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Natural Excipients in the Pharmaceutical Industry

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Abstract

Excipients in general, and natural excipients in particular, have been drawing more attention in the last few decades, and have been the subject of numerous studies. This paper begins with a definition of excipients and a general overview of the kind of attention natural excipients have begun to draw. The paper then zeroes in on alginates as natural excipients particularly noteworthy for their interesting production process and environmental impact, before closing with a general discussion of quality control both as it pertains to excipients in general and alginates in particular.

Contents

Introduction

The word excipient comes from the Latin *excipere*, meaning 'to except', and in the most basic sense excipients are everything that makes up a medicine *except* the active ingredients [1]. For a time, excipients were thought of as 'inert', as substances whose only purpose was to be cheap vehicles for the delivery of the active ingredient. That has changed, and they are now considered essential constituents of medicines which serve a variety of purposes [2][3]. They are usually classified in accordance with their function, e.g. binders or diluents; lubricants, glidants, or disintegrants; and flavorings, sweeteners, or taste-improving agents [3].

The pharmaceutical industries have been showing a particular interest in natural excipients for some of their characteristics; natural excipients are inert, biocompatible, biodegradable, have minimum toxic effects, and are cost-effective [4].

A paper by Jain et al. [3] mentions multiple examples of natural excipients, including the following:

- Starch
- Gums and Mucilage
- Polysaccharides
- Alginates

It is evident that natural excipients are plentiful. Due to the limited scope of this paper, only one process will be discussed—that of the extraction of alginate from brown seaweeds. Alginate is the general term for the salts of alginic acid, such as sodium alginate and potassium alginate [5]. Both are natural excipients [3]. Sodium alginate is used in tablet formulations as both a binder and disintegrant, and in capsule formulations as a diluent, while the use of potassium alginate is limited to experimental hydrogel systems [6].

In the next section the raw materials that go into the production of alginates are discussed.

Raw Materials

Alginate can be found in most (perhaps all) species of brown algae. Brown algae (taxonomic group Ochrophyta) are a kind of marine macroalgae, called *brown* on the basis of their photosynthetic pigment composition [5].

Figure 1: brown seaweed, courtesy of www.aphotomarine.com [7].

As was stated in the previous section, alginate is extracted from multiple kinds of brown seaweed. To be specific, as of 2018, the most industrially important species for alginate extraction are certain kelps such as *Macrocystis pyrifera*, and certain fucoids such as *Durvillaea potatorum* [5][8][9].

Alginate is found in these seaweeds as a structural component of the cell wall and intercellular regions, taking the form of insoluble mixed salts of alginic acid, mostly with calcium, but also with sodium to a lesser extent [5].

Some species of the two orders mentioned above (kelps and fucoids) have very large amounts of alginate—up to 55% of their dry weight [5]. That being said, alginate content and structure vary seasonally, and depend also on the age and part of the seaweed used, as well as environmental conditions [5][10][11][12].

Thus, the selection of the correct species and time of harvest has a substantial impact on alginate production.

