DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(6), 747-752 (1995)

THE INCOMPATIBILITIES BETWEEN CHLORHEXIDINE DIACETATE AND SOME TABLET EXCIPIENTS

Timo Pesonen, Harri Kanerva**, Jouni Hirvonen***, Tuomo Nuuja* and Juhani Pohjola

Military Pharmacy, Helsinki, Finland
*Military Academy, Helsinki, Finland
Present addresses:
**Orion-Farmos Pharmaceuticals, Espoo, Finland
***Department of Pharmaceutical Technology, University of Kuopio, Finland

ABSTRACT

The incompatibilities in a powder mixture for the manufacture of a chewable direct compression antiplague tablet preparate, were studied. The degree of loss of chlorhexidine diacetate in the presence of some common tablet excipients was studied under high relative humidity (80 % RH) and in water solution.

The most significant losses in water solution were observed with lubricants magnesium stearate and sodium lauryl sulphate. Under high relative humidity the greatest losses were, on the contrary, observed with the materials having a great water absorption capacity, such as sodium carboxymethylcellulose and sodium starch glycolate.

INTRODUCTION

Chlorhexidine (CHX) is the most effective antiplague agent used in mouth hygiene (1). The incompatibility of CHX with a great variety of materials restricts the formulation

possibilities, such as buffering of gels and liquid preparations (2,3). Incompatibilites are known to arise especially in concentrated water solutions (3,4). For solid preparations, such as tablets, incompatibilities may arise during storage under humid conditions or after administration in mouth saliva.

Recently an experimental chewable antiplague tablet preparate containing three beneficial materials for mouth hygiene i.e. CHX, fluoride and xylitol was introduced (5). The aim of the present paper was to study the incompatibility of CHX with some excipients necessary in tablet manufacturing, i.e. lubricants and disintegrants.

MATERIALS AND METHODS

Materials

The tablet mass contained three with the concept of mouth hygiene beneficial agents, i.e. 2 % w/w of chlorhexidine diacetate (i.e. CHX, Bp grade) and 0.75 % w/w of sodium fluoride (Ph Eur grade) in xylitol (direct compression grade, Sucros, Finland) with 1 % w/w of the studied excipient. The studied excipients were magnesium stearate, talc, sodium carboxymethylcellulose (NaCMC) (all Ph Eur grade), sodium lauryl sulphate (Merck, p.a. grade), sodium stearyl fumarate (Pruv®, Mendell), Hydrogenated vegetable oil (Lubritab®, Mendell), sodium starch glycolate (Explotab®, Mendell), crosslinked NaCMC (AcDiSol®, FMC) and Crosslinked PVP (Kollidon CL®, Basf).

Methods

Powder mixtures were stored on open petri dishes for two weeks under 80 % relative humidity and at ambient temperature. Three samples weighing 650 mg (responding 10 mg of CHX) were taken from each petri dish. Samples were diluted

with 100 ml of methanol. Powder mixture in water was prepared by adding 6500 mg of the studied powder mixture (responding 100 mg of CHX) into 45.5 g of distilled water and stored in 50 ml HDPE-bottle for 72 hours at ambient temperature. The degree of loss of CHX was measured using an UV-spectrophotometer (Beckman DB) at 254 nm. The coefficient of correlation for CHX standard curves in water and in methanol (range from 0 to 30 μg/ml) were 0.999 and 0.998, respectively. The absorbance of the excipient did not disturbe the measurement in water or in methanol.

Based on incompatibities the dissolution of CHX into 250 ml of water from tablets containing three different lubricants, i.e. magnesium stearate, sodium stearyl fumarate and hydrogenated vegetable oil was studied using the rotating basket method (Sotax AT 6 apparatus). Tablets, 13 mm in diameter and 623 mg in weigh, were compressed at 15 kN force.

RESULTS AND DISCUSSION

Lubricants

In water solution the most significant incompatibilities were observed between CHX and sodium stearyl fumarate, magnesium stearate and sodium lauryl sulphate (Table I). The clear incompatibility of magnesium stearate agreed with the earlier results by McCarthy with other magnesium compounds (6). The incompatability of sodium lauryl sulphate is due to its anionic nature in water solution (4). CHX as a cationic compound is incompatible with anionic compounds. Hydrogenated vegetable oil and talc reduced CHX concentration clearly lesser.

