Monash University
Victorian College of Pharmacy

Course: Formulation Chemistry II (VCF2071)

Section Two: Humectants and Preservatives

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Humectants

Humectants or moisturizers are substances that impart hydrating properties to formulations, especially those designed for use on the skin. Soft, pliable skin has a moisture content of about 20% by weight. Drug absorption through skin is increased when it has a higher moisture content. Humectants must not be confused with **emollients**, which are mainly hydrocarbon compounds (waxes, paraffins, oils). These have the effect of physically blocking or occluding evaporation, thus softening skin by retaining water in it.

Skin contains naturally occurring humectant molecules, of which the main one is sodium pyrrolidone carboxylate. This compound has been patented for use in formulations. The protonated (unionised) form has no humectant properties. Other humectant compounds in skin are salts, urea (NH_2CONH_2) and proteins.

Humectants are also used to stop food products from drying out and to maintain texture in processed foods. Food texture is a subjective quantity that is the product of a complex set of physico-chemical interactions, for which one of the fundamental variables is moisture content.

Humectant compounds have a significant proportion of water-attracting polar functions, especially hydroxyl, amide, carboxylate, ether and ester groups.

These groups are all hydrogen bonding groups

- -OH and amide groups have both H-bond donor and acceptor capability
- carboxylates, esters and ethers are H-bond acceptors only

Theory

All humectants H-bond strongly to water, reducing its vapour pressure (thermodynamic escaping tendency). In order to function properly, humectants must have low volatility. Hence, water itself is a poor humectant, as it vaporizes too easily.

The moisture activity of formulated products (processed foods, skin care products, semi-solid pharmaceuticals) can be described in terms of the partial water vapour pressure, p, above the product.

Water vapour pressures are determined for formulations and for standard conditions (p_o), and the ratio described as the **water activity** (a_w) or thermodynamic escaping tendency:

$$a_w = p/p_o = ERH/100$$

where ERH is the equilibrium relative humidity. Inclusion of humectants or moisturisers will reduce the ERH of a formulation, indicating its increased tendency to retain moisture.

Specific humectant compounds

Typical humectant or moisturising compounds are

- polyethylene glycols (macrogols, PEGs, carbowaxes), polypropylene glycols and their block copolymers, the poloxamers (pluronics, copolymers of ethylene oxide and propylene oxide)
    - made from ethylene oxide and water under pressure in the presence of catalysts – the higher the EO partial pressure, the higher the molecular weight
    - for MW > 600, polyethylene glycols are solid at RT
    - liquid polyethylene glycols are very hygroscopic
    - solid polyethylene glycols are not hygroscopic
    - polyethylene glycols are not irritant to the skin
    - PEGs are regarded as safe for injectable products (and by inference, for all other products as well)
    - PEGs can bind and inactivate various actives, including drugs and preservatives
    - PEGs have laxative effects in large amounts. High MW PEG and electrolytes are used to flush out the bowel before endoscopy or other internal examination, such as surgery
    - Polyethylene glycol (PEG) is often chemically combined with other molecules, e.g., medium and long chain alcohols, fatty acids, sorbitan esters or castor oil products. This results in surfactants, viz., the polyoxyethylene ethers (Brij series), polyoxyethylene esters (e.g., poloxyl stearates), polyoxyethylene sorbitan esters (Tween series) and polyoxyethylene castor oil derivatives, respectively. This process is called pegylation and results in hundreds of different, non-toxic compounds for formulation design purposes. World production of these compounds is in the hundreds of thousands of tonnes per year

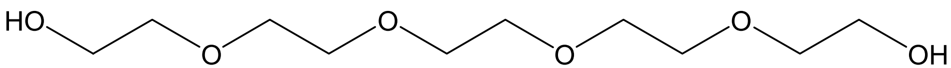


Fig: Representative polyethylene glycol (PEG, Carbowax, Hodag PEG, Lutrol E)

