# CHAPTER II

## BACKGROUND AND LITERATURE REVIEWS

### 2.1 Hydrogel

Hydrogels are composed of cross-linked hydrophilic polymers that form a three-dimension network, which swells without dissolving in water or biological fluids [12]. Hydrogels may be chemically stable or they may degrade and eventually disintegrate. Hydrogels are called 'permanent' or 'chemical' gels when they are covalently-crosslinked networks, crosslinking between chitosan and glutaraldehyde is an example of this type of hydrogel [13]. They are called 'reversible' or 'physical' gels when the networks are held together by molecular entanglements, and/or secondary forces including ionic, H-bonding or hydrophobic forces (Figure 2.1) [14].

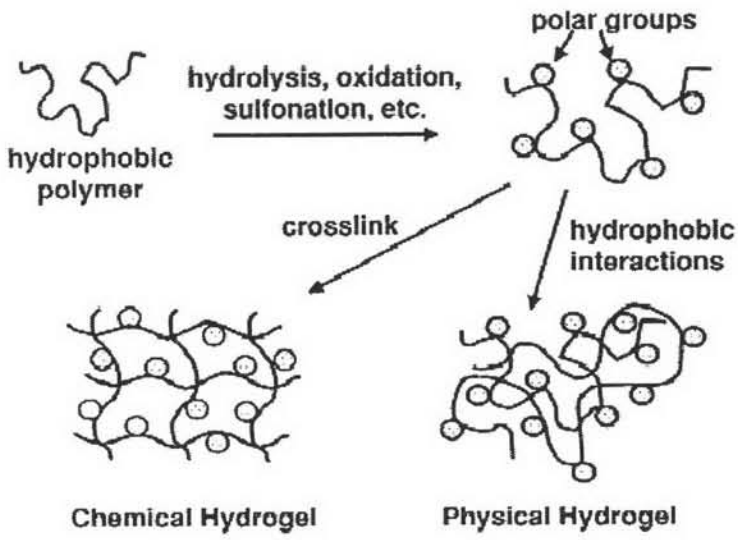



**Figure 2.1** Methods for formation of chemical and physical hydrogels [14].

### 2.1.1 Ionotropic and polyelectrolyte complex (PEC) hydrogel

The physical hydrogels are formed by a polyelectrolyte and a multivalent ion of the opposite charge. This type of hydrogel is known as an 'ionotropic' hydrogel (Figure 2.2), for example, calcium pectinate gel [15] and potassium ion in κ-carrageenan gel [16]. On the other hand, when polyelectrolytes of opposite charges are mixed, they may gel or precipitate depending on their concentrations, the ionic strength, and pH of the solution. The products of such ion-crosslinked systems are known as complex coacervates, polyion complexes, or polyelectrolyte complex (PEC). There are, for example, the complexes based on poly(acrylic acid) and chitosan of Torrado et al. [5] and chitosan-coated pectin beads of Cho et al. [4]. All of these interactions are reversible, and can be disrupted by changes in physical conditions such as ionic strength, pH, temperature, application of stress, or addition of specific solutes.

