Charpter 1

General Background

Introduction

The area of controlled release pharmaceutical is now increasingly important in the formulation, manufacturing and marketing of new pharmaceutical products. There are several advantages in using controlled release dosage form, examples of these are

- improved patient compliance
- reduction of both local and systematic adverse side effects
- better control of drug absorption
- increase the reliability of therapy.

Most peroral controlled release products have been formulated as encapsulations or tablets [Lordi, 1986]. Since the successful introduction by Smith, Kline and French in the early 1950s of their SPANSUL range of products, microencapsulation has also been widely employed in the last 40 years. Accordingly, the majority of peroral controlled release dosage forms now available are based on the microencapsulation principle. Now with the decline in the number of new drugs being introduced, greater attention is being paid to improving the efficiency of existing drugs. Microencapsulation is one of the major approach employed to achieve this goal.

Microencapsulation [Deasy, 1984; Kondo, 1979a; Kondo, 1979b; Luzzi, 1970; Li et al., 1988; Bakan, 1986] is a process of wrapping small entities in individual, protective coatings which usually composed of seamless rigid thin film. Most gaseous liquid and solid materials may be contained in microcapsule, and these materials may be either hydrophilic or hydrophobic. A variety of inorganic and organic materials can be used as wall material however polymeric substances are most frequently used. The wall material is selected appropriately

depending on the physical properties of the core materials. If the core material is oleophilic, a hydrophilic polymer is used as the wall material. When an aqueous solution is used as the core material then a water insoluble synthetic polymer is used as wall material. Examples of commonly used wall materials are shown in Figure 1 [Kondo, 1979a].

Figure 1 : Examples of commonly used wall material

PROTEINS : collagen, gelatin, casein, fibrinogen, hemoglobin, and polyamino acids
VEGETABLE GUMS : gum arabic, agar, sodium alginate, carrageenin, and dextran sulfate
CELLULOSES : ethyl cellulose, nitrocellulose, carboxymethyl cellulose, acetylcellulose, cellulose acetate-phthalate, and cellulose acetate-butylate-phthalate
CONDENSATION POLYMERS : nylon, Tetron, polyurethane, polyurea, polycarbonate, formalin napthalenesulfonic acid condensate, amino resins, alkyl resins and silicone resins
COPOLYMERS : maleic anhydride copolymers with ethylene or vinyl methyl ether, acrylic acid copolymers, and methacrylic acid copolymers
HOMOPOLYMERS : polyvinyl chloride, Saran, polyethylene, polystyrene, polyvinyl acetal, polyacrylamide, polyvinylbenzenesulfonic acid, polyvinyl alcohol, and synthetic rubber
CURABLE POLYMERS : epoxy resins, nitroparaffin, and nitrated polystyrene
WAXES : wax , paraffin resin, shellac, tristearin, monoglyceride, bees wax, haze wax, oils, fats, and hardened oils
INORGANIC MATERIALS : calcium sulfate, graphite, silicates, aluminium, alumina, copper, silver, glass, alloys, and clays.

The microcapsules can be prepared by a variety of different methods. One of the methods that has been widely used was coacervation or phase separation which is a physicochemical process. Coacervation can be subdivided into two categories, simple and complex. Briefly the simple coacervation involves the use of only one colloid, while the complex coacervation involves the use of more than one colloid. Coacervation can be induced by addition of large amount of various salts, changing the temperature or the pH or used two opposite charged colloids.

Most of the peroral controlled release dosage forms formulated by microencapsulation used hydrophobic colloid for wall material [Dakkuri, Schroeder, and Deluca, 1978; John, Minatoya, and Rosenburg, 1979; Chowdary and Murty, 1985; Chattaraj et al., 1991]. The organic solvent used with hydrophobic colloid can cause polluted air and toxic to human. Recently reports have shown that a hydrophilic polymer, *chitosan* can be successfully used as wall material for controlled release microsphere or microcapsule [Nishioka et al, 1989; Thanoo, Sunny, and Jayakrishnan, 1992; Bodmeier, Oh and Pramar, 1989].

Chitosan [Skaugrud, 1991; Skaugrud, 1989; Lower, 1984] a hydrophilic polymer is a cationic polyelectrolyte prepared by N-deacetylation of chitin, which can be obtained from crab and shrimp shell. Chitosan, as a biopolymer, is biocompatible, biodegradable and nontoxic, hence lend itself to be beneficially used in pharmaceutical applications, including the microencapsulation process [Ohya, 1993; Meshali, 1989; Bodmeier and Paeratakul, 1989; Shioya and Rha, 1989; Kim and Rha, 1989].

