CHAPTER 1

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery; 1) to target a drug to a specific organ or tissue, and 2) to control the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery system can be a major advance toward solving these two problems (1).

Pharmaceutical products which provide prolonged therapeutic action after administration are variously described as being "sustained release", "timed release", "prolonged release", "long-acting" or by similar terms implying an extended period of action for a given drug in some special dosage forms (2).

The area of sustained release pharmaceutical is now increasingly important in the formulation, manufacture, and marketing of new pharmaceutical products. The desirability, and functionality of these sustained release dosage forms are becoming well accepted by the general public, and are being recognized by regulation agencies.

For sustained release systems, the oral route of administration has by far received the most attention because there is more flexibility in dosage form design for the oral route than parenteral. Patient acceptance of the oral route is rather high. It is also a relatively safe route compared to parenteral routes.

Indomethacin is a non-steroidal anti-inflammatory drug for arthritis (3). It is usually administered orally in conventional capsules form, 1-2 capsules 3-4 times a day (4). The serious irritation and central nervous systems side effects seem to be occurred when using this dosage form and related to the high initial plasma concentration that occurs after ingestion (5). High drug concentrations in the GI tract wall, kidneys, blood, and liver may be major contributing factors to the incidence and severity of side effects (6). Oral sustained release dosage form of this drug would be capable to maintain steady plasma level, leads to reduce side effects and also the frequency of administration (7).

Matrix diffusion seems to be a good and easy system in producing oral sustained release dosage forms, especially tablet (1). It can be achieved by using appropriate type and concentration of matrix substances, followed by general manufacturing mainly included granulation and compression.

Of the substances established in Table 1, the selection criteria of polymers for matrix development in Table 2 and also properties (both physical and chemical) of indomethacin (9), celluloses are good candidate substances for the development of indomethacin sustained release tablets. Ease of compression, their ability to accommodate large percentage of drug and negligible of the processing variable on release rates are some of the other reasons for their popularity. Both hydrophilic and hydrophobic celluloses control the release of drug by diffusion process. Gel erosion is also taken into account for hydrophilic polymer. Using either cellulose or both types could achieve the zero order release pattern.

Table 1 : Polymers used in Controlled Release Devices (8).

Natural Polymers

Carboxymethylcellulose	Zein
Celluloseacetate phthalate	Nitrocellulose
Ethylcellulose	Propylhydroxycellulose
Gelatin	Shellac
Gum arabic	Succinylate gelatin
Starch	Waxes, paraffin
Bark	Proteins
Methylcellulose	Kraft lignin
Arabinogalactan	Natural rubber

Synthetic Polymers

Polyvinyl alcohol	Polyvinyllidine chloride
Polyethylene	Polyvinylidene chloride
Polypropylene	Polyacrylate
Polystryrene	Polyacrylonitrile
Polyacrylamide	Chlorinated polyethylene
Polyether	Acetal copolymer
Polyester	Polyurethane
Polyamide	Polyvinylpyrrolidone
Polyurea	Poly (P-xylylene)
Epoxy	Polymethyl methacrylate
Ethyl-vinyl acetatate copolymer	Polyhydroxyethyl methacrylate
Polyvinylacetate	

Synthetic Elastomers

Polybuladiene	Acrylonitrile
Polyisoprene	Nitrile
Neoprene	Butyl rubber
Chloroprene	Polysiloxane
Styrene-butadiene rubber	Hydrin rubber
Silicone rubber	Ethylene-propylene-diene terpolymer

Table 2 : Criteria in Selection Polymers for Matrix Development (8).

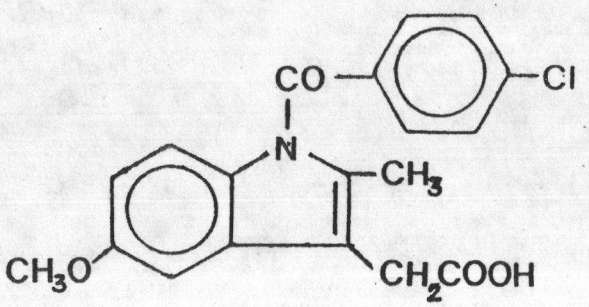
1. Molecular weight, glass-transition temperature, and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent.
2. Polymer functional group should not react chemically with the active agent.
3. The polymer and its degradation product must be nontoxic.
4. The polymer must not decompose during the entire shelf-life.
5. The polymer must be easily manufactured or fabricated into a desired product.
6. The cost of polymer should not be expensive as to make the controlled drug release devices very expensive.
7. It should be readily available.

