monographed formulation with tightly controlled specification can be a way forward.

3.2. Emollients

Alcohol in hand rubs can cause skin dryness, particularly over frequent exposure. Emollients, as well as other skin conditioners, have been shown to decrease the drying effect of alcohol on the skin (Ahmed-Lecheheb et al., 2012; Harbarth et al., 2002; Kramer et al., 2002).

Glycerin is the most commonly used humectant in hand sanitisers and other cosmetic products. Houben et al. have shown that incorporation of glycerin in hand rubs promotes hand hydration, to an extent that is directly proportional to its concentration in the formulation (Houben et al., 2006). In another study, ABHRs containing glycerin were found to increase skin hydration, but also to decrease the surface pH and superficial sebum content on the skin, although not to an extent to compromise the skin barrier function (Ahmed-Lecheheb et al., 2012). A very high concentration of glycerin can also have detrimental effects, as it can slow down the drying time and can increase the sticky sensation on the skin (especially if large or repeated doses are used) (Greenaway et al., 2018; Houben et al., 2006). Glycerol can lower the bactericidal activity of ABHRs when used at a concentration of 1.45% (v/v) (Suchomel et al., 2013). Reducing glycerol content to concentrations of 0.50% − 0.73% has been proposed as the best compromise in maintaining antimicrobial activity, while still offering the needed skin protection (Menegueti et al., 2019; Suchomel et al., 2017).

Emollients other than glycerol, can also be used to improve user acceptability and skin tolerance of the ABHRs (Suchomel et al., 2017, 2013). In a recent study, Suchomel et al. have shown that the bactericidal efficacy of an isopropanol-based hand rub was decreased by glycerol, but not by a novel humectant, made of ethylhexylglycerin, dexpanthenol and a fatty alcohol. Authors have suggested that other humectants should also be screened for their ability to maintain microbial efficacy (Suchomel et al., 2017).

Propylene glycol is the second most used humectant in cosmetic products and it is generally used for this purpose at concentrations of 2% to 5%. Being less expensive than glycerol, it can be more desirable to be used in hand sanitisers (Barel et al., 2009; Flick, 1989). Aloe Vera gel has also been used for long in various cosmetic products as a humectant, being able to retard water evaporation from formulations, yet to a lower extent than glycerin and propylene glycol. Aloe Vera gel can be used in combination with glycerol and propylene glycol to improve their water evaporation retardation effect. At high concentrations (i.e., ≥25%), Aloe Vera gel can also contribute to the firmness of formulations (Meadows, n.d.). Aloe Vera-based healthcare products, being considered natural, constitute nowadays a large and growing market (Javed and Atta-ur-Rahman, 2014). This is probably related to an increasing interest of consumers towards natural products. Thus, the incorporation of Aloe Vera gel in hand rubs can be considered a good marketing strategy for ABHRs.

3.3. Viscosity enhancers

The WHO has recommended and described the preparation of two alcohol-based formulations for local production, when commercial products are not available (WHO, 2009). Such formulations are liquids of low viscosity. Although effective, runny liquids are difficult to handle, as spillage often occurs during application. Thus, liquid formulations can leave suboptimal doses of disinfectants on the hands, potentially leading to decrease in product efficacy (Greenaway et al., 2018). For the consumer market, gel formulations are more portable and convenient to dispense on-the-go due to their ease of use and low risk of spillage compared to liquid-based products. Gel-based formulations also reduce the evaporation rate of alcohol and help alcohol to spread and penetrate through contaminating organisms (Fu et al., 2020; Howes, 2020). Gels can be obtained by incorporating viscosity enhancer excipients in the formulation. A huge variety of thickening agents for the pharmaceutical, cosmetic and food industry are available. Although the performance of these substances is well characterised in aqueous media, little is known about their behaviour in hydroalcoholic solvents.

In the next sections, rheological characteristics, preparation procedures and stability of the most commonly used viscosity enhancers in hand rubs will be discussed. We narrowed down the search by examining thickening agents that have been recommended by authentic sources as being suitable for the preparation of alcoholic gels. In particular, we have focused on viscosity enhancers suggested by the SIFAP (Italian Society of Compounding Pharmacists) in its recent newsletter (SIFAP, 2020) issued by the Federfarma (Italian Federation of Pharmacy Owners) (Federfarma, 2020) for the preparation of alcoholic gels amid CoViD-19. These viscosity enhancers include carbomer, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethyl cellulose (CMC).

3.3.1. Rheological analysis of commercial hand sanitisers

Thickeners are polymers that, differently from small molecules, cannot be univocally identified by the chemical name or CAS number, which does not take into consideration relevant features such as molecular weight, degree of substitution, ratio between substituents, etc. Indeed, each of the aforementioned viscosity enhancers is commercially available in a variety of grades, exhibiting variable thickening behaviour, rheological properties, solubility and even regulatory classification (e.g. pharmaceutical, or cosmetic, or food grade). The actual grade and the percentage of the polymer used in commercially available ABHRs are, however, not known or disclosed on the label. For these reasons, selecting the appropriate excipient for a particular application is important. To help with this, we have analysed and hereby report the viscosity and rheological behaviour of various commercially available hand sanitisers in Italy. Such measured parameters of marketed products were then used as a reference to explain how gels of similar characteristics can be manufactured using different viscosity enhancers.

The thickening behaviour of 10 commercial hand sanitisers sold in the Italian market was analysed. All the products were tested by measuring the shear stress on increasing shear rate (viscometry test) to study the effect of shear rate on viscosity (details relative to the experimental procedures are reported in Method SM 1 and Fig. SF1 in supplementary information). We only tested hand sanitisers from a single pack taken from a single batch for each product. The general behaviour of all the products is reported in Fig. 2 and Table 1. As expected, most of the ABHRs exhibited a shear-thinning behaviour, as typical of polymeric dispersions. The only exception was the product containing HEC which resembled the Newtonian behaviour and exhibited very low viscosity. Noteworthy, the product containing HEC

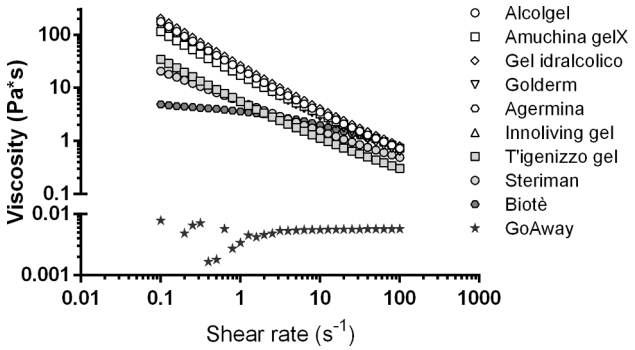

Fig. 2. Average viscosity (n = 3) of commercial hand sanitisers as a function of the shear rate measured at 20 °C.