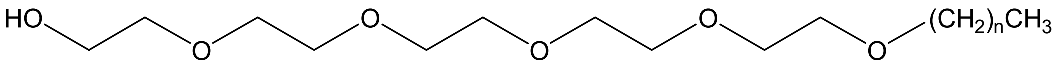
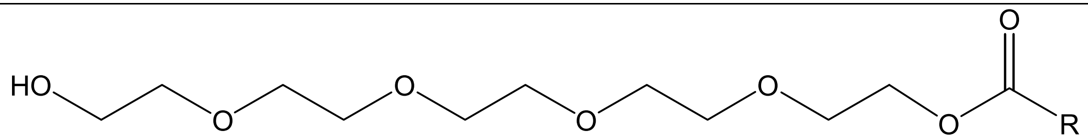
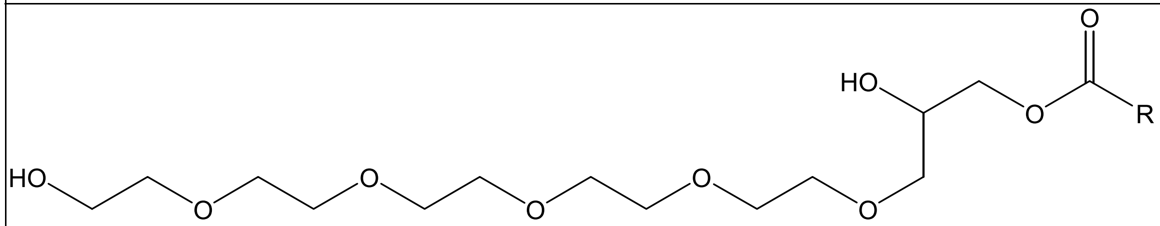