Microcapsule containing a drug core prepared using aqueous complex coacervation technique, is formed by ionic interaction of chitosan and counter polyanions [Kim and Rha, 1989]. The main mechanism for forming the membrane is the electrostatic interaction between positive charged amine group on chitosan chain and the negative charged group on counter polyanions backbone. Theoretically, it should be possible to control the porosity and permeation characteristic of membrane by controlling the physical and processing conditions that contribute to the polymer chain conformation in solution. As the solution conditions effect the chain conformation of chitosan molecules, which dictate the membrane structure, it should be possible to control the micro structure and mechanical properties of chitosan membrane by manipulating the solution conditions such as the pH, ionic strength and polymer as well as the counter-ion concentration.

Shioya et al. (1989), studied the factors which control the trans membrane permeability of the chitosan-carboxymethyl cellulose microcapsule containing cell culture, and found that the lowering of chitosan molecular weight can cause a decrease in permeability of the membrane and longer reaction time did not improve the capsule membrane.

Kim et al.(1989) had found that the pH, ionic strength and polymer concentration of chitosan solution effect the permeability of chitosan-sodium alginate microcapsule.

It has been reported that glutaraldehyde can be used as a cross linking agent for chitosan in the microencapsulation process [Thanoo et al., 1992; Bodmeier et al., 1989]. The reports revealed that increase cross linking agent, glutaraldehyde, reduce the degree of swelling and the rate of drug release.

However, no studies have been published on using chitosan-carboxymethyl cellulose microcapsule prepared by complex coacervation technique for controlled release dosage form. This study investigate the use of this technique to prepare a pharmaceutical microcapsule which has controlled drug release time of 12 hour. The model drugs used in the experiments are *indomethacin* and *pindolol*. Indomethacin is a weak acid with 2.6-11.2 hour half-life [Olin, 1987], while pindolol is a weak base with 3.0-4.0 hour half-life [McEvoy, 1992]. They are both insoluble drug.

Objectives of the study

1. To study the use of complex coacervation technique in the preparation of pharmaceutical controlled release microcapsule employed chitosan and carboxymethyl cellulose as wall material.

2. To determine the optimum processing conditions for the preparation of microcapsule using chitosan and carboxymethyl cellulose as wall material.

3. To study the effect of processing variables on the physical properties and drug release pattern of the pharmaceutical microcapsule.

4. To study the reproducibility of physical properties and drug release pattern in consecutive batch.

Literature Review

Microencapsulation

Microcapsules [Deasy, 1984; Kondo, 1979a; Kondo, 1979b] developed for use in medicine, consists of solid or liquid core material containing one or more drugs enclosed in coating as shown in Figure 2 [Deasy, 1984]. The core may also be referred to as the nucleus or fill and the coating as the wall or shell. Depending on the manufacturing process, various types of microcapsules structure can be obtained as illustrated in Figure 2, the most common type being the mononuclear spherical. Microcapsules usually have a particle size range between 1 and 2,000 micron. Products smaller than 1 micron are referred to as nanocapsules.

Microcapsules are also often described by other terms, such as coated granules, pellets or seeds, microsperules, and spansules.

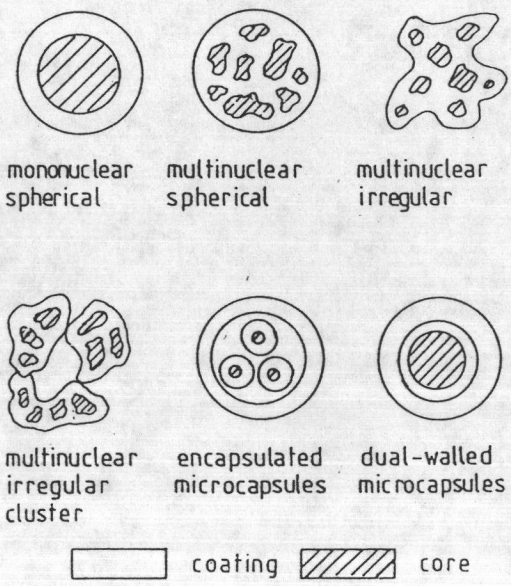

Figure 2 : Typical structures of microcapsules

Reason for microencapsulations
[Luzzi, 1970; Li et al. 1988; Deasy, 1984]

Microencapsulations can be used for a number of reasons. These include the followings.

1. Protection of reactive material from their environments.
2. Safe and convenient handling of material which are otherwise toxic or noxious.
3. Means of providing controlled and or sustained release of materials following the application.
4. Means of handling liquid as solid.
5. Tastes masking of bitter drug.
6. Masking of unpleasant odour.
7. Preparation of free flowing powder.
8. Modification of physical properties of drugs.
9. Reduce gastric and other gastrointestinal tract irritation.

Microencapsulation Procedures
[Deasy, 1984; Luzzi, 1970; Li et al, 1988; Bakan, 1986]

The microcapsules can be prepared by a variety of methods, however these methods of preparation and the techniques employed for microencapsulation overlap considerably. For the sake of simplicity, the various microencapsulation techniques may be categorised as followed.