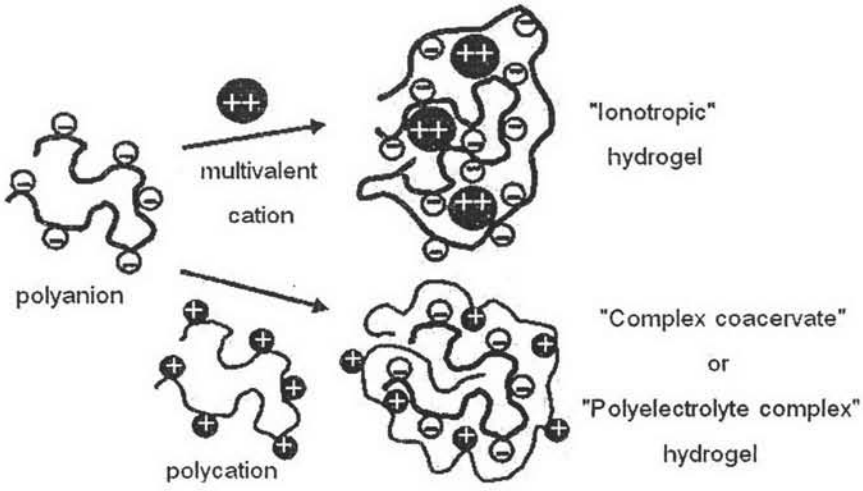



**Figure 2.2** The ionotropic and polyelectrolyte complex hydrogel [14].

### 2.1.2 Hydrogel applications

Hydrogels have received significant attention because of their distinctive material structures that make them suitable for a wide range of applications such as in nanotechnology areas (actuators, substrates, and artificial muscles), surgical implants, tissue engineering, biomaterials (membranes, biosensors), industry for the absorption and disposal of waste products and pharmaceutics (encapsulation and controlled release of drugs). Especially, in the pharmaceutical applications, polymer hydrogels have played a vastly important role in medical devices, diagnostic products, and pharmaceutical preparations.

## 2.2 Controlled Drug Release System

In its broadest sense, the concept of controlled or sustained release of biologically active agents has existed for over three decades. Early commercial applications of the technology occurred in both the pharmaceutical and agricultural industries.

The pharmaceutical field has employed the controlled release principle widely in oral medication since the early 1950s. Enteric coating of such dosage forms with pH-sensitive materials has been and remains very common. Similarly, encapsulated pellets or beads have been used, as have sparingly soluble salts, complexed systems, and porous insoluble tablets containing dispersed drug.

### 2.2.1 Advantages of controlled release

Controlled release system provides numerous benefits over conventional dosage form. Controlled release dosage forms are able to control the rate of drug delivery, the target area of drug administration and maintain therapeutic levels of drug with narrow fluctuations (Figure 2.3) [17]. This in turn can reduce toxicity and/or undesirable side effects of the drug. The serum concentration of drug released from controlled release dosage form fluctuates within the therapeutic range over a long period of time, thus making possible to reduce the frequency of drug administration and improve the treatment efficiency.

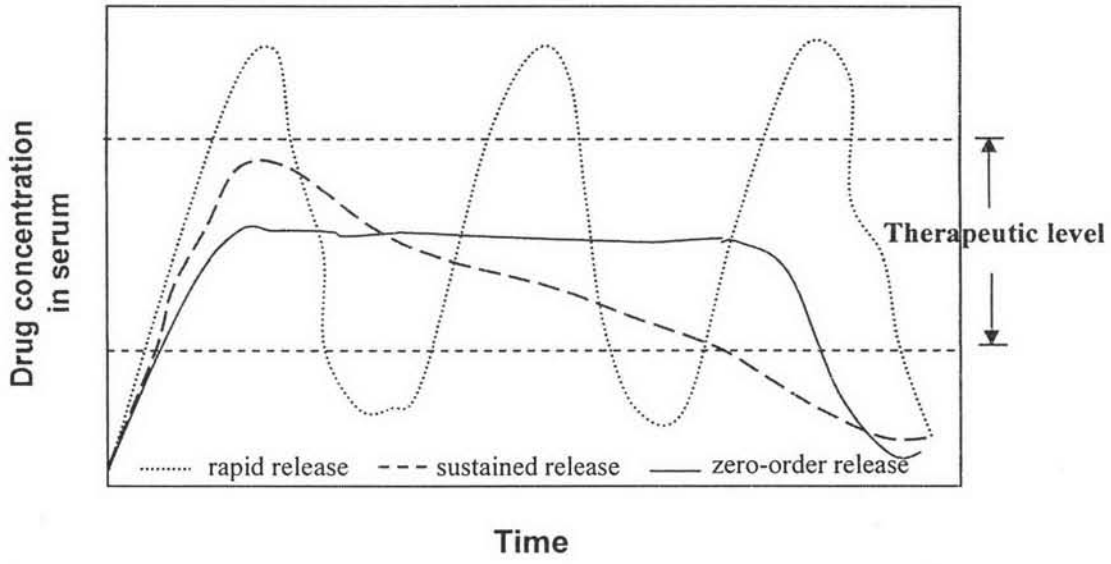



**Figure 2.3** Hypothetical serum drug concentrations of various oral dosage forms [17].

### 2.2.3 Methods of achieving controlled release [18, 19, 20]

There are five major types of controlled release device designs, as follow:

(1) Dissolution-controlled systems

(2) Diffusion-controlled systems

(3) Biodegradable systems

(4) Osmotic systems

(5) Mechanical pumps

The choice of method for achieving controlled release in a particular application depends on a number of factors such as the coat, the potency and the properties of the agent, the environment of use, and any requirement for biodegradability. Perhaps the most critical factor is the release rate required. In the following sections, three of the more superior controlled release systems (1-3) will be described in details.

