CHAPTER 2

INTRODUCTION AND REVIEW OF WORK DONE
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2.1 Introductions

2.1.1 Modified release system

2.1.1.1 Introduction

The basic goal of any drug delivery system is to provide the therapeutic amount of drug to the proper site(s) in the body to promptly achieve and then maintain the desired drug concentration (Longer and Robinson, 1985). The conventional dosage forms such as solution, suspension, capsule, tablet, etc. produce a drug blood level versus time profile similar to that shown in Figure 2.1.

![Typical drug blood levels versus time profile for intravenous and oral route of administration](image)

**Figure 2.1** Typical drug blood levels versus time profile for intravenous and oral route of administration.

The formulation is effective only for the time period when the drug blood levels are within the therapeutic range. It can be seen from the figure that administration of drug by either IV or an oral route, does not maintain drug blood levels within the therapeutic range for extended period of time. Therapeutic efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses.

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Many terms are used to describe modified release products including extended release, prolonged release, controlled release, controlled
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delivery, slow release, sustained release etc. These preparations, by definition, have a reduced rate of release of active substance (Sansom, 1999).

2.1.1.2 Terminology
The modified release system i.e. non-immediate release systems may be divided conveniently in three categories.

1. Delayed release
2. Sustained release
   a. Controlled release
   b. Prolong release
3. Site specific and receptor release
   a. Organ targeting
   b. Cellular targeting
   c. Subcellular targeting

1. Delayed release: Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of it include repeat action tablets and capsules. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range as shown in Figure 2.2.

![Figure 2.2 Typical blood levels versus time profiles for delayed release drug delivery by repeat action dosage form](image_url)
2. Sustained release: It includes all drug delivery systems that achieve slow release of drug over an extended period of time. Ideally, a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose into the gastrointestinal tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then released at a controlled rate (Li and Robinson, 1987).

a. Controlled release: Drug product is designed so that the maintenance dose release rate is equal to the elimination rate, the constant blood levels can be achieved. Such drug delivery systems are called controlled release systems.

b. Prolonged release: Prolonged release dosage forms reduce fluctuation in plasma drug levels by slowing down the absorption rate due to slower drug release rate. It extends the period of time the drug concentration is in the therapeutic range but does not maintain constant blood levels as controlled release systems. Hence it is also termed as extended release. This is illustrated in Figure 2.3.

![Figure 2.3 Drug blood level versus time profile showing the relationship between controlled release (A), Prolonged release (B), and conventional release (C)](image_url)

3. Site specific and receptor release: It should channel the active entity solely to the site of action. In the case of site specific release, the target is a certain organ or tissue (e.g.
in the treatment of arthritis or gout). While for receptor release, the target is the particular receptor for a drug within an organ or tissue (e.g. H₁ and H₂ antagonists located in tumor cells). Both these systems satisfy the spatial aspect of drug delivery. These types of drug release are difficult to achieve.

2.1.2.3 Objective
The primary objectives of modified release system are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. (Li et al., 1987).

- Sustained release formulation reduces fluctuation of drug blood levels about the mean. In cases where a constant drug level is desirable, (a) it reduces the peak blood levels (Cₘₐₓ) and thus, reducing dose related side effects, and (b) increases the minimum plasma concentrations (Cₘᵢₙ), thereby increases efficiency (Skelly and Barr, 1987).
- Sustained release formulations increase in the time interval required between doses. This provides a reduction in the total number of doses required per day. The decrease in frequency of daily doses is more convenient to the patients and can lead to improved patient compliance.

Conventional dosage forms are not able to control either the rate of drug delivery or the target area of drug administration and provide an immediate or rapid drug release. This necessitates frequent administration in order to maintain a therapeutic level. As a result, drug concentrations in the blood and tissues fluctuate widely. The concentration of drugs may be initially high, that can cause toxic, and/or side effects, then quickly fall down below the minimum therapeutic level with time elapse. In contrast, sustained release dosage forms are not only able to maintain therapeutic levels of drug with narrow fluctuations but they also make it possible to reduce the frequency of drug administration. The serum concentration of a drug released from controlled release dosage forms fluctuates within the therapeutic range over a long period of time. The serum concentration profile depends on the preparation technology, which may generate different release kinetics, resulting in different pharmacological and pharmacokinetic responses in the blood or tissues.
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For conventional drug delivery systems, the rate limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastrointestinal wall (Scheme I).

\[ \text{Drug in} \quad \rightarrow \quad \text{Drug in solution} \quad \rightarrow \quad \text{Drug at} \]
\[ \text{Dosage form} \quad \rightarrow \quad \text{form at absorption site} \quad \rightarrow \quad \text{target area} \]

Scheme I

In sustained or controlled release product, the drug availability is controlled by the kinetics of drug release rather than absorption. Kinetically the process appears as shown in scheme II.

\[ \text{Drug in} \quad \rightarrow \quad \text{Drug in solution} \quad \rightarrow \quad \text{Drug at} \]
\[ \text{Dosage form} \quad \rightarrow \quad \text{rate limiting step} \quad \rightarrow \quad \text{target area} \]

Scheme II

2.1.1.4 Classification

One of the ways to classify modified release system amongst many mentioned in literature is given below (Hui, H. and Robinson, J. R., 1987):

a. Dissolution controlled systems
b. Diffusion controlled systems
c. Dissolution and diffusion controlled systems
d. pH independent systems
e. Ion exchange systems
f. Osmotically controlled systems
g. Altered density formulation (Buoyant systems)

2.1.1.5 Which drugs are suitable for extended release formulations?

The extent of fluctuation in drug concentration at steady state is determined by the relative magnitude of the elimination half-life and the dosing interval. If a drug is given at an interval
equal to the elimination half-life, there is a two-fold difference between the maximum and minimum concentrations at steady state (Sansom, 1999).

For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxycillin has a half-life of approximately one hour, but a dosage frequency of 8 hours. This means that very large fluctuations will occur within a dosing interval, but, in view of the low toxicity of this drug, no difficulty with this approach is encountered provided the concentrations are above the minimum effective concentration during the dosing interval. On the contrary, clinical efficacy may be enhanced by the transiently high bactericidal concentration of the antibiotic e.g. aminoglycosides.

Conversely, drugs with long half-lives can be given at less frequent intervals. There is generally no advantage in formulating these drugs as extended-release formulations unless a rapid rate of change of concentration during the absorptive phase is responsible for transient adverse effects. The pharmacological effect of some drugs with short half lives is sustained by various mechanisms:

- The drug binds to the tissues e.g. tissue-bound ACE inhibitors. For these drugs, less frequent dosing is needed even though the drug may have a short half-life
- The drugs have irreversible effects e.g. the inhibition of platelet cyclo-oxygenase by aspirin
- The relationship between response and plasma/blood concentrations is relatively flat or if the dose given results in concentrations which are in the plateau region of the dose-response relationship e.g. thiazides in hypertension
- The drug is metabolized to pharmacologically active metabolite(s) which are more slowly cleared than the parent drug e.g. quinapril, trandolapril

2.1.1.6 Factors affecting drug release from sustained release systems

2.1.1.6.1 Physicochemical factors

   a. Aqueous solubility
Most drugs are weak acids or bases. Since the unchanged (unionized) forms of drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Unfortunately, the situation becomes more complex by the fact that the drug's aqueous solubility will generally be decreased in unionized form as compared to ionized form. Considering that the dosage form must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, there should be proper balance between the solubility and pka of the compound. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/mL (Jantzen and Robinson, 2002).

