Chapter 5

Literature Survey...
5.1.1. INTRODUCTION

In the rapidly developing field of medical technology, novel polymeric matrices have been used as Extended Release (ER)/Controlled Release (CR) devices for a variety of drugs. Among these, the water insoluble and swellable, hydrophilic polymers, also called hydrogels, are used as drug delivery devices for the controlled release of active agents\textsuperscript{1-4}. The release of a drug is generally controlled by one or more of the processes: namely, the molecular transport of solvent into the polymer matrix, swelling of the polymer, erosion of the swollen polymer, diffusion of the drug through the swollen polymer alteration of, physico-chemical properties (solubility, viscosity, etc.) of the drug and of the polymers, drug/polymer composition, formulation, administration form, etc. It is rather a difficult task to achieve the constant dissolution rate from the ER devices because the dissolution patterns generally show a diffusion dependent (\textit{Fickian}) release transport. However, the drug release from a hydrophilic swellable polymer depends on both the polymer relaxation rate and the drug diffusion from the barrier. Generally, the surface of the hydrated gel forms a thin barrier for the drug release to take place, which is linearly related to the exposed external surface area of the swollen matrix. The formation of such a barrier layer becomes extremely critical to the success or failure of the dosage form as a ER device\textsuperscript{5}.

In the ER of a drug through the polymer matrices, the ultimate goal is to maintain the therapeutic level of the drug in the blood. The major efforts in this area have been to achieve the zero-order release kinetics through one or many of the approaches namely

(i) Use of rate controlling barriers;
(i) Freezing in a non-uniform concentration profile of the drug across the matrix; 

(ii) Modification of the geometry of the polymeric device. 

(iv) Swelling-controlled delivery systems based on glassy hydrogels; 

(v) Copolymerization with hydrophilic monomers; and 

(vi) Hydrogel design which rupture during the course of drug release.

In recent years, there has been tremendous research activity on the ER of cardiovascular drugs through the cellulose ether based matrices, but the literature on this subject is widely scattered. The concept of poly-pharmacy, i.e., drug combination therapy, is also gaining universal acceptance, even in the treatment of hypertension.

Recent studies have shown that HPMC, a water-soluble polymer, is being frequently used in the formulation of ER dosage forms for the cardiovascular drugs. The mechanism by which HPMC retards drug release includes its ability to form rapidly a gel layer at the matrix periphery exposed to the aqueous fluid. The drug is then released from the matrix by a combination of drug diffusion and erosion of the gel. Drug diffusion through HPMC matrix therefore depends on its water solubility, though the drug release can be modified by changing several formulation factors such as the type of excipients, presence of surfactant and viscosity of HPMC.

The use of HPMC as an ER system has been well documented. Hogan reviewed the use of HPMC in pharmaceuticals. The release of drugs from compressed HPMC matrices was reviewed by Alderman. The release of drugs from HPMC matrices in terms of the mechanisms and technological factors has also been documented. From a perusal of the literature, it is observed that the mechanism proposed for the ER of HPMC matrices involves the liquid penetration into the dry matrix, hydration and swelling of HPMC, diffusion of the dissolved drug
and erosion of the polymer layer. Although extensive research has been carried out
to study the type and nature of HPMC on drug ER properties, a study on the effect of
liquid transport properties into such matrices has been somewhat neglected. *Ranga
Rao et al*²³ published a review on the swelling controlled SR systems. The polymers
covered in this review are: poly(hydroxylalkyl-methacrylates), polyvinyl alcohol,
poly(ethylene oxide), polyethylene glycol and cellulose ethers such as HPMC and
NaCMC.

5.1.2. KINETICS OF SWELLING OF HYDROGELS AND THE EXTENDED
RELEASE PHENOMENON

Hydrogels are the hydrophilic network polymers, which are glassy in the dehydrated
state and swell when come in contact with the aqueous media. In the presence of
water, hydrogels absorb a significant amount of water to form the elastic gels. Since
their introduction 20 years ago, synthetic hydrogels have been increasing in
popularity in various biomedical/pharmaceutical applications ranging from soft
contact lenses to drug delivery systems²⁴-²⁸. In addition to their inertness and good
biocompatibility, their ability to release the entrapped drug in aqueous medium and
the ease of regulating such drug release by controlling water swelling rate and the
crosslinking density made these hydrogels particularly attractive as the ER devices
for pharmaceutical products.

In many oral delivery applications, drug-loaded hydrogels are usually stored in the
dry, glassy state due to stability requirements. The release of water-soluble drugs
from such dehydrated hydrogel matrices generally involves the simultaneous
absorption of water and desorption of the drug via swelling-controlled diffusion
mechanism²⁹,³⁰. As the water penetrates into a glassy hydrogel matrix containing the
dispersed drug, the polymer swells and its glass transition temperature, $T_g$, is
At the same time, the dissolved drug diffuses through the swollen rubbery region into the external releasing medium. Such diffusion and swelling phenomena generally do not follow the *Fickian* mechanism\(^\text{32}\), but the polymer relaxation rate, in addition to drug diffusion is believed to be responsible for the observed non-*Fickian* behavior. If a polymer is thermodynamically compatible with the solvent, then its \( T_c \) is lowered below the experimental temperature so that the hydrogel swells to a rubbery state, which is accompanied by an expansion of volume. *Fickian* diffusion is generally characterized by a square root of time dependence in both the amount of liquid diffused and the penetrating diffusion front position. On the other hand, case-II transport, which is completely governed by the rate of polymer relaxation, exhibits linear time dependence in both the amount diffused and the penetrating swelling front position. However, cast II diffusion due to the balance polymer relaxation and solute diffusion was first introduced by Hopfenberg\(^\text{33}\) using gels swelled in organic media. Later, this phenomenon was confirmed in hydrogels by several researchers\(^\text{33-36}\). In most of the cases however, an intermediate situation, often called the non-*Fickian* or anomalous diffusion, exists whenever the rates of *Fickian* diffusion and polymer relaxation are comparable\(^\text{37-41}\).

Often the following empirical equation has been used\(^\text{42,43}\) to express the fraction of drug released during the initial short-time period:

\[
\frac{M_t}{M_\infty} = Kt^n
\]  

(1)

where, \( M_t \) denotes the diffusant released at time \( t \) and \( M_\infty \) denotes the diffusant at infinite time i.e., after attainment of equilibrium. \( K \) is a constant characteristic of the polymer-drug system and \( n \) is an exponent characteristic of the mode of transport. For \( n = 0.5 \), the drug release follows the well-known *Fickian* diffusion. If \( n \) varies between 0.5 and, then non-*Fickian* (or anomalous) diffusion is observed. The special case of \( n \geq 1 \) gives rise to a case-II transport, which is of particular interest because
The drug release from such devices having constant geometry will follow the zero-order kinetics, a preferred phenomenon in the SR studies\textsuperscript{44-46}.

From the foregoing discussion, it is apparent that there is a strong link between the polymer structure and the drug transport regime. Thus, the penetrant uptake has been exploited as a probe to study the polymer structure. However, the methods traditionally applied to follow the transport kinetics in polymers provide only limited information. Gravimetric techniques such as direct weighing used by Aminabhavi et al\textsuperscript{37, 41, 47, 48} have been most commonly employed. While these methods measure absorption and desorption rates, but they can give only indirect information about the structural changes in polymers and the drug-polymer interactions. However, more detailed information could be obtained using sophisticated techniques such as Electron Spin Resonance (ESR)\textsuperscript{49-51}, optical microscopy\textsuperscript{43, 46, 52} and Rutherford Back-scattering Spectrometry (RBS)\textsuperscript{53}. These techniques are indirect as they require doping or contrasting agents and are often invasive or destructive. RBS, for example, requires the polymer in the form of a film of a few \(\mu\)m thick and the penetrant must contain an element, such as chlorine or iodine, to which RBS is sensitive.

In order to calculate the values of diffusion coefficients, \(D\), of the drug from the polymer matrices, the initial sorption data from a graph of \(M_t/M_\infty\) vs. \(t^{1/2}\) have been used to compute \(D\)\textsuperscript{32}:

\[
D = \frac{\pi}{16} \left(\frac{\theta}{t}\right)^2
\]

\text{(2)}

with \(\theta = \frac{d[M_t / M_\infty]}{d\left(t^{1/2} / h\right)}\). Here, \(h\) is the thickness of the polymer layer and \(\theta\) is the initial slope of the linear portion of the sorption plot. In addition to equation (1) and (2), the Higuchi relation\textsuperscript{54} has also been used to analyze the experimental ER data.
\[ M_t = \left[ 2(A-C_\phi)C_\phi D_t \right]^{1/2} \]  

(3)

where \( M_t \) is the amount of drug released per unit surface area in time \( t \), \( A \) denotes the initial amount of loading, \( C_\phi \) is solubility of the drug in the rubbery matrix, and \( D \) is diffusivity of the active ingredient in the matrix. The derivation of Higuchi equation was based on the pseudo steady-state analysis. As a result, the predictions of release rates are in error by up to 11.3\% in the limit \( A \to C_\phi \).

Paul and McSpadden\(^5\) subsequently offered an exact analysis for the release of an active ingredient that is physically dispersed/dissolved in the polymer matrix. Thus,

\[ M_t = \frac{2C_\phi}{\text{erf}(\eta^*)} \sqrt{\frac{Dt}{\pi}} \]  

(4)

where \( \eta^* = \frac{\xi}{2\sqrt{Dt}} \) and

\[ \sqrt{\pi \eta^* \exp(\eta^*^2) \text{erf}(\eta^*)} = \frac{C_\phi}{A-C_\phi} \]  

(5)

\( \xi \) denotes the thickness of the region within which the concentration of the drug decreasing from \( A \) on the surface of the undissolved solute core within the matrix to zero at the surface of the matrix. When the drug is dissolved in the matrix, i.e., \( A \to C_\phi \), we have

\[ M_t = 2C_\phi \left( \frac{Dt}{\pi} \right)^{1/2} \]  

(6)

If drug is dispersed in the matrix, i.e. \( A >> C_\phi \),

\[ M_t = [2DC_\phi(A-C_\phi)]^{1/2} \]  

(7)

This is the same as Eq. 3 except for the coefficient 0.5 for \( C_\phi \), which is of little significance in the limit \( A >> C_\phi \).

Higuchi\(^5\) also deduced another relation for the percentage of drug released from one side of a layer of ointment in which the drug is initially uniformly dissolved. The percent drug released, \( R \), is then given as
\[ R = \frac{100Q}{hC_0} = 100 \left[ 1 - \frac{8}{\pi^2} \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp \left( -\frac{D(2m+1)^2 \pi^2 t}{4h^2} \right) \right] \]  

(8)

where \( Q \) is the amount of drug released per unit area of application, \( C_0 \) is the initial concentration of the drug in the ointment, \( D \) is the diffusion coefficient of the drug in the ointment, \( t \) is time after application and \( m \) is an integer, which varies from 0 to \( \infty \). Equation (8) is a solution of Fick's law described elsewhere\(^{57,58} \). The main assumptions involved in equation (8) are: (i) only a single type of drug is present in the ointment; (ii) \( D \) must be constant with respect to both time and position in the ointment layer; (iii) only drug diffuses out of the layer, i.e., components of the vehicle cannot diffuse out (or evaporate); and (iv) the drug reaching the receptor side of the ointment layer is removed rapidly (this is the same as the boundary condition i.e., the concentration of drug is zero at receptor-ointment boundary for \( t > 0 \)).

As a criterion to predict whether the drug transport in a polymer is diffusion or relaxation-controlled, Vrentas et al.\(^{69} \) defined the diffusion Deborah number (DEB) as

\[ \text{DEB} = \frac{\lambda_m}{\theta} \]  

(9)

where \( \lambda_m \) is mean relaxation time of the polymer-solvent system and \( \theta \) is a characteristic diffusion time defined by \( h^2/D \). In this case, the sample dimension, as well as composition and temperature is important in determining the transport mechanism. For \( \text{(DEB)} \leq 1 \) or \( \text{(DEB)} \geq 1 \), Fickian diffusion will occur either the rubbery or glassy state, respectively. When \( \text{(DEB)} \approx 1 \), non-Fickian (anomalous) diffusion including case-II transport is anticipated depending upon the relative importance of the Fickian diffusion and the polymer-relaxation processes. An estimate of drug loading was calculated by assuming that the drug is dissolved in all of the gel water and that its concentration in the gel water is the same as in the external solution. Thus,
\[ \% \text{Drug} = \frac{C_s \, V}{W_{dd}} \times 100 \]  

(10)

where \( C_s \) (in mg/ml), \( V \) (in ml) and \( W_{dd} \) (in mg) are the saturation concentration of the drug in water, the volume of water in the swollen gel, and the weight of the dry drug-loaded gel, respectively.

A conservative criterion for the zero-order release mechanism has been proposed by Peppas and Franson\(^2\) in terms of the equilibrium swelling interface number, \( S_w \) defined as:

\[ S_w = \frac{V_{\text{max}} \, h_{\text{max}}}{D} \]  

(11)

where \( V_{\text{max}} \) denotes the maximum velocity of the penetration front and \( h_{\text{max}} \) is the equilibrium thickness of the membrane. Based on the extrapolation of the plot of \( S_w \) vs. the exponent value, \( n \) of equation (1), it can be postulated that zero-order release occurs for \( S_w \ll 1 \). Lee\(^6\) also proposed a mathematical model for the release of a drug from swellable glassy hydrogels in which the drug is uniformly distributed. This model envisages a time dependent diffusion coefficient for the drug to account for the role of molecular relaxation in the diffusion process. Based on the solution of diffusion equation, it was predicted that for a value of the Deborah number for the release greater than unity DEB \( \equiv 10 \), zero-order release would be observed. Thus, the dimensionless parameters DEB and \( S_w \) are important in the conceptual understanding of the various diffusion mechanisms. However, only very limited experimental determination of \( S_w \) has been attempted\(^4\).

5.1.3. CARDIOVASCULAR DRUGS

In general, any drug that affects the heart or blood vessels, directly or indirectly, is a cardiotonic or antihypertensive drug, although this term generally connects only those drugs, which are used for their cardiovascular activity. Many such drugs are
available presently in the market and they display pronounced daily variations in their functions as well as in its hormonal and biochemical regulatory mechanisms. Nearly all groups of antihypertensive drugs show a circadian phase dependency in their effects. The British National Formulary gives an extensive list of these drugs, and some important cardiovascular drugs are listed in Table 5.1. In addition to those given in Table 5.1, there are other drugs such as anticoagulants and protamine, antiplatelet, fibrinolytic, antifibrinolytic and hemostatics, lipid lowering drugs etc.