#### 2.2.3.1 Dissolution-controlled systems

The sustained-release preparations of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier. Figure 2.4 shows that the dissolution controlled systems can be made to be sustaining in different ways. By (a) alternating layer of drug with rate-controlling coats, a pulsed delivery can be achieved. If the outer layer is a quickly releasing bolus of drug initial levels of drug in the body can be quickly established with pulsed interval following. In (b) the drug, formed as a group of beads, can be coated with a dissolving material of different thicknesses. Their release will occur in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later times will be achieved from those with thicker coatings.

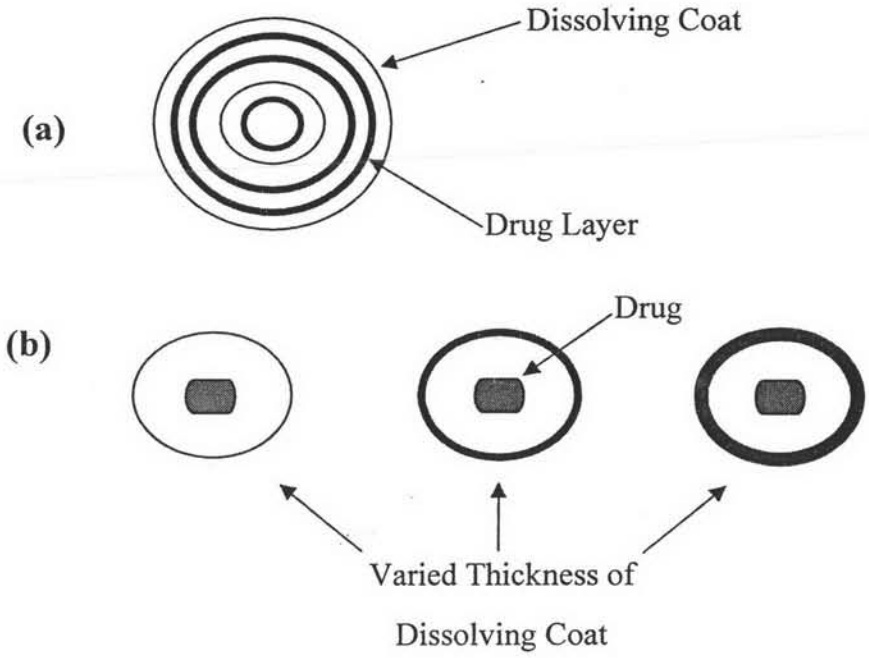



**Figure 2.4** Two types of dissolution-controlled, pulsed delivery systems: (a) single bead-type device with alternating drug and rate-controlling layers; (b) drug containing beads with differing thickness of dissolving coats [20].

#### 2.2.3.2 Diffusion-controlled systems

In diffusion-controlled systems the active agent is homogeneously dissolved or dispersed throughout the polymer mass (Figure 2.5). The release pattern depends on the geometry of the system, the identity and nature of the polymer or other carrier material, and the loading of the agent.

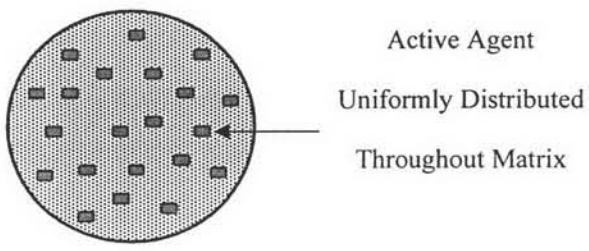



**Figure 2.5** The active agent dispersed within the polymer mass of the diffusion-controlled system.

### 2.2.3.3 Biodegradable systems

The diffusion-controlled devices previously outlined are permanent, in that the membrane or matrix of the device remains after its delivery role is completed. In some applications a device that degrades during or subsequent to its delivery role is required.

Many polymer systems have been prepared that slowly biodegrade when placed in the body. With such polymers, it is, in principle, possible to program the release of an active agent by dispersing the material within the polymer, with erosion of the polymer effecting release of the agent. A typical system is shown on Figure 2.6.

