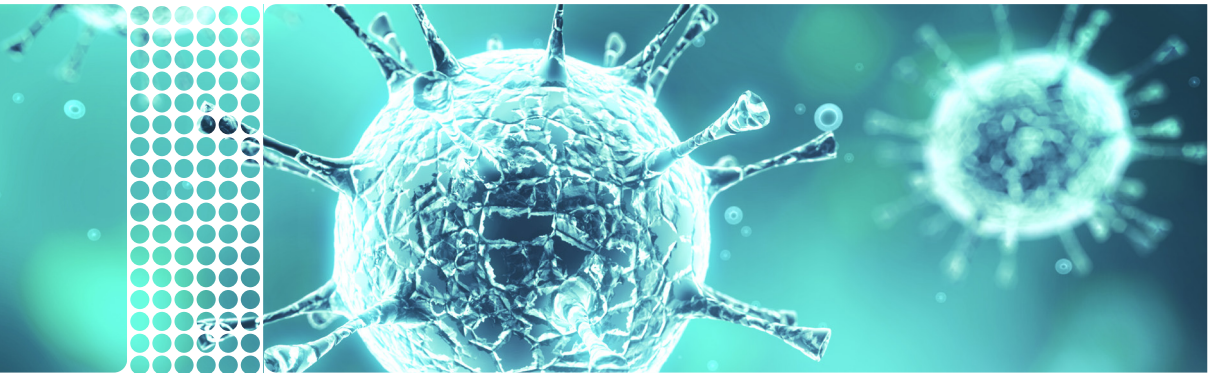

Article

Contact Scott Lamphere @ Next Level Products 23-696-1243

Quaternary Ammonium Compounds (Quats) against viruses

This article is very good at explaining highly technical information that is fairly readable for non scientist.

Summary

Quaternary ammonium compounds (Quats) such as Benzalkonium Chloride (BKC/BAK/BZK) are well-known antiseptics, effective against bacteria, fungi (yeast and mold) and algae.

But what about viruses? Quats are indeed effective against enveloped viruses. To name a few, activity against adenoviruses, enteroviruses, rotavirus, norovirus, influenza virus, severe acute respiratory syndrome coronavirus (SARS-CoV), rhinovirus, chlamydia, HIV, herpes simplex and hepatitis A and B virus have been reported.

In these pandemic times, we are being reminded of the importance of using effective, yet safe antiseptics. This has tremendous significance in the healthcare sector, where exposure to viral agents is high, and keeping workers and patients free from these agents is paramount.

Benzalkonium Chloride (BKC) is a well-established antiseptic ingredient in several ophthalmic, nasal, oral and topical formulations. In topical products, it is often reported to be effective against viruses at 0.5% concentration or less.

Benzalkonium Chloride is recommended by several national agencies as an effective compound against coronaviruses, and it presents several advantages compared to using alcohol.

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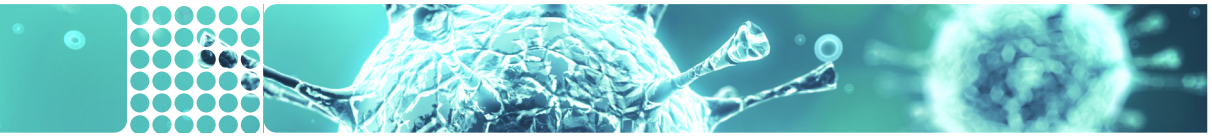

Quaternary ammonium compounds (Quats) such as Benzalkonium Chloride (BKC/ BAK/BZK) are well-known membrane-active agents interacting with the cytoplasmic membrane of bacteria and the plasma membrane of yeast.

The Quats' hydrophobic activity also makes them effective against lipid-containing viruses. Quats disrupt lipid membranes, thus are more potent against lipophilic, enveloped viruses than against hydrophilic, nonenveloped viruses. Quats also interact with intracellular targets and bind to DNA.

Benzalkonium Chloride (BKC) is a well-established antiseptic ingredient in several ophthalmic, nasal, oral and topical formulations. It is effective against bacteria, yeast, molds and enveloped viruses. For example, activity against enteroviruses[1)], rotavirus[2)], norovirus[3)4)], influenza virus[5)], severe acute respiratory syndrome coronavirus (SARS-CoV)[6)], rhinovirus[7)], chlamydia[8)], herpes simplex[8)] and hepatitis A virus[9)] have been reported.

Mode of action

The cationic "headgroup" of BKC is progressively adsorbed to the negatively charged phosphate heads of phospholipids in the lipid bilayer, and as a result, increases in concentration.

