CHAPTER 2

LITERATURE REVIEW

2.1 Sustained Release

The sustained release dosage form has become increasingly important in the present day. They are justified in view of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms.(1, 7, 8)

The advantages of sustained release dosage form are as follows: reduction in dosing frequency; reduction of the fluctuation in circulating drug levels; minimization or complete annihilation of patient compliance problems; avoidance of night time dosing; more uniform effect; and reduction in GI irritation and other dose-related side effects.

The disadvantages of sustained release dosage forms must be considered: difficulty or impossibility of stoppage of pharmacological action drug, when poisoning or intolerance occurs; reproducibility of action affected by the rate of the gastric emptying; little or no efficacy of pharmaceutical dosage form, if the drug is not absorbed by intestinal mucosa; releasing rate depends on pharmaceutical dosage form integrity; large size of pharmaceutical dosage form; low bioavailability in some cases; and more expensive cost than conventional dosage forms

The characteristics that may make a drug unsuitable for sustained release dosing (9) are the followings: short elimination half-life; long elimination half-life; narrow therapeutic index; large doses; poor absorption; active absorption; low or slow solubility; time course of circulating drug levels different to that pharmacological effect; and extensive first-pass clearance.

The sustained-release drug delivery systems could be classified in 2 types, chemical-controlled systems and diffusion-controlled systems. (9, 10)

Bioerodible systems was the first system of **chemical-controlled systems.** In this system, the polymers matrix contains hydrolytically or enzymatically labile bonds and uniformly dissolved or dispersed drug. As the polymers erodes by hydrolysis or enzymatic cleavage, the drug is released to the surrounding environment.

Drug-polymers conjugates is the other kind of **chemical-controlled systems.** This system involves drug molecules chemically bounded to a polymers backbone. The drug will be released through hydrolytic or enzymatic cleavage. The drug-polymers linkage may be covalent, ionic, or through some weaker secondary molecular forces. The polymers backbone may be either biodegradable or non- biodegradable. The drug can be part of the polymeric backbone or attached to the side-chain either directly or through a spacer group. The spacer group is generally selected in such a way that it may be hydrolyzed or degraded enzymatically under specific environmental conditions.

There are two types for the **diffusion-controlled systems.** These systems are the most popular method, and they are easier than the chemically-controlled systems.

Membrane-reservoir systems is the diffusion-controlled polymeric delivery systems that is finding increasing applications in the area of controlled release pharmaceuticals. To achieve optimum therapeutic effects, especially for drugs with short biological half-lives, it is often desirable to have a zero-order drug release. Membrane-reservoir devices, where the drug core is surrounded by a rate-controlling membrane, are often employed for this purpose. The presence of a saturated reservoir in this case is essential to maintain a constant rate of drug release.

The kinetics of drug release from such membrane-reservoir systems generally follow either a solution-diffusion mechanism or an osmotic pumping mechanism. In the solution diffusion mechanism, the drug transport occurs by first dissolving in the membrane at one interface, followed by diffusion down a chemical potential gradient across the membrane, and eventually released from the second interface into the external medium.

Matrix diffusion is the most popular diffusion controlled delivery system because of its low cost and ease of fabrication .(11, 12) Two mechanisms of drug released from

these systems have been reported. (a) Extraction of the medicament by a simple diffusional process through and from an enveloping homogeneous matrix. (b) Leaching of the medicament by the bathing fluid which is able to enter the drug-matrix phase trough pores, cracks, and intergranular spaces. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent. Intragranular diffusion is assumed, in this instance, to be insignificant. The two mechanisms are depicted schematically in Figure 2.1.

For a drug in granular matrices, the release of a solid drug from a granular matrix (Figure 2.1 - right) involves the simultaneous penetration of the surrounding medium, dissolution of drug, and leaching out of the drug through interstitial channels or pores. A granule is, in fact, defined as a porous rather than a homogeneous matrix. The volume and length of the opening in the matrix must be accounted for in the diffusional equation or Higuchi equation. Therefore, porosity (ε) and tortuosity (τ) of the matrix must be considered.