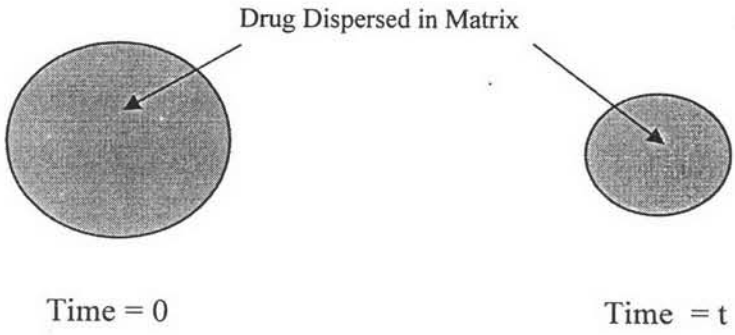



**Figure 2.6** Representation of a biodegradable system. Drug is dispersed in the matrix before release at time = 0. At time = *t*, partial release by drug diffusion or matrix erosion has occurred [20].

## 2.3 Kinetics Model of Drug Release [17, 20]

Controlled release of drugs can be achieved by incorporating solutes either in dissolved or in dispersed form into the polymers. From a mathematical modeling point of view, controlled release systems may be classified according to the physical mechanisms of release of the incorporated solute. Mathematical modeling of the release kinetics of specific classes of controlled release systems may be used to predict mechanisms of solute transport by simple comparing the release data to mathematical models.

Mathematical models can be mainly categorized into three types:

(i) Zero-order release model

(ii) First-order release model

(iii) Square-root-time release model

### 2.3.1 Zero-order release model

An ideal controlled release device is the one which can deliver the drug at constant rate until the device is exhausted of drug. Mathematically, the release rate ($dQ/dt$) from this device is given as:

$$\frac{dQ}{dt} = k_o \qquad [1]$$

Integration and rearrangement, that given:

$$Q = k_o t \qquad [2]$$

where $k_o$ is the zero-order release constant, $t$ is time, and $Q$ is the amount of drug released. This model of release is called zero-order release model.

### 2.3.2 First-order release model

The first-order release model is the second common type of the release model. The release rate in this case is proportional to the amount of drug contained within the device. The rate is then given as:

$$\frac{dQ}{dt} = k(Q_o\text{-}Q) \qquad [3]$$

where $Q_0$ is the amount of agent in the device at t = 0. On integration and rearrangement, this given

$$\frac{dQ}{dt} = kQ_o\, exp\,(\text{-}kt) \qquad [4]$$

In the first-order model, therefore, the rate declines exponentially with time, approaching a release rate of zero as the device approaches exhaustion.

On the assumption that the exposed surface area of matrix decreases exponentially with time, that drug release from most controlled-release matrices could be described by apparent first-order kinetics, thus:

$$A_t = A_o\, exp\,(\text{-}k_1 t) \qquad [5]$$

where $k_1$ is the first-order release constant, $A_o$ is the initial amount of drug and $A_t$ is the amount of drug remaining in the matrices at time $t$.

Simplifying and taking the natural logarithm (base $e$) of equation (5) yields

$$ln\, A_t = ln\, A_0 - k_1 t \qquad [6]$$

First-order model can be predicted by plotting the logarithm of the amount of drug remaining against time.

### 2.3.3 Square-root-of-time release model (Higuchi model)

The third common release model is frequently referred to as square-root-of-time ($t^{1/2}$) release. In this model, the matrix device consists of drug dispersed homogeneously throughout a polymer matrix as represented in Figure 2.7.

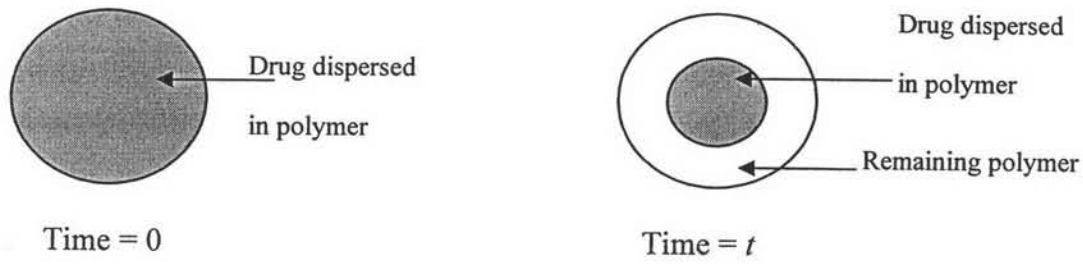



**Figure 2.7** Matrix diffusional system before drug release (time = 0) and after partial drug release (time = $t$) [20].

The drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and solid drug moving toward the interior.

The next equations, which describe the rate of release of drug dispersed in an inert matrix system, have been derived by Higuchi [21].

$$dQ = Adh - \tfrac{1}{2} C_s dh \qquad [7]$$

where $dQ$ = change in the amount of drug released per unit area

$dh$ = change in the thickness of the zone of matrix that has been depleted of drug

$C_o$ = total amount of drug in a unit volume of the matrix

$C_s$ = saturated concentration of the drug within the matrix.

From the diffusion theory,

$$\frac{dQ}{dt} = \frac{D_m C_s}{h} \qquad [8]$$

where $D_m$ is the diffusion coefficient in the matrix. Equating Eq. (7) and (8), integrating, and solving for $h$ gives:

$$Q = [C_s D_m (2C_o - C_s)t]^{1/2} \qquad [9]$$

When the amount of drug is in excess of the saturation concentration, that is, $C_0 >> C_s$

$$Q = (2C_s D_m C_o t)^{1/2} \qquad [10]$$

Which indicates that the amount of drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

$$Q = \left[ D_s C_a \frac{p}{T} (2C_o - pC_s)\, t \right]^{1/2} \qquad [11]$$

where $p$ = porosity of the matrix

$T$ = tortuosity

$C_a$ = solubility of the drug in the release medium

$D_s$ = diffusion coefficient in the release medium

This system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid-filled channels and dose not pass through the polymer directly.

For purposes of data treatment, Eq. (10) or (11) can be reduced to

$$Q = k_h t^{1/2} \quad [12]$$

where $k_h$ is a Higuchi constant, so that a plot of the amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion-controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters: (i) initial concentration of drug in the matrix, (ii) porosity, (iii) tortuosity, (iv) polymer system forming the matrix, and (v) solubility of the drug.

Since both the first-order release and the square root of time release plots are linear, as indicated by correlation coefficient, it is necessary to distinguish between the models. The treatment has been based upon using the differential forms of the fist-order and square root time equation [22].

For Higuchi model, the rate will be inversely proportional to the total amount of drug release ($Q'$), in accordance with equation.

$$\frac{dQ'}{dt} = \frac{k_h{}^2 S^2}{2Q'} \quad [13]$$

where $Q' = QS$ ($S$ is the surface area of matrix). The Higuchi rate constant ($k_h$) is obtained from the slope of the percentage drug release as a function of square root time. The rate predicted by first-order model was given by:

$$\frac{dQ'}{dt} = kA_o - kQ' \quad [14]$$

where $A = A_o - Q'$. This indicates that rate will be proportional to Q'. The first-order release constant ($k_1$) is obtained from the slope of the percentage drug remained as a function of time.

The plots of rates of release (*dQ/dt*) versus *1/Q'* are linear, indicating that the release is fitted with Higuchi model. If the plots of rates of release versus *Q'* are linear, it indicates that the first-order model is operative.

The release model for each of these classes of device is illustrated in Figure 2.8 [18]. The release models of zero-order, first-order, and square root time are depicted, respectively (equation 1, 3 and 12).

