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**Investigation on Rheological Behaviour of Dually  
Modified Tapioca Starch/Carrageenan as Gelatin  
Alternative in Pharmaceutical Hard Capsules**

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## ABSTRACT

With the goal of finding an alternative to gelatin in the processing of pharmaceutical capsules, the effects of *k*-carrageenans on dually modified tapioca starch were investigated. While film forming and mechanical properties are important in all pharmaceutical capsules, solubility at high solid concentration and thermo-reversibility are important factors for hard capsule processing. Casava starches were modified first by hydrochloric acid (0.14 N for 6, 12, 18, and 24 h at 50 °C) and secondly by propylene oxide (10, 20, and 30% of solid for 24 h at 40°C).

To improve the gel setting property of the dually modified starch, dually modified tapioca starches were combined with  $\kappa$ -carrageenan (0.25, 0.5, 0.75, and, 1%). The concentration of the  $K^+$  ion in the composite mixture was adjusted appropriately to achieve the same sol-gel transition temperature. The rheological properties of the mixtures were measured and compared, with gelatin as the reference material. The solution viscosity and sol-gel transition of the mixtures at 50 °C were comparable to those of gelatin. The viscoelastic moduli ( $G'$  and  $G''$ ) for the gel mixtures were lower than those of gelatin. The composite gels had temperatures of gelation similar to that of gelatin. Both viscosity in solution and stiffness in gels could be adjusted using high levels of  $\kappa$ -carrageenan and was relatively independent of the molecular weight of the starch. These results illustrate that dually modified tapioca starch in combination with  $\kappa$ -carrageenan has properties similar to those of gelatin, thus these starches can be used in dip-molding processes, such as those used to make pharmaceutical hard capsules.

## **CHAPTER 1: INTRODUCTION**

## **1.1 Background**

The capsule is one of the formulations of the oldest pharmaceutical in history, known especially from the ancient Egyptians. In Europe, it was not until the nineteenth century that the first gelatin pharmaceutical capsule with the patent of Mr. Dublanc pharmacist and his student Mr. Mothes. Over the years, this invention has been so successful that the production of capsules has grown rapidly in many countries. This has led to many improvements including the invention of hard gelatin capsules in 1846 by Mr. Lehuby (Podczeck and Jones, 2004).

The development of pharmaceutical capsules, used for therapeutic purposes, originates in the keen interest shown by the numerous researches in pharmacology. This has greatly expanded the range of possible formulations using pharmaceutical capsules. Today, pharmaceutical capsules are mainly based on animal gelatin from porcine or bovine. Gelatin is an animal protein that is a traditional ingredient in many fields, including food. Gelation properties at temperatures close to room temperature and formation of homogeneous films, potable, gelatin as a choice for the manufacturing of pharmaceutical capsules.

However, the use of animal gelatin in the food and pharmaceutical industry is governed by regulations becoming more stringent. The precautionary principal applied, for example, the risk of transmission by animal gelatin; the bovine spongiform encephalopathy (BSE) has questioned its use. Even if today the rules on the origin of the gelatin are very strict and that gelatin is no longer a risk to health, development of alternative products of interest to pharmaceutical and food industries. The sources from which gelatin can also be problematic for ethical or religious populations. Many people around the world do not consume products made from pork (vegetarians, Hebrews, and Muslims) or beef base (vegetarian Hindus). It is

therefore that the replacement of gelatin with other texturing agents of non-animal origin has been much research in recent years.

The most important properties that potable gelatin as capsule forming material are heat sealability of films for soft capsule processing and solubility in high concentration, film formability and thermo-reversibility for making hard capsules.

Starch as a plant based material is one of possible alternative for gelatin due to cost and accessibility. Native starches can form films, but the films have not heat sealability, also starches are non soluble biopolymer, and form non-reversible gels. So changes or supporting the structure likely improve the starch property to consider as gelatin replacement in some cases.

The proposed system is a mixture of starch and  $\kappa$ -carrageenan. Starch would give the mixture of film-forming properties and solubility in aqueous and carrageenan bring its ability to gel. The selected starch has focused on the use of such modification(s) on starch that able it to dissolve at temperatures below 100 °C and form stable solutions at high concentrations ( $\approx$  20-30%). The botanical origin of the tapioca starch is due to its proper amylose content, which improves mechanical properties of films and availability of this starch in Southeast Asia. The gelling agent has been studied was  $\kappa$ -carrageenan/ $K^+$  for its ability to form thermo reversible gels and easily adjustable thermo-physical transition temperatures. The film-forming mixtures were prepared by casting method.