Table 5.1. Cardiovascular drugs.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascodilators</td>
<td>Diazoxide, Hydralazine hydrochloride, Sodium nitroprusside, Minoxidil</td>
</tr>
<tr>
<td>Centrally acting antihypertensive drugs</td>
<td>Clonidine hydrochloride, Methyldopa</td>
</tr>
<tr>
<td>Adrenergic neurone blocking drugs</td>
<td>Guanethidine monosulfate, Bethanidine sulfate, Debrisoquine</td>
</tr>
<tr>
<td>Alpha-adrenoceptor blocking drugs</td>
<td>Prazosin hydrochloride, Doxazosin, Tetrazosin, Phenoxybenzamine hydrochloride, Indoramin, Phentolamine mesylate</td>
</tr>
<tr>
<td>Angiotension-converting enzyme inhibitors (ACE inhibitors)</td>
<td>Captopril, Cilazapril, Enalapril maleate, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril</td>
</tr>
<tr>
<td>Ganglion-blocking drugs</td>
<td>Trimetaphan camsylate</td>
</tr>
<tr>
<td>Tyrosinehydroxylase inhibitor</td>
<td>Metirosine</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Gliceryl trinitrate, Isosorbide mononitrate, Isosorbide dinitrate, Pentaerythritol tetranitrate</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Amlodipinebesylate, Diltilazem hydrochloride, Felodipine, Isradipine, Lacidipine, Nicardipine hydrochloride, Nifedipine, Nimodipine, Verapamil hydrochloride</td>
</tr>
<tr>
<td>Peripheral vascodilators</td>
<td>Cinnarizine, Nafidrofuryl oxalate, Nicotinic acid derivatives, Oxpentifylline (Pentoxifylline), Thymoxamine, Adrenaline, Dobutamine hydrochloride, Dopamine hydrochloride, Metaraminol, Methoxamine hydrochloride, Noradrenaline acid tartrate, Phenylephrine</td>
</tr>
</tbody>
</table>
The polymer, HPMC have often been used to prepare the ER matrix tablets because the polymer is nontoxic, easy to handle and does not require any special manufacturing technology for their large-scale production. A list of such excipients used commonly in the pharmaceutical industries is given in Table 5.2.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carboxymethylcellulose</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Sodium carboxymethylcellulose</td>
<td>Disintegrant</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Binder, diluent, disintegrant</td>
</tr>
<tr>
<td>Methyl cellulose</td>
<td>Binder</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Binder, coating material</td>
</tr>
<tr>
<td>Hydroxyethylcellulose</td>
<td>Binder, film former</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>Binder, granulating agent</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>In SR formulations, film former</td>
</tr>
<tr>
<td>HPMC phthalate</td>
<td>Binder in the preparation of granules with SR properties</td>
</tr>
</tbody>
</table>

5.1.4. DISCUSSION OF LITERATURE RESULTS

In this section, the published results on HPMC based hydrogel matrices where in HPMC alone or in combination of other polymers used as ER devices are critically evaluated.

5.1.4.i. Propanolol hydrochloride

Propanolol hydrochloride is a non-selective β-blocker antihypertensive drug. It has a short elimination half-life of 3 h, which makes it a suitable candidate to be delivered at a controlled rate. Hydrogel matrix SR tablet formulations containing propanolol hydrochloride were prepared by Ganga et al using HPMC, Na CMC and their
various combinations to evaluate the *in vitro* release kinetics and to study the therapeutic effects in mongrel dogs. A calculated amount of the drug and hydrogels were mixed and compressed into tablets using a Manesty E2 single punch hand operated tablet machine using flat-faced punches at a compression pressure of 16 tons psi. Specifications for the six batches of matrix tablets are given in Table 5.3.

The dissolution results were analyzed by measuring UV absorbance at 290 nm and the release rate constants were calculated for the first- and zero-order release kinetics as well as *Higuchi* equation. These data are also included in Table 5.3. Neat propranolol tablets released nearly 94% of the drug within 2 h. However, the zero-order release kinetics were seen for a selected drug, HPMC, and Na CMC combination. In dogs, the ER tablet showed 50% inhibition of isoprenaline-induced tachycardia after 2 h, which was maintained up to 4 h. At the end of 8 h, 33% inhibition of tachycardia was observed. The neat tablet showed a maximum inhibition of 60% for up to 2 h. By the end of 8 h, the dog's heart rate returned to normal. It was concluded that the hydrogel matrices provide the ER propranolol to produce improved therapeutic effects in dogs.

In a recent study by *Bodea* and *Sorin*⁶⁶, optimization of the release rate of propranolol hydrochloride from mixtures containing HPMC and Na CMC with the drug were designed. These experimental data were evaluated using a quadratic model to generate contour plots so as to assess the change in response surface to establish the relationship between dependent and independent variables. In another study⁶⁷, the effects of hydrophilic polymers on the ER of propanolol hydrochloride as a function of the drugs solubility was investigate. The release rates were analyzed theoretically.
Table 5.3. Batch specification and propranolol hydrochloride content of the tablets².

<table>
<thead>
<tr>
<th>Drug/polymer ratio</th>
<th>Tablet Drug Content (mg)</th>
<th>Rate constants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>k₁</td>
<td>k₀</td>
</tr>
<tr>
<td>Plain tablet</td>
<td>39.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug:HPMC (1:5)</td>
<td>40.00</td>
<td>-0.035</td>
<td>5.20</td>
</tr>
<tr>
<td>Drug:HPMC (1:3.5)</td>
<td>40.00</td>
<td>-0.048</td>
<td>5.97</td>
</tr>
<tr>
<td>Drug:Na CMC (1:4)</td>
<td>40.20</td>
<td>-0.074</td>
<td>7.46</td>
</tr>
<tr>
<td>Drug:Na CMC (1:6)</td>
<td>40.20</td>
<td>-0.055</td>
<td>6.84</td>
</tr>
<tr>
<td>Drug:HPMC:NaCMC (1:2:5)</td>
<td>40.60</td>
<td>-0.067</td>
<td>8.62</td>
</tr>
<tr>
<td>Drug:HPMC:NaCMC (1:0.5:3)</td>
<td>40.00</td>
<td>-0.075</td>
<td>8.75</td>
</tr>
</tbody>
</table>

k₁ - First order dissolution rate constant  
k₀ - Zero-order dissolution rate constant  
kₙ - Higuchi equation dissolution rate constant

Recently, Perez-Marcos et al⁶⁸ examined the potential of combining HPMC (Methocel K 4M) and Carbomer 974 (Carbopol 974) to extend the dissolution rate and to rationalize the role played by the polymers in the ER of propranolol hydrochloride from the matrix tablets. The tablets of 12.7 mm flat-faced were directly compressed at 197 MN/m² using the Manesty F₃ tableting machine. Tablets contained 160 mg of propranolol hydrochloride, 40, 90 or 140 mg of polymer; and 0.75% magnesium stearate as the lubricant. The ratios of polymer used were 0:1, 1:2, 1:1, 3:1 or 1:0 HPMC/Carbopol 974. Dissolution was studied at 100 rpm at 37°C and the results were analyzed at 288 nm using UV-spectrophotometry. The dissolution rates were quantified by treating the data as a function of square root of time. For HPMC/Carbopol ratio, the dissolution rate of propranolol decreased as the amount of total polymer increased (see Table 5.4). Similar dissolution rates were found from the data corresponding to 5-35% of the total drug release from matrices containing the same weight of the polymer, but a burst release occurred from formulations
Containing 1: > 3 HPMC/Carbopol 974, once 35% of the drug had dissolved. Increased quantities of free water in the gels were observed, producing a reduction in viscosity. Hydration studies on Carbopol 974 gels and matrices indicated that two different types of water were present in the scans of melting process. Also, the amount of water imbedded for Carbopol 974 was lower than by HPMC or 1.1 mixture of the polymers. The burst release during dissolution was explained by the formation of a complex between propranolol hydrochloride and Carbopol 974. Dissolution rates in the range of 5-35% were independent of the polymer ratio. The mechanism of drug release was analyzed by using the relation

$$\frac{M_t}{M_\infty} = K(t - t_0)^n$$

(12)

where $K$ is a kinetic rate constant, $t$ is release time, $t_0$ denotes the lag-time prior to dissolution and $n$ is the exponent indicative of the mechanism of release. Values of $n \approx 0.6$ indicated the release to be diffusion-controlled to zero-order release.

Wan et al.\(^6\) examined the kinetics of matrix swelling using the coupled case-I and case-II equations. Matrices were prepared from varying concentrations of one to four different viscosities of HPMC with either propranolol hydrochloride or ibuprofen and were evaluated for swelling by determining the vertical displacement using a dial

<table>
<thead>
<tr>
<th>Ratio of HPMC/Carbopol</th>
<th>Amount of polymer (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td>1:0</td>
<td>7.33</td>
</tr>
<tr>
<td>3:0</td>
<td>6.51</td>
</tr>
<tr>
<td>1:1</td>
<td>6.86</td>
</tr>
<tr>
<td>1:3</td>
<td>6.94</td>
</tr>
<tr>
<td>0:1</td>
<td>6.65</td>
</tr>
</tbody>
</table>
The thickness of the swollen layer formed around the matrix core increased with the viscosity of HPMC gel. The dynamic swelling results of this study were analyzed by using the empirical relation similar to equation (1) i.e., $\log \delta = n \log t + K$, where $\delta = \frac{[h-\delta-h]}{h} \times 100$ is the swelling index calculated from the initial thickness $h$ and the swollen thickness $h_s$ of the membrane, $n$ is exponent describing a Fickian or anomalous swelling mechanism and $K$ is a constant. For the HPMC-propranolol matrices, the swelling mechanism in water was non-Fickian with an increasing amount of HPMC. This indicated the increasing importance of case-II relaxational mechanism to the overall matrix swelling. The coefficients of both case-I and case-II mechanisms increased with increasing concentration of HPMC. However, the effect of HPMC concentration on swelling rates was less marked at higher polymer content, i.e., > 50% of HPMC of high viscosity grade and a saturation state was attained beyond 40% of HPMC content of these matrices.

Wan et al.\textsuperscript{69} also studied the liquid penetration profiles of HPMC/drug matrices using propranolol hydrochloride and ibuprofen as model drugs. In this study, a special apparatus developed earlier\textsuperscript{70} based on the capillary tube method was used to measure the volume of the liquid penetrated into the matrix after time $t$. They fitted the results to the simple Washburn equation\textsuperscript{71}:

$$V = k^m t^n$$ \hspace{1cm} (13)

where $V$ is volumetric uptake by the matrices, $m=0.5$, $t$ is time of release and $k$ is a constant. The liquid uptake kinetics data was analyzed using the relation:

$$V = k_1 t^n$$ \hspace{1cm} (14)

where $m$ is an exponent describing Fickian anomalous uptake. The Washburn equation failed to describe fully the liquid penetration into a matrix system compressed with a swelling polymer. A polynomial equation incorporating Fickian case-I diffusion and case-II relaxational models was found to be more appropriate. An increase in the polymer content shifted the ratio of contributions toward an
increase in case-I and a decrease in case-II contributions to the overall uptake. It has concluded that a polynomial equation incorporating the Fickian case-I diffusion and case-II relaxational models have been used successively to describe the liquid penetration rates into the HPMC matrices.

In view of the importance of chirality in pharmaceutical research\textsuperscript{72, 73}, a study was conducted by Duddu et al\textsuperscript{74}, on the release of propranolol hydrochloride enantiomers from a chiral HPMC formulation using high-performance liquid chromatography (HPLC). The release of propranolol enantiomers from HPMC matrices, although variable, was found to be stereoselective. The S:R enantiomer ratio was 1.07 and this was due to stereoselective diffusion of enantiomers through the chiral environment of the hydrated matrix and/or stereoselective complexation of the enantiomers with the hydrated chiral polymer. On the other hand, the release of enantiomers from the β-cyclodextrin complex was not stereoselective. It was concluded that the release of propranolol enantiomers was from HPMC matrices, but not from β-cyclodextrin inclusion complex is stereoselective. The overall release of the water soluble propranolol hydrochloride from HPMC matrix showed a dependence on (i) diffusion of water, a nonstereoselective process, through the matrix and thereby hydrating it; (ii) diffusion of the enantiomers of the drug through the hydrated chiral matrix, presumably a stereoselective process; and (iii) erosion of the hydrated matrix, a nonstereoselective process. A time plot of the mean ratio (S:R) of the cumulative percentage of (R)- and (S)-propranolol hydrochloride enantiomers released from HPMC matrices showing stereoselectivity in dissolution is presented in Fig. 5.1. The dissolution results of this study have been analyzed using equation (1) to estimate the values of $n$. For (R)-propranolol, $n = 0.767$ while for (S)-propranolol, $n = 0.777$ thereby indicating the release to be controlled by both diffusion of the drug in the hydrated matrix and erosion of the gel matrix itself.
In an effort to investigate the effect of polymer viscosity in a matrix system on drug release, 25 matrices of varying viscosity grades of HPMC (Metolose) at different HPMC concentrations and propranolol hydrochloride were prepared. The drug and HPMC were thoroughly mixed in a mixing bag for 10 min. A weighed amount of the mixture was fed manually into the die of a single punch-tableting machine (Manesty-E2, England) to produce a matrix of 300 mg and a porosity of 0.15 using flat-surface punches of 9.5 mm diameter. The dissolution experiments were carried out at 37°C in 1000 ml distilled water at 100 rpm. Matrices containing 5, 10, 25, 50 and 75% (w/w) of HPMC were prepared. Matrices formed using 5% of HPMC retarded the drug release only marginally. More than 60% of the drug was released within 30 min and 80% was released in 1 h. However, a complete drug release was obtained within 4 h. The drug release data were analyzed using Higuchi equation:

\[
\frac{W_t}{\sqrt{t}} = A \left[ DS \left( 2 \frac{W_0}{v} - S \right) \right]^{1/2}
\]

where \(W_t\) is the amount of drug released in time \(t\), \(A\) is effective diffusive area, \(W_0\) is the initial amount of the drug present in the matrix, \(v\) is effective volume of the hydrated matrix, \(D\) is diffusivity, \(S\) is solubility of the drug in the polymer matrix. These findings suggested that the diffusion layer model suggested by Ford et al. is operative. The results indicated that an increase in viscosity in the high molar mass grades of HPMC promoted water entry, whereas the reverse effect was observed with the lower molar mass grades. In addition, the solution viscosity and gel thickness vary directly with the viscosity grade of HPMC. It was concluded that solution viscosity can be varied with the thickness of HPMC forming the gel layer as well as its viscosity grade.
Fig. 5.1. Mean cumulative % ratio (S/R) vs. the time of propanolol hydrochloride enantiomers released from HPMC matrices in the four experiments showing stereoselectivity in dissolution. The vertical bars show standard deviations for four observations.

5.1.4.ii. Diltiazem hydrochloride

Diltiazem hydrochloride is a calcium channel blocker and is effective in angina. Its ER formulation is also used for treatment of hypertension. Multi-layered hydrophilic matrix tablets have been developed as ER devices for diltiazem hydrochloride with HPMC matrices and their effectiveness, reproducibility, and technological properties have been studied in vitro. The development of a formulation that is able to reproduce an inert film coating performances either to delay the core hydration rate or to prevent drug diffusion from protected surfaces was carried out by two different approaches. The first was based on the use of an insoluble inert polymer (ethyl cellulose) formulated for tableting procedure (barrier E). The second was based on hydrophilic swellable HPMC polymer that was also used in the active core.

- 160 -
formulation. A model formulation containing diltiazem hydrochloride was designed as a hydrophilic, slowly swellable, but almost non-erodible heterogeneous matrix. The active core compositions are given in Table 5.5.