Since drugs must be in solution before they can be absorbed, compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastro-intestinal transit time of the undissolved drug particles and limited solubility at the absorption site. The choice of mechanism for oral sustained/controlled release systems is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the concentration in aqueous solution, will be low. In contrast, such drugs may be effectively incorporated in matrix systems. In selecting polymers for sustained/controlled release systems, the dissolution rate of a drug must be considered. The slow dissolution rate of drug can be utilized to achieve sustained/controlled drug release by incorporation in a matrix system (Li et al., 1987).

b. Partition coefficient and molecular size
To produce a therapeutic effect in the body, the drug administered in the gastrointestinal track must cross a variety of biological membranes. Hence, partition coefficient of drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is defines as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, drugs with high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. They can localize in the lipid membranes of cells and usually
persists in the body for long periods. On the other side, compounds with low partition coefficients will have difficulty in penetrating membranes, and results in poor bioavailability (Jantzen and Robinson, 2002). The venlafaxine HCl has partition coefficient value 0.43.

c. Drug stability
Orally administered drugs can be subject to both acid and base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. Apart from these, route of drug delivery, target sites, acute or chronic therapy, the disease type are the other factors to be considered.

d. Protein binding
Many drugs bind to plasma proteins which in turn influences duration of drug action. Distribution of the bound drug into the extra vascular space is governed by equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for obtaining sustained release in the extra vascular tissues, and such drugs generally do not require a sustained release dosage form. In general, charged compound have a greater tendency to bind with protein than uncharged compounds, due to electrostatic effects. The presence of a hydrophobic moiety on the drug molecule also increases its binding potential. The drugs that bind with proteins are amitriptyline, diazepam, novobiocin, etc.

e. Dose size
For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 g is considered maximal for a conventional as well as sustained release dosage forms. Another consideration is the
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margin of safety involved in administration of large amounts of a drug with a narrow therapeutic range (Jantzen and Robinson, 2002).

f. Molecular Size and Diffusivity:
Drug must diffuse through a variety of biological membranes during its time-course in the body. Drugs in many sustained release systems must diffuse through polymeric membrane or matrix that is used to control their release kinetics. The ability of drug to diffuse through membranes is a function of its diffusivity. It is related to its molecular size (molecular weight) by the following equation:

$$\log D = -S_v \log V + K_v = -S_M \log M + K_M$$

Where D is diffusivity, M is molecular weight, V is molecular volume. $S_v$, $S_M$, $K_v$ and $K_M$ are constants.

In general, the denser the medium, the smaller the diffusivity for drugs of intermediate molecular weight (150 - 400). Diffusivities through flexible polymers are typically of the order of $10^{-8}$ cm$^2$/sec for drugs with a molecular weight greater than 500 and polymeric drugs should be expected to display very slow release kinetics (Li et al., 1987).

2.1.1.6.2 Biological factors
a. Absorption
The usual aim of drug therapy is to achieve and maintain effective concentrations of drug at the receptor site. However, the body is constantly trying to eliminate the drug, and, therefore, it is necessary to balance absorption against elimination to maintain the desired concentration (Bourne, 2002). The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Since the purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. Considering the transit time of most drugs and devices in the absorptive areas of the gastrointestinal track is about 8-12 h, the maximum half-life for absorption should be approximately 3-4 h; otherwise, the device will pass out of the potential absorptive
regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h\(^{-1}\) to give 80-95% over this time period (Jantzen and Robinson, 2002). Compounds that demonstrate too lower absorption rate constants will probably be poor candidates for sustaining systems. Generally, absorption rate of therapeutic agent is assumed to be relatively uniform over the entire length of small intestine. But if a drug is absorbed by active transport or transport is limited to a specific region of the intestine, sustain release preparation with an attempt to formulate low-density pellets, capsules, or tablets that can float on the top of gastric juice, and thereby, delay their transfer out of stomach is desirable. Other alternative is use of bioadhesive polymer which has an affinity for the gastric surface, most probably the mucin coat.

b. Distribution
The following two parameters are used to describe the distribution characteristics of a drug
(a) Apparent volume of distribution \(V_d\) and
(b) Ratio of drug concentration in tissue to that in plasma at steady state (T/P ratio).
The \(V_d\) is merely a proportionality constant which relates drug concentration in the blood or plasma to the total amount of the drug in the body. It can also influence the elimination kinetics of a drug.

c. Metabolism
Drugs that are significantly metabolized before absorption, either in the lumen or in the tissue of the intestine, can show decreased bioavailability from sustained release dosage forms. As the drug is released at a slower rate in gastrointestinal track, less total drug is presented to the enzymatic degradation during a specific period, allowing more complete conversion of the drug to its metabolite (Jantzen and Robinson, 2002).

d. Elimination and biological half life
Since the therapeutic index for most drugs is around 2, it will be necessary to dose the patients at intervals shorter than half-life. Such inconvenient regimens often result in
reduced compliance and inadequate treatment. In general, dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination (ke) or by modifying the release rate of a dosage form to decrease the rate of absorption (ka). Both approaches seek to decrease fluctuations in plasma levels during multiple dosing, allowing the dosing interval to increase without either overdosing or under dosing (Li et al., 1987). To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Drugs with short half-lives require frequent dosing in order to minimize fluctuations in the blood levels accompanying conventional oral dosage regimens. Therefore, controlled/sustained release dosage forms would appear very desirable for such drugs. However, this is limited, in that drugs with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 h, such as levodopa or furosemide, are poor candidates for sustained release preparations. On the other side, compounds with long half-lives, more than 8 h are also generally not used in sustaining forms, since their effect is already sustained (Jantzen and Robinson, 2002). As the half life increases, formulation factors become less important in the development of the dosing regimen.

The most serious restriction to the use of oral sustained release dosage forms would be the limited residence time of the dosage form in the small intestine. Generally, 0-12 hr is considered reasonable estimate of average effective absorption time after oral administration of a well-absorbed drug in a dosage form that remains intact in the gastrointestinal tract (Silber et al., 1987). Occasionally, absorption from the colon may allow continued drug delivery for up to 24 h (Jantzen and Robinson, 2002).

e. Side Effects and Margin of Safety:
For some drugs, the incidence of side effects, in addition to toxicity, is believed to be related to their plasma concentration. Sustained release system can, minimize side effect by controlling its plasma concentration.

The measure of the margin of safety of a drug is its therapeutic index. (TI)
TI = TD\textsubscript{50} / ED\textsubscript{50}

TD\textsubscript{50} is the median toxic dose and ED\textsubscript{50} is the median effective dose. The value of TI varies from as little as unity to several thousand. For very potent drugs whose therapeutic concentration range is narrow, the value of TI is small. In general, the larger the value of TI the safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into sustained release products primarily due to technological limitation of precise control over release rates.

