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Marine Polysaccharides as Multifunctional Pharmaceutical Excipients

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Abstract

This chapter is presented to depict the chance of marine polysaccharides satisfying the properties of good pharmaceutical excipients and the potential of that could be utilized as multifunctional pharmaceutical excipients in the pharmaceutical solid dosage form manufacturing as fillers, diluents/vehicles, binders, glidants, binders and disintegrants, and so on. In addition, this chapter discusses the use of marine polysaccharide holding a specific pharmacological activity in the formulation/dosage form, which is used for the same aliment/disease.

Keywords: marine polysaccharide, pharmaceutical excipients, bioavailability, drug delivery, dissolution, disintegrants, pharmacological activity

1. Introduction

Drugs, which are obtained from plants, animals, marine source or minerals, are not very often administered in their pure form. Before releasing into the market, these drugs are combined with a variety of inert substances (excipients/adjuvants) and modified into a dosage form, which is convenient to be administered by a specified route [1]. Similar to the drugs, these excipients are also obtained from many sources, namely natural, synthetic sources. Nowadays, the naturally obtained excipients have shown more interest due to the various advantages like low cost, biocompatibility, biodegradability, non-toxicity, easy availability, eco-friendly processing, superior patient tolerance and acceptance [2]. Before, it was thought that the therapeutic reaction to a drug is a characteristic of its inherent pharmacological action. However, nowadays, it is much implicit that the dose-response connection obtained after drug administration by various routes — for example, oral and parenteral — is not identical. The difference is also observed when the same medicine is administered as dissimilar dosage forms or similar



© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. (co) BY formulations produced by dissimilar manufacturers, which in turn depends upon the physical, chemical properties of the drug, the excipients present in the formulation, the technique of formulation and the way of administration [1].

Natural marine origins are among the most widely used excipients in the formulation of different dosage forms. A number of marine-based polysaccharides, such as agar, alginate, carrageenan, fucoidan, chitosan and hyaluronan are utilized in pharmaceutical dosage form as binders, vehicles, disintegrating agents, gelling agents and drug release sustaining agents [3].

The purpose of this review is to discuss potential pharmaceutical formulation development applications of marine polysaccharides, with a special emphasis in multifunctional excipients development for enhancing bioavailability, drug delivery applications. In addition, this review discusses the use of marine polysaccharide holding a specific pharmacological activity in the formulation/dosage form, which is used for the same aliment/disease, for example, incorporating the marine polysaccharide having anti-cancer activity in anti-cancer drug formulation as excipients. In fact, data has added that such excipients operate on well-distinct biological pathways and receptors in order to implement their valuable properties. If additives that work on several cancer pharmacological pathways or receptors targets are jointed together in concentrations that are at and/or more than their recommended levels, then there is a possibility exists that such a formulated dosage form may offer "standalone" control of cancer.

2. Marine polysaccharides, as multifunctional pharmaceutical excipients

A drug injected intravascularly (I.V/I.A) directly enters the blood and produces its pharmacological effects. The majority of drugs are administered extravascularly, usually through oral route. If anticipated to act systemically, such drugs can produce their pharmacological actions only when they come into the blood circulation from their site of application. In order to reach the blood circulation, orally administered formulation must disintegrate, deaggregate and dissolution of the drug in the aqueous fluid at the absorption site must occur [4]. If the drugs are not hydrophilic in nature, the absorption process of drugs like these is usually dissolution rate-limited (**Figure 1**).

Better absorption can be achieved by altering the characteristics of the dosage form using pharmaceutical excipients. Moreover, pharmaceutical excipients help in the manufacturing process by serving as a binder, diluents, wetting agent, filling agent, disintegrating agents, dissolution enhancers, and so on. [3]. Now their increasing demands and expectations



Figure 1. The two rate-determining steps in the absorption of orally administered dosage form.

with regard to quality have stimulated the development of new additives characterized by advanced assay and lesser content of impurities. Quality of formulation does depend on the quality of excipient [4]. The purpose of this study is to give a scope for the researchers to try and develop a formulation that is made up of just the drug and natural marine polysaccharides. This review is done to depict the chance of some marine polysaccharides satisfying the properties of good pharmaceutical excipients if the stability of them has been explored sufficiently.

2.1. As binder

Marine polysaccharides can serve as a good binder in the production of tablets by the wet granulation method of manufacture. In this role, binders are either added as a solution or as a solid into the powder mix (following which the granulating fluid, typically water, is added). Due to the high concentration of hydroxyl groups in the polysaccharide, generally have a high water-binding capacity that makes wet granulation easier [5]. The responsible bio-adhesives marine polysaccharides have extraordinarily high cohesive strength and binding strength to the solid surfaces, enabling the API to remain attached under tensional conditions.

2.2. As diluents

Marine polysaccharides can be employed as diluents/fillers in the formulation of tablets (by all methods) to increase the mass of the solid dosage forms that hold a low concentration of therapeutic agent and thereby render the manufacturing process more reliable and reproducible [6]. For example, chitin and chitosan are used as a diluent or filler and as a binder in direct compression of tablet processing, as a disintegrant, and so on. Chitin and chitosan have a lowest bulk and tapped density that cause good flow as well as compaction during filling and tablet compression processing. **Figure 2** shows the structure of cellulose chitin and chitosan.



Figure 2. Structure of cellulose, chitin and chitosan.



Figure 3. Disintegrants facilitating the breakdown of the tablet into granules.