<table>
<thead>
<tr>
<th>Active core</th>
<th>Composition %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem hydrochloride, USP</td>
<td>46.87</td>
</tr>
<tr>
<td>HPMC, USP (100,000 cPs)</td>
<td>36.46</td>
</tr>
<tr>
<td>Mannitol, USP</td>
<td>10.41</td>
</tr>
<tr>
<td>Ethyl cellulose, NF (20 cPs)</td>
<td>4.69</td>
</tr>
<tr>
<td>Magnesium stearate, NF</td>
<td>1.04</td>
</tr>
<tr>
<td>Colloidal silicon dioxide, NF</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Matrix tablets were partially coated on various sides with an inert impermeable film. The coating was applied manually on the tablet base or on the sidewall to have different coating combinations. These combinations are shown schematically in Fig. 5.2. The release patterns of the model formulation uncoated matrix (type-0) and of the four coating designs (types 1, 2, 3 and 4) are presented in Fig. 5.3. A progressive shifting of the release kinetics towards constant drug release was achieved by increasing the extent of surface area coated with the barrier. In order to verify the barrier layer efficiency in the control of drug release profile, batches of double-layer (type 1) and three-layer systems (type 2) were prepared by applying in one or both tablet bases or the film coat F (manually by casting) or 30 mg of the barrier layers C (by compression) as shown in Fig. 5.4. Dissolution experiments were performed on the uncoated devices, on the film-coated devices (1F and 2F), and on the tablets coated by compression with the barriers (1C and 2C). The percent amount of drug released at various time intervals was determined (at 100 rpm in 900 ml distilled water, 37°C) spectrophotometrically at 236 nm and these results are compared in Fig. 5.5. It was found that the presence of coatings reduced the drug release rate proceeding from the 'two-' to the 'three-layer' systems. With the
swellable polymeric barriers (1C and 2C) compared with the film (1F and 2F), this
effect was more pronounced. In case of ‘three-layer’ tablets, the drug release rates
decreased further, approaching zero-order kinetics. The influence of compression
force on the release patterns and on the crushing strengths was also evaluated on
these systems.

![Diagram of four coating patterns]

Fig. 5.2. Schematic drawing of the four coating patterns studied and the uncoated
matrix tablet (Type 0).

![Graph showing fraction released vs. time]

- 162 -
5.3. Release profiles of the uncoated matrix (type 0) and the four-coated patterns examined and exponent n calculated from equation (1).

![Diagram showing two and three layer systems with film and barrier coatings.]

**Fig. 5.4.** Schematic drawing of the film- or barrier-coated systems.

![Graph showing percentage released vs. time for uncoated tablets and coated systems.]

**Fig. 5.5.** Comparison of the percentage of drug release vs. the time of uncoated matrix tablets (O); two-layered-coated systems, 1F (▼) and IC (Δ); and three-layer-coated systems, type 2F(●) & 2C(○).
Swellable matrix systems with impermeable coatings that partially cover the matrix have been prepared and the ER of diltiazem hydrochloride from the plain matrix systems (plain matrix), matrices coated on one face (type 1) and matrices coated on two faces (type 2) was also studied\textsuperscript{76}. The release patterns of the three systems were significantly different. The morphological changes in the three types of systems were observed by photography. Drug release was markedly reduced because of the coating of the matrix bases. The $t_{90}$ obtained with the flow-through apparatus for the three identical matrices without coating, with coating on one face and with coating on two faces were 108, 160 and 234 min, respectively. The kinetics of drug release was evaluated by equation (1). From the values of $n$ obtained, it was found that the kinetics of plain matrix follows the anomalous behavior, which tends to approach a constant release with increasing number of coatings applied. The differences in the release patterns are displayed in Fig. 5.6. The extension of releasing surface during swelling increased more slowly as the area of the coating applied increased. Because coating changed the dimensionality of the matrix swelling, the kinetics of matrix relaxation was also changed. The drug release kinetics followed the kinetics of matrix relaxation, expressed by the external releasing surface increase of the matrix. It was concluded that the application of an impermeable partial coating to a swellable matrix reduces the amount of drug released by reducing the available releasing area of the system.

The release mechanisms of the SR swellable systems prepared by the coating methods suggested by Conte et al\textsuperscript{77} have been further studied using diltiazem hydrochloride as the drug, mannitol FO IX as the filler and HPMC as the swellable polymer. The variations in matrix relaxation and drug diffusion rates were quantified by measuring the surface area exposed during the matrix swelling and the drug release as a function of impermeable coating coverage and location. Compressed discs were coated with an impermeable coating in order to prepare the five types
Fig. 5.6. Instantaneous release rates of the three types measured from the flow through drug release.
illustrated in Fig. 5.2 with the same codes as: type 1, type 2, type 3 and type 4, as given\textsuperscript{76}. The diffusion coefficient of diltiazem hydrochloride in the swollen matrices measured in a standard diffusion cell was found to be $6.2 \times 10^{-6}$ cm\textsuperscript{2}/s. The release data of these five types are presented in Fig. 5.6. The release mechanism in all the types [(fitted by equation (1)] was found to follow the anomalous transport because the values of \( n \) varied between 0.64 to 0.84, thus showing an effect of coating on the release rates of the drug. The results of analysis of equation (1) are given in Table 5.6. The fractional release data of diltiazem hydrochloride for five different coatings are presented in Fig. 5.7 while Fig. 5.8 displays the dependence of diltiazem hydrochloride flux vs. time for the same formulations.

The release results were further correlated by the Peppas and Sahlin model\textsuperscript{78}. Four different types of matrices that were partially coated on various sides were investigated to study the role of swelling behavior on the drug release, taking into account the three-dimensional nature of swelling. The dependence of release kinetics on the matrix surface area was investigated. A new dimensionless swelling area number was defined to evaluate the significance of the relative rate of matrix swelling variation and drug diffusivity. The systems studied were produced by a partial covering of the release area of tablets by an impermeable coating.

Table 5.6. Release data of different systems\textsuperscript{77}.

<table>
<thead>
<tr>
<th>System Type</th>
<th>Kinetic constant $K \times 10^4$/s$^{-n}$</th>
<th>Diffusional exponent $n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type-0</td>
<td>19.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Type-1</td>
<td>14.0</td>
<td>0.64</td>
</tr>
<tr>
<td>Type-2</td>
<td>2.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Type-3</td>
<td>4.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Type-4</td>
<td>2.9</td>
<td>0.76</td>
</tr>
</tbody>
</table>
7.1.3. Some Miscellaneous Cardiovascular Drugs

Verapamil, a calcium channel blocker, is widely used for the treatment of hypertension, supraventricular arrhythmias, and angina pectoris. It is well absorbed after oral administration, but has only about 25% bioavailability and is also classified as a highly variable drug. Novel floatable and zero-order release formulations of verapamil using asymmetric configuration delivery systems containing 20% of HPMC K4M polymer along with other ingredients have been prepared. The amount of verapamil released was measured by spectrophotometry at 230 nm. These results showed that the gastric retention time of the delivery system was prolonged.

Fig. 5.8. Diltiazem hydrochloride flux vs. time for the five coating types prepared.

Improving the bioavailability of verapamil. The mechanism of release of verapamil hydrochloride and dipyridamole from coated swellable minimatrices was studied by comparing the release kinetics of the systems based on the inert or swellable cores.
and by measuring the permeability of the isolated membranes whose composition was identical to that of coating. The drug, polymers and filler mixtures were granulated by wetting with a 5% iso-propanol solution of Eudragit® RS. The mixtures were forced through a 710 μm screen and dried at 35°C. The granules were lubricated with a 0.5% magnesium stearate and tableted in a single punch at a punch pressure of 110 MPa. The core composition of the swellable (formulae a and b) and inert (formulae c and d) systems are given in Table 5.7.

The cores were coated in a rotating pan with 6% w/v of iso-propanol solution of a mixture composed of Eudragit® RS (58%), Eudragit® RL (15%), Eudragit® E (25%), and 2% of castor oil. The dissolution tests were performed in a simulated gastric fluid without enzymes using paddle apparatus (1000 ml, 37 °C, 100 rpm). Verampil HCl and dyphylline were assayed spectrophotometrically at 278 and 273 nm respectively. Polymer film average thicknesses of 100 μm were used for permeability studies using, a Sartorius Apparatus (Model SM 16750). The release data were fitted to equation (12). It was found that for the coated matrices the release kinetics shifts towards a constant release depending on the increase in film thickness. Furthermore, the observed value of \( n = 0.5 \) indicated the transport to be of Fickian type. The ER in this study was ascribed to a physical restriction exerted by the film on core swelling. It was concluded that the film coating was not the rate-limiting step in the drug release from swellable minimatrices.

Table 5.7. Percent core composition

<table>
<thead>
<tr>
<th>Formulae</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verampil HCl</td>
<td>30</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Dyphylline</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Methocel® K 15M</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ethocel®</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Talc</td>
<td>50</td>
<td>50</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
Dipyridamole is an antithrombotic and vasodilator, used in the long-term therapy of chronic angina pectoris with usual dosages of 50 mg three times daily. It is characterized by a dissolution rate, which is very high at acidic pH, but very low at neutral/basic pH and to date, its very few ER formulations are available. In an effort to study the extended release hydrophilic matrix containing dipyridamole by loading the swellable crosslinked NaCMC polymer with dipyridamole as drug and enteric polymer (cellulose acetate phthalate or cellulose acetate trimellitate), Giunchedi et al. devised an oral extended release formulation. The drug release was studied in vitro. Tablet formulations containing hydrophilic matrices were prepared by mixing the granules with HPMC and then tableting the resulting mixture to examine the drug release rate. Here, the dipyridamole SR formulations were prepared by the two methods: (i) three-component modified release granules made up of swellable polymer loaded with dipyridamole and an enteric polymer - the drug/enteric polymer/swellable polymer weight ratio used was 1:2:1 and (ii) extended release formulations made up of hydrophilic matrices, resulting from tableting mixtures of the modified release granules with the gelling HPMC polymer. The compositions of the modified release granules and of the extended release granules are given respectively, in Tables 5.8 and 5.9.

Dissolution experiments were carried out at 37°C and 100 rpm by the following procedures: (i) at constant pH, 1000 ml of gastric simulated fluid (pH 1.2) and 1000 ml of intestinal simulated fluid (pH 7.5), both without enzymes; (ii) with pH variation: 750 ml of 0.1N HCl (pH 1.0) from 0 to 2 h of the test and then addition of 250 ml of 0.2M tribasic sodium phosphate solution to give a pH of 6.8 in a total volume of 1000 ml. The in vitro tests at constant pH were performed on samples of 100 mg of dipyridamole in the powder form, samples of the modified release granules containing the equivalent of 100 mg, and the tablets. The tests with pH variations
were performed only on the tablets. Due to variations in the UV absorbance of the drug in different dissolution media, dipyridamole was determined spectrophotometrically at 283 nm for the tests in gastric medium or in 0.1N HCl and at 294 nm for the tests carried out in intestinal medium or in the final phosphate buffer of pH 6.8. In fact, the major element determining the duration of the drug release was found to depend on composition of the matrices rather than the pH of the dissolution medium.

Table 5.8. Compositions of the modified release granules.

<table>
<thead>
<tr>
<th>Release system</th>
<th>% DIP</th>
<th>% CAT</th>
<th>% CAP</th>
<th>% CM-XL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIPCAT</td>
<td>25</td>
<td>50</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>DIPCAP</td>
<td>25</td>
<td>—</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>DIP - dipyridamole; CAT - cellulose acetate trimellitate; CAP - cellulose acetate phthalate; CM-XL - crosslinked Na CMC.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.9. Composition of the extended release matrices.

<table>
<thead>
<tr>
<th>Matrix (Tablet)</th>
<th>DIPCAT [DIPCAP] (%)</th>
<th>Methocel K4M</th>
<th>Mannitol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (P1)</td>
<td>80</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>T2 (P2)</td>
<td>75</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>T3 (P3)</td>
<td>75</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Thus, the highest content of HPMC (T1 and P1) was characterized by the slowest release rates (at least 24 h of drug release), those containing 5% mannitol (T2 and P2) were slightly faster (~20 h of release), while 10% mannitol in the matrices (T3 and P3) did not give efficient drug release (i.e., about 70% dissolution of the drug only after 3-4 h), with the exception of P3 tablets in the intestinal fluid (about 85% dissolution of the drug after 18 h). Thus, it was concluded that the tests of modified release granules in simulated gastric fluid showed a modulation of the high
dissolution rate of dipyridamole at acidic pH and a very marked improvement in drug
dissolution in the intestinal fluid. Studies of the tablets performed at constant pH and
with pH variation showed that the matrices were capable of providing extended drug
release in acidic medium and that they moderated the dissolution behavior of
dipyridamole tablets under different physiological pH values.

Nifedipine is a calcium channel blocker used in the treatment of hypertensions,
angina, and Raynaud's phenomenon. In addition to different polymeric forms, it can
also exist in the glassy state. Since it is poorly water-soluble (6.2 mg/l at 26.5 °C), its
bioavailability is expected to depend on the dissolution rate. Solvent evaporation and
spraying methods were used to load nifedipine onto the surface of a NaCMC to
achieve an improvement in the dissolution rate. The addition of excipients for further
improvement in dissolution and better surface distribution was discussed. The
dissolution rate was not strictly dependent on drug crystallinity, but was more related
to the water interaction properties of NaCMC. In another study, the bioequivalence
in five human volunteers and the pharmacokinetic parameters of an ER hydrophilic
tables of nifedipine prepared with HPMC as a swellable polymer were investigated.
The results indicated that the hydrophilic tablets were useful as an ER formulation for
the long-term treatment of hypertension.

The significance of factors such as drug solubility, polymer molecular weight, drug
loading, compression force, and hydrodynamic conditions for the SR of nifedipine
and diltiazem hydrochloride with solubilities of <0.001%, <0.1%, <1%, and <50%,
respectively. Changes in the pectin/HPMC ratios, the HPMC molecular weight, and
hydrodynamic conditions had a significant influence on the release rate and release
duration. It was further shown that the hydrodynamic stress and intensity of fluid flow
causd greater attrition at the swollen periphery and were responsible for the
dramatic increase in release rate. This observation confirmed that the mechanism of
drug release from a swellable system is erosion-dependent. The influence of the polymer molecular weight and drug solubility on the release kinetics and the potential of the delivery system were discussed.

A transdermal delivery system (TDS) was developed for the SR of nifedipine. The physicochemical properties influenced percutaneous absorption like solubility and partition coefficient, thereby, confirming the drug’s potential for the development of a SR formulation. However, these studies when performed for permeation through hairless mouse skin from a range of hydrophilic and hydrophobic donor vehicles indicated inadequate penetration. It was concluded that 1% sodium lauryl sulfate and 20% propylene glycol in a Na CMC (3%) gel base failed to increase the drug flux to an acceptable level. These results suggested that the development of a TDS for the chemically unmodified drug in humans is likely to be unsuccessful.