2.1.1.7 Advantages of sustained release system (Longer and Robinson, 1985)

1. Avoid patient compliance problems.
2. Employed less total drug
   a. Minimize or eliminate local side effects
   b. Minimize or eliminate systemic side effects
   c. Obtain less potentiation or reduction in drug activity with chronic use
   d. Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment
4. Cure or control condition more promptly
5. Improve control of condition i.e. reduce fluctuation in drug level
6. Improve bioavailability of some drugs
7. Make use of special effects eg. Sustained release aspirin for morning relief of arthritis by dosing before bedtime
8. Economy

2.1.1.8 Limitations of sustained release system (Longer and Robinson, 1985)

1. Drug with following characteristics can not be given by sustained release dosage form.
   I. Drugs with very narrow therapeutic index.
   II. Drugs with erratic absorption from gastrointestinal track
   III. Drugs with long biological half life
   IV. Drugs which needs to adjusts dose regime
   V. Drugs with very high dose
2. The dose can not be subdivided as in conventional dosage form
3. Difficult to provide antidote for sustained release formulations
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2.1.2 Depression disorder

2.1.2.1 Introduction
Depression involves the brain's delicate chemistry specifically, it involves chemicals called neurotransmitters. These chemicals help send messages between nerve cells in the brain. Certain neurotransmitters regulate mood, and if they run low, people can become depressed, anxious, and stressed. Stress also can affect the balance of neurotransmitters and lead to depression.

Sometimes, a person may experience depression without being able to point to any particular sad or stressful event. People who have a genetic predisposition to depression may be more prone to the imbalance of neurotransmitter activity that is part of depression.

Medications that doctors use to treat depression work by helping to restore the proper balance of neurotransmitters.

2.1.2.3 Types of depression
There are several forms of depressive disorders. The most common are major depressive disorder and dysthymic disorder.

- **Major depressive disorder**, also called major depression, is characterized by a combination of symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Major depression is disabling and prevents a person from functioning normally. An episode of major depression may occur only once in a person's lifetime, but more often, it recurs throughout a person's life.

- **Dysthymic disorder**, also called dysthymia, is characterized by long-term (two years or longer) but less severe symptoms that may not disable a person but can prevent one from functioning normally or feeling well. People with dysthymia may also experience one or more episodes of major depression during their lifetimes.

Some forms of depressive disorder exhibit slightly different characteristics than those described above, or they may develop under unique circumstances. However, not all scientists agree on how to characterize and define these forms of depression. They include:

- **Psychotic depression**, which occurs when a severe depressive illness is accompanied by some form of psychosis, such as a break with reality, hallucinations, and delusions.
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- **Postpartum depression**, which is diagnosed if a new mother develops a major depressive episode within one month after delivery. It is estimated that 10 to 15 percent of women experience postpartum depression after giving birth.\(^1\)

- **Seasonal affective disorder (SAD)**, which is characterized by the onset of a depressive illness during the winter months, when there is less natural sunlight. The depression generally lifts during spring and summer. SAD may be effectively treated with light therapy, but nearly half of those with SAD do not respond to light therapy alone. Antidepressant medication and psychotherapy can reduce SAD symptoms, either alone or in combination with light therapy.\(^2\)

- **Bipolar disorder**, also called manic-depressive illness, is not as common as major depression or dysthymia. Bipolar disorder is characterized by cycling mood changes—from extreme highs (e.g., mania) to extreme lows (e.g., depression).

### 2.1.2.3 Causes of depression

There is no single cause for depression. Many factors play a role including genetics, environment, life events, medical conditions, and the way people react to things that happen in their lives.

- **Genetics**
  
  Research shows that depression runs in families and that some people inherit genes that make it more likely for them to get depressed. Not everyone who has the genetic makeup for depression gets depressed, though. And many people who have no family history of depression have the condition. So although genes are one factor, they aren't the single cause of depression.

- **Life Events**
  
  The death of a family member, friend, or pet can go beyond normal grief and sometimes lead to depression. Other difficult life events, such as when parents divorce, separate, or remarry, can trigger depression. Even events like moving or changing schools can be emotionally challenging enough that a person becomes depressed.

- **Family and Social Environment**
  
  For some teens, a negative, stressful, or unhappy family atmosphere can affect their self-esteem and lead to depression. This can also include high-stress living situations such as poverty; homelessness; and violence in the family, relationships, or community.
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Substance use and abuse also can cause chemical changes in the brain that affect mood—alcohol and some drugs are known to have depressant effects. The negative social and personal consequences of substance abuse also can lead to severe unhappiness and depression.

- **Medical Conditions**

Certain medical conditions can affect hormone balance and therefore have an effect on mood. Some conditions, such as hypothyroidism, are known to cause a depressed mood in some people. When these medical conditions are diagnosed and treated by a doctor, the depression usually disappears.

For some teens, undiagnosed learning disabilities might block school success, hormonal changes might affect mood, or physical illness might present challenges or setbacks.

### 2.1.2.4 Symptoms of depression

People with depressive illnesses do not all experience the same symptoms. The severity, frequency and duration of symptoms will vary depending on the individual and his or her particular illness.

**Symptoms include:**

- Persistent sad, anxious or "empty" feelings
- Feelings of hopelessness and/or pessimism
- Feelings of guilt, worthlessness and/or helplessness
- Irritability, restlessness
- Loss of interest in activities or hobbies once pleasurable, including sex
- Fatigue and decreased energy
- Difficulty concentrating, remembering details and making decisions
- Insomnia, early—morning wakefulness, or excessive sleeping
- Overeating, or appetite loss
- Thoughts of suicide, suicide attempts
- Persistent aches or pains, headaches, cramps or digestive problems that do not ease even with treatment
- Things that used to make you happy, don't make you happy anymore
- Crying a lot
2.1.2.5 Treatment of depression

Numerous treatments for depression are available. Standard depression treatment options include:

- Medications
- Psychotherapy
- Electroconvulsive therapy (ECT)

Emerging and less-studied treatments for depression include:

- Brain stimulation
- Complementary and alternative treatments

In some cases, primary care doctor can treat depression. In other cases, one may benefit from treatment with a qualified mental health provider, such as a psychiatrist, psychologist or social worker.

The patient should try to be an active participant in its depression treatment. Working together, the patient and doctor or therapist can decide which treatment options may be best for the situation, depending on patient’s symptoms and their severity, personal preferences, insurance coverage, affordability, treatment side effects and other factors.

2.1.2.5.1 Medications

Dozens of medications are available to treat depression. Most people find the best relief of depression symptoms by combining medications and psychotherapy. Some medications for depression are antidepressants that have been specifically approved by the Food and Drug Administration (FDA) to treat depression. Doctors also can use their medical judgment to prescribe other medications that haven't been FDA approved to treat depression but that may be effective anyway a common and perfectly legal practice called off-label use.

