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Chitin and Chitosan as Biomaterials: Going Forward based on Lessons Learnt

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Abstract

The role that chitin, chitosan, and their derivatives can play as biomaterials is apparent. Yet they remain primarily the domain of intense R&D. The search for a sensational commercial breakthrough that can generate excitement and spur continued R&D remains. This paper offers three focus points for consideration, type of potential biomedical product to work on, improvement of analytical methods for these materials, and reproducibility of reactions in producing chemical derivatives of chitin and chitosan.

Introduction

Chitin and chitosan have a role as biomaterials. This fact is indisputable based on the work done as evidenced in the scientific literature and patents published over the last 40 years. The potential applications such as wound dressings, hemocompatible coatings, drug delivery, tissue engineering, and cell encapsulation are well known today. Wound dressings and hemocompatibility coatings normally find use as external devices, while tissue engineering and drug delivery are intended for internal use that requires biodegradability except possibly when drug delivery is *per os* (Khor, 2002).

It is also very evident that from a brief inspection of the two leading Biomaterials journals, Biomaterials and Journal of Biomedical Materials Research, the number of articles with chitin or chitosan in their title is increasing since the start of the 21st Century. This augurs well for the interest of chitin, chitosan, and their derivatives in the fields of medical technology, and regenerative medicine.

Yet for all the promise in the past 40 years and their increasing relevance, chitin, chitosan and their derivatives remain "biomaterials in waiting". This has been reflected by the limited number of chitin and chitosan based medical products in select markets. Even the much publicized hemostatic chitosan-based "hemcon®" bandage that received much publicity prior to the Gulf War II, has not resulted in the much needed commercial impact that drives interest and continuing R&D (www.hemcom.com)

The need to address the presumed biological safety issues of chitin, chitosan and their derivatives by producing medical grade/quality materials with properties that are well defined, and confirming their utility in further studies, has previously been discussed (Khor, 2001). What more can be done based on all the promising biomedical applications history of chitin, chitosan and their derivatives that can transform the present *status quo* into action that realizes their true potential as biomaterials that have "arrived" defined as "erupting with profits"? The author believes that a candid reassessment of the past, confronting any shortcomings into a course of action is the basis for the future. This article addresses an updated refinement in the understanding of the role of chitin, chitosan and their derivatives in the biomedical arena. The paper is a brief presentation of a continuing series by the author at addressing the issue of chitin, chitosan and their derivatives relevance as biomaterials.

Going Forward Based on Lessons Learnt

The appropriate application for a breakthrough commercial success:

The place for chitin, chitosan and their derivatives as biomaterials in medical technology must

certainly be in applications where they are used as transient materials that play a role as medical devices or drug delivery carriers that are removed or biodegrade *in situ* once their usefulness terminates with native tissue regeneration. This is in agreement with the profile of the many applications stated in the introduction where most fall in the realm of temporary devices exploiting the inherent character of the polymeric glucosamine/N-acetyl-glucosamine backbone. Therefore, from a historical perspective, the chitin and chitosan scientists "got it right" where biomedical applications are concerned from the start and continue to do so. This sentiment was recently echoed by Professor David Williams in his keynote address at the 6th Asia-Pacific Chitin Chitosan Symposium, Singapore in May 2004 where he noted that natural substances such as chitin, chitosan and their derivatives were unlikely to find use "in long term medical devices, either structurally or as surfaces" (Williams, 2004). It is also noteworthy that two of chitin and chitosan's pioneers, Professors Muzzarelli and Hirano, played early roles in this endeavor, exploring applications in wound healing, bone substitutes and blood compatible materials (Khor, 2001).

But, should there be some refinement of the present broad scientific research momentum? The author believes that for continued R&D resulting in the growth of chitin science, there is a need to focus present efforts in the quest for that elusive breakthrough commercial success. How is this approached? It is pertinent to recall that chitin in nature is found as an intimate composite with proteins and $CaCO_3$ in its most abundant commercial source, shellfish. Even as a cell wall component, the covalent links with glucans implies an associated and not standalone configuration. Therefore, taking a page from nature, one can construe that the best way to utilize chitin, chitosan and their derivatives are in combination with other materials such as collagen, gelatin, hyaluronic acid, hydroxyapatite, etc., that best exploits the individual characteristics of the constituents, a direct correlation with the term composite as defined from an engineering perspective i.e. a (usually directional) reinforcement in a matrix. In this regard, chitin, chitosan and their derivatives have the versatility of participating in both roles as the scientific literature attests. This does not mean that the author precludes their utilization as single component materials. Rather, it is to distinguish the obvious that perhaps the best chance for a first large scale commercial success lies in mimicking nature as is the current general trend in many scientific disciplines.

