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MANUFACTURING OF TABLETS DESIGNED TO OBTAIN A CLEANING/DISINFECTING AND STORAGE SOLUTION FOR CONTACT LENSES

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ABSTRACT

In the present paper the authors describe a cleaning and disinfecting process for soft contact lenses. The process consists of immersing the lens to be treated in purified water, adding a tablet which liberates first a water soluble disinfecting compound and after a time-lag, releases a second water soluble compound. The second compound forms an oxidation-reduction system with the first one, so that the reactionnal contact of these two compounds results in their mutual degradation, giving by products which are harmless to the eye. For the formulation of the tablets, the authors had to conciliate the following systems :

- redox system (disinfecting/neutralizing)
- acido-basic system (effervescence)
- delayed release system (film coated inner core).

INTRODUCTION

Soft contact lenses have become an esthetic modality for the correction of ametropia (5). A disinfecting system is required that is effective and safe in order to protect the lens wearer from introducing infectious micro-organisms into the eyes (11, 12, 25). The aim of our studies was the realization of a cleaning and

disinfecting process for contact lenses. Many methods for soft contact lens disinfection are described in the literature (17, 19, 22, 29). All the systems used have disadvantages. These methods can be classified as physical or chemical methods.

Physical sterilization consists of immersing the lenses into a boiled saline solution. Some lens materials, e.g. HEMA-PVP copolymers are modified by the action of humid heat (15). This method cannot be used with highly hydrated lenses (70-80 % hydration). Other disadvantages in the use of this method are coagulation of deposits on the lenses and shorter duration of the lenses.

Chemical sterilization is based on the use of three kinds of solutions (disinfectant, cleaning and rinsing solutions) (4). The use of 3 % hydrogen peroxide solution, known to be an efficient disinfecting agent, also has some disadvantages (28). Due to of its ocular toxicity, lenses ought to be rinsed with a neutralizing solution (20) after soaking in hydrogen peroxide.

Furthermore, conservation of hydrogen peroxide is a problem (22). A number of articles published on soft lenses refer to boiling and hydrogen peroxide treatment as cleaning procedures (3, 10, 27, 33, 34) contributing to the confusion between cleaning and sterilizing processes (13). The fact that hydrogen peroxide swells the lens and leaves the lens crystal clear, probably has contributed to this confusion.

Other sterilization methods using chemical agents are based on the combination of several bactericidal products.
The most commonly used system consists of the combination of chlorhexidine digluconate with thiomersal (21, 30). The efficiency of the above combination is often enhanced by adding EDTA (26). Mercurothiolate (thiomersal) is not very toxic for the cornea, but is a major allergen (20). Chlorhexidine is atoxic and settles down on the soft lenses deposits. Most of the products actually used for asepticizing soft lenses are solutions (18, 24). The patent FR 7215299 (6) describes a synergistic combination of thiomersal with urea peroxide. The lenses must be rinsed after the use of these solutions.

PRINCIPLE OF THE METHOD FOR ASEPTICIZING

A chemical asepticizing system for soft contact lenses should have different properties :

- the aim of disinfection is to remove living pathogenic micro-organism : staphyloccocus aureus, escherichia coli,

pseudomonas aeruginosa and candida albicans (AFNOR Standards & F.D.A. Standards) (1).

- the system should not alter the lens physical parameters
- the chemical compounds of the systems should not be absorb on the lens
- the products should be harmless to the eye.

The cleaning/disinfecting process consists of plunging the lens to be treated into purified water, adding first a water soluble disinfecting compound and then releasing in the same medium a second water soluble compound. The second compound forms an oxidation-reduction system with the first one , so that the reactional contact of these two compounds results in their mutual degradation, leading to by-products which are harmless to the eye. The two reactive compounds are brought into contact after a time-lag. The second agent has a reducing action, and has the additional effect of destroying the proteins, so as to eliminate the blur troubling the transparency of the lens. The second agent itself possesses a bacterial action which is exerted on germs.