Purposes of the Study

1. To develop indomethacin sustained release tablet by using different cellulose derivatives as matrix system.
2. To study the influence of concentration of cellulose on the release rate of drug.
3. To study the effect of type of celluloses on the release pattern.
4. To study the effect of compressional pressure on indomethacin release pattern.
5. Using the in-vitro release rate of indomethacin to investigate its release mechanisms.
6. Carry out the pre-formulation data to manufacture indomethacin sustaianed release tablet in large-scale production.

Literature Review

1. Indomethacin



$C_{19}H_{16}ClNO_4$

MW. 357.81

Figure 1: Structural Formula of Indomethacin.

Indomethacin appears as a white to yellow-tan, odourless or almost odourless, crystalline powder with a faintly astringent taste. It is commercially available as free base and sodium trihydrate salt (9). It is practically insoluble in water but soluble in alkali solution with decomposition (9). Its solubility data are represented in Table 3. Indomethacin in both aqueous solution and solid form is light sensitive. Aqueous degradation is first order kinetic and specific base catalysed at 25°C (10).

Indomethacin has pharmacological actions similar to those of other NSAIDs. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. It is rapidly and almost completely absorbed from GI tract in healthy adults. Although the relationship between plasma drug concentrations and anti-inflammatory effect has not been precisely determined, a

Table 3 : Solubility Data of Indomethacin (10,11).

Solvent	Temp (°C)	Solubility
Water	25	0.40 mg/100 ml
Water	RT*	Practically insoluble
Phosphate buffer pH 5.6	25	3 mg/100 ml
Phosphate buffer pH 6.5	25	11 mg/100 ml
Phosphate buffer pH 7.0	25	54 mg/100 ml
Ethylalcohol 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	25 mg/gm

* = Room temperature.

therepeutic range of 0.5-3 μg/ml has been suggested (9). The volume of distribution and time to peak levels were reported to be 0.34-1.57 L/kg and 1-2 hours, respectively with 4.5 - 6 hours half-life (12). Dose of indomethacin is varied, depended on type and state of disease (13). In general the usual initial dose is 25 mg, two to four times a day. In acute gout, 50 mg may be given three or four times daily (4). A dose of 200 mg a day should not be exceeded (13).

Various dosage forms of indomethacin are available, included : (4,11,14).

Capsules	25 and 50 mg
Timed Release Capsules	75 mg
Oral Suspension	10 mg/ml
Opthalmic Suspension	10 mg/ml
Injection	50 mg/amp
Injection (Lyophilized Amp.)	50 mg/2 ml
Suppositories	50 and 100 mg.

Many investigators have reported methods to produce indomethacin sustained release dosage forms (5,7,15-21). Different mechanisms and kinetics have been purposed. Three basic mechanisms or combination of those containing the drug are as follows;

1. Erosion of a matrix (either tablet or bead).
2. Erosion of a coat surrounding the drug product (either tablet or bead).
3. Diffusion of the drug through a semipermeable membrane, gel layer with remain intact.

Materials used to retard the release of indomethacin, type of the formulations and some conclusions are also listed in Table 4.

Table 4 : Various Forms of Indomethacin Sustained Release Reported in the Past Decade (5,7,15,17-19,21).