Table 1
Analysis of rheological behaviour of some commercially available hand sanitisers.

ProductRhelogicalbehaviour		Amuchina X germ (A.C.R.A.F. S.p.a.)	Alcogel gel Igienizzante Mani (Sydex S.p.a.)	Gel idralcolico igienizzante delle mani (Th Pharma)	Innoliving gel (Innoliving S.p.a.)	Apoteke T'igienizzo (ABC Italia S.r.l.)	Biotè scudo gel igienizzante mani (PDT Cosmetici S.r.l.)	Go Away! Gel mani (OSCO PHARMA S.r.l)	Steriman Gel Igienizzante Mani (PromoPharma S.p.a.)	Golderm xbact (Shedir pharma S.r.l)	Agermina gel Igienizzante Mani (BB farma S.r.l.)
Ethanol*		74%	> 62%	N/R	50%	60%	N/R	> 61%	N/R	N/R	66%
Thickener		N/R	Carbomer	Carbomer	Carbomer	Carbomer	HPMC	HEC	Carbomer	Carbomer	N/R
Viscosity:Power law model with yield	**Power law viscosity ($Pa{\cdot}s^{PLI}$)**	8.75 ± 0.19	6.56 ± 0.14	8.24 ± 0.06	8.84 ± 0.78	2.83 ± 0.29	The model provided a yield stress < 10^{-16},	The model provided a yield stress < 10^{-16},	4.37 ± 0.23	5.33 ± 0.25	6.27 ± 0.81
	Power law index	0.43 ± 0.02	0.46 ± 0.00	0.44 ± 0.00	0.43 ± 0.01	0.51 ± 0.00	that is, it became equal to the power	that is, it became equal to the power	0.52 ± 0.00	0.48 ± 0.01	0.45 ± 0.01
	Yield stress (Pa)	8.37 ± 1.20	15.69 ± 0.78	18.09 ± 1.14	8.68 ± 1.27	2.83 ± 0.29	law model	law model	1.02 ± 0.11	12.22 ± 0.38	17.35 ± 0.98
	R^2	0.999 ± 0.000	0.999 ± 0.000	0.999 ± 0.000	0.999 ± 0.000	0.999 ± 0.000			0.999 ± 0.000	0.999 ± 0.000	0.999 ± 0.000
Viscosity:Power law model	**Power law viscosity ($Pa{\cdot}s^{PLI}$)**	16.72 ± 0.31	22.08 ± 0.93	26.27 ± 1.24	17.09 ± 0.98	6.07 ± 0.40	4.77 ± 0.04	0.01 ± 0.00	5.13 ± 0.32	17.24 ± 0.98	23.67 ± 1.28
	Power law index	0.31 ± 0.01	0.24 ± 0.00	0.23 ± 0.01	0.31 ± 0.01	0.38 ± 0.01	0.61 ± 0.00	1.01 ± 0.00	0.48 ± 0.01	0.25 ± 0.00	0.21 ± 0.00
	R^2	0.989 ± 0.004	0.966 ± 0.001	0.969 ± 0.002	0.989 ± 0.004	0.988 ± 0.001	0.998 ± 0.000	0.999 ± 0.000	0.999 ± 0.000	0.967 ± 0.003	0.961 ± 0.002
Brookfield Viscosity (Pa·s)**	**30 rpm**	4.41 ± 0.14	4.95 ± 0.17	5.81 ± 0.21	4.50 ± 0.23	1.51 ± 0.08	2.34 ± 0.01	0.01 ± 0.00	1.98 ± 0.10	4.02 ± 0.07	5.06 ± 0.31
	60 rpm	2.73 ± 0.10	2.93 ± 0.10	3.42 ± 0.10	2.79 ± 0.14	0.97 ± 0.05	1.80 ± 0.01	0.01 ± 0.00	1.43 ± 0.15	2.41 ± 0.04	2.77 ± 0.13
Notes								Presence of white particles at the bottom of the container	Appearance: slightly opaque		

* The % of ethanol amount is %w/w for the products authorized as Biocide, while the specific unit of measurement is unknown (not reported) for the cosmetic ones.
**The rpm values refer to the Brookfield Spindle LV4 (64) and were calculated from the shear rate values using the conversion factor provided by Brookfield (Brookfield engineering laboratory, more solutions to sticky problems: a guide to getting more from your Brookfield viscosimeter and rheometer; 2014).

also showed white precipitates settled on the bottom, which on shaking resulted in a cloudy system. All the other alcoholic gels containing carbomer had a characteristic plastic behaviour (refer to Table 1 for the yield stress values) with a strong shear rate dependency (power law index < 0.5 in Table 1). All the carbomer-thickened gels showed almost superimposable viscosity profiles except for "Apoteke T'igienizzo" and "Steriman Gel", which were characterised by a lower consistency. Finally, the only product containing HPMC showed the typical behaviour of a weak gel, characterised by pseudo-plasticity and a moderate shear rate dependency (power law index almost double compared to carbomer gel, but still much lower than 1). Interestingly, the HPMC-based gel exhibited a viscosity similar to that of the carbomer-based gels at the higher shear rates.

Overall, the unique and stronger shear rate dependency of carbomer-based products means that, compared to other gels, they are more solid-like on standing and become more liquid-like under agitation (shear-thinning). This dual behaviour is a desirable feature for hand rubs, as the carbomer gel will have an attractive robust consistency, a nice appearance and could still be dispensed in consistent doses - not being runny. Then, during application, the viscosity would decrease drastically under the high shear of the hand rubbing action, which will help in well spreading of the product over the surface area.

3.3.2. Carbomer

Carbomers, also known as carboxypolymethylene, are a series of synthetic, high molecular weight and cross-linked poly-acrylic acid polymers, widely used in cosmetics and pharmaceutical industries for the formulation of semisolid and oral liquid products of various consistencies. These polymers are effective thickeners, suspending agents and stabilisers at a very low concentration (0.1–3% w/w). Carbomers differ by the cross-linker and its density, and the solvent used during their polymerisation. Based on the cross-linker type, carbomers can be grouped into carbomer homopolymers (acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol), carbomer copolymers (acrylic acid and C10-C30 alkyl acrylate crosslinked with allyl pentaerythritol), and carbomer interpolymers (carbomer homopolymer or copolymer that contains a block copolymer of polyethylene glycol and a long chain alkyl acid ester). For each category, the cross-linking density can be low, medium, or high, providing polymers with a varying ability to increase the viscosity of aqueous systems. The "traditional" carbomers are still synthesised in benzene, a toxic solvent that cannot be used for pharmaceutical applications. The pharmaceutical-grade carbomers are synthesised in either ethyl acetate or a mixture of ethyl acetate and cyclohexane. For an unambiguous designation of these copolymers, numeric codes such as 910, 934, 940, 941 are used as the suffix within the carbomer nomenclature to provide an indication of their molecular weight and specific components of the polymer (Lubrizol, 2005).