This process could be applied to most of the known contact lenses (European patent 84.440016.8/2107) (2). The first agent has an oxidizing action and performs the destruction of the germs that are present on the lens.

The oxidizing compound consists of hypochlorous acid, released by a precursor (dichloro-isocyanuric acid, sodium salt (=DCCNa). The reducing compound consists of hydrogen peroxide, "in situ" released by a precursor (e.g. sodium percarbonate and urea hydrogen peroxide) (31).

The peroxiden compound reacts with the chlorine compound and is decomposed to liberate oxygen gas according to the following equations :

1st equation : sodium dichloro-isocyanurate $\xrightarrow[Na^+]{H_2O}$ X NaClO X = 2

2nd equation : sodium percarbonate or urea hydrogen peroxide $\xrightarrow{H_2O}$ Y H_2O_2 Y = 1.5 or 1

3rd equation : $NaClO + H_2O_2 \longrightarrow NaCl + O_2 + H_2O$

Thus the contact lens is efficiently cleaned and decontaminated by the sequential action of active chlorine and active oxygen.

It is important that the lenses are not removed from the solution immediately after the treatment with the sodium dichloro-isocyanurate, because the reduction component must be allowed to exert its sequential action. The reducing component must be allowed to degrade the chlorine and hypochlorite chlorine into harmless by products, water, sodium chloride and nascent oxygen and to exert its additional cleaning and decontaminating action on the lens.

SPECIFICATIONS

The components can be conviently formed into pharmaceutical solid dosage forms such as : double core tablets (14), multiple-layer tablets, solid powders in double-compartment poaches.

The solid forms have to meet the following requirements :

- determine the quantity of active ingredient to be used in 10 mL of purified water,
- the oxidizing agent (hypochlorite chlorine) has to be released rapidly,
- the reducing agent (hydrogen peroxide) has to be released with a lag time,
- as the two actives ingredients are chemically incompatible, and as this process uses a controlled dissolution of the reducing compound (hydrogen peroxide) the latter should be contained in a coated core with a polymer having a good ocular safety (methyl polymetacrylate) (figure 1).

PREFORMULATION STUDIES

The objective of these studies was to collect data yield supportive information on the drug substance and formulations. This data forms the basis of a rational pharmaceutical dosage form development (9, 23).

Stability study of the active ingredients :

Hydrogen peroxide is tested by visible spectrometry using titanium sulfate which forms a titanium peroxide (yellow coloration). The coloration is stable, and can be detected at 410 nm.

The dichloro-isocyanuric acid sodium salt releases hypochlorous acid. This compound is tested using the method of free

Table 1 : Storage conditions of the active ingredients

Storage conditions	Definition
+ 20°C	Room temperature, no controlled humidity
+ 20°C, RH	Room temperature (100 % relative humidity)
+ 37°C	Drying oven at 37°C, no controlled humidity
+ 57°C	Drying oven at 57°C, no controlled humidity

chlorine dosage with o-tolidine in acidic medium, which possesses an oxidized yellow form. This coloration allows an assay by visible spectrometry at 438 nm wavelengh.
Stability studies on the active ingredients are undertaken in order to determine their sensitivity to heat, light, moisture, and the like. The different samples of active ingredients are stored in polyethylene vials in order to investigate their stability, according to table 1.

The stability of the dichloro-isocyanuric acid sodium salt was investigated using the determination of residual chlorine (X %).

Table 2 summarizes the stability parameters (X %) estimated from DCCNa : the recorded mean values obtained are not significantly different after 13 weeks of storage at 20°C, 37°C, and 57°C respectively.
The amount of residual chlorine did not decreased markedly as the humidity was 100 % RH, after 13 weeks storage, at 20°C.

The stability of hydrogen peroxide carbamide was investigated by testing residual hydrogen peroxide.
Table 3 shows that urea hydrogen peroxide is relatively stable at room temperature (20°C), while the stability is lower during the 13 weeks at higher temperature (37°C and 57°C).