The main objective of this research project is to replace the gelatin with a composite tapioca (tapioca) starch film for manufacturing of pharmaceutical capsules especially hard capsules. The idea for hard capsule processing is to develop a new system whose characteristics in the solution and solid state would be closer to existing formulations. The

constraints imposed industrial development concentrated formulations (25-30%) prepared at temperatures below 100 °C capable of forming a gel by physical cooling and forming a film after drying.

## **1.2 Rational of study**

The main objective of this research was to replace gelatin with a composite casava starch for the manufacture of pharmaceutical capsules. The methods proposed for hard capsule processing involve creating a starch that has characteristics in the solution and solid states that are similar to those of existing gelatin-based formulations. Any gelatin alternative material would have to meet these criteria: solid concentration of 25–30% w/v, preparation temperature below 100 °C, ability to form a gel by physical cooling, and ability to form a film after drying.

The system proposed herein is a mixture of tapioca starch and carrageenan. The starch would provide the film-forming property and solubility in an aqueous environment and the carrageenan is expected to enhance the gelling property and improve the durability of the system. Thus, the modification of the starch was designed so that it can dissolve at temperatures below 100 °C and form stable solutions (in terms of rheological properties and functionality) at high concentrations (20–30%).

## **1.3 Objectives of the study**

The objectives of this study are:

1. Investigation on effects of carrageenan on dually modified tapioca starch flow properties.



2. Investigation on effects of carrageenan on dually modified tapioca starch sol-gel transition.
3. Investigation on effects of carrageenan on dually modified tapioca starch gel properties.

### 1.4 Research Flowchart

This research was designed as the following research flowchart.