The consistent increase of BKC concentration results in reduced membrane fluidity and thus, the creation of hydrophilic gaps in the membrane. In addition, the alkyl chain "tail" component of BKC 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 these effects results in the solubilisation of the bilayer constituents into BKC/phospholipid micelles. BKC also interrupts inter-cellular targets and compromises the conformational behavior of DNA[10)].

Figure 1:

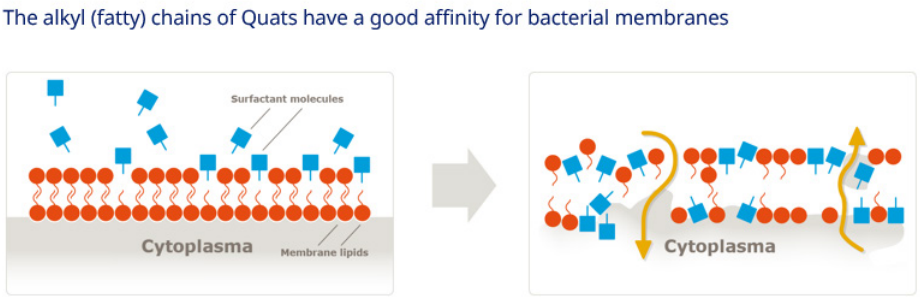

Illustration: Novo Nordisk Pharmatech A/S

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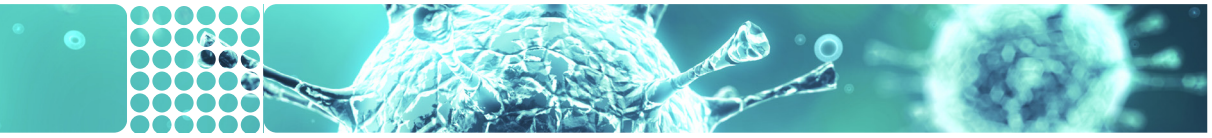

Fazlara and Ekhtelat[11] report that through membrane destruction, BKC is efficient to act against bacteria, some enveloped viruses, fungi, yeasts and protozoa.

The length of the alkyl chain groups can also greatly affect the antimicrobial activity. Methyl group lengths of C12 to C16 usually show the greatest antimicrobial activity[12].

Effective on a wide range of enveloped viruses

Enveloped viruses such as HIV, hepatitis B virus and influenza virus are all susceptible to BKC[13]. BKC was found to inactivate influenza, measles, vaccinia, canine distemper, meningo-pneumonitis, rabies, fowl laryngotracheitis, Semliki Forest, feline pneumonitis and herpes simplex viruses after 10 min of exposure at 30°C or at room temperature[14]. Saknimit et al.[15] investigated virucidal activity of BKC against the canine coronavirus (CCV) and mouse hepatitis virus (MHV), Kilham rat virus (KRV) and canine parvovirus (CPV). BKC showed sufficient efficacy and could readily inactivate coronaviruses, whereas the two parvoviruses (non-enveloped) were relatively less susceptible.

A BKC concentration of 0.1% was found virucidal for Adenovirus Ad19, Ad3, Ad7a, Ad5 and Ad37[16], which are strains causing ocular infections. Similar results were obtained at lower concentrations by other authors[17].

Belec et al.[8] demonstrated in vitro inhibition of adenovirus at varying concentrations of BAK with greater inhibition seen over longer exposure times.

Testing methods and concentrations differ greatly between scientific publications. We have summarized some results in Table 1.

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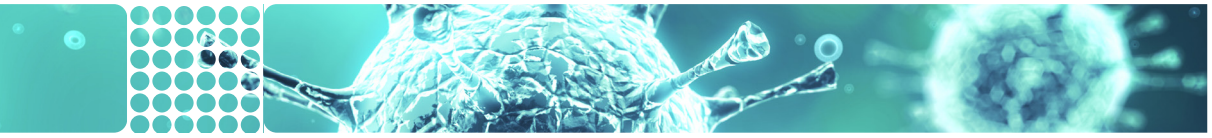

