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 [13]. 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 [14]. 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) [15].

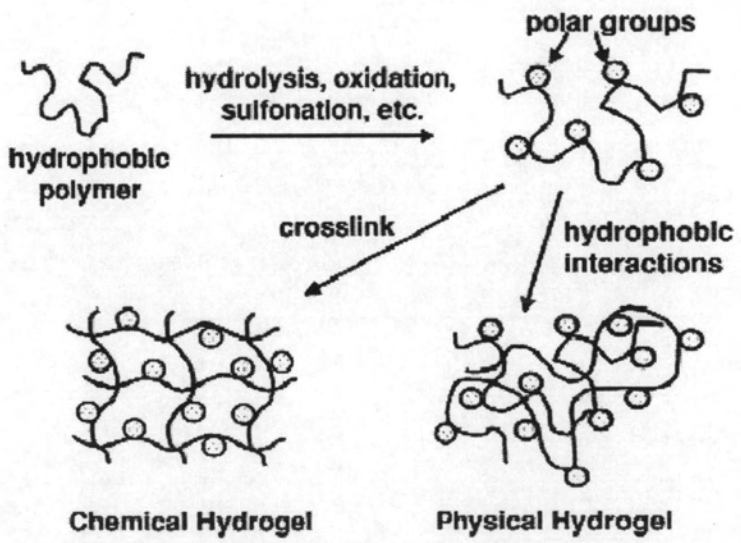

Figure 2.1 Scheme of the methods for formation of chemical and physical hydrogels.

2.1.1 Ionotropic and polyelectrolyte complexes (PEC) hydrogel

The physical hydrogels are formed by a polyelectrolyte with a multivalent ion of the opposite charge, it known as an 'ionotropic' hydrogel (Figure 2.2), for example, calcium pectinate gel [16] and potassium ion in κ-carrageenan gel [17]. Further, 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). 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.

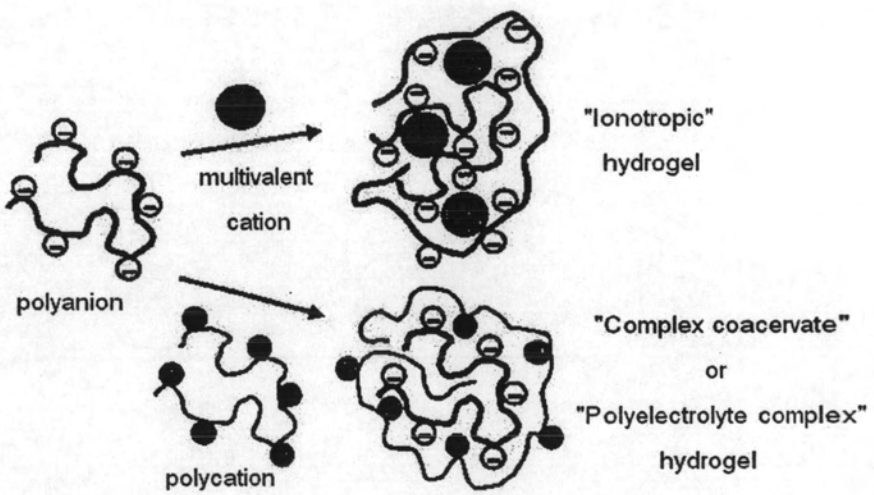

Figure 2.2 Methods for formation of chemical and physical hydrogels [15].

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 used controlled release widely in oral medication since the early 1950s. Enteric coating of such dosage forms as tablets 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) [18]. That can reduce toxic 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. That makes it possible to reduce the frequency of drug administration and improvement in treatment efficiency.