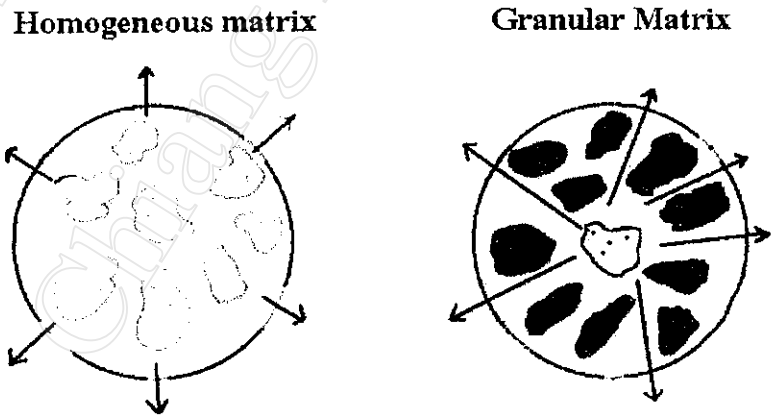

Figure 2.1 : Two methods of drug release from matrix (12)

There are some factors that influence the release rate of drug from matrix, which must be concerned in order to work properly in practice. Therefore, the design of sustained release drug from matrix system must take into consideration these important factors which

are summarized below. The importance of choice of matrix material on drug release in formulation of sustained release products is illustrated by many studies. (13, 14, 15, 16) Carli et al. (15) reported that Eudragit RS and Eudragit RL copolymers had poor surface wettability. However, these polymers were reported to have good liquid transport properties. Drug release was controlled by diffusion through matrix pores, and copolymer containing a higher percentage of hydrophilic group produced the fastest drug release rates. Nakano et al. (16) indicated that the drug release rate was fast from tablets made of low viscosity grade polymer, while the release rate was slow from tablets made of polymers of medium and high viscosity grades. Therefore, the drug release rate can be modified by changing the mixing ratio of two polymers with different viscosity grades depending on the required sustain period.

Beside the type of matrix to be considered, quantitative ratio of drug in matrix is another important factor in drug release rate because it is often necessary to design and obtain the drug delivery system having different drug concentrations for each type of drug and matrix. The study of the effect of amount of sodium salicylate in polyethylene matrix tablets from 5, 10 and 20% showed that the release rate increase is approximately proportional to the initial drug loading. (17)

Solubility of drug is one of the major factors to be considered. It is often found that a matrix which gives the desired release pattern for one drug may not be suitable for other drugs. Desai et al. (17) compared the release of sodium salicylate from polyethylene matrix to the release of caffeine, benzoic acid and benzocaine which have different solubilities of 650, 25, 3.4 and 0.4 mg/ml, respectively. It was shown that the increasing solubility of drug could give a faster release rate.

Matrix additives or formulation additives further modify release rates. Daly et al. (18) described that the addition of surfactants may modify release from hydroxypropyl methylcellulose matrices by binding to the polymer and increasing the viscosity. Lipidus et al. (19) showed that the addition of lactose increases the release rate of chlorpheniramine more than an equivalent amount of calcium phosphate, which can be explained by the

difference in solubility of the diluents and their subsequent effects on the tortuosity factor. As the water-soluble diluent dissolved, it diffuses outward and decreases the tortuosity of the diffusion path of the drug. The tricalcium phosphate did not diffuse outward, but rather became entrapped within the matrix.

It was found that compression force and compression period have no effect on drug release from elastic matrices or hydrogel matrices of which porosity value is steady or not changing. Huber et al. (20) stated that tablet hardness did not show marked differences in release characteristics as evaluated by an in vitro method. Lapidus et al. (19) utilized two different compression forces and observed no significant difference in drug-release patterns from tablets of differing density.

Influence of shape factors on kinetics of drug release from matrix tablets were investigated by several workers. Higuchi (12) was the first to derive an expression describing the release of drug through a unit tablet surface. The basic Higuchi equation may be written as

$$f_t = K_H t^{1/2}$$

where f_t = fraction of drug released at time t

K_H = Higuchi release rate constant from a single planar surface of constant area

Jambhekar et al. (21) derived cubic equations describing the release of drug through surface of a slow- release tablet. For a cylindrical shape, the fraction of drug released from the tablet at time t is given by

$$f_t = (q+2)K_r t^{1/2} - (2q+1)[K_r t^{1/2}]^2 + q[K_r t^{1/2}]^3$$

where K_r = release rate constant

q = ratio of the initial tablet diameter to thickness H_0

The data fitted adequately by the cubic equation when the entire tablet surface was exposed to the dissolution fluid and by the linear equation when only one planar surface was exposed.