Table 1: Summary: effect of BKC on viruses

Virus type	BKC Concentration	Effect	Method	Ref.
SARS-CoV	1% (1000 ppm)	Loss of culturability	Detection of viral DNA through PCR after 30 min. exposure in vitro	6)
- *Chlamydia trachomatis* - Herpes simplex virus hominis type 2 (HSV-2) - Cytomegalovirus (CMV) - Adenovirus (ADV)	0.00125% w/v (v (12.5 µg/L) 0.00125% w/v (12,5 µg/L) 0.0025% w/v (25 µg/L) 0.0005% w/v (5 µg/L) 0.0050% w/v (50 µg/L) 0.0125% w/v (125 µg/L)	>99% killing on Chlamydia trachomatis Inactivation of >99% CMV Inactivation of >95% HSV-2 and CMV 3.0 log10 reduction of HSV-2 and CMV 3.0 log10 reduction of RSV 3.0 log10 reduction of ADV	1 min. Incubation in vitro 1 min. Incubation in vitro 5 min. Incubation in vitro	8)
-Rhinovirus (RV) type 14 -Respiratory syncytial (RS) virus -Influenza A (H1N1)	0.31 µg/mL (0.031% w/v) 0.16 µg/mL 0.0016 µg/mL	Viral inhibition of: RV type 14 RS H1N1	*In vitro* Monitoring viral plaque-forming units/mL (other compounds present with BKC)	7)
SARS CoV-2 3 strains	Oral rinse contain-ing 3,5 mg/10 g solution (0.035%)	Log reduction: Strain 1≥ 3.11 Strain 2≥ 2.78 Strain 3≥ 2.61	Mouthwash with BKC as active + de-qual-inium chloride. Virucidal activity determined by quanti-ta-tive suspension test with 30-second exposure time. 1 part virus suspension mixed with 1 part organic load mimick-ing respiratory secretions and 8 parts of the oral rinse.	18)
SARS CoV	0.5%	Reduction factor >4	BKC surface disinfectants. Experiments acc. to prEN 14476.19. Eight (8) parts of compound mixed with one (1) part of virus suspension and one (1) part of organic load or MEM.	19)
Adenovirus (Ad) strains responsible for ocular infections	0.1% 0.01%	Decreases of ≥3 Log_{10} for: Ad3, Ad5, Ad7a, Ad19/64 and Ad37 Decreases between >1 Log_{10} and <3 Log_{10} for Ad4 and Ad8 Decreases of >1 Log_{10} for Ad5	*In vitro* incubation of virus/BKC mixtures for 1h at 33C. Decreases of ≥3 Log_{10} were considered virucidal.	16)
-Herpes simplex (HS) type 1 -HIV type 1 -Human coxsackie (HC) virus	0.2% w/v	Reduction of: HS type 1: >4.51 Log_{10} HIV type 1:>1.87 Log_{10} HC: >5.12 Log_{10}	1 minute exposure at room tempera-ture, in the presence of organic matter	20)
Adenovirus respon-sible for ocular infections	0.005% 0.01% 0.03%	Rare IF No IF Viral inhibition (no cell lysis and no IF)	*In vitro* administration of BKC-contain-ing eye drops over 3 days. Viral activity detected by cell lysis and IF.	17)

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Coronaviruses

Numerous studies report a virucidal effect of BKC against coronaviruses, even if as pointed out by Schrank et al.[21] in 2020, the cumulated data on BKC-based products against the family of known CoV's is not uniformly asserted. This can be seen in their review of scientific papers:

Table 2: Ability of Different QACs to Inactivate Viral Loadings Based upon Literature findings[21]

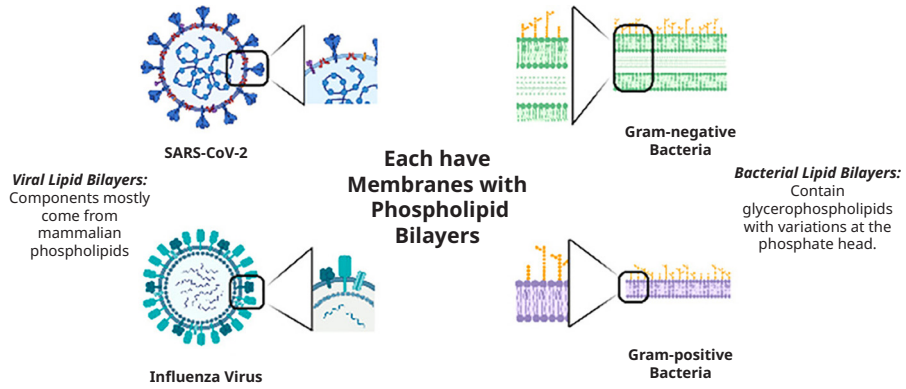
ACS Infectious Diseases pubs.acs.org/journal/aidcbc Viewpoint

Table 1. Ability of Different QACs to Inactivate Viral Loadings Based upon Literature Findings

