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The Maillard reaction of bisoprolol fumarate with various reducing carbohydrates

Mateusz Szalka [a,*], Jacek Lubczak [b], Dorota Naróg [c], Marek Laskowski [a], Krzysztof Kaczmarski [d]

[a] Product Development Department, ICN Polfa Rzeszów S.A., 35-959 Rzeszów, Poland
[b] Department of Organic Chemistry, Rzeszów University of Technology, 35-959 Rzeszów, Poland
[c] Department of Physical Chemistry, Rzeszów University of Technology, 35-959 Rzeszów, Poland
[d] Department of Chemical and Process Engineering, Rzeszów University of Technology, 35-959 Rzeszów, Poland

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ABSTRACT

HPLC analysis of drug products containing bisoprolol fumarate and lactose revealed the presence of N-formylbisoprolol, which is a final product of the Maillard reaction. Formulations containing secondary amines and reducing carbohydrates are prone to the condensation of amine and carbonyl functional groups and formation of glycosylamines in pharmaceutically relevant conditions. Further rearrangement occurs in the presence of a nucleophile and leads to the formation of 1-deoxy-1-amino-2-ketose also known as the Amadori Rearrangement Product (ARP). The influence of water content, carbohydrate, and lubricant types on the reaction rate was tested. The reaction progress was monitored by HPLC and UV–Vis spectrophotometry. The structures of intermediates were confirmed by the LC/MS^2 analysis. N-formylbisoprolol – the final reaction product – was synthesised and characterised by LC/MS^2, H^1 and C^{13} NMR.

1. Introduction

Common incompatibilities between the active pharmaceutical ingredients and excipients (tablet diluents) occur due to the Maillard reaction also known as a non-enzymatic browning reaction. Over 100 years ago Louis Maillard reported, that carbonyl compounds may react with amino acids and proteins to form the complex mixtures of brown pigments with a characteristic malt-like odour (Maillard, 1912). This reaction has been studied for many years and is described in details in the food and nutritional literature (Ledl and Schleicher, 1990; Ledl, 1990). Nowadays, the Maillard reaction was also extensively studied in the pharmaceutical systems (Qiu et al., 2005; Monajjemzadeh et al., 2009) where glucose, lactose, and maltose are commonly used as fillers in capsules and tablets (Rowe et al., 2003). In the drug product formulations the non-enzymatic browning reaction occurs between a reducing carbohydrate (mainly mono- or disaccharide) which may exist in open-chain aldehyde forms, and active substances containing primary or secondary amine functional groups (Hodge and Rist, 1953). For many years tertiary amines were not considered as substrates for the Maillard reaction. However, as described by Thumma and Repka (2009), reaction of promethazine and lactose also results in non-enzymatic browning.

Bisoprolol fumarate belongs to the beta-blocker class of therapeutic substances and is commonly used in a treatment of hypertension, coronary failure, and arrhythmia (Merck KGaA Darmstadt Germany, 2001). Chemically bisoprolol is a derivative of phenoxyaminopropanol (secondary amine); it is used as a racemic mixture for therapeutic purposes. The Concor® family of drug products was originally developed by the Merck Group and is currently registered in over 90 countries worldwide. Recently, there are many generic formulations of bisoprolol fumarate available in the European market, most of them contain reducing carbohydrates as primary tablet fillers – mainly lactose due to its low price and good compressibility.

The European Society of Cardiology strengthened the position of beta blockers in a treatment of the chronic and acute hart failures in the revised guidelines (McMurray et al., 2012). There is evidence

Abbreviations: ACE, angiotensin converting enzyme inhibitors; Al/PVdC, aluminium/polyvinylidene chloride; Ar, aromatic ring; ARP, Amadori Rearrangement Product; DMSO, dimethylsulphoxide; EMEA, European Medicines Agency; FDA, Food and Drug Administration; GC, gas chromatography; HPLC, high performance liquid chromatography; ICH, The International Conference on Harmonisation of Technical Requirements; IR, infrared spectroscopy; KF, Karl Fischer titration; MS, mass spectrometry; NMR, Nuclear Magnetic Resonance; RT, retention time; UV–Vis, ultraviolet–visible spectrophotometry.

* Corresponding author. Tel.: +48 795 521 562.
E-mail address: mateusz.szalka@valeant.com (M. Szalka).

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that beta-blockers are complementary with diuretics or ACE inhibitors (the list of abbreviations is given in the first page of this paper), and may be used simultaneously in a treatment of the diagnosed heart failure. Thus, we may expect that many new generic formulations containing two active substances from the different classes will be developed and registered at relevant authorities. The formulation scientists should not forget that a combination of amine and carbonyl compounds may result in the non-enzymatic browning reaction and formation of undesirable chemical compounds which often demonstrate a biological activity.

The first reaction step involves condensation of a carbonyl functional group of carbohydrate and an amine group from active substance to form a glycosylamine and water. The second step of this reaction was proposed by Amadori, who proved that heating D-glucose with primary amines leads to the formation of two isomers: one labile which readily undergoes rearrangement to the another more stable isomer (Amadori, 1925). Both structures of the labile and stable isomers were later identified as a glycosylamine and 1-deoxy-1-amino-2-ketose, respectively (Kuhn and Dansi, 1936; Kuhn and Weygand, 1937). Further stages of the non-enzymatic browning may occur through many different reaction pathways, including the fragmentation and dehydration of carbohydrates or the cyclisation and formation of aromatic compounds (Ledl et al., 1986). The non-enzymatic browning was observed at slow rates in the neutral and acidic conditions. However, as reported by Hodge and Rist (1953), alkaline conditions are the most favourable for this reaction. Studies of the Maillard reaction in a liquid model system confirm, that the addition of small amounts of hydroxides significantly improve the reaction rate and may lead to the formation of new degradation products. For example the formation of N-formylfluoxetine was observed in the reaction of lactose and fluoxetine hydrochloride only after the addition of potassium hydroxide (Wirth et al., 1998). It is important to highlight, that glycosylamines and Amadori Rearrangement Products (ARP) are susceptible to the hydrolysis. Thus, if the kinetic study of the Maillard reaction is being performed by tracing the ARP, then the reaction conditions should exclude aqueous solutions (Wolfrom et al., 1949; Mitts and Hixon, 1944).