The types of antidepressants

There are several different types of antidepressants. Antidepressants are generally categorized by how they affect the naturally occurring biochemicals in the brain to change mood. There are many different kinds of antidepressants, including:

- Selective serotonin reuptake inhibitors (SSRIs)
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- **citalopram (brand name: Celexa)**
- **escitalopram (brand name: Lexapro)**
- **fluoxetine (brand name: Prozac)**
- **paroxetine (brand names: Paxil, Pexeva)**
- **sertraline (brand name: Zoloft)**

These medicines tend to have fewer side effects than other antidepressants. Some of the side effects that can be caused by SSRIs include dry mouth, nausea, nervousness, insomnia, sexual problems and headache.

- **Tricyclics**
  - **amitriptyline (brand name: Elavil)**
  - **desipramine (brand name: Norpramin)**
  - **imipramine (brand name: Tofranil)**
  - **nortriptyline (brand name: Aventyl, Pamelor)**

Common side effects caused by these medicines include dry mouth, blurred vision, constipation, difficulty urinating, worsening of glaucoma, impaired thinking and tiredness. These antidepressants can also affect a person's blood pressure and heart rate.

- **Serotonin and norepinephrine reuptake inhibitors (SNRIs)**
  - **venlafaxine (brand name: Effexor)**
  - **duloxetine (brand name: Cymbalta)**

Some common side effects caused by these medicines include nausea and loss of appetite, anxiety and nervousness, headache, insomnia and tiredness. Dry mouth, constipation, weight loss, sexual problems, increased heart rate and increased cholesterol levels can also occur.

- **Norepinephrine and dopamine reuptake inhibitors (NDRIs)**
  - **bupropion (brand name: Wellbutrin)**

Some of the common side effects in people taking NDRIs include agitation, nausea, headache, loss of appetite and insomnia. It can also cause increase blood pressure in some people.

- **Combined reuptake inhibitors and receptor blockers**
  - **trazodone (brand name: Desyrel)**
  - **nefazodone (brand name: Serzone)**
  - **maprotiline**
  - **mirtazpine (brand name: Remeron)**
Common side effects of these medicines are drowsiness, dry mouth, nausea and dizziness. If you have liver problems, you should not take nefazodone. If you have seizures, you should not take maprotiline.

- **Monamine oxidase inhibitors (MAOIs)**
  - isocarboxazid (brand name: Marplan)
  - phenelzine (brand name: Nardil)
  - tranlcypromine (brand name: Parnate)

MAOIs are used less commonly than the other antidepressants. They can have serious side effects, including weakness, dizziness, headaches and trembling. Taking an MAOI antidepressant while you're taking another antidepressant or certain over-the-counter medicines for colds and flu can cause a dangerous reaction. Your doctor will also tell you what foods and alcoholic beverages you should avoid while you are taking an MAOI. You should not take an MAOI unless you clearly understand what medications and foods to avoid. If you are taking an MAOI and your doctor wants you to start taking one of the other antidepressants, he or she will have you stop taking the MAOI for a while before you start the new medicine. This gives the MAOI time to clear out of your body.

Most antidepressants are equally effective. But some pose a higher risk of serious side effects. Here's how antidepressants and other medications are generally considered when person is starting treatment for depression:

- **Typical first choices.** Many doctors start treatment with antidepressants by prescribing an antidepressant known as an SSRI — a selective serotonin reuptake inhibitor. This is because the side effects of the medications in the SSRI class of antidepressants are generally more tolerable than are those of other types of antidepressants, and they also generally work well. Other common first choices for antidepressants include serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), combined reuptake inhibitors and receptor blockers, and tetracyclic antidepressants.

- **Typical second choices.** The class of antidepressants called tricyclic antidepressants (TCAs) has been around longer than has the SSRI class, and TCAs are still effective.
But because TCAs tend to have more numerous and more severe side effects, they're often not prescribed until patient have tried SSRIs first without an improvement in its depression.

- **Typical last choices.** The class of antidepressants called monoamine oxidase inhibitors (MAOIs) is often prescribed as a last resort, when other medications haven't worked. That's because MAOIs, while generally effective, can have serious harmful side effects. They also require strict dietary restrictions because of rare but potentially fatal interactions with certain foods. Newer versions of MAOIs that one can stick on skin as a skin patch rather than swallowing may have fewer side effects.

### 2.1.2.5.2 Psychotherapy

Psychotherapy is a partnership between an individual and a professional such as a psychologist who is licensed and trained to help people understand their feelings and assist them with changing their behavior. Research increasingly supports the idea that emotional and physical health is very closely linked and that therapy can improve a person's overall health status. There is convincing evidence that most people who have at least several sessions of psychotherapy are far better off than untreated individuals with emotional difficulties.

People often consider psychotherapy, also known simply as therapy, under the following circumstances:

- They feel an overwhelming and prolonged sense of sadness and helplessness, and they lack hope in their lives.
- Their emotional difficulties make it hard for them to function from day to day. For example, they are unable to concentrate on assignments and their job performance suffers as a result.
- Their actions are harmful to themselves or to others. For instance, they drink too much alcohol and become overly aggressive.
- They are troubled by emotional difficulties facing family members or close friends.

### 2.1.2.5.3 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (also called ECT) may help people who have the following conditions:
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- Severe depression with insomnia (trouble sleeping), weight change, feelings of hopelessness or guilt and thoughts of suicide (hurting or killing yourself) or homicide (hurting or killing someone else).
- Severe depression that does not respond to antidepressants (medicines used to treat depression) or counseling.
- Severe depression in patients who can’t take antidepressants.
- Severe mania that does not respond to medication. Symptoms of severe mania may include talking too much, insomnia, weight loss or impulsive behavior.
- Schizophrenia that does not respond to medication.

How are the ECT treatments given?
ECT may be given during a hospital stay, or a person can go to a hospital just for the treatment and then go home. ECT is given up to 3 or 4 times a week. Usually no more than 12 treatments are needed to relieve depression. Treatment is given by a psychiatrist.

Before each treatment, an intravenous (IV) line will be started so medicine can be put directly into patient’s blood. It will be given an anesthetic (medicine to put you into a sleep-like state) and a medicine to relax it’s muscles. The heart rate, blood pressure and breathing will be watched closely. After patient is asleep, an electrical shock will be applied to its head. The shock will last only 1 or 2 seconds and will make patient’s brain have a seizure. This seizure is controlled by medicines so that patient’s body doesn’t move when it have the seizure.

The patient will wake up within 5 to 10 minutes after the treatment and will be taken to a recovery room to be watched. When it is fully awake, it can eat and drink, get dressed and return to it’s hospital room or go home.

2.1.2.6 Mechanism of action of Antidepressants
Therapeutic response is observed after a few weeks of antidepressant treatment; so, many adaptive changes in cellular functions occur. The neurotransmitter receptor hypothesis of antidepressant action explains the ultimate mechanism of their therapeutic action by receptor sensitivity changes.
Selective serotonin reuptake inhibitors (SSRI) are the most frequently used antidepressants. Their mechanism of action on serotonergic neuron in a depressed patient is shown on Figure 1.2.1.