All carbomers must be neutralised to pH 6.5–7.5 to achieve the maximum viscosity; the consistency of the dispersion starts to decrease at pH $\geq$ 9.0. For aqueous dispersions, a large number of neutralising agents such as sodium hydroxide, ammonium hydroxide, potassium hydroxide, L-Arginine, aminomethyl propanol, tetrahydroxypropyl ethylenediamine, triethanolamine, tromethamine, PEG-15 cocamine, diisopropanolamine and triisopropanolamine can be used. When carbomers are used for thickening of ethanol, isopropanol or hydroalcoholic mixtures (like in hand sanitisers), the neutraliser must be selected carefully to avoid the precipitation of the polymer. Metallic alkalis, such as NaOH and KOH, are recommended to be used in hydroalcoholic mixtures of up to 20% ethanol, and triethanolamine in those containing up to 50–60% ethanol. Considering the percentage of ethanol generally employed in the formulation of hand rubs (60–95%), the most suitable neutralisers are tetrahydroxypropyl ethylenediamine (Neutrol® TE), aminomethyl propanol (AMP® Ultra PC2000) and triisopropanolamine (up to 80–90% of ethanol) (Lubrizol, 2002).

Carbomers have thickening properties much higher than cellulose derivatives at a pH range of 5–9. A typical 0.5% (w/w) carbomer solution at pH 7.5 exhibits viscosities in a range of 4000–11,000 mPa·s (Carbopol® 971P), 29,400–39,400 mPa·s (Carbopol® 974P) and 40,000–60,000 mPa·s (Carbopol® 980); those are the grades commonly employed in topical products such as lotions, creams and gels (Lubrizol, 2009). An evaluation of the effect of ethanol on the consistency of the hydrogel prepared in hydroalcoholic media is not straightforward; comparison studies on hydrogels in pure water and in hydroalcoholic media are lacking. One report, that compared the flow behaviour of Carbopol® Ultrez™ 10 (0.1–0.5 w/w) in aqueous and hydroalcoholic media (15% w/v and 30% w/v ethanol) (Fresno et al., 2002), showed that the presence of ethanol decreases the consistency of the hydrogel. The decrease in consistency was more pronounced at a polymer concentration of 0.1% w/w than at 0.5% w/w, and at a low pH (pH = 4). Osei-Asare et al. also prepared a gel using 62% v/v of ethanol with 0.81% v/v Carbopol® 940, but unfortunately, viscosity data were only partially reported (Osei-Asare et al., 2020).

Some manufacturers have also provided guidance on carbomer selection for hydroalcoholic gels. Lubrizol suggested the use of Ultrez™ due to their higher transparency and ease of preparation (Lubrizol, 1998); while Ashland proposed Carbomer 980 at around 0.35% for a gel with 72% w/w of ethanol (Ashland, 2018a). Considering this and our experience, we recommend 0.3–0.6% high viscosity carbomers (Carbopol® Ultrez™ 10, or Carbomer 980) or 0.5–1% medium viscosity types (Carbomer 974) along with aminomethyl propanol as a neutralising agent for the preparation of ABHRs.

3.3.3. Hydroxyethyl cellulose

HEC is a non-ionic partially substituted poly(hydroxyethyl) ether of cellulose, available under the trade name of Natrosol™ (Ashland) or Cellosize (Dow). It is prepared by the reaction of ethylene oxide with cellulose in the presence of sodium hydroxide under controlled conditions. Each glucose unit of the cellulose backbone contains three hydroxyl groups capable of reaction. If all three hydroxyl groups of each glucose residue react, the theoretical degree of substitution (DS) would be 3, although this is not practically achievable. The introduced hydroxyethyl groups can, indeed, react again with the free ethylene oxide at basic conditions, giving a side chain containing a different number of hydroxyethyl groups. To account for this, the total molar substitution (MS) describes the average number of ethylene oxide molecules attached to each glucose residue. HEC with DS and MS of 1.5 and 2.5 respectively, is known as Natrosol™ 250. Natrosol™ 250 is available in a range of molecular weight grades (L, M, H, HH) differing in their aqueous viscosity, where the L, M, H, HH refers to low, medium, high and very high viscosity, respectively. Furthermore, the pharmaceutical-grade of the product is indicated by the abbreviation Pharm, whereas the cosmetic grade is indicated by the abbreviation CS (Aqualon, 2000; Ashland, 2018b). HEC is easily dissolved in cold or hot water, but unlike other cellulosic derivatives, it is insoluble in organic solvents. The low or medium molecular weight types are fully soluble in glycerol and have a good solubility in hydroalcoholic media containing up to 60% ethanol (Ashland, 2018b). Specifically, the manufacturer indicates that HEC is "soluble" in a 70:30 water/ethanol mixture and partially soluble in a 40:60 water/ethanol mixture, both at 25 °C and 60 °C (Ashland, 2018b).

Natrosol 250 has been used as a thickener, rheological modifier, colloidal protective, stabiliser and suspending agent. The viscosity of aqueous dispersions increases with increasing the concentration and molecular weight (MW) of HEC used. For instance, at a concentration of 2% w/w, the viscosity increases from around 20 mPa·s for L-type polymer up to around 100,000 mPa·s for HH-type. The manufacturer does not provide further information regarding the viscosity of HEC dispersions in hydroalcoholic mixtures (Aqualon, 2000). Brown et al. measured and compared the elastic modulus G' of 3% HEC (the type was not specified) dispersions in water and in hydroalcoholic mixtures containing up to 60% ethanol. The measured G' was 354 Pa in water. The consistency of the dispersion reached a maximum at 30% ethanol

(470 Pa), then decreased again at 40% or higher ethanolic concentrations. The viscosity dropped to 229 Pa in 60% ethanol due to poor hydration of the polymer in less aqueous media (Brown et al., 1998). Therefore, high molecular weight HEC (1–2%) could be suitable for the preparation of hand rub gels containing 50–60% ethanol. HEC gel formulations containing > 60% alcohol are not recommended, due to the poor solubility of the polymer and the cloudy appearance that results, as shown in Fig. SF2 (supplementary information). Since 60–95% ethanol is necessary for efficient hand disinfection, HEC does not seem to be a suitable viscosity enhancer for ABHRs.