1. Phase separation or coacervation
2. Interfacial polymerization
3. Electrostatic method
4. Mechanical method

1. Phase Separation or Coacervation

The term *"coacervation"* has been used by two Dutch scientists, Bungenberg de Jong and Kruyt, to describe the salting out or phase separation of lyophilic solid into liquid droplets instead of into solid aggregates. Two mechanisms have been suggested for the formation of microcapsule by coacervation method;

a) individual coacervate droplets maybe attached to and coalesce around core particles immiscible in the system and/or
b) single coacervate droplet may encompass one or more core particles.

The deposition of coating material is aided by a reduction in total interfacial energy of the system consequent upon the decrease in the surface area of the coating material as its droplets coalesce around the core material. The coating is then gelled by lowering the temperature and hardened by the addition of a cross linking agents such as formaldehyde or glutaraldehyde. Figure 3 [Deasy, 1984] shows the typical steps involved in microencapsulation by coacervation method.

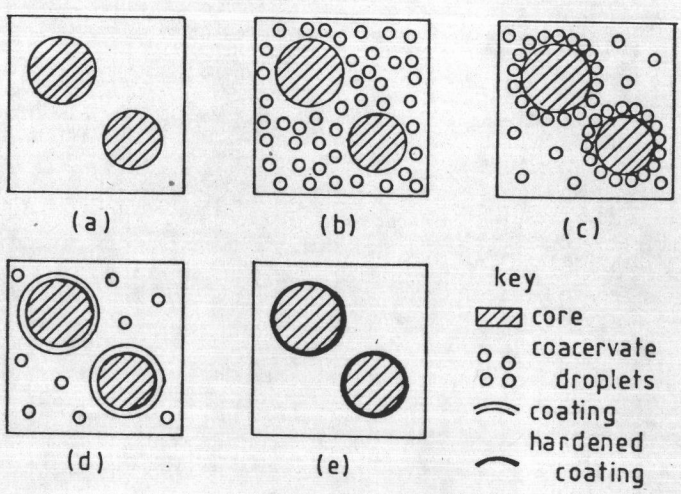

Figure 3 : Typical steps in a coacervation of microencapsution.
(a) Core particles dispersed in solution of polymer by agitation.
(b) Coacervation visible as droplets of colloid-rich phase induced by one or more agents.
(c) Deposition of coacervate droplets on surface of core particles.
(d) Mergence of coacervate droplets to form the coating
(e) Shrinkage and cross linking of the coating to rigidize it as necessary.

Finally, after washing off residual hardening agents, the microcapsules may be recover by filtration, configuration or decantation, and may be converted into a dry powder by removal of residual water using a solvent, spray or freeze drying or a fluidized bed dryer.

Size distribution, morphology of microcapsules and its drug release pattern can be manipulated by controlling the variables in the coacervation process. Examples of these processing condition variables are as following.

- Drying method [Takenaka, Kawashima, and Lin, 1980]
- Type and amount of drying agent [Takenaka et al., 1980; Nixon and Hassan, 1980]
- Coacervation temperature [Luzzi and Gerrauhthy, 1967]
- Concentration of colloid [McMullen, Newton, and Becker, 1982]
- Colloid and drug ratio and coacervation pH [Takenaka et al., 1980; Nixon and Hassan, 1980; Luzzi and Gerraughthy, 1967; McMullen et al., 1982; McMullen, Newton, and Becker, 1984]

The coacervation process can be subdivided into two categories, simple and complex coacervation. The following section describes these two types of coacervation methods.

1.1 Simple Coacervation

Simple coacervation involves the use of only one colloid, e.g. gelatin in water, and the removal of associated water from around the dispersed colloid by agents with a greater affinity for water, such as various alcohols and salts. The dehydrate molecules of polymer tend to aggregate with the surrounding molecules to form the coacervate. Likewise, electrolyte and heating can be used to coacervate an aqueous solution of methylcellulose as the solubility of this polymer decrease with a rise in temperature.

1.2 Complex Coacervation

Complex coacervation involves the used of more than one colloid. Gelatin and acacia in water are most frequently used. The coacervation is accomplished mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration. Examples of other colloids which have been found to be suitable for complex coacervation are pectin-gelatin [McMullen et al., 1982; McMullen et al., 1984], carboxymethyl cellulose-gelatin [Koh and Tucker, 1988] and albumin-acacia [Burgess, Kwok, and Megremis, 1991].

2. Interfacial Polymerization

Microencapsulation by this method is a process whereby a monomer is made to polymerize at the interface of two immiscible substances. If the internal phase is a liquid, it is possible to disperse or solubilize the monomer in this phase and emulsify the mixture in the external phase until the desired particle size is reached. At this point, a cross linking agent may be added to the external phase. Since there is usually some migration of the monomer from the internal to the external phase, and since it is preferred that the cross linking agent does not transfer to the internal phase, the bulk of any polymerization will take place at the interface.

