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## NATAMYCIN STABILITY DATA SHEET

Natamycin is a stable compound provided the powder is protected from light and moisture. Only a few percent loss of activity is observed after several years storage at room temperature. This is true for the trihydrate, the anhydrous form however is not stable. This form, prepared by heating the trihydrate in vacuo at room temperature over phosphorus pentoxide, loses 15% of activity when stored for 48 hours at room temperature in a closed bottle in the dark. Natamycin will withstand heating at up to 120°C for no more than one hour. However, any anhydrous natamycin produced during heating is unstable.

**The methanol solvate is an unstable substance as well.**

Neutral aqueous natamycin suspensions are nearly as stable as the dry powder. A neutral aqueous suspension can be boiled for a short time before a reduction in potency occurs. Aqueous solutions are quite stable at pH values between 5 and 9 if stored in the dark. At extreme pH values natamycin is rapidly inactivated with formation of various kinds of decomposition products. At a low pH the mycosamine moiety is split off. The resulting unstable aglycone reacts with either a second molecule of aglycone or with a still intact molecule of Natamycin. In both cases dimers with a triene rather than a tetraene group are formed. At the same time the epoxy group is hydrolysed to a diol. Heating at low at high pH

values, rapidly at pH 12, the lactone is saponified with formation of the microbiologically inactive natamycoic acid. Treatment with strong alkali results in further disruption of the molecule owing to a series of retroaldol reactions. Among the reaction products the following compounds could be detected:

13-hydroxy-2,4,6,8,10-tetradecapentaene-1-al , acetone , acetaldehyde and ammonia.

Natamycin is decomposed by ultraviolet radiation with loss of the tetraene structure. Thom observed that Natamycin decomposed faster in aqueous solution at pH 4 than at pH 8 upon radiation with a xenon lamp. Visible light does not inactivate natamycin unless transfer of photo-energy by e. g. riboflavin takes place.

Gamma radiation decomposes natamycin as well, it can therefore not be used to sterilize the substance.

The inactivation by peroxides or, especially at higher temperatures , by oxygen can be prevented by antioxidants like chlorophyll , ascorbic acid butylated hydroxyanisole or butylated hydroxytoluene.

Oxidative inactivation is promoted by several metal ions, especially  $\text{Fe}^{3+}$ ,  $\text{Ni}^{2+}$  and  $\text{Cr}^{3+}$ . This can be prevented by adding complexing agents like EDTA or polyphosphates.

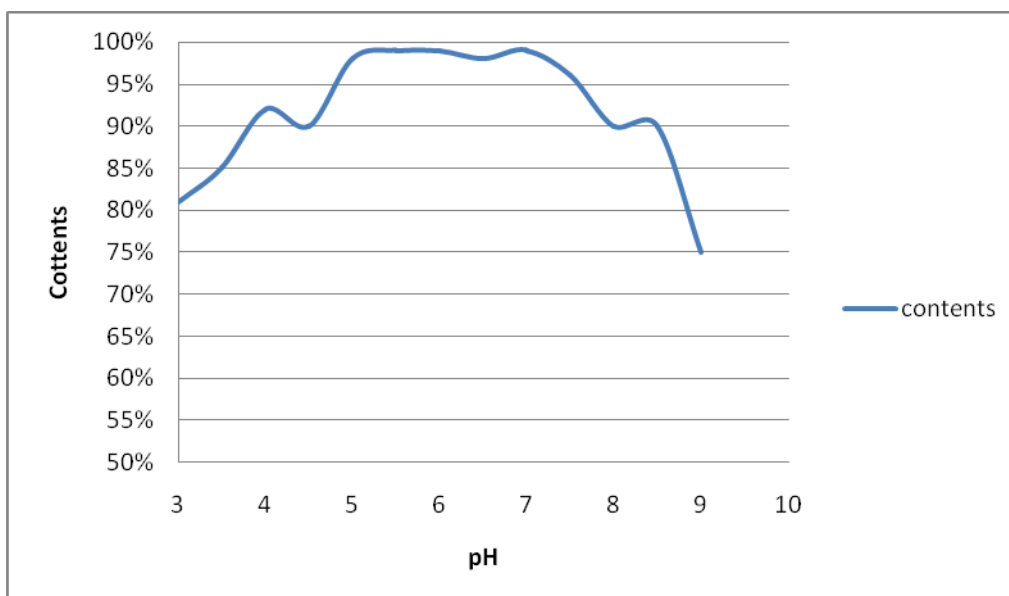
Inactivation of natamycin by light , peroxides or oxygen proceeds at the fastest rate in solution or in suspension ,less so in the solid form. Oxidative degradation of natamycin probably leads to the formation of polymers or compounds formed by addition of oxygen on the conjugated double bonds. The

latter reaction, which takes place at one end of the polyene chain, is described for several polyenes. Either an epoxy-group (filipin and lagosin) or a hydroperoxide (nystatin, or levorin and mycoheptin) is formed. Inactivation occurs also in the presence of sulphites or sodium formaldehyde sulfoxylate.

The ultimate effect of natamycin in practice is determined by the concentration employed and the stability of this antimycotic under the conditions prevailing. Factors affecting stability are: acidity (pH value), temperature, light, oxidants and heavy metals.

#### Acidity (pH value)

At pH value lower than pH 3 and higher than pH 9, the Natamycin suspension is less stable. The diagram shows how much active product remains as a 0.1% aqueous suspension after storage at a temperature of 30°C at the pH given. Most foods have a pH value between pH 4 and pH 7, i.e. within the range in which Natamycin is very stable.



The diagram clearly shows the great stability of Natamycin suspension

within a wide range of pH values.

A concentrated aqueous suspension of Natamycin at neutral pH can tolerate a temperature of 50°C for several days without any noticeable effects. It can even withstand some hours heating at 100°C.