Table 2 : Stability study of dichloro-isocyanuric acid sodium salt under different storage conditions.

Amount of residual active chlorine							
Storage conditions		Storage time (weeks)					
		0	1	2	4	9	13
+20°C	X % ± SD %	101.24 0.83	103.0 1.73	107.6 0.60	103.2 3.90	99.3 1.35	101.6 1.60
+20°C H	X % ± SD %	101.24 0.83	104.7 1.30	101.5 2.60	96.1 0.72	107.8 0.60	93.9 1.10
+37°C	X % ± SD %	101.24 0.83	99.5 2.36	107.9 2.00	121.0 1.10	97.0 0.88	110.4 0.90
+57°C	X % ± SD %	101.24 0.83	106.0 1.12	110.7 1.62	104.0 0.69	107.4 0.90	108.1 0.70

Compatibility study for active and inactive ingredients :

The aim of this study was to investigate the possible interactions between the drugs (active ingredients) and excipients (inactive ingredients) (32). This was carried out by comparing binary mixtures (active and inactive ingredients) after 1, 4 and 8 weeks. Several products were studied in mixtures with DCCNa (Table 4).

The results have shown that DCCNa can be combined with fillers like Tablettose (R)[1], Di-Pac (R)[2], Lactose EFC (R)[3] and mannitol[4].

[1] Tablettose : MEGGLE MILCHINDUSTRIE GmbH
REITMEHRING, RFG

[2] Amistar Corporation, USA - S.C.P.I. France

[3] H.M.S. (France) S.A. SUCRE DE LAIT

[4] ROQUETTE LESTREM - France

Table 3 : Stability study of urea hydrogen peroxide (hydrogen peroxide carbamide) under different storage conditions

Residual amount of hydrogen peroxide							
Storage conditions		Storage time (weeks)					
		0	1	2	4	9	13
+20°C	X % ± SD %	84.4 5.9	84.2 9.4	85.3 4.5	88.1 4.2	78.3 6.5	94.5 6.3
+20°C H	X % ± SD %	84.4 5.9	86.0 7.7	81.5 4.9	81.5 2.7	83.5 6.6	97.6 5.2
+37°C	X % ± SD %	84.4 5.9	85.5 1.8	82.6 2.4	77.6 8.5	52.1 4.0	48.5 3.5
+57°C	X % ± SD %	84.4 5.9	89.5 5.9	0	0	0	0

Table 4 : Compatibility study between DCCNa (dichloro-isocyanuric acid sodium salt) and inactive ingredients.

Lactose EFC	Anhydrous monosodium citrate	Sodium carbonate glycine
Tablettose	Anhydrous disodium citrate	Glycine
Mannitol	Trisodium citrate	Malto-dextrin
Di-Pac	Anhydrous potassium phosphate monobasic	Sodium chloride
Anhydrous citric acid	Anhydrous potassium phosphate dibasic	PEG 6000
Adipic Acid	Anhydrous sodium phosphate monobasic	Povidone
Tartaric acid	Anhydrous sodium phosphate dibasic	Explotab
Boric acid	Sodium bicarbonate	Sodium benzoate
Fumaric acid	Potassium carbonate	

Table 5 : Stability study between urea hydrogen peroxide and different inactive ingredients

Lactose EFC + Sodium benzoate	Anhydrous monosodium citrate	Potassium carbonate
Tablettose	Anhydrous disodium citrate	Anhydrous sodium carbonate
Mannitol + Sodium benzoate	Anhydrous sodium Phosphate monobasic	Calcium carbonate
Di-Pac + Sodium benzoate	Anhydrous potassium Phosphate dibasic	Sodium carbonate glycine
Anhydrous citric acid	Sodium bicarbonate	Malto-dextrin
Tartaric acid	Potassium bicarbonate	Sodium chloride
Boric acid	Sodium bicarbonate	Disodium edetate
Fumaric acid	Potassium bicarbonate	Eudragit L100
Sodium benzoate		

DCCNa is compatible with an effervescent system such as sodium bicarbonate with an acidic agent (neither citric acid, nor fumaric acid). It is possible to incorporate a buffer system (phosphate buffer) in the tablet formulation, in order to achieve a pH which is physiologically acceptable. The lubricant to be used must be soluble, since the tablet must give a clear solution. Polyvinylpyrrolidone (Povidone)[5] used as binder agent is not possible, because DCCNa is not stable with povidone.