Accordingly, tablet formulation can proceed in a systemic manner by utilizing tablet shape to adjust drug release to the desired rate. The release of drug from a cylindrical tablet or biconvex tablet may be predicted from fundamental parameters.

Examples of the influence of shape factors on kinetics of drug release from matrix tablets that have the same standard condition except shapes which are spherical, cylindrical and biconvex shape, has been shown. It was found that the release rate of drug from different shaped tablets were different depending on the shape of tablet.

A major disadvantage of matrix devices is that drug release rate continuously decreases with time. This is a consequence of increased diffusional distance and decreased surface area at the penetrating solvent front. Therefore, to achieve zero order release from matrix devices, it will be necessary to select a geometry that compensates for the increase in diffusional distance with a corresponding increase in surface area for dissolution. Anyhow, a novel approach to achieve zero order drug release recently was more preferably based on non-uniform drug distribution in a matrix instead of constant drug activity in a reservior.

Hydrophilic matrices, the formulation of drugs in gelatinous capsules or in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. (1) In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent, hydrophilic polymers. These system are called swellable controlled-release systems. (22)

2.2 Release kinetics

The pattern of drug delivered by sustained release system can be defined in many types. The important various kinetic models, which have been suggested to described the drug release, included zero-order, first-order and Higuchi square-root time release kinetic model. (23)

Zero-order kinetic model

A zero-order kinetic model is required for most controlled release dosage forms. This kinetic made constant rate of drug releasing which depended on the amount of drug. The zero-order rate can be expressed as the change of the amount of drug release (M) with time (t).

$$dM / dt = K_0$$

This can be integrated in sink condition between time t and initial time, where K_0 is the zero rate constant. The equation was obtained in which

$$M_0 - M_t = K_0 t$$

where M_0 is the initial amount of drug in dosage form

M_t is the amount of drug remaining in dosage form at time t

First-order release kinetic model

The release rate in this model is proportional to the mass of drug in dosage form. The rate is then given as

$$dM / dt = K\ (M_0 - M)$$

After integration of this equation, It gives the following equation

$$M_t = M_0 \, e^{-Kt}$$

where M_t is the amount of drug remaining in dosage form at time t

M_0 is the initial amount of drug in dosage form

K is the first-order rate constant

This equation 6 can simplified by taking in logarithms equation as

$$\ln M_t = \ln M_0 - k\,t$$

First-order pattern can be predict by plotting the logarithm of drug remaining against time. The linear relationship can be obtained if the releasing is follow first-order kinetic.

Higuchi square-root time kinetic model

The release of the medicinal compound from a planar surface of matrix by diffusion through the intergranular openings created by porosity of the matrix was described by the Higuchi square-root equation as following (12, 24)

$$Q = [\,(D\varepsilon / \tau)\,(2A - \varepsilon C_s)\,C_s\,t\,]^{1/2}$$

where Q is the amount of drug released after time t per unit exposed area

D is the diffusitivity of the drug in the permeating fluid

τ is the tortuosity factor of the capillary system of the matrix

A is the total amount of drug present un the matrix per unit volume

C_s is the solubility of the drug in the permeating fluid

ε is the porosity of the matrix

The equation was derived under the assumption as follow : the releasing of drug was maintained in pseudo-steady state, the total amount of drug present per unit volume in the matrix (C_0) substantially was greater than the saturation solubility of drug per unit volume in the matrix (C_s), the release medium was a perfect sink condition at all times, drug particles were much smaller in diameter than the average distance of diffusion in the matrix, the diffusion coefficient remained constant and no interaction occurred between drug and matrix. The plot of the amount of drug released from matrix versus the square root of time was linear relationship. The equation will given as

$$Q = K_H t^{1/2}$$

where K_H is the Higuchi rate constant

The equation may be converted into logarithmic form as

$$\log Q = \log K_H + 1/2 \log t$$

2.3 Pentoxifylline

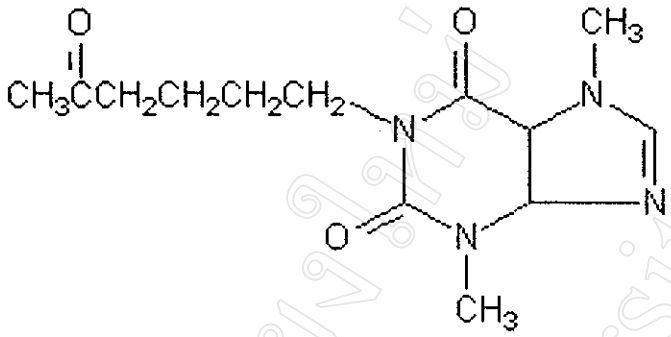

Figure 2.2 : Pentoxifylline structure (3)