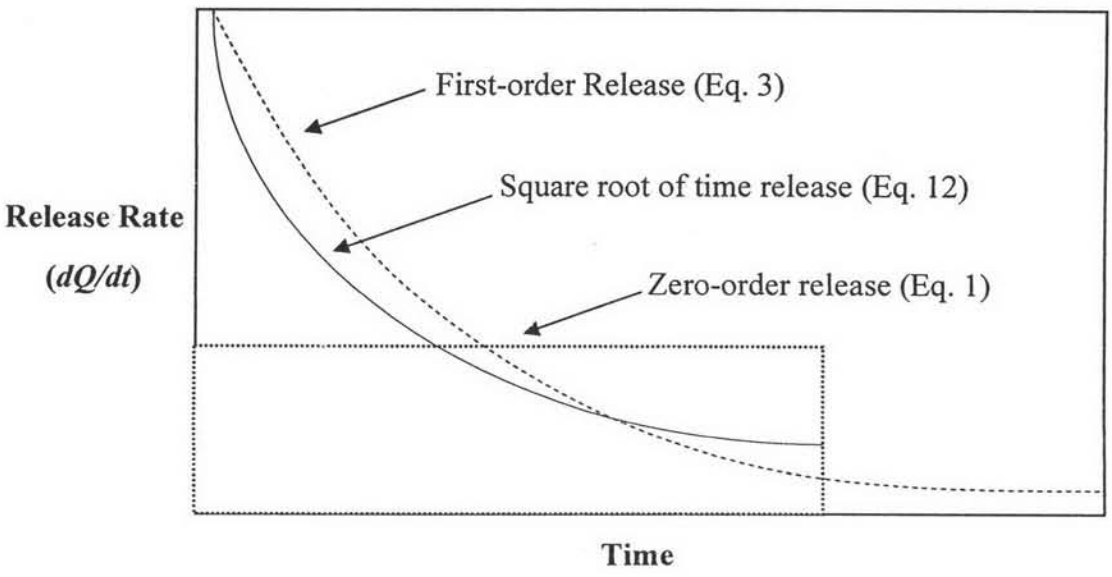



**Figure 2.8** Zero-order, first-order, and square-root of time release pattern from devices containing the same initial active agent content [18].

## 2.4 Chitosan

Chitosan, a polycationic biopolymer, was discovered by Rouget in 1859 and gives a name by Hoppe-Seyler in 1894 [23]. It is generally obtained by alkaline deacetylation of chitin, which is the second abundant polysaccharide next to cellulose. Chitin is the principal component of protective cuticles of crustaceans such as crabs, shrimps, lobsters, prawns and cell walls of some fungi such as *aspergillus* and *mucor*. In plants, chitin is present in hyphae or spores of molds [24].

### 2.4.1 Structure of chitosan

Chitosan $(C_6H_{11}O_4N)_n$ a natural linear biopolyaminosaccharide, is a copolymer of β-[1-4]-linked 2 –acetamido-2-deoxy-D-glucopyranose and 2-amino-2- deoxy-D-glucopyranose. It has one primary amine group and two free hydroxyl groups for each $C_6$ building unit (Figure 2.9). Both reactive primary amine and hydroxyl group can be used to chemically alter its properties under mild reaction conditions. The polymer differs from chitin in that a majority of the N-acetyl groups in chitosan are hydrolyzed. The degree of hydrolysis (deacetylation) has a significant effect on the solubility and rheological properties of the polymer. The amine group on polymer has a pKa in the range of 5.5 to 6.5, depending on the source of the polymer. At pH below 6.5 (dilute acid solution), chitosan is soluble as the glucosamine units can be converted into a soluble form ($R\text{--}NH_3^+$). It gets precipitated in alkaline solution (pH above 7) or with polyanions. The pH-sensitivity, coupled with the reactivity of the primary amine groups, make chitosan a unique polymer for oral drug delivery applications.

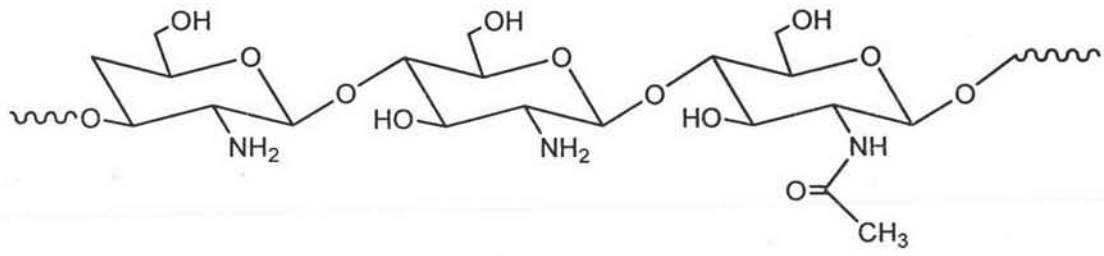



**Figure 2.9** Chemical structure of chitosan.

### 2.4.2 Chitosan in pharmaceutical application

Chitosan is currently receiving great deal of attention for medical and pharmaceutical application. The main reasons for this increasing attention are certainly its interesting intrinsic properties. Indeed, chitosan is known for its biocompatibility, low toxicity and biodegradability allowing its use in various pharmaceutical applications such as topical ocular application [25], implantation [26] and uses in pharmaceutical formulations. Chitosan were prepared for controlled drug release in stomach such as sodium diclofenac [1] and amoxicillin [27] due to its antacid and antiulcer characteristic which prevent or weaken irritation in the stomach. Chitosan also promotes wound and burn healing properties, enhances the functions of inflammatory cells such as polymorphonuclear leukocytes, macrophages, fibroblasts and it is beneficial for the large open wounds of animals [28]. Due to its positive charges at physiological pH, chitosan can bind to the negatively charges and thus make it bioadhesive to for example, mucus, fatty acid and lipid. Consequently, they can increase the retention time at the site of application and so can be used for the prolonged release of drug in small intestine [29, 30]. Moreover, it is potentially suitable for use in dietary food because it can significantly reduce the cholesterol, triglyceride level and blood glucose [31].