3. Electrostatic Methods

Preparation of microcapsules by these methods involves bringing together the wall material and the material to be encapsulated when both are aerosolized. The wall material must be liquid during the encapsulation stage and must be capable of surrounding the core material. The aerosols produced must be oppositely charged. These chambers are used for the process, two for atomization of wall and core material and the third for mixing. Oppositely charged ions are generated and deposited on the liquid drops while they are being atomized.

4. Mechanical Methods

All of the mechanical methods used for microencapsulation employ special equipment. The microcapsules produced result from mechanical procedures rather than from a well defined physical or chemical phenomenon.

Since the last decade, there have been tremendous technological advances in different types of microencapsulation coating equipment, such as spray drying, spray congealing, pan coating, fluid bed coating, and centrifugal multiorifice.

Kinetic of Drug Release from Microcapsules
[Lordi, 1986; Deasy, 1984]

Microcapsules are often irregular in shape, so that the conventional methods based on spherical, cylindrical, or other regular geometric shape often resulted in poor fit for release data. Also many microcapsules, particularly those produced by various coacervation procedures, are multinuclear or are composed of aggregates of smaller microcapsules hence their release kinetics do not follow that expected of a reservoir type device but rather that of monolithic device. This is due to the diversity of inclusion and lack of homogeneity of many polymeric coating.

Release of drug from microcapsules is a mass transport phenomenon involving diffusion of drug molecules from a region of high concentration in the dosage form to a region of low concentration in the surrounding environment through a polymeric membrane. The permeation rate must follow Fick's first law equation,

$$\frac{dM}{dt} = \frac{DkA\,\Delta c}{l_m} \qquad (1)$$

where : $\frac{dM}{dt}$ = drug passing through membrane per time unit

D = diffusion coefficient

k = partition or distribution coefficient of drug toward polymer

A = microcapsule surface area

Δc = different in concentration of drug in solution on either side of the membrane

l_m = membrane thickness

1. **Reservoir type Device**

Assuming that the thermodynamic activity of the core material is maintained constant with the microcapsule, which is spherical and has inert homogeneous coating (Figure 4 [Deasy, 1984]). Then the steady state release rate derived from equation (1) is given by

$$\frac{dM_t}{dt} = 4\pi Dk\Delta c\frac{r_o \cdot r}{r_o - r} \qquad (2)$$

where r_o = outside radius
r = inside radius

Assuming that all parameters on the right hand side of equation (2) remain constant, the function $M = f(t)$ must be a straight line. So this indicated that drug release is constant or of zero order.

If the thermodynamic activity of the core material does not remain constant because initially a saturated or unsaturated drug solution was encapsulated or because similar conditions apply during the terminal release phase, then the rate of release will become exponential or first order. The diffusion law can be expressed as

$$\frac{-d(M_o - M)}{dt} = k_c\,(M_o - M) \qquad (3)$$

or

$$\log(M_o - M) = \log(M_o) - k_c\, t \qquad (4)$$

where M_o = initial drug concentration in microcapsule
M = drug mass diffusion
k_c = first order rate constant

The function $\log(M_o - M) = f(t)$ must be a straight line, as well as the function $\log(P) = f(t)$, where P is the percentage of drug remaining in the microcapule at time t.