Pentoxifylline is a synthetic xanthine derivative. The drug is a trisubstituted xanthine derivative which is structurally related to other xanthine derivatives (e.g., caffeine, theobromine, theophylline). Pentoxifylline is a dimethylxanthine derivative which differs structurally from caffeine or theobromine by a presence of a 5-oxohexyl group rather than a methyl group or hydrogen atom, respectively, at position1. The chemical name of this drug is 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6-dione.

The Molecular formula is $C_{13}H_{18}N_4O_3$ and it has molecular weight 278.31. Pentoxifylline occurs as a white, odorless, crystalline powder with a bitter taste. The melting point of this substance is 105°C. Pentoxifylline absorbs UV at 208 and 273 maximum wavelength (2,3,4,25)

The pentoxifylline solubilities are approximately 77 mg/ml at 25°C, 191 mg/ml at 37°C in water, 63 mg/ml at 22°C in alcohol and 11 g/100 ml in benzene. The drug has pK_a of 0.28

Accepted Indications of pentoxifylline are used for peripheral vasculary disease treatments. Pentoxifylline is indicated to provide symptomatic relief of intermittent claudication associated with chronic occlusive arterial disorders of the limbs.

After administration, pentoxifylline is extensively absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. The usual recommended dosage of pentoxifylline is 400 mg taken orally three times daily.

(2,3,4,25)Plasma half-lives of pentoxifylline and its metabolites are 0.4 to 0.8 hours and 1 to 1.6 hours, respectively. There is no evidence of accumulation or enzyme induction. Excretion is primarily urinary. Less than 4% of the dose is recovered in feces. 98 % of drug was eliminate in 24 hours.

Due to the very soluble of pentoxifylline, there are many studies to retard the release of this drug and maintain drug level effectively in the patients. Copolymers of methylmethacrylate-methacrylic acid were coated on pentoxifylline pellets to retard the release.(26) Eudragit® were prepared to combine with pentoxifylline as rectal gel to control the release if drug and tested both in vitro and in vivo studies.(26) Behenic acid and palmitic acid were used as dry-coated wax matrix for pentoxifylline tablets to produce the programmable drug release. (5, 27, 28, 29, 30) Water soluble polymers such as hydroxy ethylcellulose (HEC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (sCMC) were used in matrix of soluble drug for controlled release dosage forms. (7)

2.4 Soluble Polymer

Sustained-release or controlled devices are designed to limit or slow the rate of drug release. (31) There are many polymers which could be used in this system to delay drug release. The rate, extent and duration of drug release from a controlled release device depend on a number of design variables and upon the physicochemical properties of drug. The most important are the properties of the polymer to be combined with the drug. In general, the polymer is selected from one of several classes: (1) nonbiodegradable hydrophobic polymers (e.g., polyethylene vinylacetate, polydimethylsiloxane, polyether urethane, cellulose acetate, polyethylene and polyvinyl chloride), (2) hydrogels (e.g., polyhydroxyethyl methylacrylate, cross-linked polyvinyl alcohol, cross-linked polyvinyl pyrrolidone, polyacrylamide and some dextran), (3) soluble polymers (e.g., polyethylene glycol, uncrosslinked polyvinyl alcohol, uncrosslinked polyvinyl pyrrolidone, hydroxypropyl methylcellulose) and (4) biodegradable polymers (e.g., polylactic acid, polyglycolic acid and polycaprolactone)

Drugs are combined with these polymers in a variety of methods to produce controlled-release devices. The method of fabrication affects both duration and mechanism of release.

Water soluble polymers employed in modified-release pharmaceutical systems usually swell and form gels before they ultimately dissolve. There are also those that exhibit a pH-dependent-solubility behavior. The gel layer created by polymer hydration facilitates the release of water soluble drugs by a diffusion mechanism. Drugs with poor aqueous solubilities are released by an erosion mechanism corresponding to slow dissolution of the polymer.