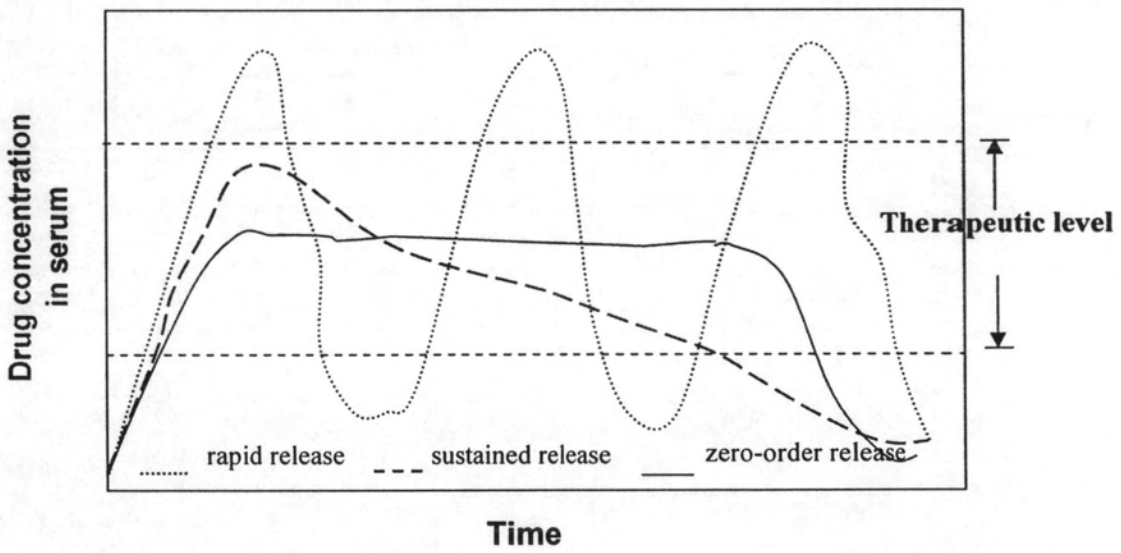

Figure 2.3 Hypothetical serum drug concentrations of various oral dosage forms [18].

2.2.2 Methods of achieving controlled release [19, 20, 21]

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.

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.

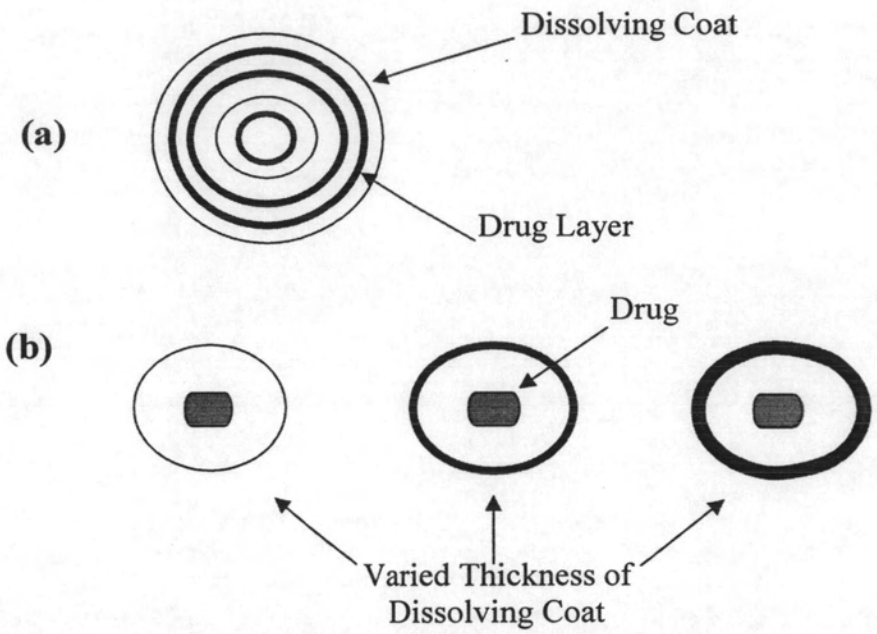

Figure 2.4 Two types of dissolution-controlled, pulsed delivery systems: (a) single bead-type device with alternating drug and rate-controlling layers; (b) drug containing beads with differing thickness of dissolving coats [21].

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.