3.3.4. Hydroxypropyl cellulose

HPC is a non-ionic water-soluble ether derivative of cellulose with remarkable aqueous thickening and stabilising properties. HPC is manufactured by Ashland and commercialised under the trade name of Klucel™. It is made by reacting alkali cellulose with propylene oxide at elevated temperatures and pressures. At these conditions, an ether linkage can be formed between propylene oxide and one or more of the three reactive hydroxyl groups of each glucose monomer unit of the cellulose chain. The degree of substitution usually varies from 1 to 3, but can be > 3 if the secondary hydroxyl group in the side chain reacts with propylene oxide (Ashland, 2017).

HPC is a cellulose derivative soluble in the broadest range of solvents, such as water (up to 40 °C), alcohols, many polar organic solvents, polyethylene glycol and propylene glycol (Klucel™hydroxypropylcellulose. Physical and chemical properties, 2017). High purity HPC (0.2% ash maximum) is produced for food (F), cosmetics (CS) or pharmaceutical applications (F Pharm). Seven further grades of HPC are available on the base of viscosity/ MW and are designated as EL, E, L, J, G, M, and H in the order of viscosity (Klucel™hydroxypropylcellulose. Physical and chemical properties, 2017).

HPC has been used as a thickening agent providing aqueous systems with a broad viscosity, ranging from < 10 mPa·s to > 10,000 mPa·s, depending on the type used (at 2% wt). In pure water, viscosity increases exponentially to the increase in concentration. Particularly, a maximum viscosity > 10,000 mPa·s can be reached in the range of 0.5–5%(w/w) for the high MW grades (i.e. H, M and G). A maximum viscosity of around 1,000 mPa·s can be reached using the intermediate MW grades (i.e. J, L) at 8–10%(w/w); while a maximum viscosity between 100 mPa.s and 1,000 mPa.s can be obtained using the low MW grades (i.e. E and EL). Limited information is available regarding the effect of ethanol on the viscosity of HPC systems. It is possible to prepare a clear hydrogel using 100% ethanol as a dispersion medium for high, medium and low MW HPC grades. However, gels prepared with 100% ethanol have a slightly lower viscosity than the systems prepared in 100% water. The percentage decrease in viscosity in pure ethanol is more marked for high and intermediate MW HPC, with respect to the low MW HPC. Moreover, the viscosity of gels of HPC in hydroalcoholic media is much higher than gels prepared with pure solvents (even water), at least for the intermediate MW polymers. For instance, 2% HPC gels in a hydroalcoholic mixture (30:70 ethanol/water) had a viscosity of 500 mPa·s, which is higher than those in pure water or ethanol (270 mPa·s and 210 mPa·s, respectively) (Klucel™hydroxypropylcellulose. Physical and chemical properties, 2017). The same trend was reported by Ramachadran et al. for the viscosity of 3% (w/w) HPC type G in 50:50 hydroalcoholic gels compared to the same gels in pure water and pure ethanol (Ramachandran et al., 1999).

Ashland (the manufacturer) suggested using the highest MW type of HPC (i.e. type H) at a concentration of 1.1% in a hydroalcoholic gel with 72% (w/w) ethanol (Ashland, 2018a). Interestingly, the viscosity profile reported for the HPC hydroalcoholic gel is superimposable to the viscosity of “Biotè scudo gel”, a commercially available ABHR thickened with HPMC (Fig. 2). Therefore, we recommend a high molecular weight HPC (~1–1.5%) for the preparation of ABHR gels.

3.3.5. Hydroxypropyl methylcellulose

HPMC, aka hypromellose in the European and United States pharmacopoeias, is a cellulose ether derived from cellulose, widely used in various industries such as pharmaceutical, cosmetic, food, paints, etc. HPMC has a cellulose backbone with methyl and hydroxypropyl substituent groups. Commercially available HPMC (e.g. Methocel, Metolose, Pharmacoat, Vivacoat, Vivapharm, Benacel) are characterised by differences in terms of abundance of methyl and hydroxypropyl groups and their molecular weights. An initial 4-digit number defines the abundancy of the substituent groups, specifically 2910 (or type E according to Colorcon) indicates a methoxy substitution of 28–30% and a hydroxypropyl substitution of 7–12%; 2208 (or type K according to Colorcon) indicates a methoxy substitution of 19–24% and a hydroxypropyl substitution of 7–12%; while 2906 (or type F according to Colorcon) indicates a methoxy substitution of 27–30% and a hydroxypropyl substitution of 4–7%. The numeric code in the nomenclature is followed by the viscosity (mPa·s) of a 2% aqueous solution. For instance, Hypromellose 2208 4 M is a HPMC having methoxy and hydroxypropyl contents of 19–24% and 7–12% respectively, exhibiting a viscosity of 4 mPa·s at 2% in water (DOW, 2002; Li et al., 2005).

HPMC is commonly used as a thickener in aqueous solutions and is extensively researched in the literature. It is also used in a large variety of binary solvent systems as per manufacturer (DOW, 2002), however, it is not much used in non-aqueous solvents. Brown et al. reported the values of storage moduli of 5% HMPC hydroalcoholic mixtures up to 80% ethanolic medium. Like HEC and HPC, the viscosity behaviour followed a bell-shaped curve, with a maximum viscosity at ~50% ethanol. The viscosity of the mixture decreased to a level equal to that of pure water when the ethanol approached 80% (Brown et al., 1998). Robert et al. studied the effect of ethanol, up to a concentration of 40% for gels containing 2% HPMC 2208 4 M, and found a similar observation to that of Brown et al. (Roberts et al., 2007).

Interestingly, the rheology of 2% HPMC 2208 4 M gels in 10–40% hydroalcoholic mixtures from Roberts et al. (2007) is similar to a commercially available ABHR, which is “Biotè scudo gel”, thickened with HPMC (Table 1). Also, the viscosity profile of 1.5% HPMC 2208 10 M gel containing 72% w/w of alcohol from Ashland (Ashland, 2018a) was similar to that of the commercially available product “Biotè scudo gel” (Fig. 2). Acknowledging that the commercial product (unknown polymer concentration) and the gels reported in the literature (known polymer concentration) have similar viscosity, the use of HPMC 10 M ~ 1.5% and HPMC 4 M ~ 2–2.5% (both types 2208 and 2910) for the preparation of ABHRs is recommended.