In continuation of their earlier studies by Skoug et al on HPMC-based SR tablets of adinazolam mesylate and alphrazolam, further efforts were made to predict the relative changes in ER rates as a function of the formulation composition for HPMC-based ER tablets of adinazolam mesylate and alphrazolam using a mathematical model based on Higuchi equation. The diffusional release of the soluble drugs from the polymeric matrices and concentration dependence of adinazolam diffusivity in dilute HPMC gels and their solutions were studied. Reasonable correlations were obtained between the experimental drug release rate ratios and the predicted drug release ratios for the ER of adinazolam mesylate and low-dose (0.5 mg) ER alphrazolam tablets. These results were found to be in agreement with the previous findings of the release mechanisms of these formulations.

The release mechanism from tablet matrices prepared with either of the two grades of HPMC polymers and panadiplon (U-78875) as a model drug with poor aqueous
solubility was investigated to define the conditions for selecting the appropriate polymers for ER formulation\(^9\). The viscosity of HPMC polymers, being related to molar mass, showed a great influence on the erosion rate of the matrix tablet. Use of a low viscosity grade HPMC was recommended for drugs that are poorly water-soluble and the release rates of the poorly soluble drugs could be controlled by the rate of tablet erosion. Tablet erosion rate could also be adjusted by the choice of viscosity grade of HPMC. The ability of ER tablet matrix systems containing HPMC to physically withstand the mechanical stresses involved in a reworking procedure was evaluated\(^{15}\). The influence of the nature of the polymer, the rework procedure, powder re-blending levels, and the compression characteristics were also been studied using chlorpheniramine maleate, medizine dihydrochloride, and ascorbic acid.

The effects of polymer hydration rate, polymer concentration, and interactions of drug/polymer/excipients on the stability and release profiles of xanthinol niacinate (xantinolium nicotinate) from hydrophilic matrix tablets have been investigated\(^{17}\) using different HPMC grades (Methocel K4M CR, K15M CR, E4M CR and E10M CR). The mechanical strength, average weight and mass variability, disintegration and dissolution of the drug were determined. The drug release was dependent on the type of polymer forming the matrix and its concentration. The dissolution rate ranged from 18 to 489 min and the total amount of the drug was released within 1 to 21 h. Methocel K4M CR in 20% concentration ensured the drug release by the zero order kinetics within 12 h.

A three-dimension (pH-time-solubility) solution test of SR release captopril tablets has been performed\(^{31}\). The results indicated that the effect of pH (ranging from 1.0 to 7.4) on the solubility of the drug was insignificant and that the solubility rate could be controlled by 20-45%, 45-70%, and 75% at 2.6, and 12 h, respectively. In addition,
5.1.4. CONCLUSIONS

The evolution of SR technology for the treatment of heart ailments is still at a primordial stage; nevertheless, some important practical applications have emerged, especially in the use of HPMC polymers. Further developments in this area seems limited only by the ingenuity shown by polymer chemists, pharmacologists and physicians involved in the SR research. However, those works in this field must astute enough to choose problems where the therapeutic benefits obtained via sustained drug delivery justify the expenditure of time, energy and investment involved in the developmental effort. For a successful development of a useful SR formulation of a cardiovascular drug, thorough knowledge is required not only of the physical and chemical properties of the drug and delivery systems, but also of the pathophysiology of the condition to be treated. This in turn, necessitates a close collaboration and communication between pharmaceutical chemist, polymer scientist, pharmacologist, physician and clinician. In some respects, the drug delivery research is more akin to engineering science than to the traditional biological/physiological research. Further research and developmental work on the SR of antihypertensive drugs through more number of other hydrogel based polymeric membranes has direct implications in this versatile and active field of research.
2. HYDROPHILIC MATRIX EXTENDED RELEASE TABLET

In the last two decades, hydrophilic matrices have become extremely popular in controlling the release of soluble drugs from solid dosage forms. Hydrophilic matrix consists of a mixture of one or more active ingredient(s) with one or more gel forming agent(s). The mixture is usually compressed into a tablet.

Swelling and matrix systems are differently identified by scientist. Lee\textsuperscript{92} called them hydrogel matrices or polymer matrices exhibiting moving boundary. Lippold\textsuperscript{93} adopted the physiochemical definition of hydrocolloid matrices. Ford\textsuperscript{96} proposed hydrophilic matrix tablet while Peppas and Korsmeyer\textsuperscript{95} used swelling controlled release systems.

5.2.1. Polymers

Polymers most widely used in preparation of hydrophilic systems include Hydroxypropylmethyl cellulose (HPMC), Hydropropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly(ethylene oxide), crosslinked homopolymers and copolymers of acrylic acid and sodium carboxymethylcellulose. They are usually supplied in micronized form because small particle size is critical for the rapid formation of gelatinous layer on the tablet surface.

5.2.2. Phenomena of Drug Release

First report on the used of compressed cellulose matrices for oral controlled release dosage form appeared in 1962\textsuperscript{96}. Higuchi\textsuperscript{97} in 1963 was first to present a detailed mathematical analysis of sustained release preparations. Bamba et al\textsuperscript{98} in 1979 further developed the mechanisms of release from matrix systems that swell at the tablet periphery to form a gel which acts as a barrier to drug diffusion. Later, from time to time, various formulation factors influencing the release of drugs from
compressed hydrophilic matrices, viz., viscosity of the polymer\textsuperscript{21}, ratio of polymer(s) to the drug\textsuperscript{21,101}, mixture of polymers\textsuperscript{21,99-100}, compression pressure\textsuperscript{99,104-105}, thickness of the tablet, tablet shape and added diluents\textsuperscript{22}, particle size of the drug\textsuperscript{21,101}, pH of the matrix\textsuperscript{106,107}, entrapped air in the tablets\textsuperscript{52}, surface area of the tablets, influence of the surfactants\textsuperscript{109}, molecular size of the drug\textsuperscript{110}, molecular geometry of the drug\textsuperscript{111} and solubility of the drug have been studies by several workers and have been reviewed. Most of the researchers working in the area of controlled drug delivery believe that, ideally drug must be released from the dosage form at a zero order rate. However, in hydrophilic swellable matrices and erosion matrices, drug release rate declined continuously in a manner that essentially follows the classical square root of the time relationship. Rangaro and Baveja\textsuperscript{111} were first to suggest the use of both an ionic and non-ionic cellulose ethers as a solution to this formulation problem.

HPMC is one of the most widely cellulose ether for producing matrix formulation\textsuperscript{99-100,112-120}. The release of water-soluble drugs through uncross-linked HPMC occurs by a combination of diffusion and dissolution of the matrix itself following hydration\textsuperscript{121}. Diffusion, however may not be significant to release of hydrophobic drugs. In general, drug release from HPMC matrix can be modified by various formulation factors, such as type of polymer, polymer concentration, drug particle size and the presence of additives\textsuperscript{22,101,109,122-123}. Ford et al\textsuperscript{22,101} investigated the influence of these formulation factors on drug release from HPMC matrix tablets. Analyzing a typical example of the release of water-soluble drugs from HPMC matrix tablets, drug release of up to 90% of the total drug fits the Higuchi equation. This indicated that erosion of the HPMC does not contribute to the release of water-soluble drugs\textsuperscript{21,101,127}. Varying the polymer concentration is most efficient in controlling the drug release kinetics. Increasing the polymer concentration reduces the drug release rates.
The addition of a hydrophobic lubricant, such as magnesium stearate, stearic acid or methyl alcohol, did not affect the release of highly water-soluble drug\textsuperscript{21}. Fore \textit{et al} have used different grades of HPMC (K100, the lowest viscosity grade amongst K4M, K15M and K100M) to study the effects of some formulation variables like drug particle size, compaction pressure, absence or presence of magnesium stearate, on the release rate of Promethazine hydrochloride from tablet matrices. Changing the size range of the drug from 45-65\(\mu\)m to 500-700\(\mu\)m produced only 12\% increase in the drug release rate; possibly due to the drug particle size of the drug controlling the release rate from HPMC matrices by altering the matrix tortuosity.

5.2.3. Effect of Compressional Pressure

Variation in the compaction pressure or absence of 0.75\% magnesium stearate did not appear to affect release rate\textsuperscript{21}.

5.2.4. Effect of Surfactants

Daly \textit{et al}\textsuperscript{100}, felt that addition of anionic surfactants like sodium dodecylsulphate (NaDS) may modify release from HPMC matrices by binding to the polymer and increasing the viscosity. More simple molecules, for example insoluble diluents such as tribasic calcium phosphate or water-soluble diluents such as lactose may modify release rates. Lapidus and Lord\textsuperscript{105}, showed that addition of lactose increased the release rate of Chlorpheniramine more than the equivalent amount of calcium phosphate, due to the former reducing the tortuosity of the diffusion pattern of the drug. Feely and Davis\textsuperscript{109} in another set of studies, studied the ability of ionic surfactants to retard the release of drug from HPMC matrices and found that hydrocarbon chain length of the surfactant does not appear to influence the liberation rate of the drug but surfactant is effective when both, polymer and the drug are ionized and of opposite charge.
5.2.5. Effect of Viscosity

Polymer viscosity is known to modify the release rate and so it is of great importance in determining the final release properties of the dosage form. There has been a considerable interest in the relationship between bulk solution viscosity and the rate of dissolution of a wide range of materials. Huber and Christensen, while investigating the release of a tracer (tartrazine) from two HPMC matrix tablets obtained that the higher viscosity grade HPMC released the tracer at a significantly lower rate than a lower viscosity grade. However, Solomon et al. indicated that the viscosity grade of HPMC only affected the lag time for potassium chloride diffusion to become quasi-stationary but did not affect the rate of release. Harwood and Schwartz, (1982) and Nakona et al. (1963) also found the release to be slower from the higher viscosity grades of HPMC. More recently, Cheong et al. have studies the relationship between polymer viscosity and drug release from HPMC polymers comes into contact with water, it absorbs water and swells to form a gel which serves as a binder to drug diffusion. The process of drug release from a HPMC- drug matrix, hydration and gelation of the polymer, dissolution of drug and diffusion of the dissolved drug through the resultant gel layer. Thus larger the amount, higher the viscosity grade of HPMC present in the matrix, more resistant the gel layer is to diffusion and greater the retardation of release of drug.

5.2.6. Method of Fabrication

In the purpose of designing a dosage form, which will utilize the matrix system, tablet matrix system is selected here. To formulate a matrix tablet, several workers have used direct compression^21,100,103,111,113,119,132-135 as a technique, which involves sieving, mixing, blending and compression of drug and polymer along with suitable excipient. Direct compression method is acceptable for the materials having good flow and compressibility and procedure is relatively simple.
Wet granulation is another technique for matrix formation\textsuperscript{136-141}. Granules formed are dried, sieved, lubricate and then compressed to obtain tablets. Wet granulation can be performed on high shear mixer or fluid bed granulators\textsuperscript{142}. Granulation is carried out using aqueous or hydroalcoholic binder.

In the present study, HPMC is used singly and the effect of different viscosity grades of HPMC and other polymer as a matrix material is evaluated. Both wet granulation and direct compression method have been tried.

Much attention today is paid to release mechanism from hydrophilic matrix. Huber et al\textsuperscript{212} suggested that drug release was controlled both by diffusion of drug and attrition of gel layer. The first basic work on release kinetic was that of Lapidus and Lordi\textsuperscript{143}, who demonstrated the applicability of diffusion equation for a semi-infinite medium. Peppas et al\textsuperscript{144-145} worked with swellable matrix model that accounts for volume change and solvent diffusion, solute release governed by solvent penetration velocity and were able to predict thickness of gel layer as function of time, rate of swelling and velocity of eroding front. More recently, Colombo et al\textsuperscript{136} stressed importance of third front, the diffusion front, identified as the interface between the still undissolved drug and the drug in the gel layer. The existence of this layer was first reported by Lee et al\textsuperscript{146-148}. Drug release is function of the dissolved drug layer that separates the diffusion front form the erosion front; the diffusion is present as long as the concentration of the undissolved drug exceeds its solubility in the swollen polymer matrix. Paula Costa et al\textsuperscript{149} have recently published a comprehensive review on modeling and comparisons of dissolution data from solid dosage form. Korsmeyer et al\textsuperscript{150} developed a simple model relating exponentially the drug release to the elapsed time. The model incorporates structural and geometric characteristic of drug release mechanism. This important value can be used to characterize the drug release
mechanism. The exponent value can be used to characterize the drug release mechanism whether it is Fickian or non-Fickian release.

5.3. EVALUATION OF EXTENDED RELEASE PELLETS AND TABLET FORMULATIONS

Although the state of science is such that in vivo testing is essential in the development and evaluation of dosage forms, assessment of the in vitro characteristics and quality of the product is also necessary. For solid controlled release dosage forms, drug release characterization is the most important amongst various in vitro tests because the in vivo absorption is determined by the release of kinetics of the dosage forms. A validated in vitro dissolution test can serve the purposes of

(a) Providing necessary quality and process control;
(b) Determining stability of the relevant release characteristics of the product and
(c) Facilitating certain regulatory determinations and judgments concerning minor formulation changes, change in site of manufacture, etc.

However, the dissolution rate of a specific dosage form is essentially an arbitrary parameter that may vary with the dissolution methodology, such as type of apparatus, medium, agitation, etc. Unless it is demonstrated that the in vitro release behavior reflects the in vivo performance in humans, the data can be of no relevant value in predicting or judging the clinical effectiveness of a drug product. Therefore, development of a dissolution testing method for controlled release formulations should have in vivo considerations. For the in vitro tests to be predictive, it should be discriminative and correlated with the in vivo performance. For the in vitro test to be reliable, the in vitro specifications must be relevant to bioavailability variables and
to the critical manufacturing variables that might be expected during normal manufacturing procedures.

Many issues and challenges related to dissolution testing of controlled dosage forms have been addressed by regulatory authorities \(^{152-154}\) and in a recent review by Khan \(^{155}\). After a prototype formulation with acceptable ranges of process and composition variables has been identified, test variables should be studied, which include variations in pH, effect of surfactants, agitation, ionic strength, etc. The key elements during the dissolution evaluation include

(a) Reproducibility of the method;
(b) Maintenance of sink conditions;
(c) Dissolution profile with a narrow limit on 1 hour specification to assure lack of dosage dumping; and
(d) At least 75% of drug release at the last sampling to assure to complete release.

Out of the seven reported USP dissolution methods and tests conditions (Table 5.10) recommended for determination of drug release from oral extended release dosage forms as follows.

1. USP Apparatus I (Basket method): preferred for tablets.
2. USP Apparatus II (Paddle method): preferred for tablets.
3. USP Apparatus III (Bio-Dis dissolution method, or modified disintegration): useful for bead type dosage forms.
4. USP Apparatus IV (Flow through cell method): for insoluble drugs.

It should be pointed out that none of the existing in vitro method can perfectly mimic the in vivo situation given the nature of the g.i.t. and factor that affects its activity, and various mechanisms employed to achieve controlled release. In vivo drug absorption from dosage forms is known to be dependent on many factors other than dissolution,
such as transit time; permeability; solubility; luminal contents; metabolism and chemical stability in the g.i.t. Nevertheless, dissolution is an essential and critical step, particularly for controlled release drug products. Even thought it is only one of the process involved in drug absorption. Therefore, the ability to predict in vivo absorption characteristics from dissolution data of a controlled release dosage form has become one of the current emphases in the development of controlled release products. Development of an in vitro/in vivo correlation (IV/IVC) for this purpose has been extensively discussed and explored over the last decade\textsuperscript{156-160}. The existence of workshops research, and publications led to the issuance of guidance on this topic by the FDA in 1997\textsuperscript{156}. The guidance presented a comprehensive perspective on the methods of developing and validating an IV/IVC and its applications in setting dissolution specifications and using in vitro tests as a surrogate for an in vivo bioequivalence study in certain regulatory submissions.