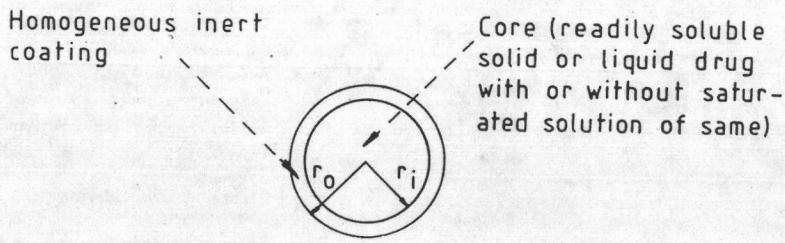

Figure 4 : Idealised spherical microcapsule

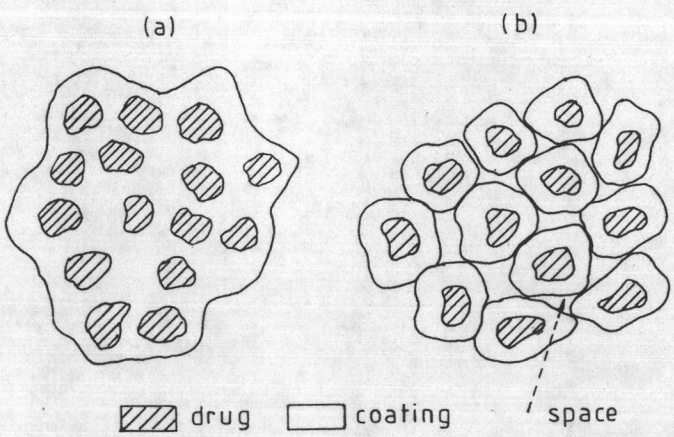

Figure 5 : Drug release from homogeneous (a) and granular (b) matrices

2. Monolithic Devices

For the drug release from homogeneous matrices model (see Figure 5a [Deasy, 1984]) assumes that the drug dissolves from the surface layer first, and when this layer has become exhausted the next layer begin to dissolve. The release rate from a slab geometry can often be used to approximate drug release from such irregular shaped microcapsules. The relevant equation for this is

$$\frac{dM}{dt} = \frac{A}{2}\left[\frac{DC_m}{t}(2C_{tot} - C_s)\right]^{1/2} \qquad (5)$$

which upon integration gives

$$Q = \frac{M}{A} = \left[DC_m(2C_{tot} - C_s)t\right]^{1/2} \qquad (6)$$

where Q = drug mass release per unit area of surface
C_{tot} = total drug loading
C_m = a portion of the drug dissolve in membrane material

For the drug release from granular type matrix (see Figure 5b), as might be observed with a cluster of microcapsule, where geometry is usually very irregular, the equation for the steady state drug release is given by :

$$Q = \left[\frac{D\varepsilon}{\tau}(2C_{tot} - C_s)C_s t\right]^{1/2} \qquad (7)$$

where ε = the porosity of the matrix
τ = the tortuousity of the matrix
C_s = saturated solubility of solute in given solvent

In general equations (6) and (7) may be expressed as

$$Q = k_1 t^{1/2} \qquad (8)$$

where k_1 = diffusion rate constant

In this case, the function $M = f(t^{1/2})$ must be a straight line to indicate that drug release pattern is square root time model and also known as *Higuchi* model.

Since both the square root of time release and first order release plot are linear, as indicated by the correlation coefficient, it is necessary to distinguish these two models [Hecquet, 1984].

For the *Higuchi* model, the rate of drug release will be inversely proportional to the total amount of drug release in accordance with the following equation.

$$\frac{dM}{dt} = \frac{k^2 s^2}{2M} \qquad (9)$$

The rate predicted by first order model was given by :

$$\frac{dM}{dt} = k_c M_o - k_c M \qquad (10)$$

This equation indicates that the rate of release will be proportional to M. The rate of release were determined by measuring the slope at different points on the percentage drug release versus times curve.

The plotted curves of the rate of release against 1/M were found to be linear, which suggested that the release was fitted with the Higuchi model. If first order model was operative then the plots of the rates of release versus M should be linear.

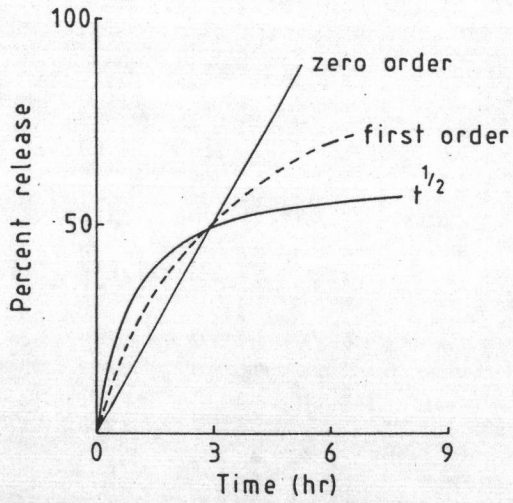

Figure 6 : Zero order, first order and $t^{1/2}$ dependent release rate for a drug with a half life of 3 hr.

Figure 6 [Deasy, 1984] show the typical from of drug release patterns. Zero order is not necessarily better than first order or $t^{1/2}$ dependent release rate. As with many products an initial greater release of active ingredient follow by a slower release for maintenance is desirable. Also, in general, reservoir type systems are more expensive and difficult to manufacture than monolithic system.