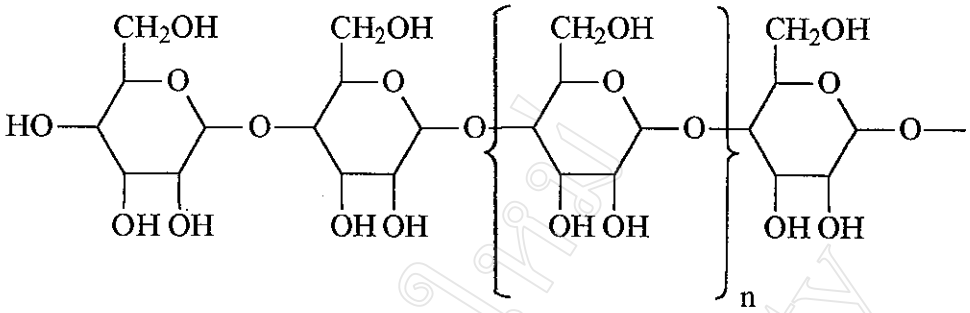

Figure 2.3 : Molecular structure of cellulose

Cellulose is a polysaccharide consisting of glucose repeat units. There are three hydroxy groups per sugar and all can be substituted. Pure-cellulose is insoluble because of its high crystallinity. However, the OH groups can be substituted to obtain various cellulose derivatives that are soluble in water due to decrease in crystallinity. The degree of substitution is defined as the average number of OH groups that have been substituted. Cellulose esters are prepared by esterification of cellulose using the proper acid and acid anhydride. Most cellulose esters are insoluble in water but are soluble in organic solvents. Some of the cellulose esters employed in pharmaceutical dosage forms are: cellulose acetates , cellulose acetate butyrate, cellulose acetate phthalate. Cellulose acetate phthalate is water soluble at the high pH-employed in enteric coatings. Cellulose acetates are semipermeable and relatively high water fluxes are possible through cellulose acetates films. They are hence used as membrane material for oral osmotic pumps. Cellulose triacetate membranes supported in micro porous polymers have also been used in controlled drug delivery. Ethyl cellulose has been extensively used in matrix tablets and also as an insoluble coating to moderate the release of drugs. Aqueous ethyl cellulose dispersions are available for coating tablets and drug containing-multiparticullates. The permeability of ethyl cellulose coating is done by adjusting ethyl cellulose and methyl cellulose or hydroxypropylmethyl cellulose content. Depending on their degree of polymerization and molecular weight some cellulose ethers dissolve in water or form gels, e.g. methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose and

carboxymethyl cellulose. The mechanism of release from these matrices depends on the aqueous solubility of the drug and the hydrophilicity of the polymer.

2.5 Hydroxyethyl cellulose

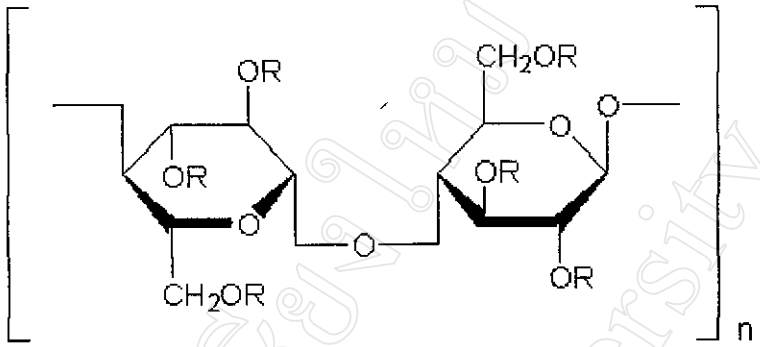

Figure 2.4 : Hydroxyethyl cellulose (R is H or [$-CH_2CH_2O-]_mH$)

Hydroxyethyl cellulose was described as a partially substituted poly(hydroxyethyl) ether of cellulose (32). It is available in several grades, varying in viscosity and degree of substitution, and some grades are modified to improve their dispersion in water. The grades are distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2 % w/v solution measured at 20 °C. Hydroxyethyl cellulose is soluble in either hot or cold water and it forms clear, smooth and uniform solutions. It is practically insoluble in acetone, ethanol, ether, toluene and most organic solvents. In some polar organic solvents, such as the glycols, hydroxyethyl cellulose either swells or is partially soluble.