Tablets are evaluated using various physicochemical parameter tests including their size, shape, color, odor, weight variation, thickness, hardness, friability, content uniformity assay\textsuperscript{161-163}.

Table 5.10. Test conditions commonly used in in vitro dissolution testing for controlled release dosage forms.

<table>
<thead>
<tr>
<th>Media</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Buffers over the full range of physiological pH (1-1.5, 4-4.5, 6-6.5, 7-7.5 for topographical plot);</td>
<td></td>
</tr>
<tr>
<td>2. simulated gastric/intestinal fluids, i.e., 1 hour acid plus pH 7.4 buffer from 1 hour on;</td>
<td></td>
</tr>
<tr>
<td>3. solutions of gradient pH: 1.2, 2.1, 5.5, 6.5, 6.7, 7.4;</td>
<td></td>
</tr>
<tr>
<td>4. water and</td>
<td></td>
</tr>
<tr>
<td>5. in some cases, surfactant may be used in dissolution media.</td>
<td></td>
</tr>
<tr>
<td>Volume of media</td>
<td>Sufficient to maintain &quot;sink&quot; conditions; the entire dose should dissolve in &lt; 33% of the dissolution media.</td>
</tr>
<tr>
<td>Mixing</td>
<td>Different agitation rates including the standard conditions. Apparatus II may be more useful at higher rpm.</td>
</tr>
<tr>
<td>Sampling Schedule</td>
<td>1. At a minimum, three time points (1-2 hour, t&lt;sub&gt;50&lt;/sub&gt; &amp; t&lt;sub&gt;80&lt;/sub&gt;).</td>
</tr>
<tr>
<td></td>
<td>2. Early sampling times for assurance against premature release:</td>
</tr>
</tbody>
</table>
1, 2, 4 hours and every 2 hour thereafter, until 80% of the drug is released.

<table>
<thead>
<tr>
<th>No. of units to be tested</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>37 ± 0.5 °C</td>
</tr>
</tbody>
</table>

5.4. METOPROLOL TARTRATE

5.4.1 DESCRIPTION

5.4.1.i. Introduction

Metoprolol tartrate is a synthetic, selective β₁-adrenoceptor blocker lacking intrinsic sympathomimetic activity. Its use is approved in Australia, Belgium, Canada, France, Germany, Zokoslovakia, India, Ireland, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, UK, USA approved in India, US, UK, etc.

5.4.1.ii. Chemical Formula, Name, Molecular Weight

\[(C_{15}H_{22}NO_3)_2 \cdot C_4H_6O_6\]  
MW 684.82

![Chemical structure of Metoprolol Tartrate](image-url)
Metoprolol tartrate is a 2:1 salt consisting of a racemic mixture of optical isomers of the base and naturally occurring dextro-tartaric acid. The compound has been described by the following chemical names.

- 2-Propanol, 1-[4-(2-methoxyethyl) phenoxy]-3-[(1-methylamino)-[R-(R*, R*)]-2,3—dihydroxybutanedioate (2:1) (salt)
- (±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol L-(+)-tartrate (2:1) (salt)
- 1-(Isopropylamino)-3-[p-(2-methoxyethyl)-phenoxy]-2-propanol (2:1) dextro-tartrate salt

5.4.1.iii. Appearance, Color, Odor

A white crystalline powder or colorless crystals, virtually odorless.

5.4.2. PHYSICAL PROPERTIES

5.4.2.i. Ultraviolet Absorption Spectrum:

The ultraviolet absorption wavelength ($\lambda_{\text{max}}$) and molar absorptivities ($\epsilon$) of metoprolol tartrate in several solvents are listed in Table 5.11.

| Solvent   | $\lambda_{\text{max}}$ (nm) | $\epsilon \times 10^3$ | Solvent   | $\lambda_{\text{max}}$ (nm) | $\epsilon \times 10^3$
|-----------|-----------------------------|------------------------|-----------|-----------------------------|------------------------
| 0.1 HCl   | 221                         | 19.5                   | Methanol  | 223                         | 21.5                   |
|           | 274                         | 2.83                   |           | 276                         | 3.11                   |
|           | 281                         | 2.31                   |           | 282                         | 2.62                   |
|           | shoulder                    |                        |           |                             |                        |
| Water     | 223                         | 23.4                   | Chloroform| 277                         | 3.36                   |
|           | 274                         | 3.60                   |           | 283                         | 2.86                   |
|           | 280                         | 2.94                   |           |                             |                        |
|           | shoulder                    |                        |           |                             |                        |
| 0.01N NaOH| 223                         | 24.0                   |           |                             |                        |
| 274       | 3.66                        |                        |           |                             |                        |
| 280       | 3.00                        |                        |           |                             |                        |
|           | shoulder                    |                        |           |                             |                        |

- 184 -
4.2.ii. **Infrared Absorption Spectrum**

The infrared (IR) absorption spectral assignments\(^{166}\) for metoprolol tartrate obtained as Nujol mull for major absorption bands are given in Table 5.12.

<table>
<thead>
<tr>
<th>Wave number (cm(^{-1}))</th>
<th>Assignment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3600-2300</td>
<td>NH(_2)^*, -OH, Aliphatic and Aromatic CH</td>
</tr>
<tr>
<td>1580</td>
<td>Carboxylic Acid Salt</td>
</tr>
<tr>
<td>1580, 1515</td>
<td>Aromatic Ring</td>
</tr>
<tr>
<td>1250, 1015</td>
<td>Aromatic Ether</td>
</tr>
<tr>
<td>1180</td>
<td>Isopropyl Group</td>
</tr>
<tr>
<td>1100</td>
<td>Aliphatic Ether, Secondary Alcohol</td>
</tr>
<tr>
<td>820</td>
<td>1,4-Distributed Benzene</td>
</tr>
</tbody>
</table>

**Table 5.12.** Infrared absorption spectral assignment for metoprolol tartrate.

5.4.2.iii. **Melting Range**

Metoprolol tartrate melts over a 1-2 degree range between approximately 120-123\(^\circ\)C\(^{166}\) when determined by USP method.

5.4.2.iv. **Dissociation Constant**

Dissociation constant (pKa) for secondary amine of metoprolol tartrate determined by potentiometric method are in the range of 8.9 to 9.5 (± 0.2) at 8 x 10\(^{-4}\) M in water at 25\(^\circ\)C\(^{166}\). The pKa values for tartaric acid are 2.93 and 4.23 at 25\(^\circ\)C\(^{164}\).

5.4.2.v. **Solubility**

Metoprolol is moderately lipid soluble\(^{167}\). The approximate solubility of metoprolol tartrate in various solvents is given in Table 5.13 at 25\(^\circ\)C\(^{166,168,169}\).
Table 5.13. Solubility of metoprolol tartrate in various solvents at 25 °C.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/ml)</th>
<th>Solvent</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Very soluble</td>
<td>Acetone</td>
<td>Slightly soluble</td>
</tr>
<tr>
<td>Methanol</td>
<td>Freely soluble</td>
<td>Acetonitrile</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Freely soluble</td>
<td>Hexane</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Freely soluble</td>
<td>Ether</td>
<td>Insoluble</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>Soluble</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.4.2.vi. Hygroscopicity\(^{166}\)

Metoprolol tartrate is a hygroscopic at high humidities. The water absorptions isotherm at 25°C indicates that the material rapidly absorbs water at relative humidities greater than 70% and conversely desorbs water as the relative humidity is decreased. No hydrate or change in crystal form has been observed.

5.4.2.vii. Distributive Ratio\(^{166}\)

Distributive ration data, expressed as the organic phase concentration divided by the aqueous phase concentration, are summed up in Table 5.14.

Table 5.14. Metoprolol distribution ratio in difference organic to aqueous phases

<table>
<thead>
<tr>
<th>Organic Phase</th>
<th>Aqueous Phase</th>
<th>Distribution Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Octanol</td>
<td>0.067 M Phosphate Buffer, pH 7.4</td>
<td>0.587 ± 0.007</td>
</tr>
<tr>
<td>1-Octanol</td>
<td>0.067 M Phosphate Buffer, pH 7.4 with 0.9% NaCl</td>
<td>0.665 ± 0.008</td>
</tr>
<tr>
<td>Hexane</td>
<td>0.067 M Phosphate Buffer, pH 7.4</td>
<td>0.0040 ± 0.0005</td>
</tr>
<tr>
<td>Hexane</td>
<td>0.067 M Phosphate Buffer, pH 7.4 with 0.9% NaCl</td>
<td>0.0047 ± 0.0001</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.1 M NaOH</td>
<td>542 ± 16</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.1 M HCl</td>
<td>0.0040 ± 0.0003</td>
</tr>
</tbody>
</table>

5.4.3. STABILITY

5.4.3.i. Solid State Stability\(^{166}\)

Metoprolol tartrate stored at room temperature and at 35°C for 5 years is physically and chemically stable. After storage at 50°C for up to 30 months, no degradation has
been observed – the only change has been that the material became slightly off-white; at lower temperatures and at shorter times intervals at 50°C, it has been completely unchanged in color. Under high humidity, the material is hygroscopic and rapidly absorbs water at relative humidities greater than 70%; however upon drying and reanalysis, the material is found to have retained its chemical and physical integrity.

5.4.3.ii. Solution Stability

No chemical change has been observed for solutions of metoprolol tartrate buffered at pH values of 4, 7 and 9, which have been stored at 60 °C for 10 days.\textsuperscript{166} Drug solutions prepared in 0.1 N HCl, pH 7 phosphate buffer and 0.1 N NaOH, refluxed for 20 hours have shown no evidence of chemical change. Ampoules containing aqueous solution of drug in 1mg/mL and 0.9% NaCl have not shown any evidence of chemical change after storage for 77 months at room temperature and at 50°C.\textsuperscript{166} A 0.4 mg/mL in 5% glucose or 0.9% NaCl was stable for 36 months when stored at 24°C in polyvinyl chloride bags.\textsuperscript{170}

5.4.4. HUMAN PHARMACODYNAMIC STUDIES

5.4.4.i. Effect on Heart Rate and Cardiac Output

Acute or chronic\textsuperscript{172-173} administration of metoprolol to normal subjects or hypertensive patients results in a reduction in heart rate and cardiac output which appears to be related to the dose of the drug.\textsuperscript{174,175,176} Stroke volume is unchanged\textsuperscript{176,175}. A dose related reduction in exercise tachycardia after oral administration of 20, 50 and 100 mg or i.v. administration of 5, 10, 15 and 20 mg was noted by Johnsson.\textsuperscript{177} For identical response, the relation between oral and intravenous doses was about 2.5:1 in comparison of the long-term haemodynamic effects of alprenolol (400 to 800 mg daily), atenolol (100 to 200 mg), timolol (10 to 20 mg) and metoprolol (50 to 300mg),
all drugs produced a comparable reduction in cardiac output but the fall in heart rate
as most pronounced with atenolol and timolol.¹⁷⁸

5.4.4.ii. Effect on Blood Pressure

Single doses of metoprolol given orally or intravenously to normal subjects or
hypertensive patients¹⁷¹,¹⁷⁷-¹⁷⁸ rapidly lowered systolic blood pressure. Although
diastolic pressure was not reduced by a single dose, it was significantly reduced by
150 to 450 daily for 3 to 4 weeks¹⁸⁰,¹⁷².

5.4.4.iii. β-Adrenoceptor Selectivity

5.4.4.iii.a. Effect on Haemodynamic Response to Sympathomimetic
 Agents

Adrenaline causes vasodilatation in muscle by activation of β₂-adrenoceptors. After
a single i.v. dose of propranolol this vasodilating action is lost, and there is
vasoconstriction, an increase in peripheral vascular resistance and a rise in blood
pressure, presumably as a result of α-adrenoceptor stimulation. After a single i.v.
dose of metoprolol, the vasodilating action of adrenaline (0.1 μg/kg/min) is largely
preserved¹⁸¹,¹⁸². The difference in interaction of the two β-adrenoceptor blocking
drugs with adrenalin is interpreted as being the result of a much less pronounced
effect of metoprolol on the adrenergic β₂-adrenoceptor compared with propranolol.
Further evidence of the selectivity of metoprolol is illustrated by its minimal effect on
lung function¹⁸³-¹⁸⁷.
5.4.4.iii.b. Effect of Lung Function and Response to $\beta_2$-Adrenoceptor Stimulants

In asthmatic patients not experiencing an exacerbation of their asthma, single\textsuperscript{183-184} or multiple oral\textsuperscript{185} (50 to 100 mg) or single i. v. doses (0.12 mg/kg; 8 mg) of metoprolol\textsuperscript{186-187} generally caused some reduction in basal FEV\textsubscript{1}\textsuperscript{183,185,186-187} FVC\textsuperscript{187} and specific airways resistance\textsuperscript{184}. This effect is less than that produced by equiactive $\beta$-blocking doses of propranolol. Unlike propranolol however, metoprolol does not significantly inhibit the branchodilatation induced by infused isoprenaline\textsuperscript{183,186}, or inhaled isoprenaline\textsuperscript{185}.

5.4.4.iv. Effect on Plasma Renin Activity

Metoprolol, given continuously or in single doses\textsuperscript{188} reduces plasma renin activity (PRA) in hypertensive and in normal subjects. It may also reduce PRA in hypertensive patients previously treated with pindolol, practolol or oxyrenolol\textsuperscript{189}.

5.4.4.v. Metabolic Effects

5.4.4.v.a. Serum Glucose and Insulin Levels

It is thought that the adrenergic receptor, which modulates insulin secretion, may be a $\beta_2$-receptor\textsuperscript{190}, which might be affected to a lesser degree by a $\beta_1$-adrenoceptor selective blocking drug such as metoprolol than by a non-selective drug such as propranolol. Newman\textsuperscript{191} reported that oral 100 mg metoprolol daily for 2 days delayed the return to normoglycaemia subsequent to insulin induced hypoglycaemia in 11 healthy fasting volunteers, whereas Davidson et al\textsuperscript{192} found a normal response following insulin hypoglycaemia in 5 fasted volunteers given intravenous metoprolol 20 mg followed by an infusion of 6 mg per hour. In 9 hypertensive males treated with metoprolol 150 to 450 mg daily for 4 to 17 weeks\textsuperscript{173} the return to normal blood glucose after insulin was not significant from that during placebo.
4.5. Plasma Lipids and Catecholamines

Although a significant rise in fasting triglycerides during metoprolol therapy has been reported by other investigators \(^{189}\), and some have found no consistent changes \(^{173,193}\).

5.4.5. PHARMACOKINETICS

Metoprolol is completely and rapidly absorbed after oral administration, is rapidly distributed to body tissue \(^{165}\). Plasma levels vary considerably between individuals, due probably to significant hepatic “first-pass elimination” which results in 50% of the administered oral dose reaching the systemic circulation \(^{194}\). Metoprolol is only slightly bound to human serum protein, namely albumin, which is reflected in its large volume of distribution \(^{194}\). The elimination half-life of Metoprolol is about 3 to 4 hours in most patients (range 2.5 to 7.5 h) and is independent of dose and duration of therapy \(^{194}\). The drug undergoes extensive biotransformation, and is excreted principally via the kidneys, only about 3% being excreted as the unchanged drug after oral administration and about 10% after intravenous administration \(^{194}\). The metabolites have no clinically important activity \(^{194}\).