Several products were studied in mixture with urea hydrogen peroxide (Table 5).

[5] BASF FRANCE - Levallois Perret

The results have shown that urea hydrogen peroxide cannot be combined with effervescent systems, or with hygroscopical raw material. Sodium benzoate must be used at low concentration to minimize interaction with urea hydrogen peroxide.

PREFORMULATION STUDY OF THE OUTER CORE

The aim is to obtain after the disintegration of the tablet a cleaning, disinfecting and storage solution for soft contact lenses. The buffer system must adjust the final pH of the solution to approximately that of the lacrymal fluid (pH 7,0 - 7,6). The buffer NaH_2PO_4 / Na_2HPO_4 (1 : 3) yields a stable solution with a pH value about 7.6.
Isotonicity results from whole components in solution. To optimize the particular dosage form with respect to processing, drug release, and stability, a number of experimental formulations have been studied, such as the following formulation.

		FUNCTION
DCCNa	4,0 mg	Active ingredient
Anhydrous disodium hydrogen phosphate	60,1 mg	Buffer
Anhydrous sodium dihydrogen phosphate	19,7 mg	
Sodium chloride	44,2 mg	Tonicity agent
Tablettose (R)	92 mg	Diluent
Sodium benzoate	10 mg	Lubricant
	230 mg	

The dissolution time of the above tablet was over a range of several days. In order to decrease the dissolution time, different tablet disintegrating agents have been tested. The disintegrating agents tested such as Ac-di-Sol (R), Primogel (R), Explotab (R), Polyplasdone XL (R), are insoluble in water.
However, low quantities of these ingredients (2 %) do not markedly change the clarity of the final solution. The major disadvantage results in the possible deposit of these ingredients on the contact lens. Furthermore, the dissolution data show that the dissolution time is not sufficiently accelerated by such a quantity of disintegrating agent. (The dissolution time is above 10 minutes).

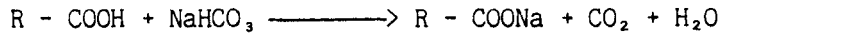
The tablet which has an initial hardness ranging between 3 and 4 kg, hardens as soon as it is immersed in water (hardness 7 kg or more).

The explanation for the relatively large increase in hardness after immersing in water is related to the fact that when water penetrates into the capillary network, the anhydrous phosphates form a gel. In order to avoid the phosphate gelification due to by too rapid a penetration of water into the tablet, a hydrophobic agent has been added to the above mentioned mixture (Aerosil R 972).

Aerosil R 972 is insoluble. However it improves the tablet disintegration (about 1 hour), but the final solution is not sufficiently clear.

The use of an effervescent system has also been studied in order to improve the disintegration.

The most compatible system is an effervescent mixture which contains sodium bicarbonate, anhydrous monosodium dihydrogen phosphate or adipic acid. The acid reacts with sodium bicarbonate by the following equation (16).



$$R - COOH + NaHCO_3 \longrightarrow R - COONa + CO_2 + H_2O$$

A formulation of the outer core is as follow :

DCCNa $2H_2O$	1.0 mg
Anhydrous monosodium dihydrogen phosphate	32.0 mg
Anhydrous disodium hydrogen phosphate	50.0 mg
Sodium bicarbonate	57.0 mg
Tablettose (R)	30.0 mg
Sodium benzoate	15.0 mg

The dissolution time of tablet with a hardness of 4 kg is about 5 minutes. The effervescence is regular and provides a mixing of the solution. Anhydrous monosodium hydrogen phosphate is used as a buffer agent and also as an acid agent in the effervescent system.