Form of Formulation	Process of Preparation	Polymer	Proposed Mechanisms
Encapsulated beads	Polymerization and phase separation	2-hydroxyethyl-methacrylate and acrylamide	Zero order upto 40% release
Microspheres	Emulsion and solvent evaporation method	Eudragit RS and Eudragit C (resins)	Zero order upto 80% release
Compressed solid dispersion	Solid dispersion	Ethylcellulose	Diffusion
Micropellets	Rigidization with formalin	Gelatin	First order
Coated granules	Air suspension coating	Ethylcellulose and glycerylmono-stearate	First order
Tablet	Physical mixing and direct compression	HPMC and diluents	Zero order
Suppository	Microencap-sulation by coarcervation	Ethylcellulose	Zero order

Biomedical research of NSAIDs therapy reported that in the case of mild or severe renal pathology, indomethacin in slow release formulation was preferred than other NSAIDs with long half-life (22). It also provided the anti-inflammatory efficacy and promoted patient compliance in the management of osteoarthritis, acute painful shoulder from buritis and/or tenditis, and alkylosing spondylitis (23-25). The pharmacokinetics, efficacy and tolerance of a new formulation of slow release indomethacin tablet were compared with those of a conventional capsule, side effects were less frequent after the slow release tablet than during the capsule period (26). Furthermore, a chronotherapeutic study of the sustained release form showed that in each state of disease an optimal time of administration should be realized to quantitate potential therapeutic gain (27).

The drug may be analyzed by various methods; spectrophotometry (11,28),fluorospectrophotometry (11), polarography (11), tritration (11,28), and mass transport techniques (11,29-31). However, the official method is spectrophotometry. It is the most simple, rapid and also highly accurate method in analysing indomethacin.

2. Hydrophilic Cellulose Derivatives

Methocel premium grades represent a complete range of highly purified, water soluble, cellulose ethers manufactured by the Dow Chemical Company (32). Various types of Methocel and their properties are represented in Tables 5-6.

Table 5 : Various Types of Methocel and Viscosity (32).

Type	Methocel (Premium grades)	Viscosity* (cps)
Methylcellulose, USP	A 15 LV	15
	A 4 C	400
	A 15 C	1,500
	A 4 M	4,000
Hydroxypropylmethylcellulose, USP 2910**	E 5	5
	E 15 LV	15
	E 50	50
	E 4 M	4,000
Hydroxypropylmethylcellulose, USP 2906**	F 50	50
	F 4 M	4,000
Hydroxypropylmethylcellulose, USP 2208**	K 35 LV	35
	K 100 LV	100
	K 4 M	4,000
	K 15 M	15,000
	K 100 M	100,000

* Normal vicosity of 2% aqeous solution at 20°C

** For USP grade hydroxypropylmethylcellulose (HPMC) , the name is followed by a four digit number. The first two digits refer to the approximate content of the methoxy group ($-OCH_3$) in percent. The second two refer to the approximate content of the hydroxypropoxy group($-OCH_2CHOHCH_3$) in percent, calculated on a dried basis (33).

Table 6: Degree of Substitution and Typical Weight Percent Substitution for Methocel Premium Grades (32).

Product	Methoxyl D.S.*	Methoxyl %	Hydroxypropoxyl Molarsubstitution	Hydroxypropoxyl %
Methocel A	1.79-1.83	29.9	-	-
Methocel E	1.86-1.90	29	0.22-0.25	8.5
Methocel F	1.71-1.81	28.4	0.12-0.15	5.0
Methocel K	1.36-1.42	22.1	0.18-0.23	8.1

* D.S. (Degree of Substitution) Weight percent or average number of substituent groups attached to each anhydroglucose unit along the chain.

2.1 Methylcellulose, MC (33)

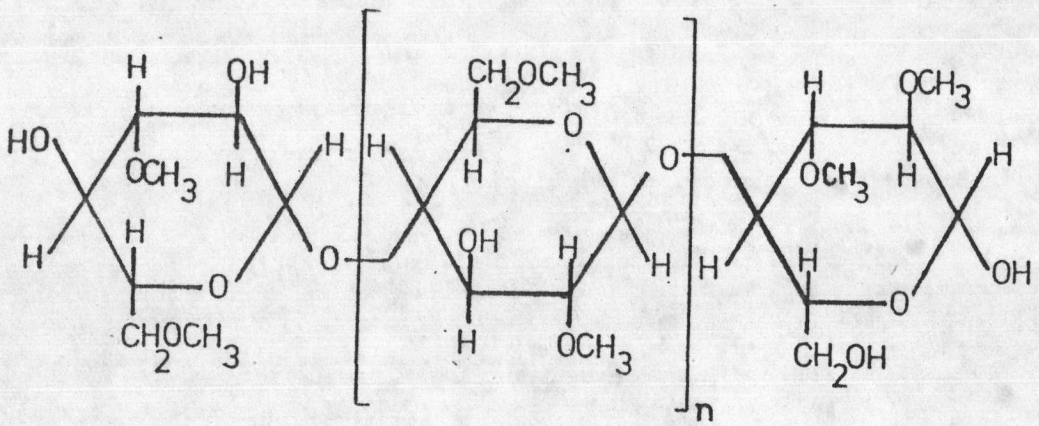


Figure 2 : Structural Formula of MC.