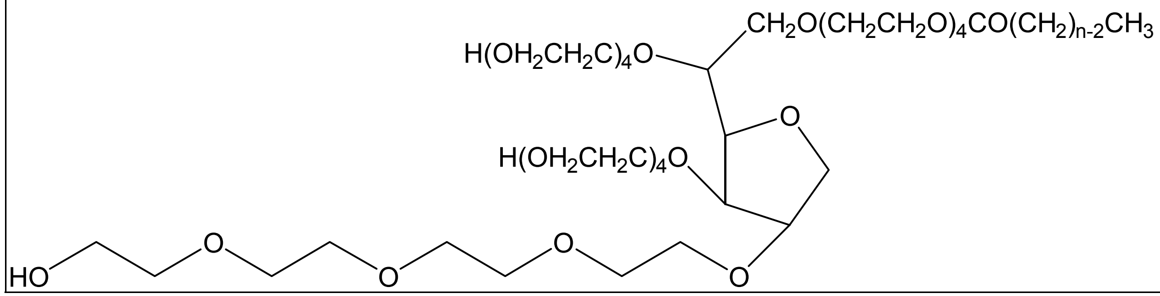
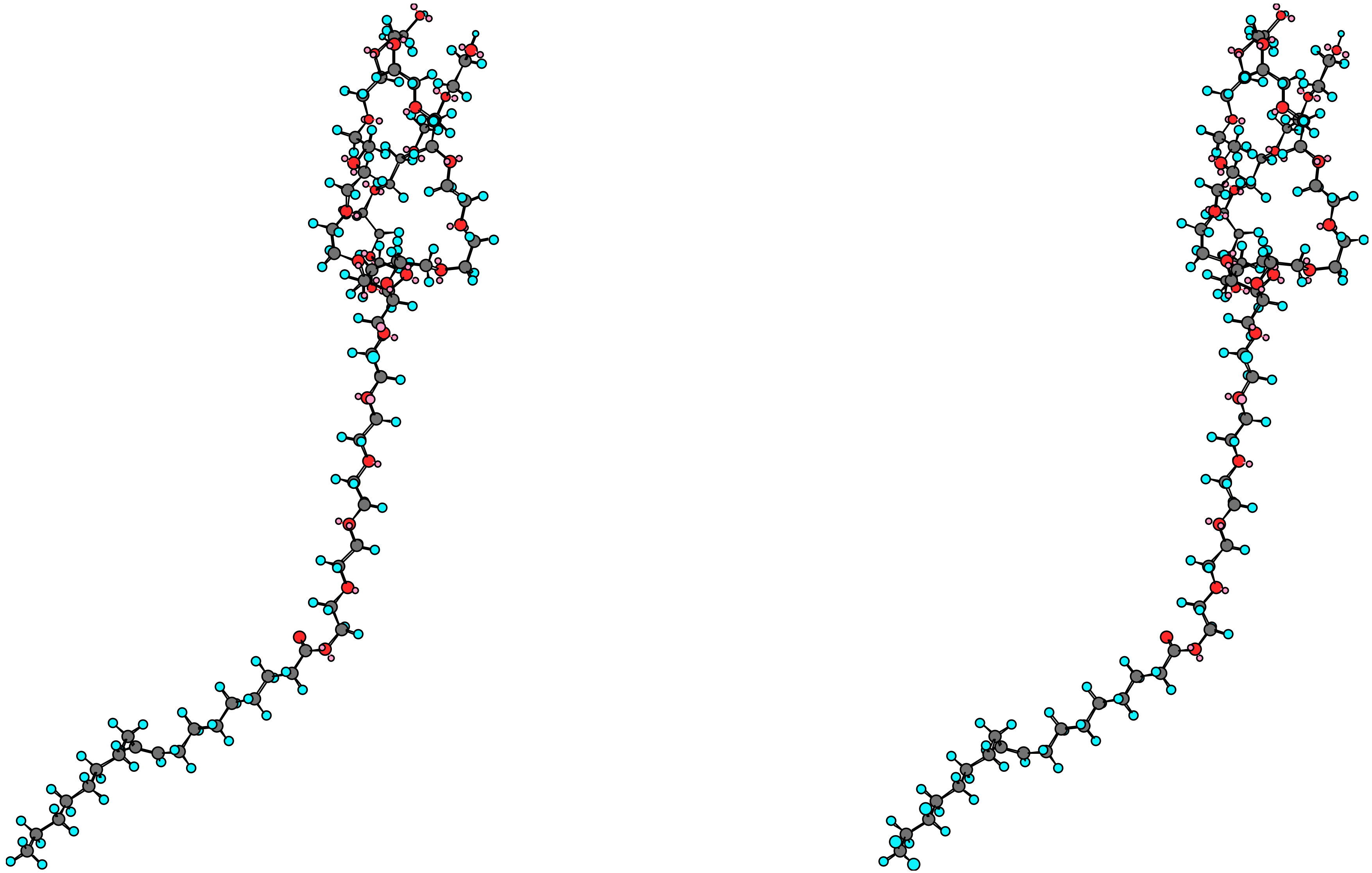


