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Loratadine: hydroxymethylation in syrup

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Loratadine, a non-sedating antihistamine, is inter alia marketed as a syrup having the composition loratadine 1 mg, citric acid 8.78 mg, flavour 2.5 mg, glycerol 100 mg, propylene glycol 100 mg, sodium benzoate 1 mg, sucrose 600 mg and water (approx. 400 mg) to make one ml. The pH of the formulation is about 2.8 and on storage it furnishes several degradation products, notably 2-hydroxymethyl- and 4-hydroxymethylloratadine. The amount formed of these degradants is related to the air headspace volume in the containers used. 25 ml of syrup kept in a tightly closed 50 ml vial for 9 weeks at 55 °C yielded approx. 0.5% of both hydroxymethyl derivatives. The degradation may be retarded or minimized by purging the containers with nitrogen or including edetate disodium in the formulation [1].

Loratadine is a basic compound that is almost insoluble in water. Hence, it is solubilized in the syrup by means of two cosolvents and citric acid. Apparently, the formation of hydroxymethyl derivatives as impurities in drug delivery systems has no precedent parallels in the scientific pharmaceutical literature and must be considered to be highly interesting. Still, surprisingly, no reports seem to have been published on the chemical mechanisms involved. The following remarks are intended as proposals and, hopefully, to stimulate interest in elaborate studies on this subject.

The most likely primary source of the one-carbon hydroxymethylation unit which is assumed to be formaldehyde, at least formally, is thought to be sucrose that is well known to hydrolyze (invert) into its constituent monosaccharides glucose and fructose; the latter may form 2-furaldehyde and formaldehyde in an acid-catalyzed dehydration via a reverse aldol reaction. Moreover, fructose may form 5-(hydroxymethyl)-2-furaldehyde and this may also possibly function as a formaldehyde donor [2]. However, formaldehyde is an electrophilic reagent and therefore an attack of it on the electron deficient 2- and 4-positions in the unaltered pyridine ring in the loratadine molecule must be considered to be unlikely. Therefore, it is proposed that loratadine may first be transformed into loratadine *N*-oxide by oxidation with atmospheric oxygen (possibly via a peroxide) and that this species subsequently undergoes hydroxymethylation by formaldehyde (or another electrophilic one-carbon donor) in the now electronrich 2- and 4-positions. Following this it is assumed that the hydroxymethylloratadine *N*-oxides are reduced by interaction with e.g. primary or secondary alcohol groups that are abundant in the syrup [3]. These hypotheses are summarized in the Scheme.

References

1 Munayyer, F. J.; Guazzo, F.; Stupak, E. I.; Chaudry, I. A.; Sequeira, J. A.: Stabilized antihistamine syrup, US Patent 6,132,758 (2000)
2 Antal, M. J.; Mok, W. S. L.; Richards, G. N.: Carbohydr. Res. **199**, 91 (1990)
3 Albini, A.: Synthesis **3**, 263 (1993)

Scheme Plausible chemical reactions leading to hydroxymethylation of loratadine in syrup at pH ca. 3