Hydroxyethyl cellulose occurs as light tan or cream to white-colored, odorless and tasteless. It is a hygroscopic powder, sensitive to moisture. Hydroxyethyl cellulose is nonionic, water soluble polymer widely used in pharmaceutical formulations.

Hydroxyethyl cellulose in commercial grades such as Cellosize® contain less than 5% w/w of water. However, hydroxyethyl cellulose is hygroscopic, the amount of water absorbed depending upon the initial moisture content and the relative humidity of the surrounding air.

The Cellosize® type has the particle size distribution less than 177 μm because 100 per cent of them pass trough a US #80 standard sieves and it has the density about 0.35-0.61 g/cm^3. Cellosize® is manufactured in several regular viscosity grades and types as shown

in table 2.1. Hydroxyethyl cellulose grades differ principally in their aqueous solution viscosities which range from 2-20000 mPa s for a 2 % w/v aqueous solution. Two types of Cellosize are produced, a WP-type, which is a normal dissolving material, and QP-type, which is a rapid dispersing material.

Table 2.1 : Approximate Viscosities of Various Grades of Aqueous Cellosize Hydroxyethyl Cellulose (Amerchol Corp) Solutions at 25 °C

Type	Grade	Concentration	Viscosity (mPa s)	
		(%w/v)	Low	High
WP	02	5	7-14	14-20
WP & QP	09	5	60-100	100-140
	3	5	220-285	285-350
	40	2	70-110	110-150
	300	2	250-325	325-400
	4400	2	4200-4700	4700-5200
QP	10000	2	5700	6500
	15000	2	15000-18000	18000-21000
	30000	1	950-1230	1230-1500
	52000	1	1500-1800	1800-2100
	100M	1	2500	3000

Hydroxy ethylcellulose (HEC) was used as a composition of matrices for controlled release of drug. The mechanism of drug release from HEC matrices were studied.(33, 34, 35, 36)

2.6 Hydroxypropyl methylcellulose

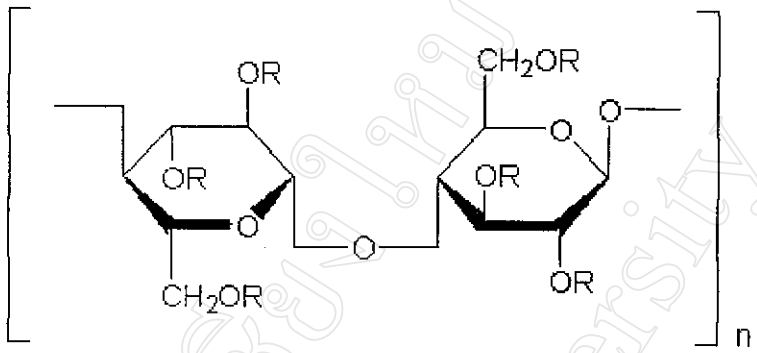

Figure 2.5 : Hydroxypropyl methylcellulose (R is H, CH_3 or [$CH_3CH(OH)C H_2$ -])

Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.(32) It was described as partly O-methylated and O-(2-hydroxypropylated) cellulose. Its chemical name is 2-hydroxypropyl methyl ether cellulose. Hydroxypropyl methylcellulose is available in several grades which vary in viscosity and extent of substitution. Grades are distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20 °C. Molecular weight is approximately 10000-1500000.

Hydroxypropyl methylcellulose appears as a odorless and tasteless, white or creamy-white colored fibrous or granular powder. It is soluble in cold water and forms a viscous colloidal solution. It is practically insoluble in chloroform, ethanol 95% and ether, but soluble in mixtures of ethanol and dichloromethane, and mixtures of methanol and dichloromethane. Certain grades of hydroxypropyl methylcellulose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propa-2-ol, and other organic solvents.