Fig: Representative polyethylene glycol ether (Polyoxyethylene alkyl ethers, macrogol ethers; Brij, Cetomacrogol, Cremophor A, Empilan) (alkyl groups are: laureth = C12; trideceth = C13; myreth = C14; ceteth = C16; steareth = C18) (e.g., laureth-20 means a C12 alkyl group with 20 oxyethylene residues)

	Fig: Representative polyethylene glycol ester (e.g., Poloxyl stearate)
	Fig: Representative polyoxyethylene castor oil derivative (Cremophor) (R = ricinoleate = 12-hydroxyoleate)
	Fig: Representative polyoxyethylene sorbitan ester (Tween)



Stereo Diagram of Tween 80 (polyoxyethylene 20 sorbitan mono-oleate)

- polyols (propylene glycol, glycerol, sorbitol, xylitol) (polyols should not be ingested in unlimited amounts as they have laxative properties – another function of their high water-absorbing tendencies) (GRAS listed)
  - ethylene glycol is **NOT** used for human products as it is metabolised to toxic products, especially oxalic acid
  - glucose
  - glycerol (also called glycerin or glycerine) is 1,2,3-propanetriol. It is used in concentrations up to 30% as a humectant. It is very hygroscopic, which is why you don't normally see it in the pure solid form (m.p. 17.8^{o} C). GRAS listed
  - sorbitol (also called D-glucitol) is a very hygroscopic solid that forms solutions containing up to 67% w/w. Originally isolated from berries, it is now made industrially from other sugars. The moisture content of sorbitol remains low until relative humidity is >65%
  - xylitol is a solid pentose sugar which (like sorbitol) is sweet but not digested by bacteria, so is non-cariogenic. Xylitol dissolves in aqueous solutions at concentrations of up to about 40%. It is only slightly hygroscopic and starts to gain moisture rapidly at relative humidities of >60%.
- polysaccharides (e.g, starch) are less used for this purpose than other humectants
  - all starches are hygroscopic and absorb moisture until they reach their equilibrium moisture content
- polyesters (e.g., triacetin, sucrose octaacetate)
  - triacetin is 1,2,3-triacetylglycerol. It is a hydrophilic triester, with some surfactant properties, including a form of micellization. Triacetin is reported safe for oral products and is GRAS listed. It is widely used in cosmetics, perfumery and food products.
  - Sucrose octaacetate is a hydrophilic polyester with humectant properties. It also has a very bitter taste, which is why it is used in anti-smoking products and in lotions designed to keep adolescents from chewing their fingernails, children from sucking their thumbs and generally putting their (usually dirty!) hands in their mouths (Formulation ingredients: Water, glycerin, sucrose octaacetate, stearic acid, propylene glycol stearate SE, cetyl alcohol, aloe vera gel, dioctyl adipate, ethyl hexyl stearate, ethyl hexyl palmitate, tocopheryl acetate, jojoba oil, panthenol, collagen, triethanolamine, methylparaben, propylparaben, diazolidinyl urea)
- anionic surfactants (e.g, sodium laurylsulphate)

Water Sorption

The water sorption capabilities of humectants may be compared by means of their osmolality values. The following percentage concentrations are iso-osmotic with serum:

Name	% w/v	molar
Propylene glycol	2.08	0.273
Glycerol	3.3	0.3584
Xylitol	4.56	0.2997
Glucose	5.0	0.278
Sorbitol	5.48	0.3008

These concentrations are those of solutions with equal water-retaining capacity. Hence, propylene glycol is about 2.5-fold more water-retaining than an equal weight of sorbitol.

Relatively large amounts of these compounds (5-30% w/w) may be needed to exert their humectant action. However, formulators must be careful not to use too much of these materials. In products for the skin or mucous membranes, excess humectant will remove moisture from these tissues, causing dehydration.

Processed foods containing excess of these hydrophilic materials will remove moisture from the membranes of the mouth and oesophagus, drying out the membranes and making swallowing difficult. Some have laxative properties, especially if given in large amounts.

Choice of humectant(s) is based on cost, compatibility, irritancy and experience

See: http://www.inchem.org/pages/jecfa.html for safety info on food additive chemicals

Preservatives

Fatty and aromatic acids, parabens, phenoxyethanol, polyhydric alcohols (polyols), quaternary surfactants, imidazolidinyl ureas, carbamates, methylisothiazolinone, glutaronitriles, EDTA

Preservatives are compounds added to formulations that are intended to minimize microbial contamination of the product **by the end user**

They are NOT allowed for removal of microbial contamination that is -

- present in raw materials used in the formulation
- introduced during processing of the formulation

No preservative may be used which does not appear in Annex VI Part 1 or 2 of the EEC Cosmetic Directive 76/768/EEC - including 7th Amending Commission Directive 94/32/EC (for European products).