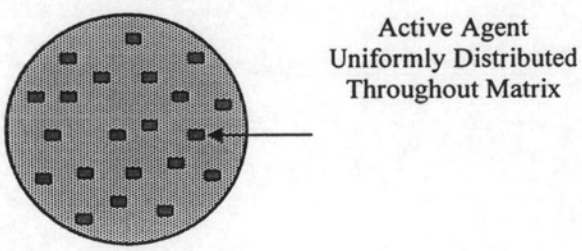

Figure 2.5 The active agent dispersed within the polymer mass of the diffusion-controlled system.

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.

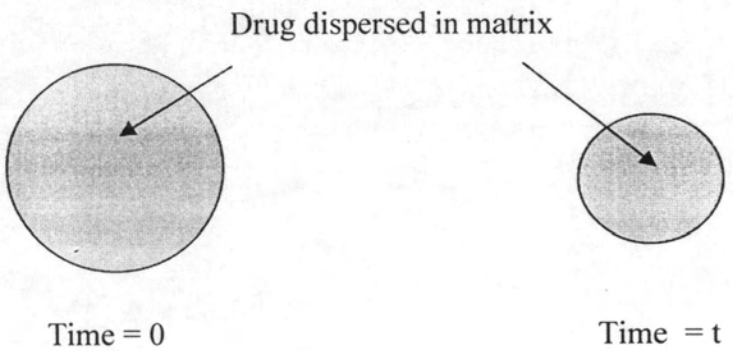

Figure 2.6 Representation of a biodegradable system. Drug is dispersed in the matrix before release at time = 0. At time = *t*, partial release by drug diffusion or matrix erosion has occurred [21].

2.3 Chitosan

Chitosan, a polycationic biopolymer, was discovered by Rouget in 1859 and gave a name by Hoppe-Seyler in 1894 [22]. 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 [23].

2.3.1 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 C6 building unit (Figure 2.7). 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.

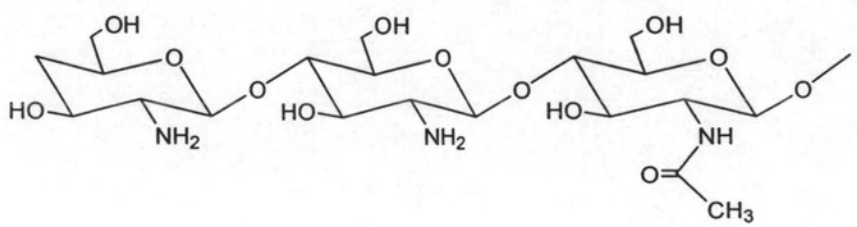

Figure 2.7 Chemical structure of chitosan.

2.3.2 Chitosan in pharmaceutical application

Chitosan has been considerable interesting in the medical and pharmaceutical fields. In addition to the good biocompatibility, biodegradability and low toxicity of chitosan, it has a number of desirable properties that make study of it interesting. Indeed, chitosan is known for it is polycationic polymer, forming gels most readily in acidic environments, such as that in the stomach. This makes chitosan interesting in relation to the development of slow release dosage forms for oral administration.

Chitosan were prepared for controlled drug release in stomach such as sodium diclofenac [1] and amoxicillin [24] 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 [25]. 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 [26, 27]. Moreover, it is potentially suitable for use in dietary food because it can significantly reduce the cholesterol, triglyceride level and blood glucose [28].

2.4 Polyethylene glycol

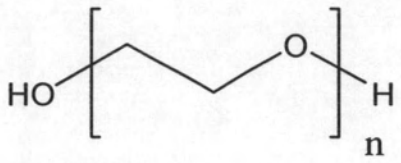

Figure 2.8 Structure of polyethylene glycol

Poly(ethylene glycol) (PEG) is family of water-soluble linear polymers formed by additional reaction of polyethylene oxide (EO) with mono ethylene glycol or diethylene glycol.

Poly(ethylene glycol) (PEG) [6] is biocompatible polymer with excellent biocompatibility and non-toxicity because it exhibits rapid clearance from the body, and has been approved for a wide range of biomedical applications [29]. Moreover, it is often blended or compound with other polymers to be use in the field of drug-controlled release, especially for the immune and protein system. Because of these properties, hydrogels prepared from PEG are excellent candidates as biomaterials.