3.3.6. Sodium carboxymethyl cellulose

CMC is a water-soluble anionic derivative of cellulose that acts as a thickening agent, rheological modifier, stabiliser, protective colloid, and a film-forming agent. CMC is made by the reaction of cellulose with sodium monochloroacetate in the presence of sodium hydroxide under strictly controlled conditions (Feddersen and Thorp, 1993). CMC is available from Ashland under the tradenames Aqualon™ CMC and Blanose™ CMC, depending on the site of production; and by other manufacturers with trade names such as Tylose CB and Walocel C. As for the other cellulose derivatives, the physical properties of CMC can be varied by the DS and MW. CMC is typically offered in three different DS such as 0.7, 0.9 and 1.2 (referred to as CMC type 7, 9 and 12) and a broad range of molecular weights indicated by the letter L (low), M (medium) and H (high). The regulatory classification is given by the letters “F” for food; “CS” for cosmetic; and “PH” for pharmaceutical compliance, according to US, European (EU) and Japanese (J) pharmacopoeia (Ashland, 2012).

CMC is soluble in water at all temperatures, and forms clear colloidal dispersions at 1–6%, with viscosity between 10 and 10,000 mPa·s. It is practically insoluble in most organic solvents, including ethanol (95%). However, it can be dispersed providing clear systems in hydroalcoholic mixtures of up to 40% ethanol. At higher

contents (up to 60% ethanol), CMC can be dispersed, but it provides opaque systems. Low-viscosity grades work better with alcoholic gels than high-viscosity types, which show clouding and polymer precipitation at higher ethanol content. The manufacturer does not provide any information regarding the effect of ethanol on the viscosity of the dispersions (Feddersen and Thorp, 1993). The only reference available is from Brown et al. who compared the viscosity of 10% CMC (the type and MW is not specified) in pure water and hydroalcoholic mixtures (up to 40% ethanol). A remarkable increase in the viscosity was observed from pure water (G' 432 Pa) to a mixture containing 30% ethanol (G'1186 Pa), followed by a drop (G' 671 Pa) at 40% ethanol which may be attributed to the poor solubility of CMC in higher alcoholic media (Brown et al., 1998). According to the literature, low viscosity CMC (being more stable in ethanol) is more suitable for the preparation of gels with a maximum ethanol concentration of 50%. In our experience, it was found that CMC dispersions precipitate and become opaque at 60% (w/w) ethanolic concentrations (Fig. F3, supplementary information). It is therefore not advisable to use CMC for ABHRs containing higher ethanol concentrations recommended for optimum germicide efficacy.

4. Preparation method for alcohol-based hand sanitiser gels

Fig. 3 summarises the different procedures that can be used for the manufacturing of ABHR gels.

4.1. Direct addition method

In the direct addition method, all the components, except for the thickener, have to be preliminarily solubilised in the water/ethanol mixture. Then, the thickener is added, preferentially sifted slowly, in the vortex of the vigorously agitated hydroalcoholic solution (with mechanical or magnetic stirring) (Aqualon, 2000; Klucel™hydroxypropylcellulose. Physical and chemical properties, 2017; Lubrizol, 1998). For carbomer thickeners, it is necessary to raise the pH to around 6.5–7 with the neutralising agent. The neutralising agent has to be added dropwise or gradually after the complete dispersion of the polymer, possibly monitoring the pH with a pH-meter (using electrodes suitable for measuring viscous or dirty samples) or a pH-indicator paper. Gel preparation using this procedure is faster with the surface-treated grades of thickeners such as Carbopol® Ultrez types for carbomer or Natrosol R-grades for HPC, due to the low lumpiness of these polymers when dispersed [for carbomer Ultrez grades the direct method should be slightly modified - for more details readers are referred to (Lubrizol, 1998)]. Also, all carbomer thickeners are faster to disperse than the others due to their pH-dependent viscosity. They remain in the liquid phase during product preparation until the pH is adjusted to neutral. This is an advantage as solvent diffusion and polymer hydration are much more rapid in liquid state than in an already formed gel system. On the other hand, the direct addition method can be slower and more difficult for HPMC and HPC gels (even for surface-treated grades), due to their high tendency to form lumps during dispersion. The direct addition method is a very effective and economical procedure, as long as an efficient stirring system is available for production.

4.2. Reverse addition method

This procedure requires the thickeners to be pre-wetted with a water-miscible organic solvent. In our experience (this is the standard procedure used in pharmaceutical practice), the best results can be obtained using glycerol or propylene glycol as wetting agents at 1:1 to 1:4 polymer:wetting agent ratio. The wetting procedure is usually operated using mortar and pestle. When a homogenous wet slurry is obtained, the hydroalcoholic solution (containing all the other components previously dissolved) can be gradually added, always under vigorous stirring with the pestle. The addition of the neutralising agent for carbomer polymers follows the same procedure reported in the direct addition method. The reverse addition method is only suitable for the production of small batches when magnetic or mechanical stirring systems are not available. Therefore, we recommend this procedure for small-scale extemporaneous compounding in community or hospital pharmacies.

4.3. Other methods

The preparation of gel containing high viscosity grades of HPMC or HPC could be sometimes difficult due to the tendency to form lumps. A