Process Description & Flow Chart

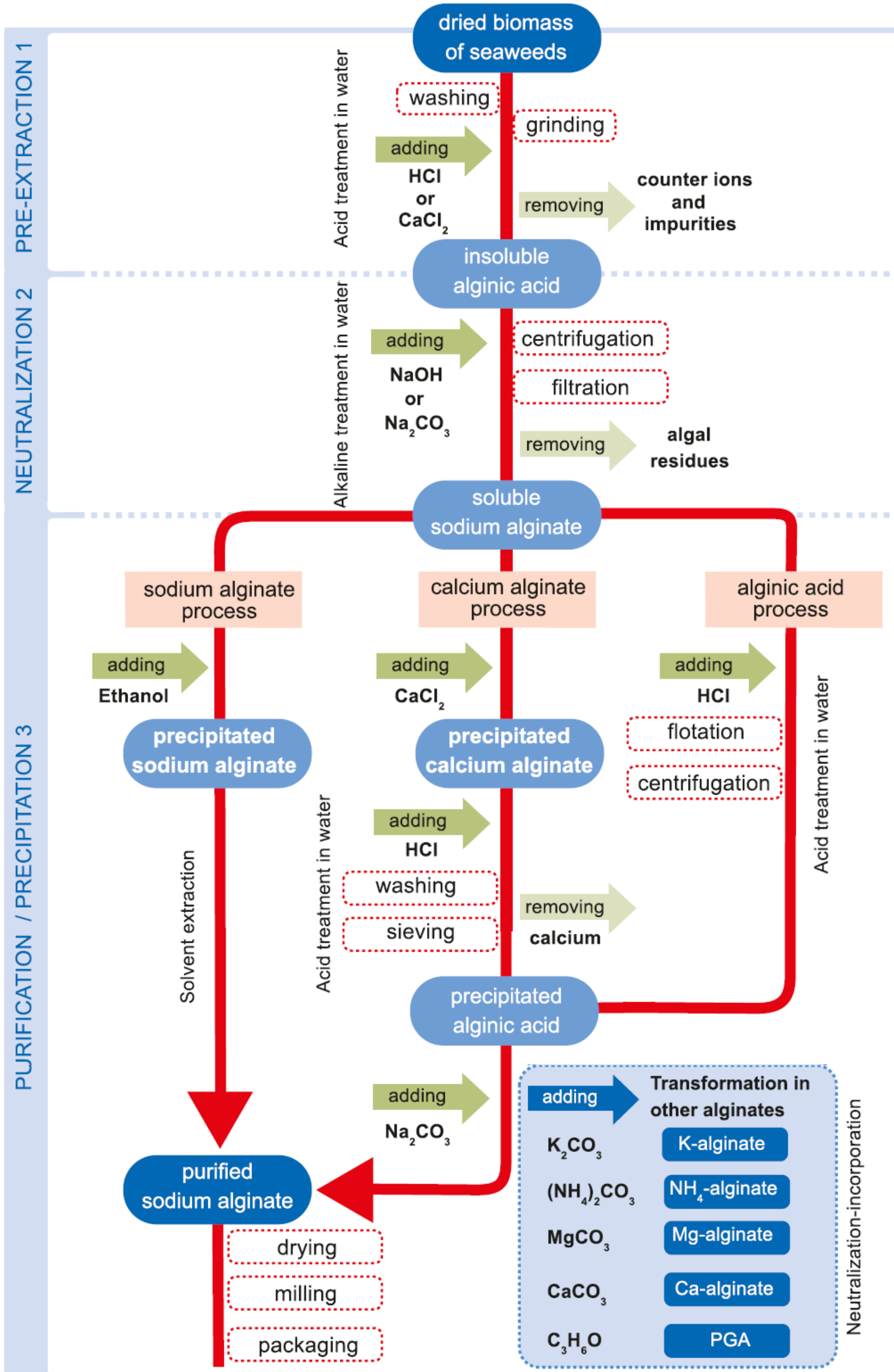

Figure 2: Alginate extraction process, courtesy of César Peteiro [5].

Alginate extraction form brown seaweeds can be separated into three key stages, as shown in the figure above: pre-extraction, neutralization, and purification.

The process as a whole consists of first transferring the insoluble alginic acid salts from the cell wall matrix and then converting them into water-soluble salts, which are then precipitated and purified. The process summarized below is described in detail by Peteiro [5].

The first step consists of washing, grinding, and treating the seaweeds with selected chemicals. The seaweeds usually enter having already been dried. Grinding is done to decrease reaction time. The purpose of the chemical treatment is to increase yield and remove counterions as well as potential impurities.

The second step sees the insoluble alginic acid present in the seaweeds converted to water soluble sodium alginate via the addition of an alkaline solution e.g. sodium carbonate (Na_2CO_3) or sodium hydroxide (NaOH). This is done at a temperature between 60 - 80° C, and with constant mixing. Centrifugation and filtration are used to remove algal residues, so that a one-phase sodium alginate-water mixture is obtained.