Mechanisms of Action

Preservatives operate by various mechanisms – these will be discussed in Microbiology classes. The potencies of preservatives vary from one organism to the next – details of these will also be discussed in Microbiology

Toxicology of Preservatives

Many different compounds are used in formulations. Some are used only in products that are intended for "rinse-off" use, i.e., the preservative stays on the skin only for a short time and is then washed off, e.g., in hair care and shower products. This should be covered in your toxicology class (3rd year).

Problems

Preservatives present various physicochemical problems in formulation, e.g., compatibility, potency loss, stability. These problems are made worse in formulations of increasing complexity. The following is an example of the type of "real-world" problems that a formulator may encounter:

PRODUCT YELLOWING
Being a new member of the formulators discussion group, I have a comment on the problems with products turning yellow after addition of antioxidants. It is my experience that you should watch out for the preservative used in the products. Especially Methyldibromo Glutaronitrile (Euxyl K 400) can produce some unexpected discolorations. I have seen this preservative produce massive discolorations with such components as Coco-betaine, PEG-40 Hydrogenated Castor oil and triethanolamine. I don't know if Euxyl k 400 reacts with the antioxidants, but it is worth looking into.

Best Regards
HB
Allison A/S
hb@allisonmail.com

Moderator replies: Thank you for sharing this with us Henrik, this is really useful information and what Baggers is all about.

Partitioning of preservatives

Preservation of creams can cause problems due to the **partitioning** of the preservative between the aqueous and oily phases of emulsions. The micro-organisms live in the aqueous phase, but most preservatives partition into the oil phase, where they have no effect and are wasted.

More preservative then has to be added to get the concentration in the aqueous phase up to the active level. Consequently, the total preservative amount in the formulation is excessively high and toxicity might occur.

Equations that can be used to calculate the concentration of preservative that is needed in a two-phase system can be found in Martin, Physical Pharmacy (4th Ed., pp. 240-241) and in Florence and Attwood, Physicochemical Principles in Pharmacy (3rd ed., pp. 279-280)

The amount of preservative remaining in the aqueous phase (C_w) is related to the total amount of preservative (C) with partition coefficient (P) in a two-phase system, where the oil-water phase volume ratio is F, as follows:

$$C_w = \frac{C(F+1)}{R(PF+1)} \qquad F = \frac{V_O}{V_t + V_O}$$

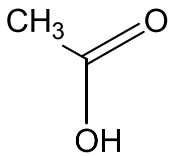
where R is the preservative/emulsifier ratio and V_0, V_t are the oil volume and total volume, respectively. C_w must equal or exceed the Minimum Inhibitory Concentration (MIC), which is a function of preservative and micro-organism types.

Of the older preservatives, only EDTA remains in the aqueous phase, but its action is very weak and insufficient by itself – an additional preservative is needed for synergy.

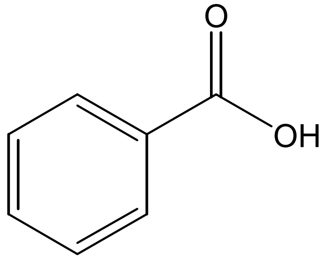
Some of the newer preservatives (e.g., quaternium-15) have been designed so that this problem does not occur.

Specific preservative compounds

Aliphatic and aromatic acids



acetic acid

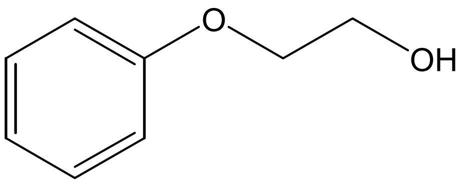


benzoic acid

Carboxylic acids, both aliphatic (e.g., acetic acid) and aromatic (e.g., benzoic acid) have weak preservative activity.