The appropriate supply of raw materials

Having established that choosing the appropriate application is the foundation for commercial success, what follows? There are two vital ingredients to complete this presentation, the quality of raw material, to be discussed first, followed by the chemical modification of other suitable forms.

The quality of raw material for biomedical applications is essential, considering the Regulatory requirements for medical technology products prevailing today. What is good quality? In the context of supplying chitin, chitosan and their derivatives, it may not be the source of material or purity that matters, but more importantly, how thorough was the characterization of the material.

There are 3 possible sources of chitin as raw materials; isolation from traditional shellfish sources such as crabs and shrimps; harvesting of fungal mycelia from bioreactor processes; and synthesizing from monomeric/dimeric units using chemical and/or enzymatic strategies.

1) For chitin, the accessible quantity from typical sources of supplies i.e. shellfish such as crabs, shrimp, crayfish, lobsters, etc. is not a concern, but their quality is. If the shellfish were harvested from regions of polluted water for example, the probability of heavy metals association increases and this has to be ascertained. The isolation/processing methods also determine the molecular weights and the degree of acetylation, therefore the biopolymer's properties. There is also a concern for the amount of residual protein.

2) For fungal sources, the thorough removal of associated glucans may pose a challenge as to the true composition of the raw material. There is also typically a final deproteinization step requiring chemical or enzymatic processing (Teng *et al.*, 2001).

3) For chemical synthesis the challenges are in ascertaining the complete removal of enzymes, chemical based catalysts and strong binding solvents. These

challenges will also extend to the derivatives of chitin and chitosan as they require some form of chemical or enzymatic manipulation to produce the desired derivative.

Therefore, regardless of the manner chitin and/or chitosan is made available, providing the molecular weight range, the degree of acetylation, the amount of residual protein and ash, and for derivatives, how accurately the degree of substitution can be ascertained as well as the site (C-6, C-3 and/or C-2) are the more relevant key issues that have to be decisively resolved.

In other words, each process to obtain good quality raw material has identifiable shortcomings that must be addressed. Not necessarily by improving the process, rather the more thorough demonstration that unambiguously defines the raw materials' properties well, for example the absence of potentially harmful impurities. This requires effort in developing refinements to present analytical methods that would provide the confidence in the quality of raw material that a manufacturer of chitin-based biomedical products can include in their dossier submission to regulatory agencies.

The appropriate chemistry

The chemical modification or derivatization of chitin and chitosan into a myriad of materials with varied properties that extends their versatility is the differentiation factor over its closest biopolymer/ biomaterials competitors such as hyaluronic acid and collagen.

Traditionally, the heterogeneous reactions of alkali-chitin to produce chitin derivatives and the reactions of chitosan in dilute acid solutions have been the mainstay in chitin-chitosan chemistry. Subsequently, the tosyl-chitin and trityl-chitin reactions offered some elegant alternatives to the alkali-chitin method. In recent times, the homogeneous reactions of chitin in lithium chloride-dimethylacetamide solutions offer another channel for generating chitin derivatives. Coupled with the exciting use of enzymes that can sponsor substitution reactions under mild conditions, the opportunities are vast for chitin and chitosan to design materials to suit specific biomedical applications.

On a scientific level the demonstrations so far have been impressive, but as biomaterials, some further sophistication remains. The first is of course the improvement in consistently obtaining a reliable and specific narrow range in the degree of substitution. This is necessary to prove reproducibility both in synthesis and properties. This practice must become more habitual where developing biomaterials are concerned considering the variability that already exists in biopolymers. In addition, there is a need to shortlist one or two candidates from the many and perform exhaustive evaluation as to their suitability for a defined biomedical application. In particular, it is well known that scaling up a laboratory success is no small feat. It is therefore imperative that the production of the shortlisted candidate be explored on a larger scale for commercial viability as well as retention of the valuable features obtained at the laboratory level. Only with focus and a concerted effort can the breakthrough occur.

Conclusions

It has more than 40 years since research on assessing chitin and chitosan and their derivatives as biomaterials began. All indications are that they can be superb biomaterials. It awaits the one breakthrough and commercial success to propel the promise into reality. A partial action list has been suggested in this article for the chitin-chitosan scientific community to consider taking up to speed up the process. What better testimony to the efforts of the pioneers who have passed on, retired or move on to senior administrative positions (and therefore participating less vigorously than they would like) than to see what their founding contributions in chitin, chitosan and their derivatives finally attain the stature as great biomaterials.

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