QAC	conc. (% w/v)	type of assay	virus tested	exposure time	quantified viral load reduction (log_{10})	effective viral load reduction (>99.9%)? (Y/N)
BAC	0.04	QCT	HCoV	1 min	3.0	N
BAC, HCl	0.04 (pH 1.0)	QCT	HCoV	1 min	>3.0	Y
BAC, EtOH	0.04, 70	QCT	HCoV	1 min	>3.0	Y
BAC	0.2	suspension	HCoV	10 min	0.0	N
BAC	1	suspension	SARS-CoV	5−30 min	reduced growth; RNA still detectable by RT-PCR	Y
Mikrobac Forte (BAC)	0.5	suspension	SARS-CoV	30, 60 min	≥6.13	Y
Kohrsolin FF (BAC)	0.5	suspension	SARS-CoV	30, 60 min	≥3.75	Y
BAC	0.01	suspension	TGEV	5 min	≥3.0	Y
CG	0.008	QCT	HCoV 229E	5 min	<3.0	N
CG, EtOH	0.008, 70	QCT	HCoV229E	5 min	≥3.0	Y
mix of BAC/CG	0.066	QCT	HCoV 229E	10 min	4.0	Y
DDAC	0.0025	suspension	CCoV	3 d	>4.0	Y
BAC	0.00175	suspension	CCoV	3 d	3.0	N
BAC, EtOH	0.1, 79	suspension	MHV	30 s	≥3.0	Y

In general, Quats are reported to be effective against influenza viruses[21]. Hence, Schrank et al. postulate the potential efficacy of such compounds against SARS-CoV-2, based on the comparable outer membranes structure (relatively similar phospholipid bilayers) between influenza and SARS-CoV-2 virus. See Figure 2 below:

Figure 2:



Comparing the viral envelopes (membranes) to that of bacterial membranes. Note that both influenza and SARS-CoV-2 have phospholipid membranes similar to that of mammalian phospholipids due to method of infectivity and replication. Figure made in Biorender.

Illustration: Ref. 21)

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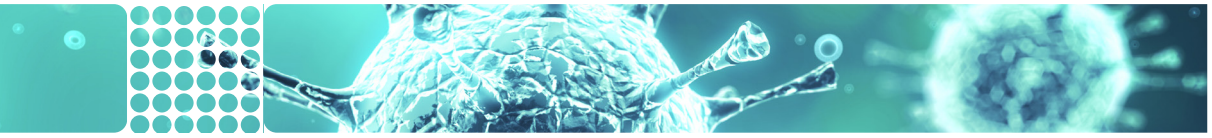

SARS-COVID: Quats are recommended by several governmental agencies

The use of Quats-based disinfectants to deactivate SARS-CoV-2 has been recommended by several jurisdictions. For example, the US Environmental Protection Agency (EPA) has provided a list of suitable disinfectant products: US Environmental Protection Agency "List N": disinfectants for use against SARS-CoV-2" (US EPA, Washington, DC, 2020):
https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2

As of 16th April 2020, List N contained 370 recommended products. Of these, 171 (48%) products contain Quats ingredients alone, and a further 33 products contain Quats formulated with at least one other class of active ingredient.

Quats up to 0.2% are also among proven disinfectants suggested by the US CDC against enveloped SARS-CoV-2.

BKC remains on the FDA list for hand sanitizers:
https://chemicalwatch.com/76526/us-fda-bans-28-substances-from-hand-sanitisers

Are Quats/BKC a good choice for healthcare sanitization?

Chemical-based disinfection is easily achieved by alcohol contact (ethanol or isopropanol) or other classic anti-viral and anti-bacterial compounds found in many commercial products. Alcohol offers momentary disinfection by contact and evaporation, while longer lasting effects that can be pro-vided by less volatile active compounds such as Quats (BKC), remaining on surfaces. Alcohol-based hand sanitizers (ABHS) are less user-friendly on skin than Quats-based, non-alcohol hand sanitizers (NABHS). ABHS predominate in health care settings given their low cost, however they are more worrisome due to their flammability and abuse potential.

For more information

If you would like to learn more about our pharmaceutical grade Quats portfolio and applications, please visit our home page novonordiskpharmatech.com.

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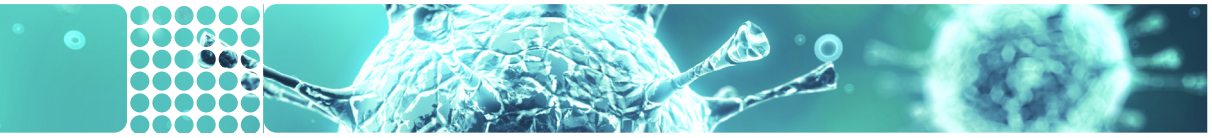

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