# Synthesis of strength hydrogel based on chitosan as drug delivery system with less cytotoxicity

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**Abstract**

***Hydrogels have known significant development in several areas, as efficient drug delivery systems. The present study mainly focused on their recent research classification, preparation and alternatives as cross linking agents, considering challenges, particularly the synthesis of a hydrogel based on chitosan with effectively no toxicity. The relationship between the hydrogel structure and the drug release mechanism were also considered.***

***Keywords:*** *chitosan, drug delivery system, genipin, hydrogel.*

## I. Introduction

Ordinary medication organization frequently requires high doses or repeated administration to empower a restorative impact; this can bring down general viability and patient consistence, and results in serious reactions and even harmful situations. Therefore, researchers have worked for years to promote drug delivery systems (DDS) which are able to improve drug efficacy with less toxicity and required dosage. One can cite membranes, nanoparticles, liposomes and hydrogels which are the main concern of the present study[1].

Hydrogels are cross-linked systems similar to the different types of polymers that are able to retain a

large amount of water or a digestive fluid due to the

presence of hydrophilic groups such as – OH, CONH–, –CONH2–, and –SO3H[2]. This feature encouraged their use in several areas such as contact lenses, encapsulation of cells and controlled release of drugs [3], Agriculture food technology, etc.

## II. Hydrogel structure

Hydrogels have a structure which looks like a fishing net (Figure 1) where the open spaces are the mesh size through which the liquid and the molecule drug can diffuse. They are characterized by a mesh size varying between 5 and 100 nm but which can be reduced by increasing the concentrations of the polymer or the cross linker. The mesh size is the controlling factor of the diffusion of drugs through a hydrogel [1]. There are several criteria upon which hydrogels can be classified. Figure 2 shows the most adopted categories as shown on Table 1.

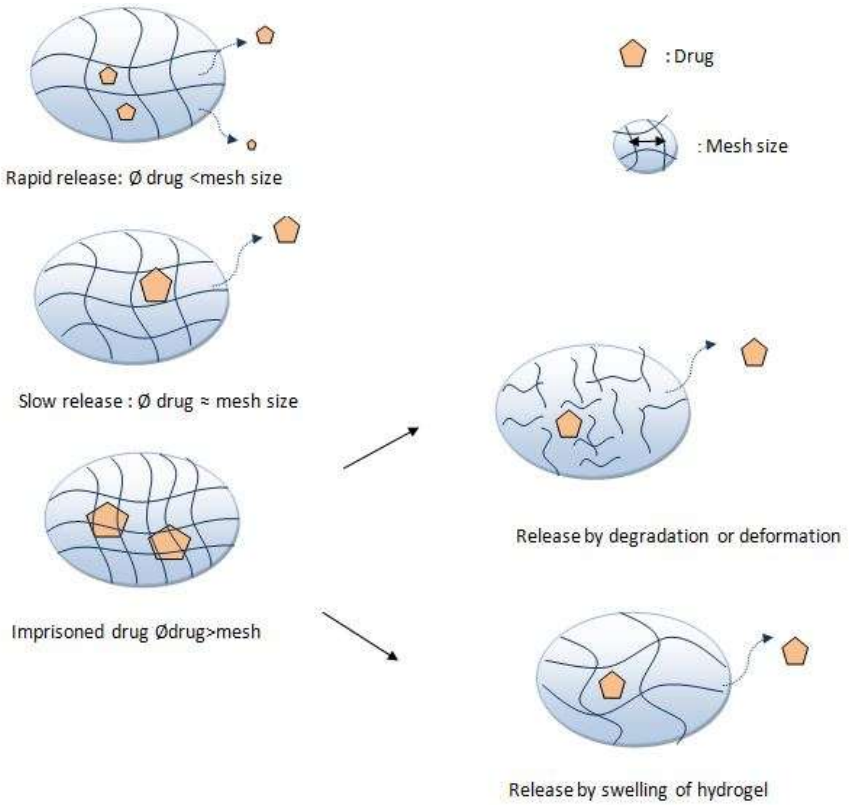


**Figure 1.** Relationship between drug molecule and mesh size

**Table1.** Classification of hydrogel

| | |
|---|---|
| **Origin** | **Natural:** alginate, cellulose, chitin, chitosan, Dextran, hyaluronic acid, pectin, starch and xanthan gum<br>**Synthetic:** poly (vinyl alcohol), polyacrylamide, poly (ethylene oxide) and poly (ethylene glycol) |
| **Type of Cross linking** | **chemical** (permanent bonds)<br>**physical** (reversible) |
| **Physical Appearance** | Matrix<br>Film,<br>Microsphere<br>Nanoparticles |
| **Technique of preparation** | Homopolymer Hydrogels<br>Copolymer Hydrogels<br>Multipolymer Interpenetrating Polymeric Hydrogel (IPN) |

## III. Pharmaceutical Applications Chitosan

Chitosan is a natural polysaccharide obtained by partial deacetylation of insoluble naturally available chitin [4] extract from exoskeletons of crustaceans, [5] fungi and insects [6].

Composed of glucosamine and Nacetyl glucosamine units (figure 2), it is nontoxic, biocompatible, and biodegradable ; for this reason chitosan hydrogels have been widely used in drug delivery systems [7].