The purpose of the third step is to extract the alginate from the mixture. This is done in one of three ways, known, respectively, as the ethanol route, the $CaCl_2$ route, and the HCl route, summarized below:

- Ethanol route: the sodium alginate is obtained by the addition of ethanol and solvent extraction or evaporation. The product obtained is sodium alginate.
- $CaCl_2$ route: the addition of $CaCl_2$ produces calcium alginate, which may be separated by sieving. The calcium alginate may be reacted with HCl to form alginic acid, which can be converted into any desired alginate (sodium, potassium, etc.).
- HCl route: the middle man ($CaCl_2$) is cut out, and alginic acid is produced directly.

It is worth emphasizing that any kind of alginate can be obtained from alginic acid. The above flow chart describes multiple processes that share the aim of producing sodium alginate specifically, but the processes for the production of other alginates are not significantly different.

Environmental Impact

The harvesting of brown seaweeds is not without impact, and awareness of that impact has been growing. There has lately been an increase in governmental control concerning the exploitation of brown seaweeds populations—with harvest quotas, for example, being set in some countries [5]. It is also worth noting that the harvesting of the kelp *Macrocystis* has been reduced due to concern about the environmental effects that result from it [5][9].

All this because the harvesting of kelps (in particular) affects other species. Kelps play a role similar to that of forests. They are founding species, providing habitat, food, and protection for a large number of organisms in coastal ecosystems [5][14].

It is sufficient to state that fucoids are important as well [15].

However, a solution to the problem above has presented itself: aquafarming.

According to Peteiro [5], aquafarming has already established itself in Asia as a commercially viable alternative to the harvesting of wild seaweeds, and current practices of kelp farming there have contributed to meeting increasing demand as well conserving natural populations and ecosystems. There's also growing interest in Europe and the Americas in the mariculture of kelp species, and it is widely recognized that a transition from extraction to cultivation is necessary to meet the challenges described above.

Quality Control

In this section we first abandon specificity, and discuss good practices in the quality control of excipients in general, under the explicit assumption that quality control practices for excipients in general apply just as well to natural excipients in particular. After that we return to specificity, and discuss the quality control of sodium alginates in particular, so that our discussion of alginate extraction is complete.

According to the World Health Organization [16], quality control as it pertains to excipients begins with a quality control unit having both the responsibility and authority to approve or reject all components, in-process materials, packaging materials, and finished excipients, as well as procedures, specifications, and process changes. It is also generally important that quality records be kept, and that all measuring and test equipment be properly calibrated and well maintained.

The quality control strategy recommended by the WHO can be divided into three categories:

1. Quality control of starting materials:

   Starting materials must be verified prior to use. There should be clear standard operating procedures for the approval of starting materials, and there should always be some evidence of an attempt by the excipient manufacturer to establish identity.

2. Quality control of the process as a whole:

   The process must be inspected and tested by either monitoring the process or drawing samples. The results of the tests must always conform to acceptable tolerances or established process parameters. There should be instructions that delineate how to use the inspection and test data to control the process.

3. Quality control of the finished product:

   Stability studies should be conducted and if the excipient has a limited shelf life or special storage conditions, then these restrictions must be placed on the label.

Now we return to our discussion of alginates in particular. In a paper by Fiona Johnson et al. [17], three methods for the study of the molecular characteristics of alginates were compared: circular dichroism, nuclear magnetic resonance, and viscosity measurements using a controlled-stress rheometer. Circular dichroism was described as a rapid and simple means of assessing the MG ratio (M for D-mannuronic acid, and G for L-guluronic acid, which together make up alginic acid). Nuclear magnetic resonance is more complex, but yields detailed information about the block structure of alginates. Finally, viscosity measurements are built on multiple assumptions, so the results obtained (mostly to do with molecular mass) from them are considered only approximate, but they nevertheless provide useful information—especially with regards to the characterization of samples to assess, for example, possible degradation on processing or storage. In the conclusion of the study, it is stated that alginates are complex in structure and that their molecular characteristics are of prime importance in terms of understanding the function they serve.

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