Before treatment (Figure 2.4 A):

- There is relative deficiency of 5-HT in serotonin neurone in a depressed patient.
- Number of serotonin receptors is up-regulated, including presynaptic autoreceptors as well as postsynaptic receptors.
- Releasing of serotonin from synaptic knob can be affected: 1. positively by activity of serotonin transporter or by tryptophan (serotonin precursor) availability; 2. negatively by activation both presynaptic inhibitory receptors, 5-HT₁B or α₂-AR, and somatodendritic receptors, 5-HT₁A.

After acute administration of SSRI (Figure 2.4 B):

- A considerable part of serotonin transporters is blocked and serotonin remains for a longer time in extracellular space. This causes serotonin to increase in the somatodendritic area mainly.
- Negative feedback mediated by inhibitory presynaptic and somatodendritic receptors is increased and both frequency of firing of action potentials and amount of serotonin released from presynaptic button is decreased.

After chronic treatment by SSRI (Figure 2.4 C):

- The increased 5-HT at the inhibitory somatodendritic receptors causes them to down-regulate and/or desensitise. It results in increase of frequency of firing of action potentials and in increase of the amount of serotonin released to synaptic cleft. The marked increase of serotonin release in the axon terminal is delayed as compared with the processes after acute administration of SSRI. This delay may explain why therapeutic action of antidepressants is not immediate.
- The increased 5-HT at the axon terminal causes down-regulation and/or desensitization of postsynaptic and presynaptic receptors. This desensitization may mediate the reduction of side effects of SSRI.

Mechanism of action of α₂-adrenoreceptor blockers is shown on Figure 2.5; mechanism of action of reversible inhibitors of monoamine oxidase A (RIMA) is on Figure 2.6.
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A) before treatment

Figure 2.4 Mechanism of action of selective serotonin reuptake inhibitors (SSRI)

B) acute administration of SSRI

C) chronic treatment by SSRI

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Figure 2.5 Mechanism of action of α2-adrenoreceptor blockers

Figure 2.6 Mechanism of action of reversible inhibitors of MAO-A (RIMA)
2.1.3 Venlafaxine hydrochloride

2.1.3.1 Introduction

Venlafaxine is structurally a novel antidepressant for oral administration. It is a bicyclic phenylethylamine chemically and structurally unrelated to tricyclic, tetracyclic or other available antidepressant agents (Harwood, 2005).

2.1.3.2 Nomenclature (Susan, 1996, Leaflet of Effexor XR Capsules)

Chemical name: (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride

Or

(R)-1-[(a-(dimethylamino) methyl]-p-methoxybenzyl]) cyclohexanol hydrochloride

Generic name: Venlafaxine hydrochloride

Empirical formula: C_{17}H_{27}NO_{2}. HCl

Structural formula:

Molecular weight: Venlafaxine HCl: 313.87
Venlafaxine: 277
O - desmethyl venlafaxine : 263

28.3 mole of Venlafaxine HCl \approx 25 \text{ mole of Venlafaxine}
2.1.3.3 Physical properties (leaflet of Effexor XR)

**Appearance**: White to off white crystalline solid.

Taste is bitter.

**Solubility**: 572 mg / mL in water (freely soluble in water)

**Partition coefficient**: 0.43 (octanol: water)

**Melting Point**: 215-217°C

**Molecular volume**: 261.6 ± 3.0 cm³

**Infra Red Spectrum (IR Spectrum)**: Mentioned in Figure 2.7

**Differential Scanning Calorimetry (DSC)**: Mentioned in Figure 2.8

**X- Ray Powder Diffraction (XRD)**: Mentioned in Figure 2.9

![Infra Red Spectrum (IR Spectrum) of Venlafaxine HCl](image-url)
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Figure 2.8 Differential Scanning Calorimetry (DSC) of Venlafaxine HCl

Figure 2.9 X-Ray Powder Diffraction (XRD) of Venlafaxine HCl
2.1.3.4 Clinical pharmacology

2.1.3.4.1 Pharmacodynamics

Venlafaxine HCl is novel antidepressant. Antidepressant action is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite O-desmethyl venlafaxine are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. It does not possess monoamine oxidase inhibitory activity as well as has no significant affinity for muscarinic, histaminergic or α-1 adrenergic receptors in vitro. Hence, it does not associate with anticholinergic, sedative and cardiovascular side effects like other psychotropic drugs.

2.1.3.4.2 Pharmacokinetics

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean ±SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 L/kg and 5.7 ± 1.8 L/kg, respectively.

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%. Food did not affect the bioavailability of venlafaxine or its active metabolite. Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N, O-didesmethylvenlafaxine, and other minor metabolites. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.
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2.1.3.5 Dosage and administration

For the treatment of Major Depressive Disorder the recommended starting dose is 75 mg/day, administered in a single dose. For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by day 4.

2.1.3.6 Indications

Venlafaxine is indicated in major depressive disorders, is also indicated for symptomatic relief from anxiety and hot flashes.

2.1.3.7 Market products

Effexor XR capsules 150 mg
Effexor XR capsules 75 mg
Effexor XR capsules 37.5 mg
2.1.4 Polymers used in the study

2.1.4.1 Hypromellose

2.1.4.1.1 Introduction

The European Pharmacopoeia describes hydroxypropyl methylcellulose (Hypromellose) as partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in various grades that vary in viscosity and extent of substitution. It is an odorless, tasteless and inert hydrophilic polymer with no ionic charge.


Synonyms: Hydroxypropyl methylcellulose, H PMC, Methocel, Methylcellulose propylene glycol ether, Methyl hydroxypropylcellulose, Metolose, Tylopur.

Chemical Name: Cellulose hydroxypropyl methyl ether

CAS Registry Number: 9004-65-3

Empirical Formula and Molecular Weight: Hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Molecular weight is approximately 10000—150000.

Structural formula:

![Structural formula of Hypromellose]

Where R is H₃, CH₃ OR CH₃ CH (OH) CH₂

2.1.4.1.2 Typical properties:

- Acidity/alkalinity: pH = 5.5-8.0 for a 1% w/w aqueous solution.
- Ash: 1.5-3.0 % depending upon the grade.
- Autoignition temperature: 360 °C
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- Density (tapped): 0.5 - 0.7 g/cm³ for Pharmacoat.
- Melting point: Browns at 190 - 200 °C, chars at 225 - 230°C. Glass transition temperature is 170 - 180 °C.
- Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane.
- Viscosity: A wide range of viscosity types are available.
- Stability and storage conditions:
  - Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity. The gel point is 50-90 °C depending upon the grade of material.
  - HPMC powder is a stable material although it is hygroscopic after drying.
  - HPMC powder should be stored in a well-closed container, in a cool, dry place.

2.1.4.1.3 Application in pharmaceutical formulations and technology:

- In oral products, HPMC is primarily used as tablet binder, in film coating (2-10%) and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water soluble drugs from a matrix.
- Hydroxypropyl methylcellulose is widely used in oral and topical pharmaceutical formulations.
- Lower viscosity grades are used in aqueous film coating solutions while higher viscosity grades are used with organic solvents.
- Concentrations of 0.45 to 1% w/w may be added as a thickening agent to vehicles for eye-drops and artificial tear solutions.
- HPMC is also used as suspending and thickening agent in topical formulations, particularly ophthalmic preparations.
- HPMC is used as an adhesive in plastic bandages as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.
2.1.4.1.4 Regulatory status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA’s Inactive Ingredients Guide, in nonparenteral medicines licensed in the UK.