5.4.5.i. Absorption

Studies with oral and intravenous titrated Metoprolol indicated the drug is rapidly and completely absorbed \(^{195,196}\). Absorption appears to take place over a wide part of the intestine as radioactive doses given as ordinary or slow-release tablets of varying dissolution rates were completely recovered in the urine \(^{195}\). The estimated half-life of the absorption process is about 10 to 12 mins \(^{196}\) when metoprolol is administered as a weakly acidic solution. The rate of absorption is influenced by the dissolution rate of the oral preparation; peak plasma levels being attained 1.5 hour after ordinary tablets and 4 hour after slow release tablets. Plasma drug concentrations after i.v.
administration are higher than after an oral dose\textsuperscript{177} and for an identical reduction in exercise heart rate the ratio between oral and i.v. doses is about 2.5\textsuperscript{177}.

About 40% of an oral dose of 5 mg metoprolol is available to the systemic circulation\textsuperscript{195} although bioavailability increases to about 50% as the dose is increases to 100 mg\textsuperscript{177}. Plasma metoprolol levels vary between individuals and reach a peak at about 1.5 hour after oral administration\textsuperscript{171}: \textsuperscript{195}. Ingestion of slow release tablets resulted in lower peak plasma levels of metoprolol, which were attained at about 4 hours. Although the mean area under the plasma concentration-time curve tended to be greater after the ordinary tablet the difference was not statistically significant\textsuperscript{195}.

Direct proportionality between plasma concentration and dose was obtained with intravenous doses above 10 mg and oral doses above 50 mg, but the ratio of the increase with dosage was higher at lower dosage levels. The increased bioavailability with increasing doses suggests the presence of some saturated disposition process of low capacity, especially after oral administration\textsuperscript{177}.

5.4.5.ii. Distribution

Metoprolol reaches concentrations in the erythrocytes ~20% higher than in plasma\textsuperscript{196}. Wood\textsuperscript{197} reported 267 ng/mL metoprolol in the cerebrospinal fluid while the plasma concentration was 341 ng/mL, in the patient receiving 50 mg 3 times daily. Metoprolol has a high volume of distribution of 5.6 L/kg\textsuperscript{196}, which appears to be due mainly to the low degree of binding to human plasma proteins\textsuperscript{198}. Metoprolol is only about 11% bound to human serum protein and appears to be bound solely to serum albumin\textsuperscript{198-199}. In the same study, alpranolol was found to be 85% bound to serum proteins. After oral administration of metoprolol, the plasma concentration curves do not show any clear-cut distribution phase (α-phase), but this phase is
early apparent after an intravenous dose\textsuperscript{196} when the half-life of the distribution phase is about 12 mins.

5.4.5.iii. Metabolism and Excretion

Only \( \sim 3\% \) of an oral dose and \( \sim 10\% \) of an i.v. dose of metoprolol is recovered in the urine as unchanged drug\textsuperscript{196}. Metoprolol is extensively metabolized in the liver. The hydroxy derivative of metoprolol, which accounts for \( \sim 10\% \) of the urinary activity, has some \( \beta \)-adrenoceptor blocking activity, but this appears to be of no clinical significance\textsuperscript{200}. Three main metabolites of metoprolol have been isolated and accounts for 85\% of the total urinary excretion\textsuperscript{201}. The main metabolite of metoprolol is an amino acid formed by O-demethylation and oxidation\textsuperscript{201}.

In healthy subjects, the renal clearance is 109 ml/min for the unchanged drug and 120 ml/min for the metabolites\textsuperscript{196}. This value indicates that glomerular filtration mainly determines the excretion of metoprolol; although the existence of tubular secretion and reabsorption of about equal efficacy cannot be disregarded\textsuperscript{196}.

About 95\% of an oral or intravenous dose of metoprolol is recovered in urine over a period of 72 hours. Whereas the elimination half-life of the total metabolites after oral administration is about 3 hours, that after an intravenous dose is \( \sim 5 \) hours, indicating that the route of administration might influence the metabolic pathways of metoprolol.

The elimination half-life of metoprolol in most patients is \( \sim 3 \) - \( 4 \) hours (range 2.5 to 7.5) and is independent of dose. The elimination half-life (3.7 hours) in elderly patients\textsuperscript{202} is about the same as in younger health volunteers\textsuperscript{177, 185}. However, the interindividual variation in peak plasma levels and elimination half-lives seemed to be more pronounced in the elderly patients. The finding that the elimination half-life is
most the same after single doses or long-term administration indicated that metoprolol does not inhibit or induce its own metabolism\textsuperscript{171}. However, there is some cumulation after a morning dose on long-term therapy being 45% higher than those after a single dose\textsuperscript{171}.

5.4.5.iv. Plasma Concentration and Clinical Effects
A significant relationship between the effect of metoprolol on heart rate and blood pressure during exercise and the logarithm of plasma drug concentration was reported by \textit{Regardh et al}\textsuperscript{95}, but the relationship between plasma concentration and percentage reduction of systolic blood pressure in hypertensive patients was not significant in the study of \textit{Bengtsson et al}\textsuperscript{71}. Similarly, there was no correlation between the plasma concentration and the change in diastolic blood pressure after 4 months of therapy with metoprolol in 24 hypertensive patients’ studies by A direct correlation between plasma metoprolol and reduction in exercise tachycardia in patients with angina pectoris was noted by \textit{Keyrilainen and Uusitalo}\textsuperscript{203}.

5.4.5.v. Old Age
Several studies\textsuperscript{204-206} indicate that age-related physiological changes have negligible effects on the pharamcokinetics of metoprolol.

5.4.5.vi. Pregnancy and breast-feeding
The clearance of metoprolol was increased four fold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant women\textsuperscript{207}. The disposition of metoprolol was investigated in newborn infants of mother treated with metoprolol 50 to 100 mg twice daily\textsuperscript{208}. In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the post-natal period, then declined over the next
15 hours; 5 of these infants had no detectable metoprolol concentrations in the umbilical plasma. No infant demonstrated signs of beta blockade.

5.4.5.7. Renal Impairment

A study of the pharmacokinetics of metoprolol and its renally excreted metabolite α-hydroxymetoprolol in normal and subjects with renal impairment\textsuperscript{209}. Following a single dose of a sustained-release tablet of metoprolol, similar plasma-metoprolol concentrations and values for the area under the concentration/time curve were reported in both groups. Mean plasma concentrations of α-hydroxymetoprolol were increase two to three fold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

5.4.6. THERAPEUTIC TRIALS

Controlled therapeutic trials in patients with angina pectoris or essential hypertension have shown metoprolol to be effective β-adrenoceptor blocking drug in these diseases.

5.4.6.i. Angina Pectoris

In patients with stable uncomplicated angina pectoris, metoprolol has shown to be more effective than placebo in reducing the frequency of anginal attacks and glyceryl trinitrate consumption and in increasing total work before onset of chest pain. In comparisons with propranolol, no significant differences could be detected between the two drugs\textsuperscript{210-211}, whilst in another study reported metoprolol was superior to propranolol\textsuperscript{212}. Thus on the basis of present evidence it appears that metoprolol is an effective prophylactic drug in angina pectoris. Metoprolol has been shown to be superior to placebo in reducing the frequency of anginal attacks and consumption of
An increase in dosage of metoprolol has not necessarily been reflected in an increase in clinical benefit\(^{210}\). It was reported that although doubling the dose of metoprolol from 12 to 240 mg daily was associated with an increase in plasma concentrations in all patients, clinical benefit was not uniform. However, there was a tendency for clinical benefit to increase with the higher dose. An apparent lack of further clinical benefit upon increasing the daily dosage from 60 to 150 mg was reported by Ekelund et al\(^{180}\), but the two placebo periods differed. Three patients experienced fewer anginal attacks during the placebo period between the low and high doses than during the period of active treatment with metoprolol 60 mg daily.

On the basis of total work on a cycle ergometer, 3 patients responded adequately to 60 mg metoprolol daily but not to the 150 mg dose. These findings tend to support the need for individual dosage adjustment in patients with angina pectoris treated with a \(\beta\)-adrenoceptor blocking agent.

5.4.6.ii. Hypertension

5.4.6.ii.a. Comparison with Placebo

Double-blind studies comparing metoprolol with placebo in patients with mild to moderate essential hypertension\(^{193,215-216}\) have shown that metoprolol is superior to placebo under controlled conditions, with statistically significant values.

5.4.6.ii.b. Comparison with other drugs

Metoprolol in fixed\(^{217-219}\) or in individually titrated doses\(^{192}\) has been shown to have antihypertensive activity similar to that of other \(\beta\)-adrenoceptor blocking drugs at equivalent \(\beta\)-blocking dosages, and to a \(\alpha\)-methyldopa\(^{220}\) and hydrochlorothiazine\(^{221}\).
and superior to that of relatively low doses of trichlormethiazide\textsuperscript{219}. No statistically significant difference between the antihypertensive activity of metoprolol 50 or 100 mg 3 times daily and 40 or 80 mg propranolol 3 times daily was found by Bengtsson\textsuperscript{218}. However, Bosman \textit{et al}\textsuperscript{217} reported that 120 mg or 240 mg metoprolol daily was superior to propranolol in maintaining diastolic blood pressure. In comparison of metoprolol and thiazide diuretic, metoprolol 150 or 300 mg has been shown to be comparable with hydrochlorothiazide 50 mg to 100 mg\textsuperscript{221} and superior to tirchlormethiazide 2 to 4 mg daily\textsuperscript{219}.

\textbf{5.4.6.i.c. Metoprolol Combined with Other Drugs}

Metoprolol 150 or 300 mg daily alone or combined with hydrallazine 75 or 150 mg daily was reported by Tuomilehto and Pakarinen\textsuperscript{222} to be effective in reducing sitting diastolic pressure to less than 95 mm Hg (9) or by more than 10\% (6) in 15 or 17 patients who have failed to respond to previous antihypertensive therapy.

\textbf{5.4.6.ii.d. Long-Term Treatment of Hypertension}

Studies in which metoprolol alone in individually titrated doses of up to 450 mg daily has been given for periods of 3 months or more\textsuperscript{172-173,223} have reported a significant fall in blood pressure, which has been maintained throughout the study. In a multicenter trial\textsuperscript{223} involving 76 patients with previously untreated hypertension and 61 patients who were unsatisfactorily controlled by, or intolerant of previous therapy, metoprolol alone (75 mg to 450 mg daily) led to a decrease in diastolic pressure to ≤95 mm Hg in 62\% of the previously untreated group and in 50\% of those previously treated with other drugs. Most of the reduction in blood pressure was evident in the first month of treatment.
Is the Efficacy of Metoprolol in Hypertension Influenced by Frequency of Administration?

Available literature suggests that once daily metoprolol is comparable in efficacy to a twice or thrice daily regimen in which the same total dose is given, reducing blood pressure in patients with mild to moderate hypertension. Bengtsson\textsuperscript{193} reduced the frequency of administration from thrice to twice daily in patients whose blood pressure has already controlled with a thrice-daily regimen. In this study the dosage as well as the frequency of administration was reduced (150 to 100 mg and 300 to 200 mg) but there was little difference in mean blood pressure after the change of the twice-daily regimen. Further data\textsuperscript{224} suggest that in most patients studied, moderately elevated blood pressure can be satisfactorily controlled by once daily administration of metoprolol.

5.4.6.iv. Role Of Metoprolol In Hypertension

Studies with metoprolol indicate that it is as effective in lowering elevated blood pressure as any other β-adrenoceptor blocking drug given in a dose, which produces a similar reduction in exercise-induced increase in heart rate (i.e. at equi-β-adrenoceptor doses).

As metoprolol is a β\textsubscript{1}-selective adrenoceptor-blocking drug, it may cause fewer tendencies to impair peripheral circulation, heart failure and hypertensive reactions in states of catecholamine excess. "Caridoselectivity" lessens the risks of branchospasm, but does not impart any advantage with regard to its antihypertensive action. Metoprolol may be better than non-selective β-adrenoceptor blocking drugs in the treatment of hypertension in patients who also experience Raynaud's phenomenon. β\textsubscript{1}-Adrenoceptor selectivity may possibly also be an advantage in patients with diabetes mellitus, who are receiving insulin or oral hypoglycemic
and those with angina or heart failure controlled by diuretics and digitalis
dose, but conclusive evidence for any advantage of β₁-selective agents in these
conditions has yet to be demonstrated. Metoprolol is not suitable with partial agonist
activity (e.g. patients at risk from A-V conduction impairment), but its lack of partial
agonist activity may be of value in patents with muscle cramps, thyrotoxicosis, or
in those who have a high-dose hypertensive response to pindolol. As with other β-
adrenoceptor blocking drugs, metoprolol is probably best given along with a diuretic
and vasodilator in the more severe cases of hypertension.

5.4.7. SIDE EFFECTS

In therapeutic trials in patients with angina pectoris or hypertension, metoprolol has
been well tolerated and any side effects reported have been moderate or mild and
have generally not interfered with normal daily activities.

In studies that have employed questionnaires with lists of possible side effects, the
frequency of adverse effects has been similar during placebo and metoprolol.

During a 6-month study in patients with angina pectoris, a greater proportion of side-
effects (33%) interfered with normal daily activity during the first month than at 3
months (18%) and 6 months (17%). In this study, tiredness, insomnia, and gastric
upset were the most frequently reported side-effects with metoprolol during long term
treatment, although during subsequent double blind comparison with placebo in the
same patients, the frequency of these and other side-effects on the check list were
similar during both periods. Dizziness and tiredness have been the most frequently
reported side effects in some other studies.
4.8. ADVERSE EFFECTS, TREATMENT AND PRECAUTION

4.8.i. Effects on bones and joints

Five cases of arthralgia associated with the use of metoprolol had been reported to the FDA\textsuperscript{227}. A polymyalgia rheumatic-like syndrome has also been reported in one patient\textsuperscript{228}.

5.4.8.ii. Effects on the gastro-intestinal tract

Reports on retro-peritoneal fibrosis in patients who had been taking metoprolol and nifidipine\textsuperscript{229} and of sclerosing peritonitis in a patient receiving metoprolol\textsuperscript{230}.

5.4.8.iii. Effects on hearing

Loss of hearing in a patient receiving metoprolol appeared to be dose related\textsuperscript{231}, hearing gradually improved over several months once the drug was withdrawn.

5.4.8.iv. Effects on lipid metabolism

Beta-blockers may increase serum triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in patients taking atenolol and metoprolol\textsuperscript{165}.

5.4.8.v. Effects on the lever

Acute hepatitis associated with metoprolol as been reported in a 56-year-old woman\textsuperscript{232}. The hepato-toxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.
1.8.vi. **Carcinogenicity/Tumorigenicity**

A 2-year study in dogs given up to 105 mg/kg per day orally, a 2-year study in rats up to 800 mg/kg per day orally, and a 21 month study in mice given up to 750 mg/kg per day orally found no evidence of carcinogenicity, although the incidence of small benign adenomas of the lung was higher in the treated female mice. A repeat of the 21-month study in mice found no increased incidence of any type of tumor\(^{167}\).