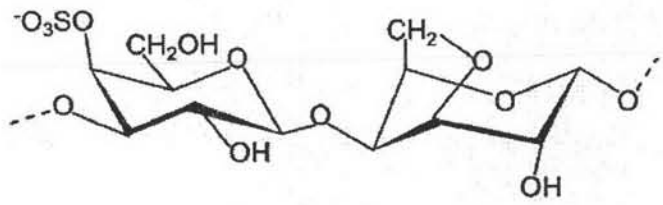
## 2.5 Carrageenan

Carrageenan is the main natural gelling polysaccharide that is extracted from difference species of marine red algae of the class *Rhodophyceae*. It has long been commercially used in the cosmetics and food industries as viscosity building, gelling and stabilizing agents. Due to its gelling, viscosity building properties and proven safety, there has been an interest in the use of carrageenan as sustained release materials [6].

### 2.5.1 Structure of carrageenan

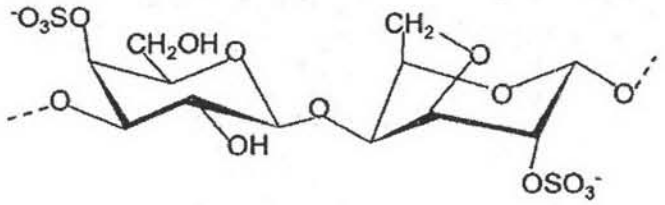
Carrageenan is polydisperse linear sulfated galactans. Its main chain consists of alternating copolymers of 1,4-α- and 1,3-β-D-galactopyranose and 3,6-anhydro-D-galactopyranose. It comes in three major types designated by Greek letter as κ (kappa), ι (iota) and λ (lambda) where the main structural difference among them is in the sulfate group degree of substitution and difference in terms of their gelling properties. The κ-, ι- and λ- carrageenan dimer have one, two and three sulfate ester groups, respectively, as shown in Figure 2.10 [32, 33]. The highly sulfate λ-carrageenan dose not gel, but the other two types κ- and ι- carrageenan, are able to generate gels with different characteristics which can influence the release behavior of mixtures [34].

**Kappa Carrageenan**



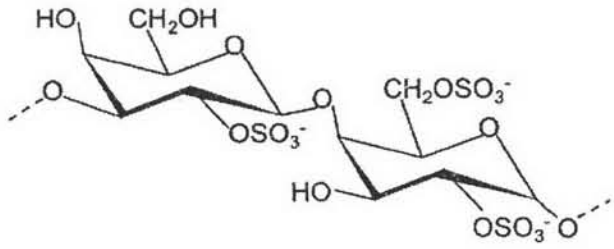

D-galactose-4-sulfate 3,6-anhydro-D-galactose

**Iota Carrageenan**




D-galactose-4-sulfate 3,6-anhydro-D-galactose-2-sullfate

**Lambda Carrageenan**




D-galactose-2-sulfate D-galactose-2,6-disulfate

**Figure 2.10** The structures of the three main carrageenan types kappa (κ ), iota (ι) and lambda (λ).

### 2.5.2 Carrageenan in pharmaceutical application

Since carrageenan is used in the food industry and is regarded as safe for human consumption, it has been used increasingly in the pharmaceutical field. Due to its viscosity enhancing, carrageenan has recently gained interest for the drug sustained release.

The matrix tablets containing carrageenan were found to be useful for tailoring the release of theophylline, sodium salicylate and chlorpheniramine maleate for 8-12 hours. Its release profile approached zero-order kinetic which is usually desirable for sustained release dosage form [6].

Sipahigi and Dortunc [35] used carrageenan to control verapamil HCl release from bead prepared by ionotropic gelation method. The results showed that about 70% of drug was released in 5 hour from the prepared carrageenan bead.

Tapia et al. [9] evaluated the possibility of using mixtures and/or PEC from chitosan-carrageenan as prolonged drug release systems. The drug release was controlled by the capacity of carrageenan to promote the entry of water into the matrices.