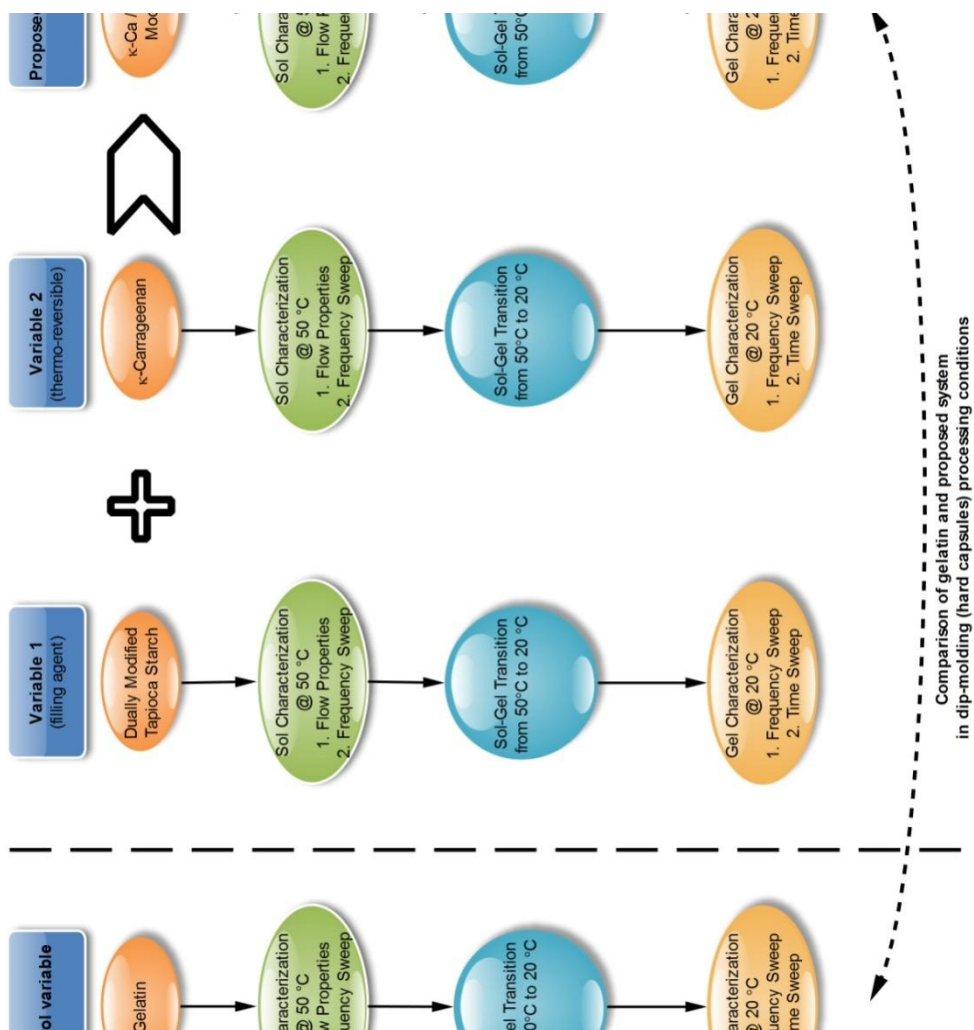


Figure 1.1: Research flowchart

## **CHAPTER 2: LITERATURE REVIEW**

## **2.1 PHARMACEUTICAL CAPSULES**

The capsules, also called caps (from the Latin word meaning capsulatus container), are solid preparations consisting of a hard or soft shell, shape and capacity variables, usually containing a unit dose of active ingredient. The contents of capsules can be solid, liquid or pasty. The soft capsules mean capsule consists of a single party whose shape can be cylindrical, spherical, ovoid, etc. It usually contains a plasticizer which gives the properties of flexibility where the adjective that means. The hard capsules are made up of two parts (head and body) of cylindrical shape with a diameter slightly different for their engagement. The hard capsules contain very little plasticizer which makes them rigid.

The first patent on the use of gelatin capsules for therapeutic use has been filed in 1834 by MM. J.G.A. Dublanc and Job Moths. Many attempts were undertaken to mask the unpleasant taste of certain drugs in vogue at that time (turpentine, Copaiba). The solution that met the most success was the invention of a cap based on a gelatin film containing the drug. MM. Dublanc and Moths then develop a process for manufacturing capsule; which is to dip a brass cylindrical object in an aqueous solution of gelatin flavored and sweetened, then remove and place it vertically for drying. After evaporation of water, gelatin is in the form of a solid film covering the walls of the cylinder, forming a capsule. The capsules, which can be regarded as soft capsules are then filled and sealed with a drop of gelatin solution. Moths has only continued to work on improving the process of development and the use of gelatin capsules. The incredible success of his capsules in the following years led to their use worldwide. For more details, you can refer to a book on history of pharmaceutical capsules, their method of manufacture and their characteristic (Podczeck and Jones, 2004). We limit ourselves in the following sections describe the characteristics of pharmaceutical hard capsules, because main part of this thesis focused on hard capsules.

### **2.1.1 Pharmaceutical hard capsules**

In the mid-nineteenth century, the remarkable growth of Mothes pharmaceutical soft capsules, leads the development of many alternative procedures. In 1846, slightly more than ten years after the invention of the first capsule-based gelatin, MJC Lehuby published a patent under the heading “My drug envelopes”. It is the first to suggest a capsule consisting of two parts which are produced by dipping the fingers of casting metal in a gelatin solution and then drying them. The capsules are cylindrical and consist of two half cylinder with a diameter slightly different for easy assembly. It is important to note that this process has been improved by the inventor over the years, was originally intended to produce hard capsules based on tapioca starch, and then based on a mixture of carrageenan and gelatin then called lichen capsules. However, these formulations have been abandoned due to their fragility in comparison with gelatin.

Unlike the early success experienced by the Mothes soft gelatin capsules, development of hard capsules has been delayed by technical difficulties posed by the manufacture of the head and body of the capsule. It was not until the early twentieth century to emerge in the U.S. the first industrial production of hard capsules made from gelatin. From 1931, the Parke, Davis & Co., managed to develop a machine capable at the same time to produce the head and body of the capsule and assembling them. The production of hard capsules is still based on this process. Some minor changes have been made over the years, mainly to automate and optimize the various stages of production. The largest producers of pharmaceutical capsules are now Capsugel (USA) and Shionogi Qualicaps (Japan) companies.