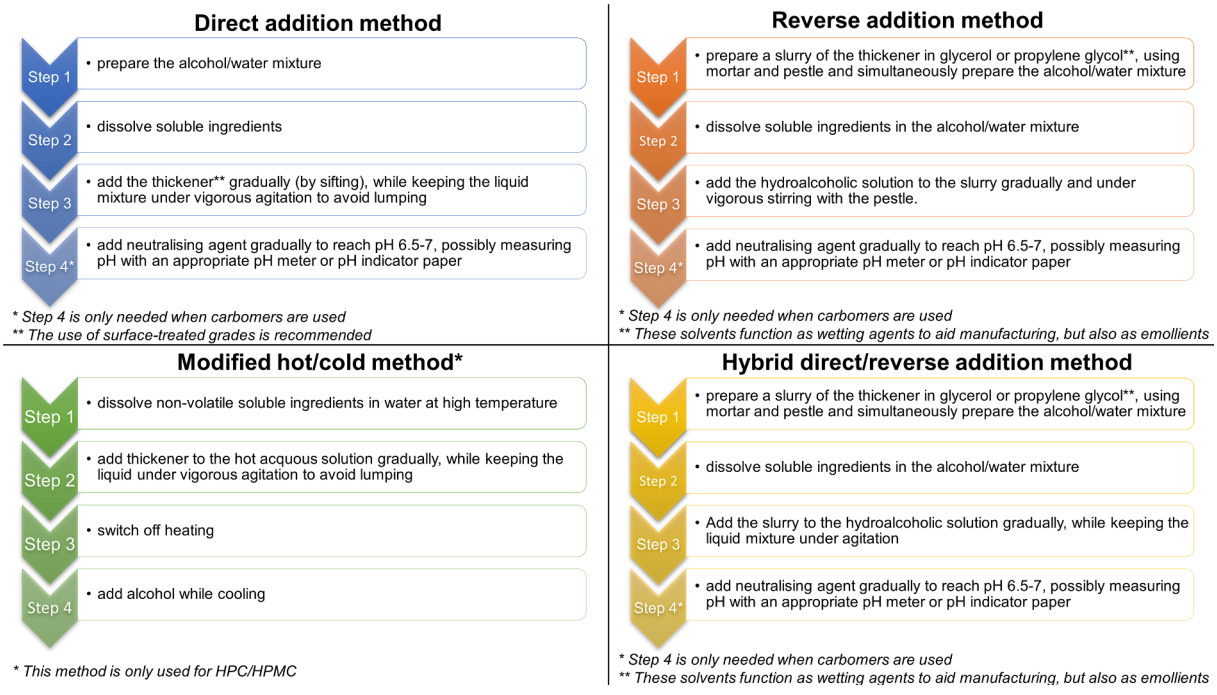

Fig. 3. Schematic diagram summarising possible methods for the manufacturing of hand sanitiser gels.

common procedure to avoid such problem and to speed-up the preparation is represented by the "hot/cold" technique (DOW, 2002). However, such a procedure is unsuitable for alcoholic gels because of the potential loss of ethanol content during the preparation, due to evaporation. Roberts at al. reported the preparation of 2% HPMC 2208 4 M hydroalcoholic gels containing 40% ethanol using a modification of the standard "hot/cold" technique (Roberts et al., 2007). Briefly, an aqueous gel is prepared with the "hot/cold" technique and then, while cooling, ethanol (and other volatile components, if any) is added under stirring. Although, this procedure could represent an interesting alternative to the previously reported methods, there is not enough information to support its use in the preparation of hydroalcoholic gels containing ≥ 60% ethanol.

Another preparation method that can be used to prevent lumping, especially for HPMC and HPC, is a combination (hybrid) of the direct and reverse addition methods. Briefly, a wet slurry is prepared similar to the reverse addition method and then it is gradually added under mechanical or magnetic stirring to the hydroalcoholic mixtures, as in the direct addition method (Ashland, 2017; DOW, 2002).

5. Products available on the market and regulatory aspects

A market research was carried out in Italy at the beginning of April 2020 amid the CoViD-19, to review the range of commercially available ABHR products in local pharmacies, supermarkets and online retailers. Table 2 provides a summary of these products including their composition, alcoholic content, type of thickeners and legal classification, extracted from the products' label. Various products sold online, with essential information missing on the label, were not included in the Table.

Comparing the thickening agents used in the formulation of hand rubs, it is evident that most of the products are made viscous by the use of carbomer and an amine-based neutralising agent (i.e. aminomethyl propanol or triethanolamine). The only exceptions were represented by two products thickened by either HPMC or HEC; and a third product in which carbomer neutralised by sodium hydroxide was used. Interestingly, these three hand gels were among the ones on which we performed the rheological analysis (Table 1), whereby they showed different rheological behaviour compared to most other analysed products. The product containing HEC was practically liquid, with a white precipitate at the bottom, that could be explained by a decreased polymer solubility at high ethanolic concentration. Indeed, the manufacturer of HEC indicates that this polymer possesses good solubility in hydroalcoholic media containing up to 60% ethanol (Ashland, 2018b), hinting at a decrease in polymer solubility at higher ethanolic concentrations. As for the carbomer gel neutralised with sodium hydroxide, it was slightly opaque and less viscous compared to the majority of the carbomer products (Table 1). Noteworthily, sodium hydroxide is not recommended as a suitable neutralising agent for carbomer-based hydroalcoholic gels by the manufacturer, due to possible polymer precipitation (Lubrizol, 2002), as stated earlier. Therefore, it can be concluded that the standard combination of carbomer/amine-based neutralising agents seems to form a product with good gel quality.

Another interesting aspect that arises from the products' analysis in Table 2, is their regulatory status. These products are marketed in Europe following two different regulatory pathways: the Cosmetic Products Regulation (Regulation (EU) N° 1223/2009, 2009) and the Biocidal Products Regulation (Regulation (EU) N° 528/2012, 2012). The label claims on the product determine the choice of the regulation market. If the product is used to cleanse or clean the skin, then it is subjected to the Cosmetic Products Regulation. While if the use of the product aims at disinfecting the skin from potentially infectious organisms, or if the action of the product goes beyond the general use of personal hygiene, then the hand sanitiser should follow the Biocidal Products Regulation. The marketing authorisation procedures and labelling requirements significantly differ between the two regulatory pathways. Specifically, a biocide has to be authorised by a competent authority (National Health Authority or European Commission) after the evaluation of a dossier containing all the information regarding the safety and effectiveness of the product. The product label must report the concentration of the "active ingredient" (including alcohol), the uses for which the product is authorised including all warnings, hazard and precautionary statements. On the other hand, evidence of safety is the key requirement for a cosmetic product. For the market authorisation, the company has to notify the Product Information File (PIF) to the cosmetic products notification portal (CPNP), which makes the information electronically available to competent authorities or poison centres. The product label must contain the list of ingredients (in descending order of weight), particular precautions or warnings and the cosmetic activity unless it is clear from its presentation.

This implies that the biocide and cosmetic hand rubs can have different amounts of ethanol in the products. All alcohol gels in Table 2 commercialised as biocides report the ethanol concentration in the label, which is always in the range 60% to 95%, suggested as a safe and effective concentration for disinfection by the US FDA and WHO (Boyce et al., 2009; FDA, 1994). Conversely, reporting the concentration of ethanol is not mandatory for cosmetic sanitisers. Of the 13 alcoholic gels approved as cosmetics, the amount of ethanol is reported only in 5 products, where one contained only 50% alcohol. Surprisingly, in three products water is listed as the first ingredient followed by ethanol, suggesting an ethanolic concentration of even < 50% (by weight). Such cosmetic products, although good for cleaning the skin, are not fit for use as disinfectants. This can be misleading for the general public, as they might not be aware of the product suitability amid the CoViD-19 pandemic. Consumers aiming to buy an effective hand disinfectant might unintentionally pick up from the shelves a very similar hand gel product, which is however not a disinfectant (i.e. a cosmetic). It is crucial, in this context, that pharmacists and retailers promptly advise customers to choose the appropriate product for the right purpose, i.e. disinfection or simple cleaning. Overall, during a pandemic, providing consumers with the correct information on hand sanitisers should be a priority of utmost importance. Perhaps, also regulatory agencies could consider revisiting the current regulations to better safeguard consumers.