## 2.6 Sodium Diclofenac

Sodium diclofenac (DFNa) is a synthetic, non-steroidal anti-inflammatory drug (NSAIDs). It is widely used for relief of pain and inflammation. DFNa was manufactured and marketed under the proprietary name Voltaren®.

### 2.6.1 Physicochemical properties [36]

DFNa is a series of phenylacetic acid derivatives. Its structure element includes a phenylacetic acid group, a secondary amino group, and a phenyl ring containing chlorine atoms, as presented in Figure 2.11.

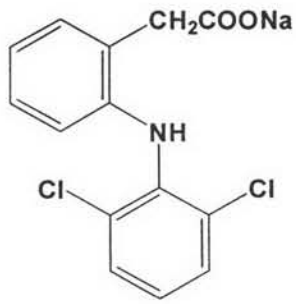



**Figure 2.11** Chemical structure of sodium diclofenac.

Chemical formula : $C_{14}H_{10}Cl_2NO_2Na$

IUPAC name : Monosodium-2-(2,6-dichloroanilino)phenylacetate

CAS No. : 15307-79-6

Molecular weight : 318.13

Description : White to off-white crystalline, slightly hygroscopic powder

Melting point : 283-285 °C

pKa : 4.0

**Table 2.1** The aqueous solubility of sodium diclofenac in the pH range 1.2 to 7.5[37].

| pH | Solubility (%w/v) |
|---|---|
| 1.2 | less than $4x\ 10^{-4}$ |
| 3.0 | less than $4x\ 10^{-4}$ |
| 4.0 | 0.0021 |
| 5.0 | 0.0086 |
| 6.0 | 0.0590 |
| 7.0 | 0.1870 |
| 7.5 | 0.1690 |

### 2.6.2 Uses and administration [10]

DFNa has been used in human medicine for many years. It possesses analgesic, antipyretic, and anti-inflammatory activities by inhibition of prostaglandin synthesis (cyclo-oxygenase).

The drug has been used for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and primary nocturnal enuresis. It may also be useful for short-term treatment of acute musculoskeltal injury, and dysmenorrheal. The daily dose varies between 75 to 200 mg/person; given in three or four divided doses depending on the route of administration (oral, rectal, intramuscular, intravenous or topical) and on the disease to be treated and may be used up to 12 weeks.

### 2.6.3 Pharmacokinetics and metabolism [11]

DFNa is rapidly and completely absorbed after oral administration, peak concentration in the plasma is reached within 2 to 3 hours. Administration with food can slow the rate but dose not alter the extent of absorption. Its half-life in plasma is approximately 1 to 2 hours. DFNa accumulates in synovial fluid after oral administration, which may explain the duration of therapeutic effect that is considerably longer than the plasma half-life. DFNa is metabolized in the liver into 4-hydroxydiclofenac, the principal metabolite, and other hydroxylated forms. The metabolites excreted in the urine (65%) and bile (35%).

### 2.6.4 Adverse effects

DFNa produces side effects in roughly 20% of patients, and approximately 2% of patients discontinue the therapy as a result [10]. The most common adverse effects of DFS are gastritis, peptic ulceration, and depression of renal function, all of which result primarily from prostaglandin inhibition [11]. Other side effects include headache, dizziness, insomnia, and blurred vision and other ocular reactions.

## 2.7 Glutaric Acid

Glutaric acid is an anionic crosslinking agent. It consists of three-carbon atoms and dicarboxylic acid groups in linear chain. The COOH groups can be converted to the $COO^-$ groups, by ionic interaction with positively charged materials such as chitosan. The interaction is reversible depending on pH of the solution, which consequently affect the controlled release of drugs.

### 2.7.1 Physicochemical properties

The structure of glutaric acid was presented below.

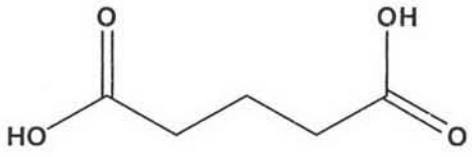



**Figure 2.12** Chemical structure of glutaric acid.

Chemical formula : $C_5H_8O_4$

IUPAC name : Pentanedioic acid, 1,3-Propanedicarboxylic acid

CAS No. : 328-42-7

Molecular weight : 132.12

Description : Colorless crystalline

Melting point : 96 °C

Boiling point : 200 °C

Density : 1.429 (water = 1)

Solubility : over 50% in water (at room temperature)