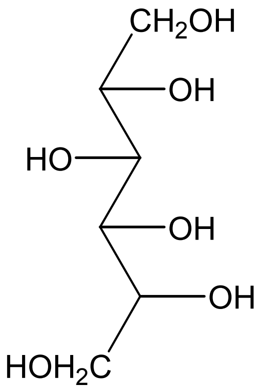
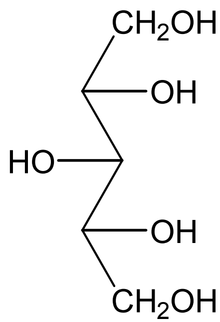
The active form is the free acid, so the pH of such formulations is critical to maintaining efficacy. As the pKa values of relevant carboxylic acids are generally in the range 4-5, pH values must not be greater than pKa+1 at the very worst. Even then, the amount of active must be 10-fold greater than if pH = pKa – 1, to achieve equal potency.

Phenoxyethanol



Phenoxyethanol is used as an antibacterial preservative in concentrations of 0.5 to 1.0% w/v. It is a liquid which freezes at 14^{o} C and boils at 245^{o} C. It does not dissolve easily in water, but heating can be used to aid dissolution. It is chemically stable and has no ionizing groups, so its activity is not pH-sensitive.

Polyhydric alcohols (polyols)

Glycerol $CH_2OHCHOHCH_2OH$ Propylene glycol $CH_3CHOHCH_2OH$	Sorbitol 	Xylitol 

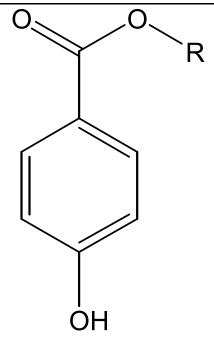
The polyhydric alcohols have mild antimicrobial properties. They are used widely in cosmetics, processed foods and pharmaceuticals.

They all have high water solubility and are hygroscopic.

Their antimicrobial properties are due to their ability to dehydrate organisms (including spores), by adsorbing water through hydrogen bonding to the numerous hydroxyl groups. Glycerol is known to kill some spores that could survive boiling nitric acid.

They generally react with chemical oxidizing agents. Their action is not pH-sensitive.

Parabens



All phenols (hydroxybenzene compounds) have antibacterial properties, but many of them have other undesirable effects. The parabens are the short chain alkyl (R = methyl, ethyl, propyl or butyl) esters of the phenolic compound, p-hydroxybenzoic acid. They are widely used as preservatives in cosmetics, foods, personal care products and pharmaceuticals.

The parabens are not very water soluble:

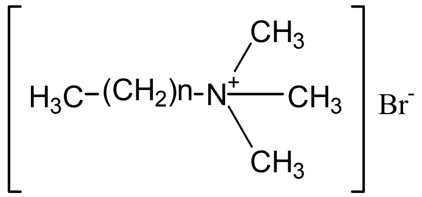
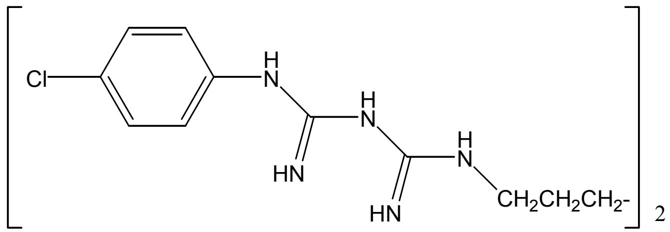
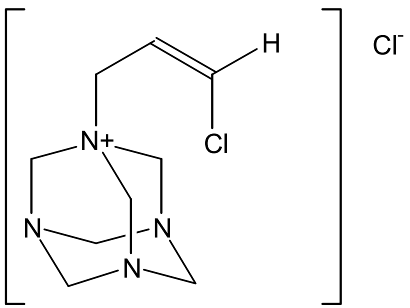
Paraben	Solubility	Partition coeff (vegetable oils)
R = methyl	2.4 mg/mL	4-8
R = ethyl	0.85 mg/mL	14-19
R = propyl	0.4 mg/mL	52-66
R = butyl	0.2 mg/mL	280