Generalized formula : $H(OCH_2CH_2)_nOH$

name : Polyethylene glycol

Molecular weight : 5100-7000

Description : White and hygroscopic flake

Melting point : 60-63 °C

Solubility : Water and many polar organic solvent such as acetone, alcohol.

Stability : low volatility and thermally stable at temperature lower than 300°C without O_2.

2.4.1 Polyethylene glycol in pharmaceutical application

Because of the non-toxicity of PEG, it is used in variety products, especially in the medical and pharmaceutical fields such as often used in cryoprotection, pharmaceutical preparation, tissue culture, and organ protection

In addition, PEG was used in combining with chitosan films for controlled release of ciprofloxacin hydrochloride. The increasing proportion of PEG could increase the cumulative release amount of drug. Moreover, the thermosensitive hydrogel of the chitosan chloride and PEG and small amount of α-β-glycerophosphate were used as the nasal drug delivery system to improve the absorption of the hydrophilic macromolecular drugs. In addition, the hydrogel of PEG and chitosan helped to decrease nasal mucociliary clearance rate release drug slowly.

2.5 Sodium tripolyphosphate

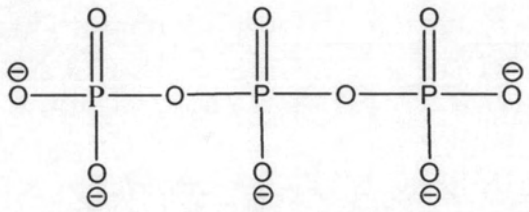

Figure 2.9 Structure of TPP

Sodium tripolyphosphate (TPP), $Na_5P_3O_{10}$, is the sodium salt of triphosphoric acid. TPP is a solid inorganic compound which presented the multivalent anions which is suitable for interacting with cationic polymer, such as chitosan. In another words, the ionic cross-linking of chitosan and TPP were created for improving the strength of chitosan beads

The important property of TPP is the pH-dependent charge numbers which were calculated according to the reported pK_a as followed: $pK_{a1} = 1$, $pK_{a2} = 2$, $pK_{a3} = 2.79$, $pK_{a4} = 6.47$ and $pK_{a5} = 9.24$ [8]

Generalized formula	: $Na_5P_3O_{10}$
name	: Pentasodium tripolyphosphate
Molecular weight	: 367.86
Description	: White or colorless crystals, granules or powder
Melting point	: 622 °C
Stability	: Stable, incompatible with strong oxidizing agents, strong acids, hygroscopic.

2.6 Sodium Diclofenac

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

2.6.1 Physicochemical properties [30]

DS 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. It was presented in Figure 2.10.

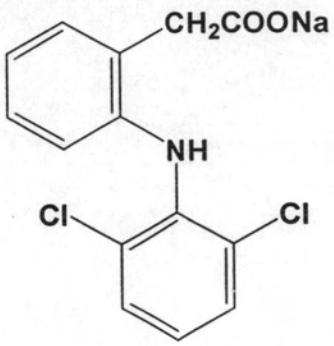

Figure 2.10 Chemical structure of sodium diclofenac.

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 [31].

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 [11]

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 [12]

DS is rapidly and completely absorbed after oral administration, peak concentration in 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 1.2 to 1.8 hours [32]. DS accumulates in synovial fluid after oral administration, which may explain the duration of therapeutic effect that is considerably longer than the plasma half-life. In the liver, DS is metabolized to 4-hydroxydiclofenac, the principal metabolite, and other hydroxylated forms. The metabolites were excreted in the urine (65%) and bile (35%).

2.6.4 Adverse effects

DS produces side effects in about 20% of patients, and as a result, approximately 2% of patients discontinue the therapy [11]. The most common adverse effects of DS in oral route are abdominal cramps, abdominal pain, abdominal distention, diarrhea, flatulence, indigestion, peptic ulceration, and depression of renal function, all of which result primarily from prostaglandin inhibition [12]. Other side effects include headache, dizziness, insomnia, and blurred vision and other ocular reactions.