6. Appraisal of formulation selection

Building upon the information and outlook provided in the previous sections of this review, a guide on formulation selection for the development of hand sanitisers is presented in Table 3. Here, functional ingredients are grouped in classes, and possible options within the same class are evaluated and compared in terms of time/ease of preparation, the equipment required (for the preparation), cost of material, antimicrobial efficacy, product appearance/acceptability, ease of use, and moisturising capacity/dermatological profile. CAS number of materials is also indicated.

7. Conclusion and final perspective

In response to the health, habits and market patterns extreme changes brought about by the current CoViD-19 outbreak, we review here the current knowledge and trends on the formulation of hand rubs. The article also presents a detailed guide on ingredients' selection, and formulation design and manufacture of quality hand sanitisers. The main outcomes of the analysis presented in this review are listed below:

- Evidences show that hand sanitisation is a main infection preventive measure during a pandemic, justifying the emphasis by the various healthcare organisations across the world, the huge increase in sales witnessed during the CoVid-19 outbreak, and the consequent shortage of hand sanitisers. The European Commission has recently highlighted the tendency of many economic operators to consider

Table 2
Label information of commercial hand sanitisers available in Italy during April 2020.

Product	Composition	Ethanol*	Thickener	Regulation
Agermina gel Igienizzante Mani (BB farma S.r.l.)	Ethanol 66 g; excipients and water up to 100 g.	66%	N/R	Cosmetic
Alcogel gel Igienizzante Mani (Sydex S.p.a.)	Denatured alcohol; water; benzyl alcohol; propylene glycol; glycerin; Sorbitol; carbomer; aminomethyl propanol; PEG-75 ethoxylated lanolin.	> 62%	Carbomer- aminomethyl propanol	Cosmetic
Amuchina gel aloe (A.C.R.A.F. S.p.a.)	Denatured alcohol.; water; glycerin; aloe barbadensis leaf juice powder; parfum; aminomethyl propanol; acrylates/ c10-30 alkyl acrylate crosspolymer.	N/R	Carbomer- aminomethyl propanol	Cosmetic
Amuchina X germ (A.C.R.A.F. S.p.a.)	Ethanol (96%) 74 g; excipients and water up to 100 g.	74%	N/R	Biocide**
Amugem igienizzante rapido (Cerichem Biopharma srl)	Denatured alcohol; water; propylene glycol; carbomer; aminomethyl propanol; citrus aurantium bergamia fruit oil.	N/R	Carbomer- aminomethyl propanol	Cosmetic
Apoteke T'igienizzo (ABC Italia S.r.l.)	Denatured alcohol.; water; aloe barbadensis leaf juice; citrus lemon peel oil; carbomer; propylene glycol; triethanolamine; PEG-40 hydrogenated castor oil, limonene; sodium benzoate; potassium sorbate; citric acid.	60%	Carbomer- triethanolamine	Cosmetic
Biotè scudo gel igienizzante mani (PDT Cosmetici S.r.l.)	Alcohol; water; isopropyl alcohol; glycerin; hydroxypropyl methyl cellulose; aloe barbadensis leaf juice; parfum.	N/R	HPMC	Cosmetic
Cien gel igienizzante mani (Mann & Schröder GmbH)	Water; denatured alcohol; glycerin; parfum; carbomer; limonene; linalool; aminomethyl propanol.	N/R	Carbomer- aminomethyl propanol	Cosmetic
Esosan gel mani (Ecolab S.r.l)	Ethanol 62 g; excipients up to 100 g.	62%		Biocide**
Fresh&clean gel mani igienizzante con antibatterico	Denatured alcohol ; water; glycerin; peg-75 lanolin; propylene glycol; benzyl alcohol; parfum; acrylates/c10-30 alkyl acrylate crosspolymer; peg-40 hydrogenated castor oil; trideceth-9; aminomethyl propanol; butylated hydroxytoluene ; citral; citronellol; geraniol; limonene; linalool.	N/R	Carbomer- aminomethyl propanol	Cosmetic
Gel idralcolico igienizzante delle mani (Th Pharma)	Alcohol; water; isopropyl alcohol; glycerin; propylene glycol; citrus lemon fruit extract; carbomer; aminomethyl propanol.	N/R	Carbomer- aminomethyl propanol	Cosmetic
Go Away! Gel mani (OSCO PHARMA S.r.l)	Water, alcohol; glycerin; polyquaternium 7, isopropyl alcohol; hydroxyethyl cellulose, parfum.	> 61%	HEC	Cosmetic
Golderm xbact (Shedir pharma S.r.l)	Denatured alcohol; water; isopropyl alcohol; glycerin; carbomer; chlorhexidine digluconate; benzalkonium chloride; parfum; triethanolamine; citronellol; limonene; linalool.	N/R	Carbomer- triethanolamine	Cosmetic
Innoliving gel (Innoliving S.p.a.)	Water, alcohol; isopropyl alcohol; Mek; PEG-75 ethoxylated lanolin; parfum; carbomer; triethanolamine; citral; geraniol; hydroxycitronellal; limonene; linalool.	50%	Carbomer- triethanolamine	Cosmetic
LH gel (LH Amedics)	Ethanol 62 g; excipients and water up to 100 g.	62%	N/R	Biocide**
Lysoform gel disinfettante per le mani (Unilever Italia)	Ethanol 70 g; excipients and water up to 100 g.	70%	N/R	Biocide**
Primagel plus gel disinfettante per le mani senza risciacquo (Allegrini S.p.a.)	Ethanol 65 g; excipients and water up to 100 g.	65%	N/R	Biocide**
Steriman Gel Igienizzante Mani (PromoPharma S.p.a.)	Denatured alcohol; water; propylene glycol; carbomer, glycerin; sodium hydroxide; citral; citronellol; geraniol; hydroxycitronellal; linalool, limonene; CI42090.	N/R	Carbomer- sodium hydroxide	Cosmetic

* The % of ethanol amount is %w/w for the products authorized as Biocide/PMC, while the specific unit of measurement is unknown (not reported) for the cosmetic ones.
** In Italy, alcohol gels fall in the category of "Products containing an active ingredient not yet approved and under revision, in accordance with Regulation 528/2012 / (EU)". Thus, they can be placed in the Italian market pursuant to Presidential Decree 392/98, as "Presidi Medico-Chirurgici" (PMC), and it is compulsory to report the PCM regulatory status in the label.