In oral products, hydroxypropyl methylcellulose is primarily used as a tablet binder, in film-coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix. Depending upon the viscosity grade, concentrations between 2-10% w/w are used as film-forming

solutions to film-coat tablets. Lower viscosity grades are used in aqueous film- coating solutions while higher viscosity grades are used with organic solvents. Hydroxypropyl methylcellulose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. In comparison with methylcellulose, hydroxypropyl methylcellulose produces solutions of greater clarity, with fewer undispersed fibres present, and is therefore preferred in formulations for ophthalmic use. Concentrations of between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions. Hydroxypropyl methylcellulose is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hydroxypropyl methylcellulose is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Hydroxypropyl methylcellulose are used as excipients in sustained release tablets. (37) The mechanisms by which sustained release is achieved in matrix tablets depends on many variables. The hydroxypropyl methylcellulose, which is present throughout the tablet, partially hydrates on the outer tablet to form a skin as a pseudo gel, controlling the rate of tablet erosion, the overall dissolution rate and the consequent drug availability. The matrix system functions after ingestion with the initial wetting and formation of a gel-like layer. Grade of hydroxypropyl methylcellulose used depends on the required rate of hydration and dissolution of the remainder of the tablet. The hydroxypropyl methylcellulose must, however, hydrate and form a gel layer quickly enough to prevent the tablet core becoming wet and dissolving. Once a protective gel layer is formed two rate mechanisms continue. Firstly the pseudo gel permits additional water to penetrate into the tablet, thus extending the gel layer further into the tablet. Secondly, the outer gel layer begins to fully hydrate and to be dissolved by the gut fluids. A steady balance of erosion and gel layer formation can be achieved, and further tablet wetting and erosion continues until the entire tablet has dissolved. For water soluble drugs the dissolution rate is

controlled by diffusion through the gel layer and drug release resulting from tablet erosion. For water insoluble drugs, the mechanism is dependent strictly on tablet erosion. Rates of release of drug are dependent on the hydration rates, gel strength and polymer concentrations in the matrix of the various grades and particle sizes of polymer. The solubility of the active ingredient and excipients also affects release rate.

The different types of commercial hydroxypropyl methylcellulose (Methocel) is classified by rate of polymer hydration. The hydroxypropyl methylcellulose K type has the fastest rate of hydration follow by E, F and A type, respectively.

Solid dispersions of drug in HPMC retarded the release of several drugs.(38) Proportion of HPMC and excipients were influenced with the release rate of drugs.(39) The reproducibility of HPMC in sustained-release tablet matrix systems was evaluated and the results showed well reproducibility of dosage form.(40, 41)

The very soluble, potassium chloride, combined with HPMC showed a sustained release profile both in vitro and in vivo studied.(42)

2.7 Polyvinyl pyrrolidone

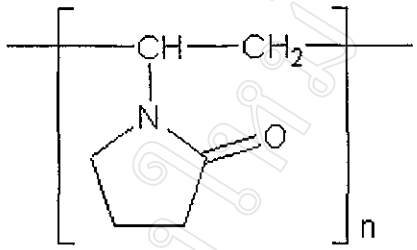

Figure 2.6 : Molecular structure of polyvinyl pyrrolidone (PVP)

The chemical name of polyvinyl pyrrolidone is 1-ethenyl-2-pyrrolidone homopolymer and the other names are povidone or polyvidone. (32) The polyvinyl pyrrolidone is described as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120.

Table 2.2 : Approximate molecular weights of different grades of polyvinyl pyrrolidone

K-value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

Polyvinyl pyrrolidone is a fine, white to creamy-white colored, odorless or almost orderless, hygroscopic powder. Polyvinyl pyrrolidone with K-valves equal to or lower than 30 are manufactured by spray-drying and exist as spheres. Polyvinyl pyrrolidone K90 and higher K-valve polyvinyl pyrrolidone are manufactured by drum drying and exist as plates. Polyvinyl pyrrolidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. It is freely soluble in acids, chloroform, ethanol, ketones, methanol and water. Polyvinyl pyrrolidone is practically insoluble in ether, hydrocarbons and mineral oil. The viscosity of aqueous polyvinyl pyrrolidone solutions depends on both the concentration and molecular weight of the polymer employed.

Polyvinyl pyrrolidone is used in a variety of pharmaceutical formulations. It is primary used in solid dosage forms. In tableting, polyvinyl pyrrolidone solutions are used as binders in wet granulation processes. Polyvinyl pyrrolidone solutions may also be used as coating agents. Polyvinyl pyrrolidone is additionally used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with polyvinyl pyrrolidone. (32)

Polyvinyl pyrrolidone in many types was used to modified the drug profiles of sustained release tablets (HPMC and PVP systems).(43) PVP increased the release rate of drug in formulation. (44)