2.1.4.1.5 Nomenclature for methocel 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 hydroxypropyl methylcellulose (HPMC) products. 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 in millipascal-seconds (mPa s) of that product measured at 2% concentration in water at 20°C. Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name is mention below:

Table 2.1 Four types of HPMC as per USP 28

<table>
<thead>
<tr>
<th>Substitution type</th>
<th>Methoxy (%)</th>
<th>Hydroxypropoxy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min.</td>
<td>Max.</td>
</tr>
<tr>
<td>1828</td>
<td>16.5</td>
<td>20.0</td>
</tr>
<tr>
<td>2208</td>
<td>19.0</td>
<td>24.0</td>
</tr>
<tr>
<td>2906</td>
<td>27.0</td>
<td>30.0</td>
</tr>
<tr>
<td>2910</td>
<td>28.0</td>
<td>30.0</td>
</tr>
</tbody>
</table>
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2.1.4.1.6 Polymer structure and manufacturing

Methocel have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units (Figure 2.10). During the manufacture of cellulose ethers, cellulose fibers are treated with caustic solution, which in turn is treated with methyl chloride and/or propylene oxide. The fibrous reaction product is purified and ground to a fine powder.

According to the major chemical differences in their percent of methoxyl and hydroxypropoxyl substitution and degree of polymerization (measured as 2% solution viscosity), four Methocel products have been defined. Methylcellulose is made using only methyl chloride. These are Methocel A cellulose ethers (methylcellulose, MC, USP). For hydroxypropyl methylcellulose (HPMC) products, propylene oxide is used in addition to methyl chloride to obtain hydroxypropyl substitution on the anhydroglucose units (Figure 1.6). HPMC products include Methocel E (HPMC 2910, USP), Methocel F (HPMC 2906, USP), and Methocel K (HPMC 2208, USP) cellulose ethers. The hydroxypropyl substituent group, -OCH2CH (OH) CH3, contains a secondary hydroxyl on the number two carbon and may also be considered to form a propylene glycol ether of cellulose. The ratio of hydroxypropyl and methyl substitution influences HPMC properties such as organic solubility and the thermal gelation temperature of aqueous solutions.

Figure 2.10 Structure and substitution levels in Methocel products

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2.1.4.1.7 Why hypromellose 2208?

Of hydrophilic polymers, hydroxypropyl methylcellulose is the most popular material for the preparation of controlled-release dosage forms and it has been employed since the 1960s. One of its most important characteristics is high swellability, which has a significant effect on the release kinetics of an incorporated drug. Also its ease of compression, non-toxic nature, ability to accommodate a large percentage of drugs, and the minimum influence of processing variables on the release of drugs from matrices are some of the reasons for its popularity.

A prerequisite for achieving controlled drug release from HPMC matrix formulations is fast formation of a gelatinous layer. In other words, the polymer must hydrate fast enough to form a gel layer before the contents of the formulation dissolve prematurely (Alderman, 1984; Ferrero Rodriguez et al., 2000). In tablet formulations the hydration rate of HPMC type 2208 has turned out to be adequate, whereas types 2906 and 2910 do not hydrate fast enough to prevent the rapid disintegration and dissolution of tablet formulations. There are slight differences in the hydration rates of the different polymer substitutions, in practice there is little effect seen on the release rate during the first 10 minutes. The rate of hydration is in order of K>E>F>A. Thus methocel K premium grades are fastest hydrating followed by methocel E premium, methocel F premium and methocel A premium grades. The grades with substitution types are mentioned in the Table 2.2.

2.1.4.1.8 Factors affecting release from tablets containing hypromellose type 2208.

There are several factors that can affect the release rate of a drug from HPMC type 2208-based matrices, e.g. HPMC viscosity grade, HPMC/drug ratio, HPMC and drug particle size, drug solubility and formulation additives etc. Of these factors, the viscosity grade and concentration of the HPMC are those most often used in regulating drug release.

1. Molecular weight and viscosity of hypromellose

HPMC, being a semi-synthetic material derived from cellulose, is a linear polymer comprised of etherified anhydroglucose rings. For products typically used in controlled release applications, the degree of polymerization (DP) is adjusted to a range between 100 and 1500. The difference in molecular weight of various Methocel products is reflected in the viscosity of an aqueous solution of a standard concentration. Viscosity of polymer solutions is the result...
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of hydration of polymer chains, primarily through H-bonding of the oxygen atoms in the numerous ether linkages, causing them to extend and form relatively open random coils. A given hydrated random coil is further H-bonded to additional water molecules, entrapping water molecules within, and may be entangled with other random coils. All of these factors contribute to larger effective size and increased frictional resistance to flow.

Several studies have demonstrated that increasing the viscosity grade of HPMC type 2208 decreases the drug release rate from both tablet and hard capsule matrix formulations (Alderman, 1984; Ford et al., 1985a, b, c; Wan et al., 1992; Sung et al., 1996; Tros de llarduya et al., 1997; Li et al., 2003). This is due to the increase in the gel layer viscosity, causing the drug to diffuse slower through the gel layer.

In addition, the greater the viscosity of the gel, the more resistant the gel is to dissolution and erosion. Consequently, the gel layer can be a controlling factor in drug release. In some studies, depending on the model drugs and formulations used, the release rate of the model drugs was not further decreased even though the HPMC type 2208 polymer was changed from a lower viscosity grade to a higher viscosity grade, e.g. from 4000 to 15,000 mPa s or from 15,000 to 100,000 mPa s (measured as a 2% w/w solution at 20°C) (Ford et al., 1985b, c; Sung et al., 1996). It was suggested that the HPMC matrix formulations studied have a "limiting HPMC viscosity", i.e. the drug release rate no longer decreases when the viscosity grade is increased above a certain level, e.g. 4000 or 15,000 mPa s (Sung et al., 1996).
Table 2.2 Methocel grades by substitution type.

