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Review

Gelatin structure and composition linked to hard capsule dissolution: A review

Anne Duconseille [a], Thierry Astruc [a], Naira Quintana [b], Filip Meersman [b], Véronique Sante-Lhoutellier [a, *]

[a] INRA de Clermont-Ferrand-Theix, UR370 QuaPA, F-63122 St Genès Champanelle, France
[b] Rousselot NV, Meulestedekaai 81, 9000 Gent, Belgium

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ABSTRACT

Gelatin obtained from pig skin constitutes about 50% of world production and is mainly composed of collagen extracted from skin by acidic baths and thermal treatments. The gelatin is used to make various products, notably hard gelatin capsules (HGC) which of varying solubility in water. This issue has been known for many years and has been, and remains, a subject of study and debate. The main reason for low gelatin dissolution rates is its tendency to form cross-links in the denatured collagen chains under specific conditions which stabilize the gel network and prevent dissolution. As it is extracted from animal tissues, gelatin may contain molecules other than collagen (sugars, lipids and other proteins) which may react with collagen chains to form covalent bonds. Although this biopolymer has been the subject of numerous publications, its structure and composition is not well defined. Indeed, there are many differences from an article to another. Consequently, the causes of HGC dissolution are not well identified and controlled.

Contents

* Corresponding author. Tel.: +33 4 73 62 47 08; fax: +33 4 73 62 42 68.
E-mail address: veronique.sante@clermont.inra.fr (V. Sante-Lhoutellier).

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1. Introduction

Gelatin derived from animal tissue has been known since antiquity and was first used as glue as far back as 6000 BC. During the 16th century, at the court of Henry VIII of England, gelatin was an ingredient of dishes at every banquet. Over time, its manufacture became industrialized and its applications have increased in number (Schrieber & Gareis, 2007). It is now widely used in the food, photographic and pharmaceutical industries.

The most abundant sources of gelatin production are pig skin (46%), bovine hides (29.4%) and pig and cattle bones (23.1%). Fish gelatin represented less than 1.5% of total gelatin production in 2007 (Gomez-Guillén et al., 2009). In this review we focus on the most abundant part of the production, i.e. pig skin gelatin, taking account of knowledge on all gelatin origins.

This biopolymer consists of proteins (85–92%), mineral salts and water. It is produced by the partial hydrolysis of collagen (Schrieber & Gareis, 2007). Depending on the raw material used (source and age of the animal), collagen does not have exactly the same structure, composition and properties, and gelatin does not either. Indeed, 28 different types of collagen have been identified (Ricard - Blum, 2010). During the gelatin-making process, proteins are extracted from skin and bone by acid or alkaline baths and thermal pre-treatments. A thermal process is then used to separate proteins from the rest of the raw material (Schrieber & Gareis, 2007). Depending on the manufacturing process, the extract is then deionized, sterilized and dried, but more steps can be added. The dried matter obtained is called gelatin. There are two types of gelatin, A and B, produced from acid and alkaline pre-treatments, respectively.

Gelatin is used as the main ingredient of the hard capsules used in the pharmaceutical industry. An important property of these hard capsules is that they melt in water at a temperature above 30 °C and easily release drugs they contain in the human digestive tract due to temperature, gastric pH and digestive enzymes. However, to be sold on the market, a hard capsule has to pass the dissolution test in water according to the specifications in the United States Pharmacopeia 711 harmonized with the corresponding texts of the European Pharmacopoeia and the Japanese Pharmacopoeia (U. S. Pharmacopeial Convention, 2012). Sometimes gelatin hard capsules present an insufficient dissolution rate in water. This dissolution issue has been known since 1974 and was revealed by studying chloramphenicol capsules (Khalil, Ali, & Abdel Khalek, 1974). Since then, many publications have dealt with the gelatin dissolution and shown that this issue is still a concern. The main cause of this poor dissolution is the tendency of gelatin to form cross-links in high relative humidity and temperature conditions or in the presence of chemical compounds such as aldehydes (Ofner, Zhang, Jobeck, & Bowman, 2001). In gastric fluids, cross-linked hard capsules can be dissolved easily in the same way as non cross-linked hard capsules (Meyer et al., 2000). This observation led to the modification of the United-States Pharmacopeia monograph on gelatin capsule dissolution testing in which the use of enzymes in dissolution media is allowed in some circumstances, i.e. in the two-tier test (Cole, Cad, & Benameur, 2008). However, specifications vary according to the pharmacopeia and water is still generally commonly used as a dissolution medium (Chiwele, Jones, & Podczeck, 2000). An alternative to gelatin was developed in the industry with other polymers like HPMC (Hydroxypropyl methylcellulose) most likely to replace gelatin (Al-Tabakha, 2010). However, the properties of HPMC are different from those of gelatin and hard gelatin capsules (HGC) are still the second most used form of oral dosage after tablets (around 70% for tablets and around 28% for HGC in 2000) and the trend is increasing, showing that other polymers are not about to replace gelatin in hard capsules (Stegemann, 2002).

Cross-link formation depends on many parameters. The main difficulty is to order the factors affecting cross-links according to their nature and impact on dissolution. The raw material used plays an important role in the degree of cross-linking. Indeed, in young animals, collagen molecules present few cross-links which confer elasticity to skin. But with aging, more cross-links are found in the collagen network, forming an extremely stable structure. The gelatin-making process also influences the cross-link degree, more particularly during acid or alkaline pre-treatments which partly cleave collagen cross-links to give a denatured collagen structure (Schrieber & Gareis, 2007).

The raw material and the manufacturing process may play an important role in the dissolution rate of HGC, but other factors like the presence of various reactive compounds have to be taken in account. Indeed, there are many different molecules in pig skin and, despite pre-treatment and thermal extraction, the extract may contain not only denatured collagens but also other extracellular matrix components such as proteoglycans, elastin or fibronectin which interact with collagen in connective tissue. The latter molecules may create cross-links with the denatured collagens and reduce gelatin dissolution. Moreover, sugars or lipids may also be extracted from the raw material during the manufacturing process and be involved in cross-link formation.

The aim of this review is to provide a state of the art on knowledge of gelatin and identify the factors affecting gelatin dissolution. Thus it aims at contributing to better understanding of this issue and providing an overview of research in this field.

2. Collagen composition and structure

Skin is mainly composed of type I collagen and, to a lesser extent, type III collagen (Bruckner, 2010)(see Table 1). Collagen is composed of three α chains forming a triple-helix structure. The α-chain consists of continuous repetitions of Gly-X-Y amino acid sequences where X is mostly proline and Y is mostly hydroxyproline (Bailey & Light, 1989). The latter amino acid is specific to the collagen molecule (Hofman, Hall, Cleaver, & Marshall, 2011). Because of this primary sequence full of proline and hydroxyproline residues, which are regularly located in the α-chain in the motif Gly-Pro-Hyp, the α-chain adopts a left-handed helix type conformation which is unstable in individual state. Indeed, proline and hydroxyproline have rings which force the chain to form a helix due to steric hindrance (Okuyama, Miyama, Mizuno, & Bachinger, 2012). When three chains are linked together they form a very stable right-handed triple helix (Bailey & Light, 1989). This triple-helix is stabilized by intra and inter-chain hydrogen bonds. In this dense structure, glycine residues are oriented in the center while