The general mechanism of the Maillard reaction (glycosylation) for glucose and a secondary amine is presented in Fig. 1a. The mechanism of the Amadori rearrangement in a presence of the catalytic amounts of acid was originally proposed by Kuhn and Weygand (Kuhn and Dansi, 1936) and involved a protonation of nitrogen in the glycosylamine, a formation of ammonium ion which stays in the equilibrium with a Schiff base and then further rearrangement to 1-deoxy-1-amino-2-ketose. This mechanism was also presented by Hodge (1955), who remarked that the attraction of a proton by nitrogen is more probable than by a weakly basic oxygen. In 1950s Gottschalk (1952) and Isbell and Frush (1958) proposed the mechanism of the Amadori rearrangement which included the protonation of oxygen atom, immediate ring opening of glycosylamine and further rearrangement to the Amadori product (ARP). Simon and Kraus (1970) in their mechanistic studies on the Amadori rearrangement point that O-protonation is much more favourable for the ring opening than N-protonation. In fact, protonation of the oxygen atom turns it into a better leaving group, thus, the ring opening should occur more readily. It is difficult to unambiguously determine according to which mechanism the Amadori rearrangement occurs in pharmaceutical systems. It may also be possible that final reaction mechanism includes at first attraction of a proton by the basic nitrogen, and when transfer of a proton to the oxygen atom and further rearrangement. The general mechanism of the Amadori rearrangement proposed by Kuhn and Weygand is presented in Fig. 1b.

The scope of our study is to demonstrate the Maillard/Amadori reactions of bisoprolol with various reducing carbohydrates in the solid model systems. Which were designed to test the influence of water, various tablet diluents, and lubricants on the reaction rate. We are also alerting that the Maillard/Amadori reactions may occur in the commercially available tablets stored in the climatic chambers with accelerated conditions as indicated by the International Conference on Harmonisation (ICH) (European Medicines Agency, 2003).

It is difficult to carry out the complete kinetic studies because of the complexity of both the Maillard reaction and the Amadori rearrangement. In addition, the intermediates and final products of conversion may degrade according to several reaction pathways, which often lead to the regeneration of amine moiety (Labuza and Massaro, 1990; Labuza and Baisier, 1992). All obtained results were carefully considered and used in a preparation of the theoretical reaction mechanism.

In our studies the reaction was monitored by the reversed phase HPLC and UV–Vis spectrophotometry. Water content was determined by the Karl Fischer titration. The molecular masses of intermediates were confirmed by LC/MS^2. The structure of the final product was compared to a synthesised working standard and confirmed by the LC/MS^2 and NMR analysis.

2. Materials and methods

2.1. Materials

Bisoprolol fumarate was obtained from ICN Polfa Rzeszów S.A., Poland.

Potassium dihydrogen phosphate (anhydrous), formic acid, and sodium hydroxide were obtained from POCH, Poland.

Acetonitrile HPLC grade, dimethylsulphoxide for GC, isopropyl alcohol HPLC grade, Karl Fischer titration reagent 5.0, Karl Fischer methanol-free solvent were obtained from Merck GmbH Germany.

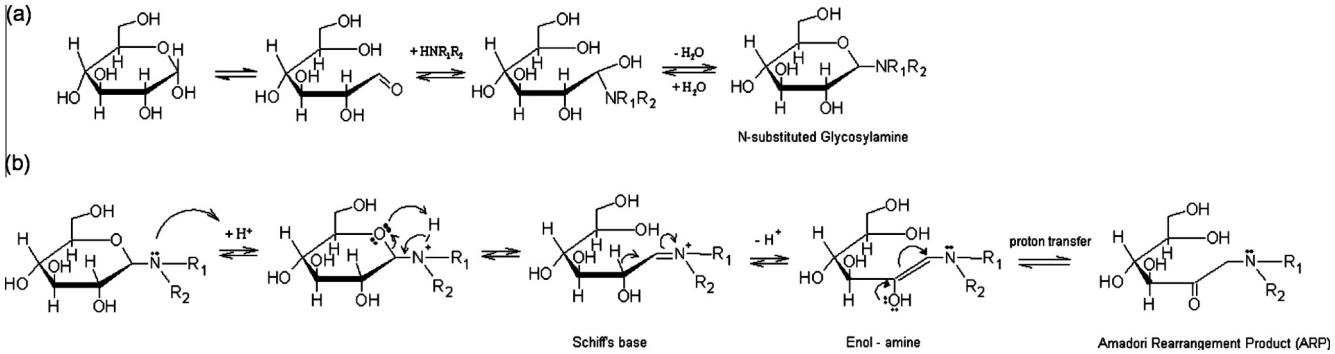

Fig. 1. Generally proposed: (a) The Maillard reaction pathway – glycosylation and (b) mechanism of the Amadori rearrangement in acidic conditions.