5.4.8.vii. **Mutagenicity**

Metoprolol was not found to be mutagenic in several tests including a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian – microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei\(^{167}\).

5.4.8.viii. **Pregnancy/Reproduction**

No adverse effect on fertility was observed in rats given up to 55.5 times the maximum human daily dose of 450 mg\(^{167}\).

5.4.9. **CONTRAINDICATIONS**

Metoprolol should not be used if there is a risk of congestive heart failure, unless the patient is satisfactorily controlled with a diuretic and/or digitalis, and then given only cautiously; nor should it be used in patients with right ventricular failure secondary to pulmonary hypertension. Significant cardiomegaly of any cause is an indication for considerable caution, as with other β-adrenoceptor blocking agents.

The drug should not be used in patients with sinus bradycardia (rates of less than 60 per minute) unless the patient is being paced, in patients with second or third degree atrioventricular block, in patients with cardiogenic shock.
5.4.10. PRECAUTIONS

- As with other β-adrenoceptor blocking drugs, patients with mild or latent cardiac insufficiency should be given a diuretic and/or adequate dosed of digitalis prior to receiving metoprolol.
- Metoprolol may be administered with caution to patients with bronchitis and a tendency to wheezing, provided that bronchodilator therapy with a β₂-adrenoceptro stimulant drug such as terbutaline, salbutamol etc is administered concomitantly. Although it is best to avoid any β-adrenoceptor blocking drug in asthma, some consider that low doses of metoprolol (up to 100 mg daily) may be given if it is thought essential in asthmatic patients, who must also be receiving optimum regular therapy with β₂-stimulant or institute combined oral and inhalation therapy in these patients.
- Metoprolol therapy must be reported to the anesthetist prior to general anaesthesia for surgery.
- Caution should be observed when treating when patients with unstable diabetes mellitus, as adjustment of the dose of the hypoglycemic agent may be necessary.

5.4.11. DOSAGE

5.4.11.i. Hypertension

Initially, 25 to 50 mg night and morning. This dose may be increased 100 to 200 mg twice daily depending on the response. Higher doses of up to about 400 mg daily may be given if required. There is some evidence that once daily administration may be effective in hypertension. Metoprolol may be given as part of a combined treatment regimen with a diuretic and/or a third drug (such as peripheral vasodilator)
where combined therapy is necessary to control blood pressure. Elderly patients may require lower maintenance dosages of metoprolol because of delayed metabolizing.

5.4.11.ii. Angina Pectoris

The usual dosage in angina pectoris is 50 mg 3 times daily. The 100 mg tablets may be administered thrice or twice daily to meet individual patients' needs, although thrice daily administration of metoprolol is preferable during the initial period of treatment of angina pectoris.

5.4.12. OVERDOSAGE

A case of massive intoxication with metoprolol has been reported in a 19-year-old male who ingested 10,000 mg (160 mg/kg). The plasma level was 12,200 ng/gm plasma and 5,700 mg/Gm at 7 and 10 hours respectively. Initial treatment was gastric lavage, infusion of balanced electrolyte solution and sodium bicarbonate and control of blood pressure with metaraminol. After these measures, the patient was comfortable and without signs of cardiovascular depression 12 hours after admission.

5.4.13. OFFICIAL MONOGRAPHS FOR METOPROLOL

The USP 27 contains following monographs for metoprolol:

- Metoprolol fumarate, pp 1100-1101
- Metoprolol tartrate, pp 1101.
- Metoprolol tartrate Injection, pp 1101-1102.
- Metoprolol tartrate Tablets, pp 1102.
- Metoprolol tartrate - Hydrochlorothiazide tablets, 1102-1104.
In Indian market, there are – brands of product, with – route of administration (oral, injectable) and of which – controlled /extended release products in different strengths, Details are given in Table 5.15\textsuperscript{236-237}.

Table 5.15. Marketed products of Metoprolol and in combinations available in India

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
<th>Packing</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Drug Dosage Form</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaloc</td>
<td>AstraZeneca Pharma</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 25 mg, 50 mg, 100 mg</td>
</tr>
<tr>
<td></td>
<td>India Ltd., Bangalore.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 x 5 mL</td>
<td>Metoprolol Tartrate 1 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Ampoule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopressor</td>
<td>Novartis India Ltd., Mumbai.</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 50 mg, 100 mg</td>
</tr>
<tr>
<td>Metocard</td>
<td>Torrent Pharm. Ltd., Ahmedabad.</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 50 mg, 100 mg</td>
</tr>
<tr>
<td>Mepol</td>
<td>Taurus labs.</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 50 mg</td>
</tr>
<tr>
<td>Metaprox</td>
<td>Cardicare, Bangalore.</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 50 mg</td>
</tr>
<tr>
<td>Metolar</td>
<td>Cipla Ltd., Mumbai.</td>
<td>10 Tablets</td>
<td>Metoprolol Tartrate 25 mg, 50 mg, 100 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 x 5 mL</td>
<td>Metoprolol Tartrate 1 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Ampoule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolar-XL</td>
<td>Cipla Ltd., Mumbai.</td>
<td>10 Capsules</td>
<td>Metoprolol Tartrate 12.5 mg, 25 mg, 50 mg, 100 mg</td>
</tr>
<tr>
<td><strong>Composition Drug Dosage Form</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaloc-H</td>
<td>AstraZeneca Pharma</td>
<td>10 Tablets</td>
<td>Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg</td>
</tr>
<tr>
<td></td>
<td>India Ltd., Bangalore.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolar-H</td>
<td>Cipla Ltd., Mumbai.</td>
<td>10 Tablets</td>
<td>Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg</td>
</tr>
<tr>
<td>Metozide</td>
<td>Torrent Pharm., Ltd., Ahmedabad.</td>
<td>10 Tablets</td>
<td>Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg</td>
</tr>
<tr>
<td>Selopress</td>
<td>AstraZeneca Pharma</td>
<td>10 Tablets</td>
<td>Metoprolol tartrate 100 mg, hydrochlorothiazide 12.5 mg</td>
</tr>
<tr>
<td></td>
<td>India Ltd., Bangalore.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug Index, June-Aug., 2003\textsuperscript{236}; Indian Drug Review, 2004\textsuperscript{237}. 
5.5. HYDROXYPROPYL METHYLCELLULOSE – CONTROL RELEASE POLYMER

5.5.1. Introduction

The word comes from the greek *polumeres*, which means ‘having many parts’\(^\text{239}\). Polymers are large molecules consisting of repeated chemical units (‘mers’) joined together usually in a line, like beads on a string\(^\text{239}\). The Dictionary of Science Technology, 1995\(^\text{240}\) defines “polymer” as a large molecule formed by the union of at least five identical monomers; it may be natural, such as cellulose or DNA, or synthetic, such as nylon or polyethylene; polymers usually contain many more than five monomers, and some may contain hundreds and thousands of monomers in each chain.

5.5.2. Definition

Progress in polymer science made it increasingly apparent that some changes were needed in the basic terms used in polymer science. A need for clear and unambiguous definition of basic terms relating to polymers lead to second new glossary of terms formulated by the 1996 IUPAC Commission\(^\text{241}\) containing 187 terms pertaining to polymer science.

**Polymer Molecule (definition)\(^\text{241}\):** A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetition of units derived, actually or conceptually, from molecules of low relative molecular masses.
Monomer (definition)\textsuperscript{242}: A substance consisting of molecules, which can undergo polymerization, thereby contributing constitutional units to the essential structure of a macromolecule.

5.5.3. Hydroxypropyl methylcellulose (HPMC)

5.5.3.i. Synonyms\textsuperscript{164,243}

Cellulose 2-hydroxypropyl methyl ether; hypromellose, Gonak; Goniosol; Tearsol; Methocel HG; Ultra Tears; lacril; Cellulose; hydroxypropyl methyl ether; Cluminal MHPC; Methocel; Metolose; Pharmacoat.

5.5.3.ii. Method of Preparation\textsuperscript{244-245}

The polymer is prepared by reacting alkali-treated cellulose first with methylcellulose to introduce methoxy groups and then with propylene oxide to introduce propylene glycol groups at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups linkages to the anhydrous rings of cellulose. The resulting products are commercially available in different viscosity grades. The reason for its wide spread acceptance include –

(i) Solubility characteristic of polymer in gastro intestinal tract and in organic and aqueous solvent systems.

(ii) Non-interference with tablet disintegration and drug availability.

(iii) Flexibility, resistance and absence of taste and odor.

(iv) Stability in presence of heat, light, air or reasonable levels of moisture.

(v) Ability to incorporate color and other additives into the film without difficulty.

The interactions with this polymer is rare. HPMC closely approaches the desired attributes of an ideal polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of HPMC with other
polymer or plasticizer is used to eliminate bridging or filling problems. This polymer is also used considerably in glossy solutions.

The approximate grade of methylcellulose is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups linkages to the anhydrous rings of cellulose. The resulting products are commercially available in different viscosity grades. The details are given earlier in this chapter.

5.5.4. Commercial Products

METHOCEL is a trademark of The Dow Chemical Company for a line of cellulose ether products. An initial letter identifies the type of cellulose ether, its "chemistry." "A" identifies methylcellulose (MC) products. "E," "F," and "K" identify different hypromellose products (Fig. 1). METHOCEL E and METHOCEL K are the most widely used for controlled-release drug formulations. The number that follows the chemistry designation identifies the viscosity of that product in millipascal-seconds (mPa·s), measured at 2% concentration in water at 20°C. In designating viscosity, the letter "C" is frequently used to represent a multiplier of 100, and the letter "M" is used to represent a multiplier of 1000. Several different suffixes are also used to identify special products. "P" is sometimes used to identify METHOCEL Premium products, "LV" refers to special low-viscosity products, "CR" denotes a controlled-release grade, and "LH" refers to a product with low hydroxypropyl content. "EP" denotes a product that meets European Pharmacopoeia requirements; "JP" grade products meet Japanese Pharmacopoeia requirements.
5.5.5. Properties

- Structure

![Chemical structure of METHOCEL E 10M Premium CR](image)

- Appearance

  White or off-white, yellowish-white, grayish-white, practically odourless, hygroscopic fibrous powder or granules$^{247-248}$.

- Carbonization temperature: 280-300 °C$^{248}$.

- Surface Tension

  42-56 dyn/cm (2% aqueous solution)$^{248}$.

- Practically insoluble in hot water, dehydrated alcohol, acetone, chloroform, and ether; forms a colloidal solution in cold water; soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform. A 1% solution in water has a pH of 5.5 to 8.0 granules$^{247}$. The solubility varies with viscosity, the lower the
viscosity is, the higher solubility has. The different HPMC is different in some properties and its solubility in water is not affected by pH granules.

- The lower methoxy content in HPMC, the higher gelation temperature, the lower solubility in water and surface activity granules.

- HPMC has also other characteristics such as thickening property, pH stability, water retention, excellent film-forming property and good disperse and adhesion power granules.

- Ionic Charge:

No ionic charge (i.e., not a polyelectrolyte), do not complex with metallic salts and ionic organics to form insoluble precipitates. So they minimize interaction problems when used in acidic, basic, or other electrolytic systems, thus presenting less compatibility problems. Work well with soluble and insoluble drugs and at high and low dosage levels.

- Gel Formation:

Undergoes a reversible transformation from sol to gel upon heating and cooling, respectively.

- Gel Point:

(i) 50 – 90°C, depending upon the Grade.

(ii) HPMC dissolves in both organic solvents and water over the entire biological pH range.

(iii) Aqueous solutions of HPMC gel on heating. Drastic increase in viscosity is observed near 60°C. Therefore problems might be encountered at temperatures higher than this.

(iv) In gastric - fluid – soluble film coating, the water solubility of the film over the entire biological pH range directly influences the bioavailability of the active ingredients.
Table 5.16. Dissolution times of film from 6 cps HPMC in various solvents.

<table>
<thead>
<tr>
<th>Test Fluid</th>
<th>Dissolution Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 °C</td>
</tr>
<tr>
<td>pH 1.2 (0.066 N HCl, 0.034 N NaCl)</td>
<td>2 min 01 sec</td>
</tr>
<tr>
<td>Water</td>
<td>1 min 51 sec</td>
</tr>
<tr>
<td>pH 7.5 (0.1 M phosphate buffer)</td>
<td>2 min 20 sec</td>
</tr>
<tr>
<td>pH 10 (Kolthoff buffer)</td>
<td>2 min 00 sec</td>
</tr>
</tbody>
</table>

Table 5.16 shows the dissolution times of film from 6 – cp – type HPMC (thickness 80 μm) in various fluids at 20, 37 and 50°C. There was no marked difference at 20°C. At 37°C, slight elongation of the dissolution time was observed in 0.1 M phosphate buffer (pH 7.5) and Kolthoff (pH 10), and the elongation was increased at 50°C. These changes are perhaps due to salting-out effect of increasing buffer concentration. At 50°C, the temperature is close to the thermal gelling temperature of HPMC so that the film becomes less soluble, and even if it disintegrates it remains in small fragments. From these data, it is expected that the film can be dissolved readily in the gastro intestinal tract at 37°C.

5.5.6. Molecular Weight and Viscosity

Hyromellose, being a semi-synthetic material derived from cellulose, is a linear polymer comprised of therified anhydroglucose rings. The degree of polymerization (DP) is varied in production to give a polymer with the desired properties. For products typically used in controlled release applications, DP is adjusted to a range between 100 and 1500. Like all polymers, hyromellose macromolecules exist as a distribution and may be characterized by parameters such as the number average
molecular weight \( M_n \), the weight average molecular weight \( M_w \), and the polydispersity \( \frac{M_n}{M_w} \).

5.5.7. Incompatibilities Granules\(^{247}\)

It has been reported with a number of compounds including chlorocresol, hydroxybenzoates, and phenol. Large amounts of electrolytes increase the viscosity of methylcellulose mucilages owing to salting-out of methylcellulose, in very high concentrations of electrolytes; the methylcellulose may be completely precipitated.

5.5.8. Adverse Effects Granules\(^{247}\)

Large quantities of methylcellulose may temporarily increase flatulence and distension and there is a risk of intestinal obstruction or condition likely to lead to intestinal obstruction. Oesophageal obstruction may occur if compounds like methylcellulose are swallowed dry.

5.5.9. Precautions Granules\(^{247}\)

Methylcellulose and other bulk laxatives should not be given to patients with intestinal obstruction or condition likely to lead to intestinal obstruction. They should be taken with sufficient fluid to prevent faecal impaction or oesophageal obstruction. Bulk laxatives lower the transit time through the gut and could affect the absorption of other drugs.

5.5.10. Safety\(^{250}\)

Human and animal feeding studies have shown HPMC to be safe.
11. **Use and Administration Granules**

The physicochemical properties of HPMC\textsuperscript{251} are strongly dependent on its chemical structure, and influences the following parameters: (i) methoxy content, (ii) hydroxypropyl content and (iii) molecular weight.