MC is a long-chain substituted cellulose ether of 50-15,000 anhydroglucose unit containing 26-32% methoxyl groups ($-OCH_3$). It is a white to slightly off-white, essentially odourless and tasteless powder or granules. It swells in cold water and produced a clear to opalescent, viscous, colloidal suspension. It is insoluble in hot water, saturated salt solutions, alcohol, ether and chloroform but soluble in glacial acetic acid and in a mixture of alcohol and chloroform. MC is slightly hygroscopic and should be stored in a well-closed container. Irreversible decrease in viscosity is caused by heating and cooling.

It is practically non-toxic,the probable oral lethal dose in human is greater than 15 mg/kg. MC is biological inert and not absorbed from the bowel.

Low or medium viscosity grades are preferred in using as a binder. It may be used in solution or as part of a

powder mix to modify disintegration/dissolution patterns. Usual concentration of 1 - 20% MC may be used as gelling, suspending, thickening, emulsifying and also tablet coating agent. High viscosity grades may act as disintegrants by swelling or contact with disintegration medium, usual concentration is 1-5%. 0.5-1.0% of high viscosity grades are preferred for eyedrops vehicles.

2.2 Hydroxypropylmethylcellulose, HPMC (33)

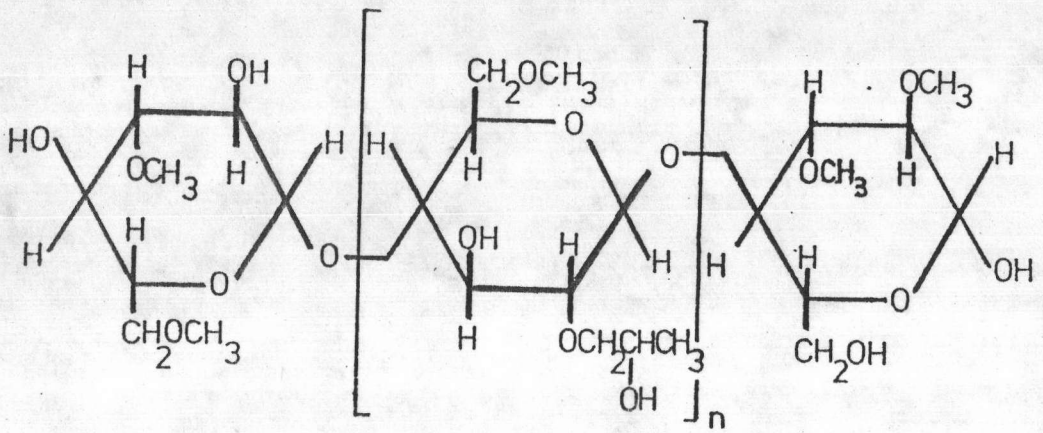


Figure 3 : Structural Formula of HPMC

HPMC is an odourless, tasteless white or creamy-white fibrous or granular powder. It is soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform but soluble in mixture of methylalcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixture of methylene chloride and isopropyl alcohol and other organic solvents. HPMC is very stable in dry conditions. Solutions are stable at pH 3.0-11.0. It is incompatible in the extreme pH conditions and with oxidizing materials. Human and animal feeding studies have shown to be safe. HPMC can be used as a film-former, thickening agent, protective colloid, emulsifier,

suspending agent and stabilizer. High viscosity grades are used to retard the release of water soluble drugs.

H. Lapidus and N.G. Lordi investigated the drug release from compressed hydrophilic matrix of HPMC 15,000 cps (34). Water-soluble drugs (chlorpheniramine maleate, sodium salicylate) and water-insoluble drugs (benzoic acid, benzocaine) were used as model drugs. The dissolution profiles when plotted against square root of time were linear. In addition, the effect of temperature, added diluent and type of polymer on release patterns measured from plane surfaces and whole tablets were also reported.