Under high relative humidity all the studied lubricants reduced CHX concentration quite similarly. Only magnesium

Table I. The remaining amount of chlorhexidine (%) after storage in the presence of different excipients under different conditions. SEM in parenthesis.

excipient	water solution	80 % RH
magnesium stearate	48.6	75.0 (5.4)
talc	79.4	94.8 (0.5)
sodium lauryl sulphate	53.4	81.6 (4.5)
sodium stearyl fumarate	45.1	91.5 (2.6)
hydrogenated vegetable oil	79.5	88.0 (3.1)
crosslinked NaCMC	46.1	70.8 (0.4)
NaCMC	43.8	70.9 (1.5)
sodium starch glycolate	73.7	87.2 (2.7)
potato starch	79.8	92.0 (0.7)
crosslinked PVP	84.3	88.0 (6.6)

stearate showed a slightly greater and talc slightly smaller reduction. The hygroscopocity of the lubricants is low. Thus, on the contrary to disintegrants, their water absorption ability is neglible or limited. The water causing or accelerating the incompatibility between CHX and lubricant must thus have been absorbed by the basic powder mass.

The dissolution profiles of all the three tablet formulations were similar (Figure 1). However, tablets containing magnesium stearate and sodium stearyl fumarate showed clearly smaller maximum dissolution of CHX than tablets containing hydrogenated vegetable oil. This agreed completely with the results in Table I.

The maximum amount (%) of dissolved CHX was clearly greater during dissolution test than during storage test in distilled water. This might be due to both shorter testing time and smaller total CHX concentration of the dissoluti-

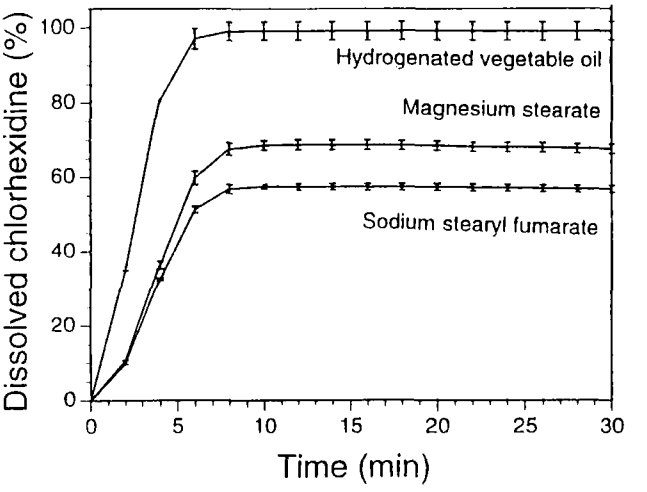

Figure 1.

Dissolution of chlorhexidine (%) from tablets containing different lubricants. Bars represent SEM.

on test (3,4). The effect of time was studied by continuing the dissolution test with magnesium stearate tablets up to 8 hours. During the last 7½ hours CHX concentration was reduced about 10 per cent from the dissolution level at 30 minutes.

Disintegrants

In water solution crosslinked PVP was the most compatible disintegrant with CHX whereas sodium carboxymethylcellulose (AcDiSol and Ph. Eur. grade) which is commonly used e.g. as a gel forming agent in pharmaceutical CHX preparations reduced CHX concentration over 50 per cent. This was as in the case of sodium lauryl sulphate due to the anionic nature of sodium carboxymethylcellulose (6).

Under high relative humidity the greatest incompatibility with CHX was again seen with carboxymethylcelluloses.

Potato starch was the most compatible disintegrant with CHX (Table I). This might, however, be partly due to the smaller water absorption ability of this disintegrant. The other studied disintegrants may be classified as so called superdisintegrants (7), which may absorb water over double of their own weigh.

CONCLUSIONS

Clear differences in the compatibility of CHX between different disintegrants but also different lubricants was observed. A lubricant is almost exclusively necessary in tablet formulation. The most compatible lubricant was talc which, however, is actually a glidant. Magnesium stearate, the usual choice as a lubricant was incompatible with CHX. Thus hydrogenated vegetable oil could be considered as a choice for a lubricant in a tablet formulation containing CHX. The need of a disintegrant in tablet formulation containing CHX must be carefully considered. If it is necessary to incorporate an effective disintegrant, the best one is crosslinked PVP.

REFERENCES

1. M. Addy, J. Clin. Periodont., 13, 957 (1988)
2. L. Eskelinen and L. Riutta, Farmaseuttinen aikakauskirja Dosis, 7, 184 (1991)
3. Martindale The Extra Pharmacopoeia 29th edition, The Pharmaceutical Press, London, 1989
4. Handbook of Pharmaceutical Excipients, The Pharmaceutical Press, London, 1986
5. T. Pesonen, T. Nuuja and J. Pohjola, 'Abstract book of Pharmacy World Congress', Washington DC 1991, p. 122
6. T.J. McCarthy, J. Mond. Pharm., 4, 321 (1969)
7. R. Shangraw, A. Mitrajev and M. Shah, Pharm. Technol., 4, 49 (1980)