The swelling and solubility behavior of HPMC depends on the molecular weight, degree of substitution, cross-linking and grafting. Non-crosslinked polymer absorbs water, swell, and dissolve (erode); cross-linked HPMC swells to some equilibrium state, at which the retractive force of the network balances the swelling force. The formation of a gel layer is of evident importance by the drug release from HPMC systems. Initially, the polymer is in a glassy state. Upon exposure to the respective biological fluid, water penetrated into the device and decreased the \( T_g \) of HPMC (acting as a plasticizer). With increasing water concentration, this reduction of the \( T_g \) also increases. At a critical concentration of water, the \( T_g \) equals the temperature of the system, and the polymer undergoes the transition from the glassy to the rubbery state. The increasing mobility of the macromolecular chains results in drug diffusion coefficients orders of magnitude higher than those in the glass state.

The reason for its wide spread acceptance include –

- Solubility characteristic of polymer in gastro intestinal tract and in organic and aqueous solvent systems.
- Non-interference with tablet disintegration and drug availability.
- Flexibility, resistance and absence of taste and odor.
- Stability in presence of heat, light, air or reasonable levels of moisture.
- Ability to incorporate color and other additives into the film without difficulty.
- The interactions with this polymer are rare.
The various grades of hydroxypropyl methylcellulose are widely for its various applications.

- **Emulsifying, suspending and thickening agent**

  Low viscosity grades are used to reduce the surface tension produced in the preparation of emulsions and in liquid oral dosage forms as replacements for sugar-based syrups or other suspension bases.

- **Thickening agent**

  High viscosity grades are used for thickening topically applied products such as gels and creams.

- **Granulating agent**

  In the manufacture of tablets low or medium viscosity grades are used as binding agents. High viscosity grades act as tablet disintegrants by swelling on contact with the disintegration medium.

- **Tablet coating**

  HPMC closely approaches the desired attributes of an ideal polymer for film coating. When used alone, the polymer has the tendency to bridge or fill the debossed tablet surfaces. A mixture of HPMC with other polymer or plasticizer is used to eliminate bridging or filling problems. This polymer is also used considerably in glossy solutions. For tablet coating, high-substituted low viscosity grades are usually used.

- **Artificial Tears**

  A 0.5 to 1% solution of high viscosity grade has been used as a vehicle for eye drops and as artificial tears and contact lens solution but hypromellose is now generally preferred for this purpose.

- **Wetting solution for contact lenses**

  A wetting solution for contact lenses. Its demulcent action decreases the irritant effect of the lens on the cornea. It also imparts viscous properties to the wetting solution, which assists the lens in staying in place.
Laxative

Mild and high viscosity grades are used as bulk laxatives since by taking up moisture they increase the volume of the faeces and promote peristalsis. They are usually given in the form of granules or tablets, in a dosage of 1 to 6 gm daily in divided doses taken with plenty of fluid. They are also given in similar doses with a minimum amount of water for the control of diarrhoea and in the management of osmotics and also used in the management of diverticular disease. Methylcellulose has also been used as an aid to appetite control in the management of obesity but there is little evidence of efficacy.

- Controlled Drug Delivery

Details are given in earlier section.

- Food industry

Methylcellulose is also employed as an emulsifier and stabilizer in the food industry.

- Miscellaneous

In adhesives, asphalt emulsions, caulking compounds, tile mortars, plastic mixes, cements, paints. As sticker for agriculture sprays and dusts.

5.6. LACTOSE MONOHYDRATE – EXCIPIENT\textsuperscript{249,251, 253-254}

Synonym: Milk sugar, saccharum lactis, α-D-Lactose Monohydrate)

5.6.1. Description

White to off white or creamy-white crystalline particles or powder.

5.6.2. General Properties

- Empirical formula:  a) C\textsubscript{12}H\textsubscript{22}O\textsubscript{11} (anhydrous),  b) C\textsubscript{12}H\textsubscript{22}O\textsubscript{11}H\textsubscript{2}O (monohydrate)

- Molecular weight:  a) 342.30,  b) 360.31
Structure

\[
\begin{align*}
\text{LACTOSE MONOHYDRATE}
\end{align*}
\]

5.6.3. Typical Properties

- **Density**
  - Particle: 1.52 g/cm\(^3\) (\(\alpha\) lactose monohydrate)
  - Bulk: 1.17 g/cm\(^3\) (anhydrous)
  - Tapped: 1.36 g/cm\(^3\) (anhydrous)

5.6.4. Solubility

Soluble in ammonia and acetic acid. Slightly soluble in dilute alcohols. Insoluble in chloroform, ether and absolute alcohol. In water, the details are given below.

<table>
<thead>
<tr>
<th></th>
<th>Water</th>
<th>Cold</th>
<th>Boiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha) lactose monohydrate</td>
<td>20 g in 100 ml</td>
<td>38.4 g in 100 ml</td>
<td></td>
</tr>
<tr>
<td>(\beta) Lactose</td>
<td>45 g in 100 ml</td>
<td>91 g in 100 ml</td>
<td></td>
</tr>
</tbody>
</table>

- The \(\beta\)-D-Lactose content is less than 3%.
6.5. Types

Lactose occurs in 3 forms: α monohydrate, α anhydrous, β anhydrous. Odorless; sweet tasting. β-lactose is more soluble and slightly sweeter than α form.

- **α-lactose monohydrate**

  Is the usual milk sugar and the lactose of pharmacy. One gram dissolves in 5 mL water, in 2.6 mL boiling water; very slightly soluble in alcohol. Insoluble in chloroform, ether. $K_a$ at 16.5 °C = 6.03 $\times 10^{-13}$.

- **β-lactose monohydrate**

  One gram dissolves in 2.2 mL water at 15 °C, in 1.1 mL boiling water. After few days crystals of less soluble α-monohydrate appear from standing solutions.

5.6.6. Official Specifications

The details are given in Table 5.17.

Table 5.17. Pharmacopoeial Specifications for Lactose Monohydrate

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Compendial Limits$^{253}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety.</td>
</tr>
<tr>
<td>Identification</td>
<td>A. Infrared Absorption.</td>
</tr>
<tr>
<td></td>
<td>B. Chromatographic (TLC). Not more than 4 discernable spots as that of Reference Standard.</td>
</tr>
<tr>
<td></td>
<td>C. A solution to which when ammonium hydroxide is added gives red color.</td>
</tr>
<tr>
<td>Clarity and color of solution</td>
<td>10% solution is clear and nearly colorless. Optical density at 400 m is not more than 0.04.</td>
</tr>
<tr>
<td>Melting point</td>
<td>121 - 124 °C</td>
</tr>
<tr>
<td>Specific rotation</td>
<td>Between +54.4 ° and +55.9 ° determined at 20° in 1.0% solution containing ammonium hydroxide.</td>
</tr>
<tr>
<td>pH</td>
<td>Between 6.0 and 7.0, in a 2.0% w/v solution.</td>
</tr>
<tr>
<td>Microbial Limits</td>
<td>The total aerobic microbial count does not exceed 100/gm,</td>
</tr>
<tr>
<td></td>
<td>the total combined molds and yeasts count does not exceed 50/gm, and it meets the requirements of the test for absence of <em>Escherichia coli</em>.</td>
</tr>
<tr>
<td>Acidity or alkalinity</td>
<td>Dissolve 6 gm by heating in 25 mL of carbon dioxide – free</td>
</tr>
</tbody>
</table>
water, cool, and add 0.3 mL of phenolphthalein TS; the solution is colorless, and not more than 0.4 mL of 0.1 N sodium hydroxide is required to produce red color.

<table>
<thead>
<tr>
<th>Property</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss on drying</td>
<td>Dry it at 80 °C for 2 hours. The monohydrate from loses not more than 0.5% of its weight, and the modified monohydrate form loses not more than 1.0% of its weight.</td>
</tr>
<tr>
<td>Water</td>
<td>Between 4.5% to 5.5%, determined on a preparation containing lactose monohydrate in a mixture of methanol and formamide (2:1).</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>Not more than 0.1%, determined on a specimen ignited at a temperature of 600 ± 25 °C.</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Not more than 5 µg/mg.</td>
</tr>
<tr>
<td>Protein and light absorbing impurities</td>
<td>1% (W/V) when measured in the range of 210 to 300 nm, the absorbance divided by the pathlength in centimeters is not more than 0.25 in the range of 210 to 220 and is not more than 0.07 in the range of 270 to 300 nm.</td>
</tr>
</tbody>
</table>

5.6.7. Applications

- Solid dosage form: Diluent, bulking agent, filler and excipient for compressed and molded tablets and capsules.
- An ingredient in infant foods.
- Lyophilized products: Added to freeze dried solutions to increase plug size and aid caking.
- Sugar coating: Lactose is used in combination with sucrose for sugar coating solutions.

5.6.8. Use

Both α and β forms of lactose are employed, with the α-form predominating; as a nutrient in preparing modified milk and food for infants and convalescents.

- In baking mixtures.
- Pharmaceutical Aid – (tablet and capsule excipient and diluent).
- To produce lactic acid fermentation in ensilage and food products.
- As chromatographic adsorbents in analytical chemistry.
- In culture media.
Therapeutic category (Veterinary)
Added to cow's milk for feeding orphan foals.

5.6.9. Incompatibilities
The 'browning reaction' is base catalyzed and may therefore be accelerated if alkaline lubricants are used.

5.6.10. Safety

Intolerance to lactose in persons with a deficiency of intestinal lactase and may lead to abdominal cramps, diarrhea, distension and flatulence. In lactose tolerant individuals, the enzyme lactase hydrolyzes lactose in the small intestine to glucose and galactose, which are absorbed. It is not uncommon for humans to lose the ability to hydrolyze lactose as they mature. The incidence of adult lactase deficiency (hypolactasia) varies considerably among different populations.

5.7. MAGNESIUM STEARATE – EXCIPIENT

- Synonym: Metallic stearate, Magnesium salt.

5.7.1. Description
Octadecenoic acid magnesium salt. Fine, white, precipitated or milled, impalpable powder of low bulk density. Odor and taste are slight but characteristic. The powder readily adheres to the skin. The commercial preparation also contains palmitate.

5.7.2. General Properties

- Empirical Formula: \( \text{C}_{38}\text{H}_{70}\text{MgO}_4 \)
- Molecular Weight: 591.3
5.7.3. Typical Properties

- **Solubility**
  Insoluble in water, alcohol and ether. Slightly soluble in hot alcohol and benzene.

- **Stability and storage conditions**
  Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container.

- **Incompatibilities**
  Acidic substances; alkaline substances; iron salts. Avoid mixing with strong oxidizing materials. Use with caution with drugs, which are incompatible with alkali.

5.7.4. Mechanism of Action

In order to reduce die wall friction and therefore obtain greater uniformity in the compact, lubricant magnesium stearate at 5% of tablet weight is added in the tablet formulation. Tablet lubricants act by interposing a film of low shear strength at the interface between the die-wall and the compact, thus reducing the friction.
Tablet lubricant may act in one or all of the three ways: (i) as anti-adhesive to prevent tablet-form sticking to the die wall and the punch faces; (ii) to reduce sliding friction at the die wall; and (iii) as glidants that will promote free flowing properties of the powder or granules into the die.

It is evident that tablet lubricants act by interposing a film of lower shear strength at the interface between the die-wall and the compact, thus reducing the friction force. Die-wall lubricants must have low shear strength. From mechanical considerations, as low a value of shear strength as possible is desirable. This suggests that liquid lubricants (hydodynamic lubricants) might be more suitable than the solid lubricants (boundary lubricants) normally used.

Tablet lubricants are most effective when used in a fine degree of subdivision. Since their function is related to surfaces, the greater the degree of subdivision, the greater the area they can cover. Therefore, they are usually passed through 60-mesh or finer screens before their incorporation into the granulation. Lubricants usually are added at the very last step before compression, since they must be present on the surfaces of the granules and in-between them and the parts of the tablet press.

Table 5.18. Shear strength values of various lubricants.

<table>
<thead>
<tr>
<th>Lubricants</th>
<th>Shear strength (kg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium stearate</td>
<td>20.0</td>
</tr>
<tr>
<td>Potassium stearate</td>
<td>31.3</td>
</tr>
<tr>
<td>Sodium stearate</td>
<td>33.9</td>
</tr>
<tr>
<td>Talc with grain</td>
<td>63.2</td>
</tr>
<tr>
<td>Talc across grain</td>
<td>80.0</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>9.3 – 20.2</td>
</tr>
</tbody>
</table>

5.7.5. Pharmacopoeial Specification

The details are given in Table 5.19.
Table 5.19. Pharmacopoeial Specifications for Magnesium Stearate

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Compendial Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Magnesium stearate is a compound of magnesium with a mixture of solid organic acids, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. The fatty acids are derived from edible sources. It contains not less than 4.0% and not more than 5.0% of Mg, calculated on the dried bases.</td>
</tr>
</tbody>
</table>
| Identification       | A. Chemical Test: The ether extract complies with identification test for magnesium.  
                         B. Chromatographic (HPLC). The retention times of the peaks corresponding to steric acid and palmitic acid in the chromatogram of the System suitability solution; as obtained in the Relative content of stearic acid and palmitic acid test. |
| Microbial Limits     | The total aerobic microbial count does not exceed 1000/gm, the total combined molds and yeasts count does not exceed 500/gm, and it meets the requirements of the test for absence of Salmonella species and Escherichia coli. |
| Acidity or alkalinity| Transfer 1.0 gm to a 100-ml beaker, add 20 mL of CO₂-free water, boil on a steam bath for 1 minute with continuous shaking, cool, filter. Add 0.05 mL of bromothymol blue TS fo 10 mL of the filtrate: Not more than 0.05 mL of 0.1 N hydrochloric acid or 0.1 N NaOH is required to change the color of the indicator. |
| Loss on drying       | Not more than 6.0% of its weight at 105 °C.                                        |
| Specific Surface Area| The P/P₀ range lies between 0.05 to 0.15 using outgassing conditions of 2 hours at 40 °C. |
| Limit of chloride    | The test solution shows no more chloride than corresponds to 1.4 mL of 0.020 N hydrochloric acid (0.1%). |

5.7.6. Functional Category

- USP: Tablet and/or capsule lubricant
- BP/EP: Lubricant; Pharmaceutical aid
- Other: Glidant, Anti-adherent
- It is generally used at 0.25 – 2.0%.
- It is also used in baby dusting powders.

5.7.7. Safety

It is described as an inert or nuisance dust. Classified as non-hazardous by the department of Transportation Regulations. Dust clouds of magnesium stearate may be explosive.


T. M. Aminabhavi, H. T. S. Phayde, Molecular transport characteristics of santoprene thermoplastic rubber in the presence of aliphatic alkanes over the temperature interval of 25 to 70°C, Polymer 36, 1023-1033 (1995).


T. Higuchi, Rate of release of medicaments, from ointment bases containing drugs in suspensions, J. Pharm. Sci. 50 (1961) 874-875.


HPMC Dow Bulletin.


J. P. Skelly et al, Pharm. Res., 7 (9), 975-982 (1990)


Greatvista Chemicals, Hydroxypropyl Methylcellulose (HPMC), http://www.greatvistachemicals.com/industrial_and_specialty_chemicals/hydroxypropyl_methylcellulose.html