MC, HPC (hydroxypropylcellulose) and CMC (sodium carboxymethylcellulose) were used as hydrophilic matrix of directly compressed metoprolol tartrate and alprenolol HCl tablets (35). By optimizing the ratio between drug, HPC, MC and CMC, zero order release could be obtained. Reproducibility of this zero order release pattern was confirmed and found that the variations in the values of release rates (slopes) from batch to batch was not significant. Erosion and diffusion were suggested to be the important mechanism of release.

Tablets of chlorpheniramine maleate dispersed in MC showed the release rate which controlled by drug diffusion rather than polymer dissolution (36).

Dissolution studies of indomethacin controlled release tablets showed that for a poorly water soluble drug, not only was the drug to polymer ratio important in controlling the release but both viscosity grade of HPMC and particle size of the drug were to recognize, greater than more water soluble drugs. Furthermore, erosion of the HPMC matrix was suggested to be the only mechanism by which poorly soluble drugs released from HPMC matrix (37).

A formulation containing cetperazine as active drug, Aerosil 200, CMC and HPMC in the ratio of 1:0.7:4.4 gave a linear release for about 12 hours, both in vitro and in vivo studies. The release of drug from this formulation was found to be independent of hardness of tablet and pH of the dissolution medium (38).

HPMC was used to produce hydrophilic matrix of propanolol HCl, aminophylline and promethacin HCl. It was found that a plot of percent drug dissolved against square root of time produced a straight line and the major factor controlling drug release was the drug:HPMC ratio (39,40).

Quibron® is one of the most unique and interesting sustained release products of theophylline as it contains almost no excipients (95% drugs). The patent describes a granulation of anhydrous theophylline with 5% HPMC which is blended with the 0.5% magnesium stearate and compressed (41).

3. **Hydrophobic cellulose derivatives**

3.1 Ethylcellulose (33)

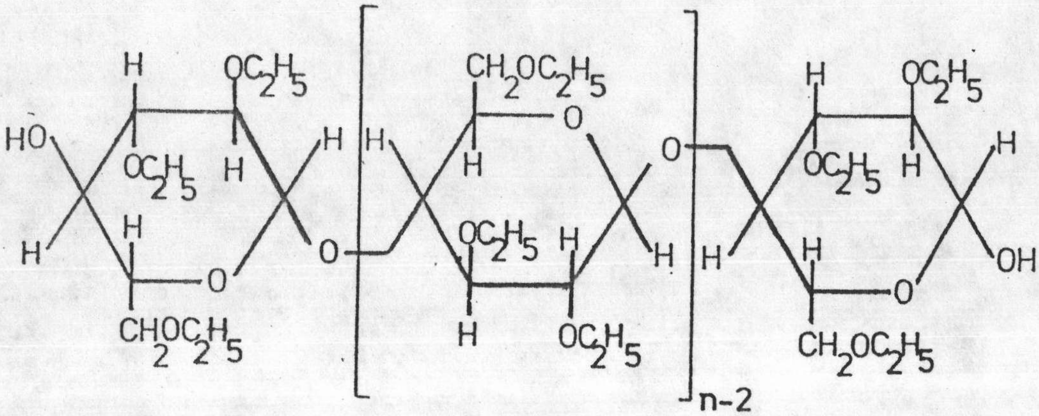


Figure 4: Structural Formula of Ethylcellulose with Complete (54.88%) Ethoxy-substitution.

Ethylcellulose appears as a tasteless, free flowing, white to light tan powder. The various types of ethylcellulose are not affected by water. Ethylcellulose is insoluble in water, glycerin and propylene glycol, but soluble in varying degrees in certain organic solvents, depending upon the ethoxyl content. The solubility data of ethylcellulose is listed in Table 7.

Ethylcellulose is resistant to alkali , both dilute and concentrated, and to salt solutions. It can withstand dilute acids for a limited period of exposure. It is subject to oxidative degradation in the present of sunlight or UV light at elevated temperatures. Ethylcellulose is incompatible with paraffin wax and microcrystalline wax. It is presented to be a non-toxic substance.