2.3. As disintegrants

Disintegrants are materials added to the dosage forms that enhance the breakup or disintegration of tablet formulations into smaller particles that dissolve faster than in the absence of disintegrants. These materials have the main role to oppose the efficiency of tablet binder and physical forces that behave under compression to form the tablets. Tablet disintegrant usually considered as the rate determining step (RDS) in a faster drug release. Marine polysaccharides may behave as a good disintegrating agent by increasing the porosity, wettability and wicking or capillary action and operate by swelling in the presence of aqueous fluids in tablet formulations to facilitate the breakdown of the tablet into granules upon entry into the stomach [7] (**Figure 3**).

2.4. As dissolution enhancers

Marine polysaccharides may serve as a dissolution enhancer for the poor soluble drug. These powders can reduce cohesive forces holding a tablet dosage form together and induce the breakup into smaller granules, thus increasing the effective surface area for dissolution (**Figure 4**).



Figure 4. Dissolution enhancer facilitating dissolution for the poor soluble drug.

2.5. As drug delivery carriers

Marine polysaccharides have been widely used to synthesize drug delivery carriers. They are bio-compatible, non-toxic and bio-degradable and stimuli-responsive makes marine polysaccharides appropriate sources for the building of complex loading devices with a release that can be effectively controlled [4]. **Table 1** shows the compilation of marine polysaccharides utilized as drug delivery carriers, and **Figure 5** illustrates the mechanisms of various marine polysaccharide carriers and its method of preparation.

Drug delivery devices can be constructed using various methods and can be synthesized in a variety of shapes, such as hydro gels, micro or nanoparticles and capsules, capable of protecting a variety of bioactive agents such as proteins and nucleic acids.









Figure 5. Illustrating the mechanism of various marine polysaccharide carriers and their method of preparation.

3. Pharmacological activity of marine polysaccharides and potential possibilities of standalone effects when incorporating as excipients

Marine polysaccharides stand for a number of abundant bio-active substances in marine organisms. In fact, numerous marine macro- and microorganisms are good quality possessions of carbohydrates with miscellaneous applications due to their bio-functional efficacies. By involving on cell propagation and cycle, and by modulating metabolic pathways, marine polysaccharides have numerous pharmacological efficacies, such as antioxidative, antibacterial, antiviral, immuno-stimulatory, anticoagulant and anticancer effects. Besides the polysaccharides, monosaccharides are useful for humans and can cure many diseases, mainly those linked to metabolism deficiency such as diabetes.

There has been growing facts in recent years that pharmaceutical additives may not be harmless, "inert" components of a formulation, but may hold either "stand alone" pharmacological activity or may act to modify the pharmacological efficacy of the API. Because most excipients have historically derived from food or food products, they have been assigned—and in most cases, experimentally confirmed—to have widespread pharmacological activity based on the ingestion of those products. Marine polysaccharides holding a specific pharmacological activity can be incorporated as an excipient in the formulation/dosage form, which is used for the same aliment/disease. **Table 2** shows the pharmacological activity of marine polysaccharides, and **Figure 6** illustrates the mechanism of action involved in the pharmacological activity of marine polysaccharides.

S. no	Marine polysaccharide	Source	Pharmacological activity
1.	Alginate	Brown sea weed	
2.	Carrageenans	Red algae	Anticoagulant [37], Anti-tumour [38], Immuno-modulator [39], anti-hyperlipidaemic [40], Antioxidant [41], Antibacterial, viral [42], bird flu, dengue, Hepatitis A, HIV [43]
3.	Fucoidans	Brown algae	Anti-tumour [44, 45], anti-thrombin [19], anti-coagulant, anti-inflammatory, anti-adhesive and anti-viral [46], burn treatment [47]
4.	Ulvans	Green algae	Anti-viral, anti-oxidant, anti-coagulant, anti-tumour, anti-hyperlipidaemic and immune system enhancer [48]
5.	Chitosans	Marine animal (chitin)	Antimicrobial [49], anti-tumour and inflammatory [50]
6.	Hyaluronans	Marine animal (glycosaminoglycans)	Wound treatment [51], supplement for arthritis [52]
7.	Chondroitin sulfate	Marine animals (whale and shark)	Anti-coagulant [53], supplement for arthritis [53]
8.	Dermatan sulfate	Ray skin (glycosaminoglycans)	Anti-coagulant [54]
9.	Heparan sulfate	Ray skin (glycosaminoglycans)	
10.	Keratan sulfate	Ray skin (glycosaminoglycans)	Anti-adhesive, osteoarthritis [54]
11.	Agarose	Red algae	Glucose intolerance in type 2 diabetes mellitus, weight loss, anti-bacterial [40]

Table 2. Pharmacological activity of marine polysaccharides.



Figure 6. Illustrating the mechanism of action involved in the pharmacological activity of marine polysaccharides.

However, the majority of the pathways or modes of action has not been revealed in humans. In addition, fairly only some have been investigated in-vitro. These in-vitro findings are unable to extrapolate into their actions in-vivo in humans. There should be well-controlled human clinical investigations using such a mixture of additives are essential prior to any rationalization for effectiveness can be asserted.

Ideation of using "marine polysaccharide bio-active excipients" is possible for diseases that are chronic in nature and for whom gradual and lasting beneficial efficacy may be observed from the modulation of signalling pathways that direct to incremental but visible improvements in the quality of life. Such "marine polysaccharide bio-active excipients" may not be efficient for acute diseases for which radical interventions are necessary.

4. Conclusion

Marine polysaccharides have a huge potential as multifunctional pharmaceutical excipients for commercial needs. However, there is a need to characterize, check compatibility of these polysaccharides to produce pharmaceutical grade additives that could find the utility in drug dosage form. In addition, research is warranted in pharmacodynamic interaction of these marine polysaccharides and particular drug when using for same aliments.

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