Chitosan

[Skaugrud, 1989; Skaugrud 1991; Lower, 1984]

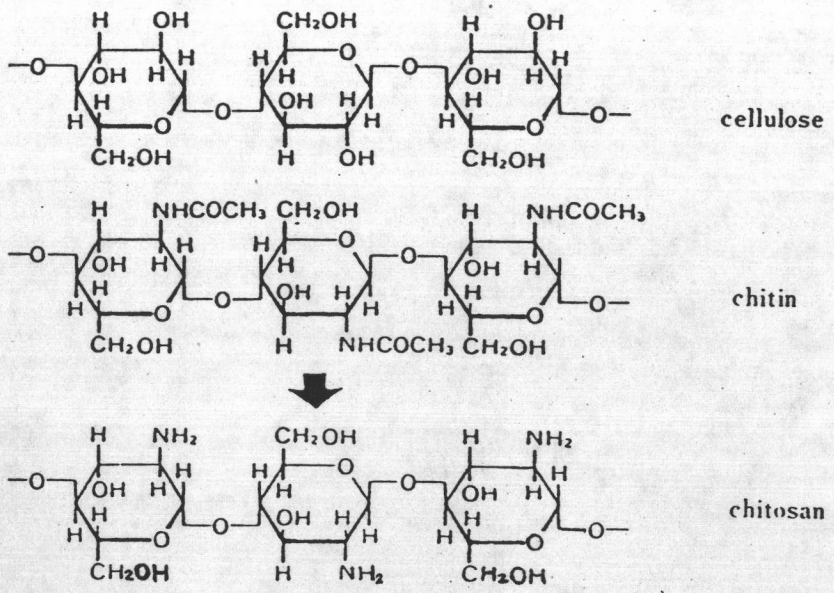

Figure 7 : Structure of cellulose chitin and chitosan

Chitosan [(1→4)-2-amino-2 -deoxy-β-D-glucon] is a hydrophilic cationic polyelectrolyte prepared by N-deacetylation of chitin (Figure 7). Chitin and chitosan, similar to cellulose, are long linear chain molecules of (1-4) linked glycans. Repeating unit in chitin is 2-acetamide-2b-deoxy-D-glucose (N-acetylglucosamine), while for chitosan it is an inhomogeneous mixture with the deacetylated form (glucosamine).

The molecular weight of chitosan, for commercial product, varies within the range of 10,000-1,000,000 Dalton, depend on its processing conditions. The mole fraction of deacetylated units (glucosamine), define as the degree of deacetylation will usually range from 70%-90%.

Physicochemical Properties

1. Solubility

Chitosan is soluble in organic acid such as adipic, acetic, formic, lactic, malic, propionic and succinic acid. Alternatively chitosan is also soluble in mineral acid such as hydrochloric, nitric and perchloric acid, however it is insoluble in sulphuric and phosphoric acid. Chitosan is considered to be a weak base, therefor certain amounts of acid is required to bring the glucosamine units to its soluble form, $R-NH_3$.

2. Rheology

Due to its high molecular weight and molecular's linear unbranched structure, chitosan is an excellent viscosifier in acid environment. It behaves as a pseudoplastic material showing decrease viscosity with increase shear.

3. Cross-Linked Chitosan

Reacting chitosan with a controlled amount of multivalent anions will result in cross-linking between the chitosan molecules. Network formed will have the ability to keep a large amount of water, by some estimates this can be as much as 95% or more. Cross-linking can be done in acid, neutral or basic environment, depending on methods applied. Several gelling counter ions are available, such as molybdate(vi) [Draget et al., 1992], glutaraldehyde [Yison, Wenjun and Tongyin, 1990; Koyama and Taniguchi, 1986; Nakatsuka and Andrady, 1992], epihalohydrin [Mayer et al., 1991], oxo acid [Muzzarelli, 1989] and some of which are shown in Table 1 [Skaugrud, 1989].

4. Chelating Agent

Chitosan can form complexes with certain metal, such as Hg, Cd, Pb, Zn, Co, Ni, Cr, Cu, Fe, Mn, Ag, Au and Pt, even though the mechanism probably is not completely understood.

Table 1 : Counter ions for ionotopic gelation of chitosan

Low molecular weight	High molecular weight	Hydrophobic
Pyrophosphate	Alginate	Octylsulphate
Tripolyphosphate	Polyaldehyde-carbonic acid	Laurylsulphate
Tetrapolyphosphate	Poly-1-hydroxy-1-sulfonate-propene-2	Hexadecylsulphate
Hexametaphosphate	Polyaldehyde-carbonic acid	Cetylsterylsulphate
$Fe(CN)_6$/ $Fe(CN)_6$		

Applications of Chitosan

Chitosan has been reported to have useful applications in the medical, cosmetic and pharmaceutical area. Its main applications in these areas are summarise in Table 2 [Skaugrud, 1989].

1. Medical Application

Chitosan has been used as blood coagulant, a wound healing accelerator, soft and hard contact lens and artificial kidney membrane.

2. Cosmetic Application

The main application area in cosmetic are in hair care and skin care consumer products.