Table 7 : Solubility of Ethylcellulose in Various Solvents (33).

Solvent	Solubility (g/ml)	
	I*	II*
Water (25°C)	0.010	< 0.001
Water (37°C)	0.012	< 0.001
Alcohol (25°C)	0.015	0.053
Alcohol (37°C)	0.025	0.066
Propylene glycol (25°C)	0.025	0.025
Propylene glycol (37°C)	0.025	0.025
Hexane (25°C)	< 0.002	< 0.002
Hexane (37°C)	< 0.006	< 0.006

* Suppliers : I Hercules Ltd.
II Dow Chemical Co.

The applications of ethylcellulose in solid dosage form are as follows,

1. Binder in tablets.

Drug blending and wet granulation with a solvent such as alcohol produce a tablet which tends to exhibit poor dissolution. In tablets preparation of water soluble drugs (acetaminophen and theophylline)(42) and sparingly water solube drugs (ibuprofen and indomethacin)(17), tablets prepared by directly compressed from solid dispersion prolonged drug release. In both cases the prolongation of drug release was primarily associated with an increase in amount of ethylcellulose rather than the viscosity grade. Matrix containing metoclopramide as an active drug and ethylcellulose as a matrix polymer showed a linear relationship between the amount of drug dissolved and the square root of time (43).

Microcapsules of theophylline with ethylcellulose were prepared by coacervation technique using silicon dioxide as separant. Tablets were prepared from microcapsules, microcapsules with theophylline fat embedded granules, and microcapsules with HPMC 4000. The release of drug from microcapsules was first order whereas that from all tablet formulations was diffusion controlled (44).

Ethylcellulose used in combination with HPMC and corn starch produced a sustained release granule of nifedipine and a linear relationship upto above 40% release was obtained based on the Higuchi's equation (45).

2. Coating material

Ethylcellulose by itself forms a water insoluble film coating. Caffeine and salicylic acid incorporated into ethylcellulose films exhibited diffusion controlled release.

The release of indomethacin from granules could be retarded by ethylcellulose-glycerylmonostearate film and the kinetics of drug release appeared to be first ordered (18).

Microcapsules of captopril coated with ethylcellulose 9,14,93 and 300 cps could be directly compressed into tablet. The release pattern was achieved first ordered kinetics followed by Higuchi's equation (46).

3.2 Hydroxypropylmethylcellulose phthalate, HPMCP (33).

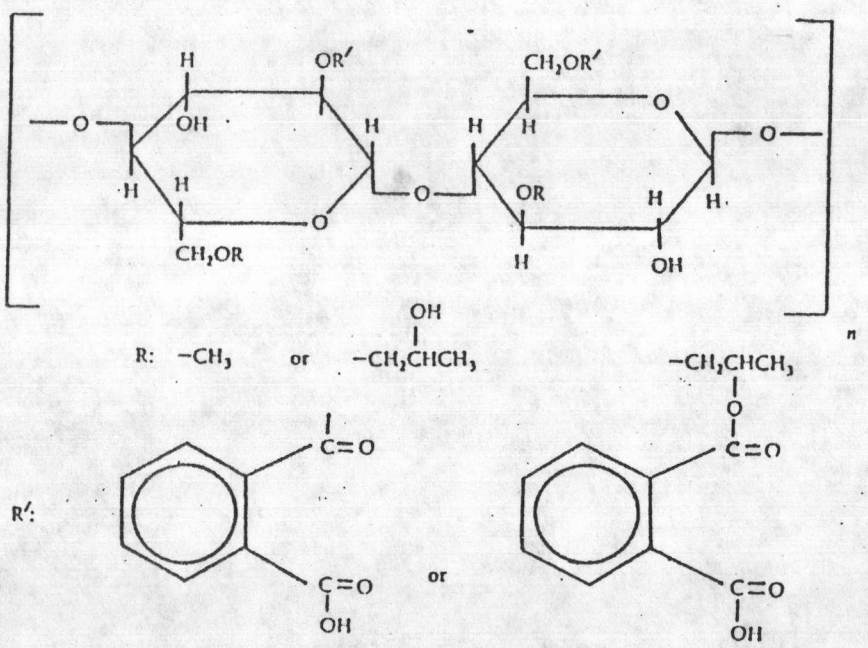


Figure 5 : Structural Formula of HPMCP.
The molecular weight of all commercial grades are in the range of 2,000-100,000.