<table>
<thead>
<tr>
<th>METHOCEL™ Product</th>
<th>Chemical Type</th>
<th>Methoxyl Content, %</th>
<th>Hydroxy-propyl Content, %</th>
<th>Viscosity of 2% solution in water, cps</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOCEL™ A15 Premium LV</td>
<td>Methylcellulose, USP</td>
<td>27.5 - 31.5</td>
<td>0</td>
<td>12 - 18</td>
</tr>
<tr>
<td>METHOCEL™ A4C Premium</td>
<td>Methylcellulose, USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHOCEL™ A15C Premium</td>
<td>Methylcellulose, USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHOCEL™ A4M Premium</td>
<td>Methylcellulose, USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHOCEL™ E3 Premium LV</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>2.4 - 3.6</td>
</tr>
<tr>
<td>METHOCEL™ E5 Premium LV</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>4 - 6</td>
</tr>
<tr>
<td>METHOCEL™ E6 Premium LV</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>5 - 7</td>
</tr>
<tr>
<td>METHOCEL™ E15 Premium LV</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>12 - 18</td>
</tr>
<tr>
<td>METHOCEL™ E50 Premium LV</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>40 - 60</td>
</tr>
<tr>
<td>METHOCEL™ E4M Premium</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>3000 - 5600</td>
</tr>
<tr>
<td>METHOCEL™ E10M Premium CR</td>
<td>Hypromellose 2910</td>
<td>28 - 30</td>
<td>7 - 12</td>
<td>7500 - 14,000</td>
</tr>
<tr>
<td>METHOCEL™ F50 Premium</td>
<td>Hypromellose 2906</td>
<td>28 - 30</td>
<td>4 - 8</td>
<td>-</td>
</tr>
<tr>
<td>METHOCEL™ F4M Premium</td>
<td>Hypromellose 2906</td>
<td>28 - 30</td>
<td>4 - 8</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2.2 Methocel grades by substitution type.

<table>
<thead>
<tr>
<th>METHOCEL™ Product</th>
<th>Chemical Type</th>
<th>Methoxyl Content, %</th>
<th>Hydroxy-propyl Content, %</th>
<th>Viscosity of 2% solution in water, cps</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOCEL™ K3 Premium LV</td>
<td>Hypromellose 2208</td>
<td>19 - 24</td>
<td>7 - 12</td>
<td>2.4 – 3.6</td>
</tr>
<tr>
<td>METHOCEL™ K100 Premium LV</td>
<td>Hypromellose 2208</td>
<td>19 - 24</td>
<td>7 - 12</td>
<td>80 – 120</td>
</tr>
<tr>
<td>METHOCEL™ K4M Premium</td>
<td>Hypromellose 2208</td>
<td>19 - 24</td>
<td>7 - 12</td>
<td>3,000 – 5,600</td>
</tr>
<tr>
<td>METHOCEL™ K15M Premium</td>
<td>Hypromellose 2208</td>
<td>19 - 24</td>
<td>7 - 12</td>
<td>11,250 – 21,000</td>
</tr>
<tr>
<td>METHOCEL™ K100M Premium</td>
<td>Hypromellose 2208</td>
<td>19 - 24</td>
<td>7 - 12</td>
<td>80,000 – 120,000</td>
</tr>
</tbody>
</table>
2. Introduction and Review of Work Done

2. Hydration and Erosion Rates of hypromellose

The kinetics of gel growth is also very similar for all substitution types of HPMC; the observed apparent differences in swelling behavior are attributed to differential expansion of the glassy core (Rajabi-Siahboomi et al., 1994). When the HPMC-based matrix formulation comes into contact with a thermodynamically compatible aqueous solvent, the solvent penetrates into the free spaces on the surface between the macromolecular chains. When the solvent has sufficiently entered into the matrix the characteristic glassy-rubbery transition temperature (Tg) of the polymer is decreased to the level of the experimental temperature and relaxation of the polymeric chains takes place (Siepmann and Peppas, 2001). The amount of water bound to HPMC is related to both the substitution and the polymer molecular weight. Within the gel layer, there obviously exists a moisture gradient from the outside surface in contact with liquid to the inner dry core. Water appears to exist in at least three distinct states within a hydrated gel of pure polymer (McCrystal et al., 1997). Upon complete polymer hydration at the outer surface, chain disentanglement begins to occur, i.e., erosion of the matrix. The rate of erosion is related to molecular weight over a wide range by an inverse power law. In addition, erosion rate is affected by the composition and ionic strength of electrolytes in the liquid medium and, by the composition and level of drugs and other additives within the matrix.

To achieve controlled release through the use of a water-soluble polymer such as HPMC, the polymer must quickly hydrate on the outer tablet skin to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core. Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role. Evidence suggests that the chemistry of HPMC encourages a strong, tight gel formation compared to other cellulosics. As a result, drug-release rates have been sustained longer with HPMC than with equivalent levels of methylcellulose (MC), hydroxyethylcellulose (HEC), or carboxymethylcellulose (CMC). For these reasons, HPMC is very often the polymer of choice over other cellulosics.
The HPMC swells, causing the dimensions of the system to increase and the concentrations of the polymer and drug to change markedly. Water-soluble drugs dissolve in the solvent and diffuse out of the matrix according to concentration gradients. If the drug is poorly soluble in the solvent, dissolved and non-dissolved drug coexist within the polymer matrix and the non-dissolved drug is not available for diffusion. Poorly soluble and insoluble drugs are mainly released when the outermost gel layer of the matrix is eroded. The erosion rate depends on the viscosity of the HPMC type used. The resulting drug release mechanism (Fickian, non-Fickian or Case II release) depends on the rates of drug diffusion, matrix relaxation and matrix erosion, and also on the dissolution of the drug in the gel.

3. Size of tablet containing hypromellose
The size of the tablet may influence the drug release rate and the amount of polymer needed to obtain controlled release. Usually, the smaller the tablet is the greater the polymer content required (Alderman, 1984). Further, as the tablet size is increased, the drug release rate may be decreased due to changes in surface-to-volume ratios and in the degree of initial gel formation.

4. The particle size and size distribution of the hypromellose
The particle size and size distribution of the HPMC type 2208 powder affect the hydration rate of the HPMC, and thus the rate of gel formation and drug release from tablet matrices (Alderman, 1984). The coarser the HPMC powder particles are, the slower the gel formation and the greater the drug release rate. The effect of the particle size of the drug on the release rate from HPMC type 2208 matrices depends on the solubility of the drug (Ford et al., 1985a, b, c; Tros de Ilarduya et al., 1997). Ford and co-workers (1985a, b, and c) noticed that decreasing the particle size of freely water-soluble drugs insignificantly affected the release rate, but when the model drug was poorly water-soluble, the release rates increased as the particle size of the drug decreased.

5. Drug solubility
Drug solubility also affects the release rate from HPMC matrices: increased solubility of the model drug results in a higher release rate from HPMC type 2208-based tablet formulations
2. Introduction and Review of Work Done

(Colombo et al., 1995; Ferrero Rodriguez et al., 2000). This is probably due to a higher concentration gradient through the gel layer, which increases the diffusion coefficient of the drug (Colombo et al., 1995). The water-solubility of drugs has an effect also on the release kinetics of drugs from HPMC type 2208 matrices (Ford et al., 1987; Ranga-Rao et al., 1990). Ranga Rao and co-workers (1990) studied the release of 23 drugs of various solubilities from HPMC type 2208 matrix tablets and reported that several sparingly, slightly and very slightly soluble drugs were released at a nearly zero order rate from the matrices, whereas the mode of release of water-soluble drugs was non-Fickian. Ford and co-workers (1987) reported similar observations when they studied the release of seven soluble and insoluble drugs from HPMC type 2208 matrix tablets.