PREFORMULATION OF THE INNER CORE

Since urea hydrogen peroxide can be used only with single inactive ingredients such as Tablettose (R) Di-Pac (R) and sodium benzoate,

the phosphate buffer, as well as the effervescent mixture and the agent responsible for osmolarity should be included in the outer effervescent core in order to minimize the incompatibilities.

The composition tested is described hereunder :

Urea peroxide	1.5 mg
Tablettose	70.5 mg
Sodium benzoate	8.0 mg
	80.0 mg

The tablets dissolve in 10 ml of purified water in less than 10 minutes. The use of a coating agent is a way of solving the problem of incompatibility, and also of performing a delayed release system (8). In order to protect and delay the release of urea hydrogen peroxide, a pH 7 soluble copolymer can be used (e.g. methylpoly-metacrylate copolymer EUDRAGIT L 100) (7).

Another way to protect the inner core is to perform a granulation with urea hydrogen peroxide Eudragit L or S, in order to produce a water soluble matrix depending on the pH value of the dissolution medium.

The urea peroxide granulated with Eudragit L is mentioned below as "Percarbamide P 27". The tablets obtained are dissolved in water after 20 minutes without mixing.

The composition obtained is the following :

Percarbamide P 27	2.5 mg
Tablettose	50.0 mg
Sodium benzoate	5 mg

A double core tablet, according to the formulations given above has been prepared. These tablets have been tested on lenses. After 10 days of use, a dicalcium orthophosphate deposit appeared on the lenses, resulting from the reaction between tears calcium and phosphate buffer. In order to avoid this disadvantage, disodium edetate has been added to the inner core composition. The use of disodium edetate results in a loss of about 13 % of active ingredient during 96 days of storage of the urea hydrogen peroxide. In order to stabilize this active ingredient, the coating with Eudragit L

Table 6 : Stability of sodium percarbonate as a powder.
R.T. = room temperature.

	+ 4°C	R.T.	+ 37°C	+57°C
T 0	101 %			
T 1 week	109.4 %	103 %	98.8 %	30.6 %
T 2 weeks	101 %	100 %	89 %	14 %
T 1 month	101.6 %	103.5 %	93.6 %	-
T 2 months	107 %	98.4 %	70.5 %	-
T 3 months	102.3 %	100.0 %	65.2 %	-

100 seemed to be a good solution, but this composition was not stable over a long storage time.
Another precursor of hydrogen peroxide, sodium percarbonate shows a greater stabiliy in comparison to percarbamide (Table 6)).

The following composition can be considered as a valuable example of an inner core candidate :

Sodium percarbonate.....0.85 mg
Tablettose.....71.15 mg
Sodium benzoate.....8.0 mg

MANUFACTURING PROCESS

The manufacturing process is as follow :

Preparation of inner core tablet :

These tablets are made by intimately mixing a fine powder of sodium percarbonate or urea hydrogen peroxide with compressible sugar or lactose and sodium benzoate. The mixture is pressed into a tablet on a rotary tabletting press. The tablet is then coated with a coating solution (Eudragit L 100 in isopropanol).

Preparation of the outer tablet :

The sodium dichloro-isocyanurate is added to a mixture of sodium benzoate and sodium bicarbonate and then a dry granulation is performed. A wet granulation is made with the others ingredients.

Preparation of the double core tablet :

The wet and dry granulations are mixed together, then the mixture obtained is pressed into a tablet on a rotary double coating press.

CONCLUSION

The great number of stability studies carried out during the preformulation testing shows the difficulty of the problem to be solved.

The choice of tabletting agents and their respective amounts, has been dependent upon pH, transparency final solution, freezing point (osmolarity), ocular safety. This study has shown that only a small number of inactive ingredients could be used, and has allowed the balance of the following systems :

- redox system (disinfecting / neutralizing),
- acido-basic system (effervescence),
- delayed release system (film coated inner core).

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