HPMCP is chemically and physically stable at ambient conditions for at least 3 to 4 years, and at 40°C/75% RH for 2 to 3 months. Specific incompatibilities are unknown. Morethan 90% HPMCP C-14 labelled was excreted unchanged in the feces within 72 hours. There was no evidence of wide-spread radioactivity in the

Table 8 : The Average Molecular Weight of HPMCP (33).

Grade	Average Molecular Weigh
HP-45	20,000
HP-50	20,000
HP-55	20,000
HP-55F	20,000
HP-55S	33,000

The numbers following HP in each grade designation refers to the pH value (X 10) at which the polymer dissolves in aqeous buffer solutions. The designation S in HPMCP HP-55S indicates a higher molecular weight grade, to give films with greater resistance to cracking. The designation F in HPMCP HP-55F indicates a product with smaller paticle size, the mean size being approximately 20 microns.

Table 9 : Degree of Substitution in Various Grade of HPMCP (33).

Substituted groups	Content (%)		
	HP-45	HP-50	HP-55
Methoxy groups	19-24	20-25	18-22
Hydroxypropyl groups	5.5-9.5	5-10	4-9
Carboxybenzoyl groups	18.5-21.0	20-24	27-35

The degree of alkyloxy and carboxybenzoyl substitution determines its polymer properties and in particular the pH at which it dissolves in aqeous media.

blood and body tissues, with the exception of the liver and kidney in which very low levels of radioactivity were detected.

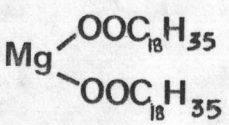
HPMCP can be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug release properties. The release rate is pH-dependent. The composition of HPMCP HP-50 and ethylcellulose was used in preparing nifedipine sustained release granules as aforementioned (45).

4. Talcum [$Mg_6(Si_2O_5)_4(OH)_4$]

Talc appears as a very fine, white to graywish white, impalpable, odourless, crystalline powder. It adheres readily to skin but soft to touch and free from grittiness. It is incompatible with quaternary ammonium compounds.

It is commonly used in solid dosage forms. Application in pharmaceutical formulation or technology is listed in Table 10. Different concentrations of talcs were reported to vary significantly in their effects on the stability of aspirin (33).

5. Magnesium Stearate (33)



$C_{36}H_{70}MgO_4$
MW. 591.3

Figure 6 : Structural Formula of Magnesium Stearate

Magnesium stearate is a fine, white precipitated or milled, impalpable powder of low bulk density. Its odour and taste are slight but characteristic. The powder is unctous, and readily adhere to the skin.

Table 10: Applications in Pharmaceutical Formulation or Technology of Talc (33).

Use	Concentration (%)
Lubricanth or glidant in tablet and capsule manufacture	1-4
Filler for tablet or capsule	5-30
Dusting powder	90-99

Magnesium stearate is described as an inert or nuisance dust classified as non-hazardous by the Department of Transportation Regulations. It is used in pharmaceutical formulation as a tablet and capsule lubricanth, glidant or anti-adherent in the range of 0.25-2.0%.

Due to its hydrophobic nature, magnesium stearate may retard the dissolution of a drug from solid dosage form, and it is therefore advisable to use as low concentration as possible. An increase in the coefficient of variation of mixing and a decrease in dissolution rate was observed when it was blended with the tablet granulation. A large decrease in dissolution rate occurred during the first minute of mixing. The tablet crushing strength also decreased continuously during the first 10 minutes of mixing with magnesium stearate. It may also increase tablet friability. Blending times with magnesium stearate should be carefully controlled.

6. Systems to achieve oral sustained release (1)

6.1 Diffusional Systems

Basic theory of this system is that diffusion entails the movement of drug molecules from a region of higher concentration to one of a lower concentration. The release rate of drug from this system is determined by its diffusion through a polymer. There are two types of diffusional devices :

1) Reservoir Devices

This type occurs as a core of drug surrounded by a polymeric membrane. Common methods used to develop this type include microencapsulation of drug particles and presscoating of whole tablets or particles. If the encapsulating material is selected properly, diffusional will be the controlling process. Some materials used as the membrane barrier coat, alone or

combination, are hardened gelatin, methyl and ethylcellulose, polyhydroxy methacrylate, hydroxypropylcellulose, polyvinylacetate, and various waxes.