3. Pharmaceutical Application

Chitosan has many applications in pharmaceutical, examples of recent reports of its uses in this area are,

- as a direct compression diluent [Sawayanagi, Numbu and Nagai, 1982] ,
- as a vehicle for sustained release [Nigalaye, Adusumilli and Bolton, 1990; Hou et al., 1985; Kawashima et al., 1985; Miyazaki, Ishii and Nadai, 1981],
- enhancement of dissolution rate of insoluble drug [Shirashi et al., 1990],
- as a tablet binder [Upadrashta, Katikaneni, and Nuessle, 1992]
- as disintegrant in pharmaceutical tablet [Parichat Chomto, 1992]
- formulation of film dosage form [Miyazaki, Yamaguchi, and Takada, 1990; Kanke et al., 1989]
- gel preparation [Draget, 1992]
- microencapsulation for anticancer, cell culture and other drugs [Nishioka et al., 1989; Thanoo et al., 1992; Bodmeier et al., 1989; Ohya et al., 1993; Meshali et al., 1989; Bodmeier and Paeratakul, 1989; Shioya and Rha, 1989; Kim and Rha, 1989].

Table 2 : Main applications for chitosan

Application	Function
1. Immobilise enzymes/living cells	Gel immobilisation matrix increase stability, compatible with phosphate
2. Personal care products	
hair care	substantive to hair and skin
skin care	form clear protective coating, moisture retention
viscosifier	build viscosity in amphoteric/non-ionic shampoo
cosmetics	viscosity building, coating, moister retention, non-allergic
3. Biomedical	
lower cholesterol	anticholesteric
wound care	accelerate wound healing
eye bandage	forms tough protective properties coating
drug delivery	biodegradable, bioerodable, non-toxic
contact lens	crosslinked to give porous, grindable lens material, non-allergic
dental	bioadhesive
absorbable sutures	biodegradable, accelerate wound healing
orthopaedic	temporary bioengineering material
4. Biotechnology	
immobilise enzymes	complexes with proteins
immobilise living cells	forms gel matrix (e.g. beads)
encapsulated cells	replace polylysine in algin bead process
filtration	membrane can be cast, film
recover valuable protein	complexes with proteins, flocculate
chromatography	support enzymes/cell stabilisers

Sodium Carboxymethylcellulose

[American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986]

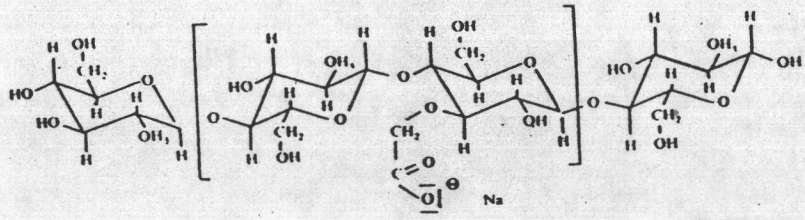

Figure 8 : Structure formula of carboxymethylcellulose

Synonyms : Sodium cellulose glycolate, sodium CMC, CMC

Empirical Formula : $\left[C_6H_7O_2(OH)_{3-x}(OCH_2-COONa)_x\right]_n$

Molecular Weight : 90,000 - 700,000

Physicochemical Properties :

Carboxymethylcellulose (CMC) is a white to yellow odourless, hydroscopic powder or granular material having a faint paper like taste. It is soluble in water at all temperature, giving clear solution, practically insoluble in most organic solvents. CMC is incompatible with strongly acidic solutions and with soluble salts of iron and some other metals such as aluminium, mercury and zinc.

Functional Category :

- USP suspending and/or viscosity increasing agent, tablet binder, coating agent
- BP pharmaceutical aid
- Other disintegrant, thickener, suspension stabiliser.

Safety : generally recognised as safe.

Indomethacin

[The United States Pharmacopoeia Convention, 1992]

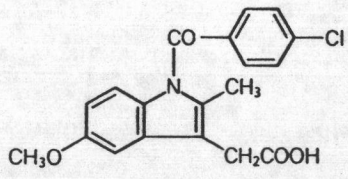

Figure 9 : Structure formula of indomethacin

Chemical Name : 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

Empirical Formula : $C_{19}H_{16}ClNO_4$

Molecular Weight : 357.81

Physicochemical Properties [Klaus, 1984] :

Indomethacin appears as a pale yellow-tan crystalline powder that is odourless or almost odourless. Its pk_a is 4.5. The solubility data of indomethacin is shown in Table 3. Indomethacin is sensitive to light and is unstable in alkaline solution.

Pharmacology [McEvoy, 1992] :

Indomethacin has pharmacological actions similar to those other NSAIDs. The drug exhibits anti-inflammatory, analgesic and anti-pyretic activity. The exact mechanisms have not been clearly established, but many actions appear to be associated principally with inhibition of prostaglandin synthesis. Indomethacin inhibits the synthesis of prostaglandin in body tissues by inhibiting cyclooxygenase, an enzymes that catalyses the formation of prostaglandin precursors (endoperoxides) from arachidonic acid.