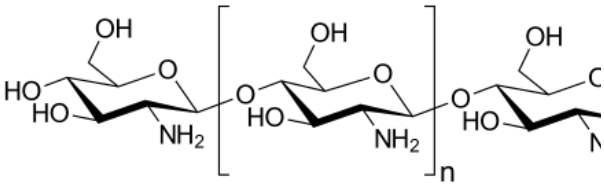


**Figure 2.** The chemical structure of chitosan

In addition to its distinctive physicochemical properties chitosan is also a bioactive agent which has shown to be attractive in pharmaceutical and biomedical applications. Depending on their size, surface charge, hydrophilic/lipophilic balance and specific transmembrane ability, a polymer drug carrier can change pharmacological and immunological activity of drugs and their delivery. The following section illustrates the unique features of chitosan as a pharmacologically active delivery system.

### III.1 Antibacterial Activity of Chitosan

At an acidic pH, chitosan possesses an antimicrobial activity against many bacteria and fungi. One of the suggested mechanisms behind this property is that the positive amino group of the glucosamine units interacts with negative charged components in microbial cell membranes and alters their barrier properties, thereby preventing the entry of nutrients or causing the leakage of intracellular contents [8]. This eventually leads to the cellular breakup of the bacteria or fungi [9, 10]. Another suggested mechanism is that chitosan penetrates into the cell and binds to the DNA of the bacteria and subsequently inhibits protein synthesis [11]. Factors such as molecular weight, degree of deacetylation, pH of the chitosan solution, position of glucosamine unit, etc. do all influence the biological activity of chitosan [12]. It has been reported that high molecular weight chitosan inhibits Escherichia coli's activity almost completely by stacking outside the cell and inhibits the permeation of nutrition in comparison to low molecular weight chitosan.

### III.2 Antioxidant Activity of Chitosan

Antioxidants are compounds that protect the body against oxidative damage by inhibiting or delaying the oxidation of cellular oxidisable substrates caused by reactive oxygen species (ROS) and degenerative diseases. Superoxide anion (-O2-), hydroxyl radical (OH) and hydrogen peroxide are the ROS produced by sunlight, ultraviolet light, ionizing radiation, chemical reactions and metabolic processes which have a wide variety of pathological effects such as stroke, cancer, diabetes, atherosclerosis and cardiovascular disease. Low molecular weight partly deacetylated chitosan exhibits antioxidant properties and can be considered as a natural antioxidant [13]. Peng and co-workers reported that chitosan inhibits the activity of Linolenic acid peroxidation by 83.7% against hydroxyl radicals [14]. It was observed that sulfate and sulfanilamide derivatives of chitosan, having various molecular weights, increase the antioxidant and scavenging activities [15, 16]. From the range of derivatives of chitosan, it was found that the major factor for free radical scavenging activity is the amino group [17]. Among the four forms of amino groups, the primary amino group, imino group, secondary amino group and the quaternised amino group, the latter showed the highest antioxidant activity against hydroxyl radicals. Therefore it can be concluded that high positive charge density increases antioxidant activity [18].

### III.3 Antitumor Activity of Chitosan

Decreasing the molecular weight of chitosan causes an increase in water solubility, transformation of crystal structure and alteration of thermo stability without change in chemical structure. This improves the antitumor activity of chitosan. In order to elucidate the structural features of low molecular weight chitosan and its effect in inhibiting angiogenesis, Prashanth and co-workers injected chitooligo saccharides intraperitoneally into mice [18]. They observed apoptosis in Ehrlich ascites tumour and over 90% decrease in the ascites volume. Copper complexes of chitosan at the ratio of 0.11 mol copper per one chitosan residue, induces cleavage of DNA and arrested the cell cycle progression in tumour cell lines such as 293 and HeLa. But normal human lung fibroblast cell lines were not affected by the complex [19]. Water soluble

chitosan derivatives were also used as antitumor drug or gene delivery vectors [20-21].

The choice of the cross linking agent is a very important factor because it plays on the strength of the hydrogel, among the most used cross linking agents we note glutaraldehyde, tripolyphosphate, these latter gives a very strong hydrogel On the other hand, they have a high risk of toxicity, particularly glutaraldehyde, which can alter the biocompatibility of the chitosan delivery system.

The genipin is a great alternative because it is biocompatible and ensures a stable hydrogel

Genipin (figure 3) is extracted from the fruit of *Gardenia jasminoides* Ellis.

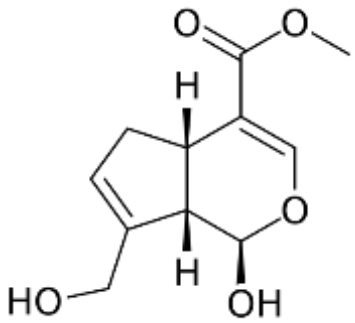


**Figure 3.** The chemical structure of genipin

Genipin is recently used to develop a drug delivery system. Wu Zhang et al [22] have developed a chitosan-based hydrogel cross linked with Genipin for the controlled release of tetracycline the in vitro and in vivo cytotoxicity test proving the biocompatibility of the genipin with sustained release of the drug.

## IV. Conclusion and perspectives

DDS have had a great deal of interest, and researchers have devoted every means to introduce them from the laboratory to the production and marketing. The difficult challenge is to provide the patient DDS which has therapeutic efficacy with less toxicity, use the Genipin as cross linking agent, despite all the benefits he has (strength system, less toxicity and biocompatibility). Hence a perspective is introduced it into the preparation of hydrogel nanoparticles for encapsulation of protein drugs cells.

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