Aspects of disinfectant formulation in the galenic laboratory in the pharmacy

Veronika Šimunková, PharmDr, PhD[1, *], Daniel Krchňák, DiS[1]

[1] Department of Galenic Pharmacy, Faculty of Pharmacy, menius University in Bratislava, Slovakia

[*] Correspondence: simunkova@fpharm.uniba.sk

The current difficult situation, as a result of the Covid-19 pandemic, has caused a demand for something that we took for granted and did not realize that there might be a shortage. However, the deteriorating availability of disinfectants has given us, pharmacists, the opportunity to show the continuing legitimacy of galenical pharmacy and individual preparation of drugs in 21st century. Although disinfectants are now more available than during the "first wave" of COVID-19, it is certainly a good pharmacy business card if it can expand its range with a portfolio that is perceived by the public as "hand-made" and at a more affordable price compared to high prices from commercial manufacturers.

The compilation of recipes requires both basic knowledge of microbiology so that we can reliably determine for which group of microbes the product will be effective and technological knowledge so that we can formulate the product appropriately and thus ensure it´s stability and good applicability. When formulating new prescriptions for disinfectants in a pharmacy, we must be aware of three basic aspects, relating to the following areas:

1. **Choice of antimicrobial substance**

Alcohols. These hydroxy derivatives of hydrocarbons are used as disinfectants either alone or in combination with other antimicrobials, in which case they also act as vehicles. They act rapidly (at a concentration of 70% within 30 seconds) on a wide range of vegetative bacteria, viruses and microscopic filamentous fungi. The alcohols themselves are sporistatic and have sporicidal effects in combination with selected surfactants or in combination with hydrogen peroxide. They are used in disinfectants in concentrations of 60 - 80% (V / V). The most used e.g. ethanol (*Ethanolum* (*96 per centum*) Ph. Eur. 10), for which the effective concentration optimum is generally considered to be 71%, despite the variability of the results of experimental work. A more effective alcohol is isopropyl alcohol (*Alcohol isopropylicus* Ph. Eur. 10), which is used separately e.g. for preoperative skin disinfection in concentrations of 60 - 70%. Isopropyl alcohol at a concentration of 60% shows the same bactericidal activity as 77% ethanol, on the other hand, ethanol is more effective against some types of viruses. In vitro experiments confirmed the efficacy of both isopropyl alcohol and ethanol at the indicated concentrations against SARS-CoV-2 virus. The disadvantage of isopropyl alcohol is, in addition to higher skin irritation, also twice the toxicity (p.o.), compared to ethanol. Alcohols in certain concentrations show technological incompatibility with carbomer (acrylic and polyacrylic acid derivatives, trade name *Carbopol*®) and sodium carboxymethylcellulose (disruption of gel structure to liquefaction). It has been reported in the literature that a maximum of 35% ethanol can be incorporated into carbomer gels without rapid reduction in gel viscosity.

Chlorhexidinium digluconate (*Chlorhexidini digluconatis solutio* Ph. Eur. 10). It is a disinfectant belonging to the group of diguanides. It has a bactericidal effect on gram-positive and gram-negative bacteria and on enveloped forms of viruses. The mechanism of action is disruption of membrane integrity and inactivation of membrane enzymes (at lower concentrations), up to coagulation of the cytoplasm (at higher concentrations). It has the highest bactericide and virucide activity at neutral to slightly alkaline pH, when it occurs as a dication. It is incompatible with anionic surfactants (they can reduce effectiveness). It is used in disinfectants in concentrations of 0.5–4%, possibly in combination with alcohols or quaternary amine salts. A commercially available pharmacopoeial substance is a 20% aqueous solution.

Benzalkonium chloride (*Benzalkonii chloridum* Ph. Eur. 10). This cationic surfactant, which belongs to the quaternary amine salts, is readily soluble in both water and ethanol and can therefore be used in combined disinfectants. Thanks to its surface-active properties, it wets surfaces well, which increases its availability and disinfection effect. The mechanism of action is damage to the integrity of the cytoplasmic membrane of bacteria, subsequent leakage of cytoplasmic components and cessation of metabolism. In vitro experimental work has shown that the antimicrobial is also effective against SARS-CoV-2 virus at a concentration of 0.2% (w / w). Its effective pH optimum lies in the neutral to slightly basic range. In combination with anionic and nonionic substances, mixed micelles are formed and incompatibility occurs. Benzalkonium chloride from 0.1% (w / w) in carbomer bases shows incompatibility (turbidity and flow of the gel) and therefore a different gelling agent must be used in the formulation of the gels.

2. Galenical form of disinfectant.

The least technologically demanding is to formulate disinfection into a solution. The vehicle is most often water, ethanol, isopropyl alcohol or a mixture thereof in a suitable ratio. In the case of crystalline disinfectants, these are simply dissolved in a solvent (e.g. alcohol, which in some cases may potentiate the disinfecting effect of the substance itself). The low viscosity of the solution ensures that the disinfectant active substance reliably gets into all the unevenness of the skin. Gels are a more technologically demanding form. Compared to solutions, they require a certain amount of technological experience to prepare, but especially time, which can be a problem in the current stressful situation in pharmacies. It is also necessary to take into account the possible incompatibilities of the gelling agents with the active ingredients and excipients. If we manage to solve these critical aspects - gels are a more popular form of disinfection compared to solutions. They are well applied to the hands and if we give their composition a certain "upgrade" in the form of humectants, e.g. urea or glycerol (to minimize skin dryness), substances that promote epithelialization and skin regeneration, or odor correction - they can take on the character of a cosmetic product with a specific focus.