Table 3 : Solubility data of indomethacin

Solvent	Temp(°c)	Solubility
Water	25	0.40 mg/100 ml (a)
Water	25	0.52 mg/100 ml (b)
Water	25	0.88 mg/100 ml (c)
Water	RT	Practically insoluble
Phosphate buffer pH 5.6	25	3 mg/100 ml (a)
Phosphate buffer pH 5.6	25	5 mg/100 ml (b)
Phosphate buffer pH 6.2	25	11 mg/100 ml (a)
Phosphate buffer pH 6.2	25	16 mg/100 ml (b)
Phosphate buffer pH 7.0	25	54 mg/100 ml (a)
Phosphate buffer pH 7.0	25	80 mg/100 ml (b)
Ethyl alcohol (95%)	RT	1 in 50
Chloroform	RT	1 in 30
Ether	RT	1 in 45
Methanol	25	32 mg/gm
Benzene	25	4 mg/gm
n-Butanol	25	19 mg/gm
sec-Butanol	25	27 mg/gm

(a) form I , (b) form II , (c) form III

Pharmacokinetic [Olin, 1987] :

Indomethacin can be rapidly and almost completely absorbed from GI tract in the healthy adults. At therapeutic concentration, indomethacin is approximately 99% bound to plasma protein. The volume of distribution and time to peak level of indomethacin have been reported to range between 0.34 and 1.57 L/kg and 1.5 hours respectively with 2.6-11.2 hour half life.

Use and Administration [John, 1980] :

- Gout : initial 100 mg, then 50 mg 3 time a day until pain is relieved, then dosage is rapidly reduced until discontinue.
- Antipyretic : oral 2-3 times a day
- Antirhumatic : oral 50 mg 2-3 times a day
- Acute bursitis or tenitis: oral 75-100 mg a day in 3-4 divided doses.

Pindolol
[McEvoy, 1992]

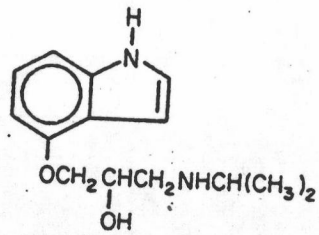

Figure 10 : Structure formula of pindolol

Chemical Name : 2-propanol,1-(1-H-indol-4-yloxy)-3-[(1-methylethyl)amino]
-1-(indol-4-yloxy)-3-(isopropylamino)-2-propanol

Empirical Formula : $C_{14}H_{20}N_2O_2$

Molecular Weight : 248.32

Physicochemical Properties [Moffat, 1986] :

Pindolol is a white crystalline powder. Its meting point range between 171-173 °c and its pk_a is 9.7. It is practically insoluble in water but slightly soluble in dehydrated alcohol and chloroform, and also sparingly soluble in methanol.

Pharmacology and Pharmacokinetics [McEvoy, 1992] :

Pindolol is a non-selective β-adrenergic blocking agent, inhibit both β_1 and β_2 - adrenergic receptor. It can be rapidly absorbed from GI tract. Reported bioavailibilty ranges from 50-95%. Peak plasmas concentration of 45-167 ng/ml are reached within 1-2 hours after administration of a single 20 mg dose. Approximately 40-60% of pindolol is bound to plasma proteins. In healthy adults the drug has an

apparent volume of distribution (V_d) of 1.2-2.0 L/kg; V_d may be decreased by 50% in ureamic patients. Pindolol is distributed into milk. Pindolol has a plasma half life of 3-4 hours in healthy adults. Approximately 60-65% of pindolol is metabolised in the liver to hydroxylated metabolites which are then excreted in urine as glucuronides and ethereal sulphates.

Use and Administration :

Pindolol is used in management of hypertension and chronic stable angina pectoris that is straight or exercise induced (not resting angina).

- Hypertension : usual initial and maintenance dosage for adult is 5 mg twice daily and 10-30 mg daily given in 2-3 divided dosages respectively.
- Chronic stable angina pectoris : 15-40 mg daily given in 3-4 divided dosages.

Glutaraldehyde
[John, 1990]

Synonyms : Glutaral, glutaric dialdehyde, pentaedial.

Empirical Formula : $C_5H_8O_2$

Molecular Weight : 100.12

Physicochemical Properties :

Glutaraldehyde is a colourless liquid with a pungent odour, boils at about 188 °c with decomposition, stable in light, oxidise in air, polymerise on heating. Glutaraldehyde concentrate is a 50% (w/w) solution in water. It is soluble in water and in alcohol.

Usage :

- A disinfectant superior to formaldehyde. It is microbicidal against all micro organism, including spores and viruses.
- It is employed as a tissue fixative for optical and electron microscopy, being bifunctional, glutaral cross-linked protein in tissue and thus limits movement during staining and handling.

Safety [Susan, 1989] :

LD_{50} of 25% solution orally in rats is 2.38 ml/kg; by skin permeation in rabbit is 2.56 ml/kg.