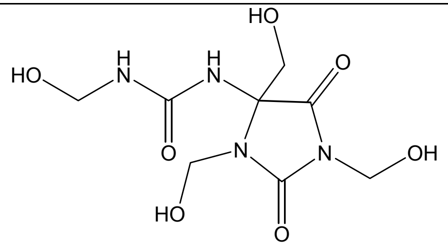
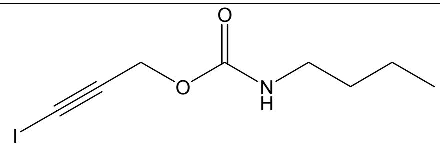
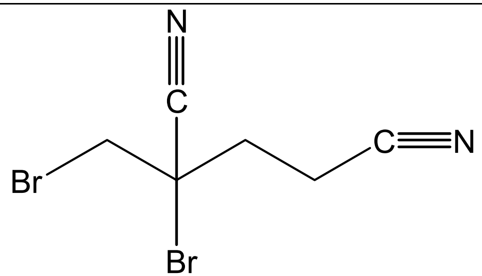
Their poor water solubilities mean that they are often used in combination, both with each other and with other preservatives, where their combined activity is additive. The parabens also partition readily into vegetable oils, esters and long chain alcohols, hence are rapidly lost from the aqueous phase of emulsion formulations. They can irritate skin in high concentrations.

The parabens are sufficiently stable to be sterilized by high temperatures in slightly acidic aqueous solutions. Their stability is reduced at high and low pH values.

Incompatibility of parabens with non-ionic emulsifiers occurs through absorption into micellar structures. This interaction is likely to also involve adsorption of the parabens onto the surface of the micelles, as it is easily disrupted by polyols such as propylene glycol (10%). Other excipients that also are incompatible with the parabens are bentonite, magnesium trisilicate, talc, tragacanth, sodium alginate and sorbitol.

Quaternary ammonium compounds

	alkyltrimethylammonium bromide (cetrimide is a mixture with n = 11-15, mainly 13)	The quaternary ammonium antibacterials are used in many situations, including cosmetics, personal care products, and pharmaceuticals. They are highly water-soluble, but their solubility in non-aqueous solvents is low, especially quaternium-15. All of these cationic compounds are potentially incompatible with organic anions, through charge-charge interactions. This applies especially to anionic soaps. Non-ionic surfactants can reduce the activity of chlorhexidine and cetrimide through micellization, but this does not apply to quaternium-15. Cetrimide itself also forms micelles. Quaternium-15 forms yellow colours with some fragrances, e.g., those containing citral.
	chlorhexidine (always used as a salt, usually the very water soluble gluconate)	
	quaternium-15 (Dowicil 200) (active concentration, 0.02 to 0.2%) Quaternium-15 is a chemical modification of a very old antiseptic called methenamine	

  Diazolidinyl urea Iodopropynyl butylcarbamate	**Imidazolidinyl ureas and carbamates** Diazolidinyl urea is a member of the imidazolinyl urea antibacterials. The preservative system Germall Plus is a combination of 99% diazolidinyl urea and 1% iodopropynyl butylcarbamate. Germall Plus is claimed to be free of chemical inactivation and to be compatible with virtually all cosmetic ingredients
 Methyldibromoglutaronitrile (recently reported to have an increased incidence of allergic skin reactions: 0.7% in 1991 rising to 3.5% in 2000)	**Glutaronitriles** Methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyano-butane; Tektamer 38). Combination (20%) with 2-phenoxy-ethanol (80%) is the product Euxyl K400. Widely used in cosmetics, e.g., body lotions, creams, shampoos and sunscreens at a maximum concentration of 0.5% w/w in cosmetics and 0.125% w/w in sunscreens.
EDTA has very weak antibacterial properties that require the presence of a second antibacterial, e.g., one or more of the parabens, to exert synergistic effects	**Other miscellaneous antibacterials** • DMDM hydantoin • methylisothiazolinone and analogues
General preservatives reference: Kabara JJ, Ed., Cosmetic and Drug Preservation: Principles and Practice. Dekker, NY (1984) (Pharmacy Library 668.55 C834)	