Table 3
A guide to selecting ingredients for the development of hand sanitisers.

Ingredient	Options	Time/ease of preparation	Equipment required	Material cost1	Antimicrobial efficacy	Product appearance/ acceptability	Ease of use	Moisturising capacity/ dermatological profile	Expert opinion
Disinfectant	Ethanol (CAS 64–17-5)	–	–	****/**[2]	****	***	–	****	Most commonly used; combination with other alcohols is possible. High skin tolerance. Most effective against non-enveloped viruses.
	Isopropanol (CAS 67–63-0)	–	–	***	***	**	–	***	Recommended by health agencies like ethanol. Stronger smell than ethanol.
	N-propanol (CAS 71–23-8)	–	–	**	***	**	–	***	Use is less common. Effective, yet not listed by as many of health agencies.
Emollient	Without	****	–	****	****	–	–	*	Cannot counteract the drying effect of alcohol on skin. Option discouraged.
	Glycerol (CAS 56–81-5)	***	–	***	***	***	–	****	Most commonly used. It can reduce antimicrobial efficacy and leave a sticky feel on skin, yet concentration can be adjusted to minimise these effects. A quantity of 0.5–0.7% is suggested.
	Propylene glycol (CAS 57–55-6)	***	–	***	–	***	–	****	Considered cheap.
	Others	***	–	–	–	–	–	–	Possible, assuming that they are inexpensive, miscible with water and alcohols and well tolerated by skin. Aloe Vera gel offers attractive marketing strategy.
Viscosity enhancer	Without	****	****	****	–	*	*	–	WHO proposes two cheap formulations (without viscosity enhancer), recommended when commercial products are unavailable. Runny formulations are effective, yet difficult to handle and less attractive for consumers.
	Carbomer (CAS 9003–01-4)	**	***	***	–	****	****	–	Used in most of the commercial products. Excellent transparency, touch feeling and handleability (due to its plastic behaviour). The necessity to being neutralised represents its strength (as it does not build up consistency during the solubilisation) and its weakness (since adding the right amount of base requires a certain expertise) at the same time. It possesses the highest thickening ability. A quantity of 0.3–0.6% and 0.5–1% is suggested for high and medium viscosity grades, respectively.
	HEC (CAS 9004–62-0)	***	***	***	–	*	**	–	It is an unsuitable thickener in media containing > 60%-65% of ethanol. Considered cheap.
	HPC (CAS 9004–64-2)	**	**	**	–	***	***	–	None of commercial products tested were prepared with HPC. It possesses a similar behaviour to HPMC. A quantity of 1–1.5% is suggested for high molecular weight grades.
	HPMC (CAS 9004–65-3)	**	**	**	–	***	***	–	HPMC gels in hydroalcoholic media are transparent and behave in pseudoplastic manner. The gel preparation could be slightly tricky due to increasing viscosity during HPMC dissolution. A quantity of 1.5% and 2–2.5% is suggested for 10 M and 4 M viscosity grades, respectively.
	CMC (CAS 9000–11-7)	***	***	***	–	–	–	–	None of the commercial products tested were prepared with CMC. It is an unsuitable thickener in a media containing > 50% of ethanol. Considered cheap.

(*continued on next page*)

Table 3 (*continued*)

Ingredient	Options	Time/ease of preparation	Equipment required	Material cost1	Antimicrobial efficacy	Product appearance/ acceptability	Ease of use	Moisturising capacity/ dermatological profile	Expert opinion
Other additives	Without	****	****	****	****	***	****	****	The two formulations recommended by the WHO do not contain any colour or dye.
	Perfumes and colours	***	***	**	–	****	****	–	Fragrances and dyes are present in certain commercial products. Such ingredients maybe incorporated, as long as they have no impact on antimicrobial activity and do not cause toxicity and/or allergenicity.

**** optimal; ***good; **moderate; *scarce; - indicates information is not relevant or not available.

[1] Cost comparison are made by referring to Sigma-Aldrich database or to the catalogue of ACEF Spa, an Italian raw material distributor for pharmaceutical, cosmetic, galenic products and nutraceuticals. For each category of ingredients, the cost comparison has been made using the same data source within the various options of the same ingredient. The amount needed for each preparation has been taken into consideration for the cost evaluation.

[2] For ethanol, the price difference depends on whether it is the denatured type or the standard one.

the possibility to shift and/or increase the production of hand cleaners and disinfectants to respond to the current needs (European commission, 2020). Businesses producing hand sanitisers and compounding pharmacists are now challenged to keep up with the exceptionally high demand for such products.

- Most gel formulations contain carbomers and an amine-based neutralising agent to form the gel matrix. Other gelling polymers could also be used, in theory, as alternatives; however, such polymers do not often provide hydroalcoholic gel products of the same ideal rheological behaviour and appearance, touch feel, ease of use and stability. Carbomer remains, in our opinion, the gold standard gel former in alcohol-based hand sanitisers.
- Substandard products can be available in certain markets. When the low standard is related to the selection of less appropriate excipients or formulation procedures, but the alcoholic concentration is maintained between the accepted standard of disinfection (i.e. 60–95% for ethanol), the risk for consumers is mainly a reduced perception of product quality and attractiveness, and reduced ease of use; while overall product efficacy is maintained. The poorly formulated products may also be subject to inappropriate use and sanitisation technique.
- Much more worrying is the presence of hand cleaners on the market containing low ("substandard") and/or unknown concentrations of alcohol that are not commercialised as disinfectants. There is a tangible risk that consumers might, and are using, hand cleaners, which product appearance is very similar to hand disinfectants, while being unaware that such products cannot ensure disinfection and are not fit for use amid the CoViD-19 pandemic. To minimise this risk: 1) customer counselling by pharmacists and retailers regarding the selection of appropriate products for CoViD-19 infection control is highly necessary; 2) online purchase of hand sanitiser from unknown or unreliable e-commerce sites by the public is discouraged; 3) awareness campaigns to educate the public on discriminating between products fit for general hygiene/cleansing from those for disinfection fit the for CoViD-19 infection control should be promoted; and finally, 4) regulatory bodies should revisit current regulations on hand sanitisers to better safeguard consumers.
- The demand for the hand sanitisers amid the CoViD-19 pandemic is likely to remain high for long, until more efficient infection preventive measures become available, such as a SARS-CoV-2 vaccine. Moreover, public awareness on the importance of hand sanitisation during this pandemic is likely to have long term effects on hygiene habits across the world. The public is likely to endure the routine use of hand sanitisers, even beyond the CoViD-19 era, as a new norm of self-hygiene.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.119431.

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