Carbomers (*Carbomera*, Ph. Eur. 10; *Carbopol®*) and cellulose derivatives - hydroxyethylcellulose (HEC, hyetellose, Hydroxyethylcellulose Ph. Eur. 10), methylcellulose (MC, Methylcellulosum Ph. Eur. 10), hydroxypropyl-methylcellulose are used as gelling agents. (HPMC, hypromellose, Hydroxy-propylmethylcellulose Ph. Eur. 10). Most of them are commercially available.

The concentration of the gelling agent in the preparation is chosen according to the desired consistency (viscosity) of the preparation and according to which packaging material is intended to be used. When choosing a gelling agent, we are limited primarily by the choice of a suitable effective antimicrobial agent, as we must not allow the possibility of possible incompatibility.

3. Choice of packaging material for the chosen galenical form of the disinfectant

Proper adjustment is no less an important final aspect of product preparation. In addition to protecting the product from external influences, it must provide a convenient and practical application of the disinfectant. The disadvantage of the solution is the impractical application to the hands when using narrow-neck incompressible vials as packaging. This disadvantage can be solved by using a spray applicator on a narrow-necked dark glass vial or by adjusting to a box. However, due to the higher vapor permeability of polyethylene, they are not entirely suitable for long-term storage. Commercially produced disinfectant gels and solutions are often adjusted in PETE (polyethylene terephthalate) packages, which have improved mechanical properties, are less vapor permeable and have better chemical resistance. In the case of gels, narrow-mouth vials are useful, but a clear attractiveness and improvement of product application can be achieved by using pump vials or plastic extrusion containers. An essential part of the packaging is, of course, the label, which must not lack, inter alia, the qualitative composition of the preparation and the concentration of the active disinfectant.

Examples of recipes suitable for the preparation of disinfectants in the galenical laboratory:

Disinfectant gel with 72% ethanol.

Composition:	894 g (≈ 1,000 ml)
Ethanol 96% (V/V)	667.5 g
Purified water	178.0 g
Glycerol 85% (w/w)	26.7 g
Methylcellulose	17.8 g
Lavandulae aetheroleum	4.0 g

Technological process:

Ethanol 96%, lavender silica, glycerol 85% are weighed into a beaker and mixed. The methylcellulose is then dispersed in the solution. While stirring (preferably using a shaft stirrer), purified water is added and mixed until a clear to slightly opalescent thin gel is formed.

Composition interpretation:

Ethanol at a concentration of 72% (w/w) acts as a disinfectant. Methylcellulose acts as a gelling agent, increasing the viscosity of the preparation. Glycerol is used as a humectant at a concentration of 2.55% (w/w). Purified water acts as a vehicle. It creates an environment for the formation of the gel structure of methylcellulose. Lavender essential oil is a corrective fragrance. However, it can also be theoretically assumed that it "potentiates" the disinfecting effect of the preparation, as most essential oils show antimicrobial activity.

Disinfectant solution with 75% isopropyl alcohol according to WHO (modification of the recipe according to D. Krchňák).

Composition:	843 g (≈ 1,000 ml)
Isopropyl alcohol	591.0 g
Hydrogen peroxide 3% (w w)	41.5 g
Glycerol 85% (w/w)	20.8 g
Purified water	189.7 g
Limonis aetheroleum	gtt X (decem)

Technological process:

Isopropyl alcohol, lemon silica, 3% hydrogen peroxide, purified water and finally glycerol 85% are gradually weighed into the beaker. The solution is stirred until the glycerol is dissolved.

Composition interpretation:

Isopropanol at a concentration of 75% (V/V) acts as a disinfectant. Hydrogen peroxide at a concentration of 0.125% (V/V) acts synergistically with the isopropyl alcohol present as a sporicidal substance, which helps to eliminate possible contamination of the product with spores. The mechanism of action is the oxidative production of free hydroxyl radicals, which have a germicidal effect. Glycerol at a concentration of 1.45% (V/V) acts as a humectant. Purified water acts as a vehicle to dilute isopropyl alcohol to the desired concentration. Lemon oil is a fragrance corrector. However, it can also be theoretically assumed that it "potentiates" the disinfecting effect of the preparation, as most essential oils show antimicrobial activity.

References

EDQM. European Pharmacopoeia, 10.5 th ed. Strasbourg, France. 2021.

MLYNARČÍK, D., MÁJEKOVÁ, H., DUBNIČKOVÁ, M. Farmaceutická mikrobiológia. Bratislava: Univerzita Komenského. 2017.

ROWE, R., C., SHESKEY, P., J., QUINN, M. E. Handbook of Pharmaceutical Excipients, 6 th edition. London: Pharmaceutical Press. 2009.

WHO Guidelines on Hand Hygiene in Health Care. Geneva: World Health Organization. 2009.

SKLENAŘ, Zbyněk. et. al. Magistraliter receptura v dermatologii. Praha: Galén. 2009.

XILING, Guo. et al. In vitro inactivation of SARS-CoV-2 by commonly used disinfection products and methods. Sci Rep, 2021, 11.

OGILVIE, Benjamin H., et al. (2021). Alcohol-free hand sanitizer and other quaternary ammonium disinfectants quickly and effectively inactivate SARS-CoV-2. Journal of Hospital Infection, 2021, 108.

SpecialChem. What is PET Plastic? online: <https://omnexus.specialchem.com/selection-guide/polyethylene-terephthalate-pet-plastic>