2) Matrix Devices

Products of this type are identified as drug dispersed within an insoluble matrix of some sort. The three major types of materials used in the preparation of matrix devices are

2.1 insoluble plastic
- methylacrylate
- methylmethacrylate
- PVC
- PE etc.

2.2 hydrophilic polymers
- methylcellulose
- HPMC
- CMC etc.

2.3 fatty compounds
- carnauba wax
- glyceryltristearate etc.

The most common method of preparation is to mix the drug with the matrix material and then compress the mixture into tablets. The rate of drug release from this type has been described by Higuchi (47,48).

6.2 Systems Utilizing Dissolution

In principle, a drug with a slow dissolution rate will yield an inherently sustained blood level. For highly water soluble drug, this can be done preparing an appropriate salt or derivatives, by coating the drug with a slowly dissolving material, or by incorporating it into a tablet with a slowly dissolving carrier. Two common formulations relying on dissolution to

determine release rate of drug are encapsulated and matrix dissolution systems.

6.3 Osmotic Systems

The key to this system is the ability of the drug solution inside the tablet to attract water by osmosis through the semipermeable coating. The tablet imbibes fluid at a constant rate determined by membrane permeability and by osmotic pressure of the core formulation, the drug solution will be pumped out of the tablet or particle through the orifice in the coat at a controlled rate equal to the volume uptake. Some materials used as the semipermeable membrane include polyvinylalcohol, polyurethane, cellulose acetate, ethylcellulose, and polyvinylchloride.

6.4 Ion Exchange Resins

Ion exchange resins are water-insoluble crosslinked polymers with salt forming groups in repeating positions on the polymer chain. Drug is bounded to the resin by repeated exposure of the resin to the drug in a chromatographic column, or by prolonged contact of the resin with the drug solution. Drug release from the drug-resin complex depends on the ionic environment, such as, pH and electrolyte concentration, within the GI tract, as well as properties of the resin. Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract followed by diffusion of the free drug molecule out of the resin.

6.5 Prodrugs

It is a compound formed by chemical modification of a biologically active compound which will liberate the active compound in vivo by enzymatic or hydrolytic cleavage.

7. Mechanism of drug Release from Matrix System

The mechanism by which sustained release is achieved from matrix tablets is dependent on certain variables (47); solubility of the drug, types of polymer, diluents etc.. The principle mechanism for sustained release is relied on dissolution or diffusion.

7.1 Diffusion mechanism

In this case diffusion rate of drug dispersed in an insoluble matrix is the release rate determining step. Drug release from this system usually be described by Higuchi's equation (48) :

$$Q = DE/T(2A - EC_s)C_s t^{1/2} \quad \text{---------- (1)}$$

Q = the ammount of drug release per unit surface area of tablet

t = time

D = Diffusion coefficient of the drug in the release medium

C_s = the solubility of drug in the medium

E = the porosity of the matrix

T = the tortuosity of the matrix

A = the total amount of drug in the matrix per unit volume

In general, Higuchi's equation is usually derived and used as in equation (2)

$$Q = kt^{1/2} \quad \text{---------- (2)}$$

k = Diffusion rate constant

7.2 Dissolution mechanism

Dissolution rate is controlled by the diffusion of the solute across "stagnant" layer (assumed to exhibit between solid and solution at the solid solution interface)(49,50). When Fick's law of diffusion is applied to this diffusion controlled phenomenon under laminar flow conditions. The dissolution rate is expressed as the following equation :

$$dm/dt = DO(C_s - C_b)/h = kO(C_s - C_b) \quad \text{——————} \quad (3)$$

m = the amount of solid dissolve into solution at time = t

O = the surface area of solid exposed to the dissolution medium

D = Diffusion coefficient of solute in the dissolution medium

h = the thickness of dissolution layer

k = the dissolution rate constant

C_b = Concentration of solute in bulk solution