6. Formulation additive

Formulation additives also modify the release rate of drugs from HPMC matrices. The addition of lactose or calcium phosphate to HPMC type 2208-based tablet and capsule formulations generally increases the release rate of drugs (Alderman, 1984; Ford et al., 1987; Sung et al., 1996; Nokhodchi et al., 1999). Sodium carboxymethylcellulose (NaCMC) and microcrystalline cellulose are insoluble and swellable additives often used as fillers or disintegrants. When these are incorporated into HPMC type 2208-based tablet matrices, the gelatinous layer tends to expand, causing more of the drug to be released in the early stages of dissolution (Alderman, 1984; Nokhodchi et al., 1999).

Also the effect of different surfactants on the release of drugs from HPMC type 2208-based matrix tablets has been evaluated (Feely and Davis, 1988; Nokhodchi et al., 1999). Ionic surfactants (e.g. sodium dodecylsulphate, n-hexadecylsulphate and n-octadecylsulphate) retarded the drug release only when these were ionized and had opposite charges (Feely and Davis, 1988). Nokhodchi and co-workers (1999) have reported that incorporating sodium lauryl sulfate into HPMC matrices increased the drug release. This was probably due to the pores/channels that the surfactant formed in the matrix, thereby increasing the effective surface area by a method other than wetting.
2.1.4.2 Polyethylene oxide

2.1.4.2.1 Introduction

Polyethylene oxide is non ionic hydrophilic matrixing agent available in various grades (Table 2.3). Manufactured by Dow chemicals under the trade name of POLYOX water soluble Resin NF for pharmaceutical application. Similar to hypromellose low viscosity grades are recommended for tablet binding, tablet coatings, transdermal drug delivery systems, mucosal bioadhesives etc. while higher viscosity grades are useful for controlled release matrix dosage systems. They are having good flow properties and are suitable for direct compaction as well as can be used for melt granulation, wet granulation etc.

Table 2.3 List of polyox manufacture by Dow chemicals (Dow site)

<table>
<thead>
<tr>
<th>POLYOX water soluble Resin NF product</th>
<th>Approx. Molecular weight</th>
<th>Viscosity Range at 25°C in cps</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSR N-10</td>
<td>100,000</td>
<td>30-50</td>
</tr>
<tr>
<td>WSR N-80</td>
<td>200,000</td>
<td>55-90</td>
</tr>
<tr>
<td>WSR N-750</td>
<td>300,000</td>
<td>600-1,200</td>
</tr>
<tr>
<td>WSR-205</td>
<td>600,000</td>
<td>4,500-8,800</td>
</tr>
<tr>
<td>WSR-1105</td>
<td>900,000</td>
<td>8,800-17,600</td>
</tr>
<tr>
<td>WSR N-12K</td>
<td>1,000,000</td>
<td>400-800</td>
</tr>
<tr>
<td>WSR N-60K</td>
<td>2,000,000</td>
<td>2,000-4,000</td>
</tr>
<tr>
<td>WSR-301</td>
<td>4,000,000</td>
<td>1,650-5,500</td>
</tr>
<tr>
<td>WSR Coagulant</td>
<td>5,000,000</td>
<td>5,500-7,500</td>
</tr>
<tr>
<td>WSR-303</td>
<td>7,000,000</td>
<td>7,500-10,000</td>
</tr>
</tbody>
</table>

Nonproprietary Names: USPNF: Polyethylene oxide

Synonyms: Polyox; polyoxirane; polyoxyethylene.

Chemical Name: Polyethylene oxide

CAS Registry Number: 25322-68-3
Structural Formula

USPNF 23 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula (CH₂CH₂O)ₙ, where n represents the average number oxyethylene groups. It may contain up to 3% of silicon dioxide (Owen, 2005).

2.1.4.2.2 Typical properties

- Angle of Repose: 34°
- Density (true): 1.3 g/cm³
- Melting point: 65 - 70 °C.
- Solubility: Soluble in water and a number of common organic solvents such as acetonitrile, chloroform and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycols, and most alcohols.
- Viscosity: A wide range of viscosity types are available (Table 1.3.2.1).

2.1.4.2.3 Applications in Pharmaceutical Formulation or Technology

The polyethylene oxide has many applications in pharmaceutical industries because of its biocompatibility, hydrophilicity and versatility.

- Polyethylene oxide of low molecular weights can be used as a tablet binder at concentrations of 5-85%.
- The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate or sustained-release matrix formulations (Table 1.3.2.1).
- Polyethylene oxide has been shown to be an excellent mucoadhesive polymer. Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water-formulations to provide improved viscosity stability.
- Polyethylene oxide films demonstrate good lubricity. This property has been utilized in the development of coatings for medical devices.
- Polyethylene oxide can be radiation crosslinked in solution to produce a hydrogel that can be used in wound care applications.
2. Introduction and Review of Work Done

2.1.4.2.4 Regulatory Status

Included in the FDA inactive ingredients guide (sustained release tablets). Included in the Canadian list of acceptable non-medicinal ingredients.

2.1.4.2.5 Factors affecting release from polyethylene oxide matrix

There are several factors that can affect the release rate of a drug from Polyox based matrices, e.g. PEO viscosity grade, PEO /drug ratio, PEO and drug particle size, drug solubility and formulation additives etc. Of these factors, the viscosity grade and concentration of the PEO are those most often used in regulating drug release. For water soluble drugs, the drug release is primarily controlled by the diffusion of the drug through the hydrogel layer produced on the surface of the tablet.

1. Molecular weight:

To increase the molecular weight while maintaining a constant polymer concentration can drastically reduce the release rates. The increased molecular weight leads to an increase in gel strength which tends to decrease the diffusion of the drug; however, there is a maximum molecular weight beyond which no further change in release rate is affected. Figure 2.11 shows the effect of molecular weights of polyox water-soluble resins on the release rate. As can be seen, an increase in molecular weight from 5,000,000 to 7,000,000 does not appreciably alter the release rate for the water-soluble active, caffeine. (Dow site (a))

![Figure 2.11 Effect of molecular weight of polyox water-soluble resins on in vitro release rates of caffeine from a matrix tablet](image-url)
2. Polymer concentration:
Increasing polymer concentration increases the gel viscosity on the surface of the tablets, which will retard the diffusion of the drug from the gel layer. Figure 2.12 shows caffeine release from matrix tablets produced from polyox WSR-303 NF (7,000,000 molecular weight). When polymer concentration was changed from 10 to 60 percent in the formulation, no drastic changes in the release rate was observed. At a very low polymer concentration, the initial drug release is larger, but the rate of release is very similar to that obtained for higher polymer concentrations.

![Graph showing caffeine release from matrix tablets](image)

**Figure 2.12** Effect of polymer concentration on in vitro release rates of caffeine from a matrix tablet with polyox WSR-303 NF

3. Drug Loading
The drug loading does not affect significantly the release rates. The almost little change in the release rate takes place when the caffeine concentration is increased from 50 to 150mg in 500-mg tablets. Figure 2.13 summarizes matrix tablet release data obtained by changing the drug concentration of caffeine in polyox water-soluble resins.

4. Drug solubility
The release is faster in case of highly soluble drug as it can easily diffuse out from the gel layer of polyox as compared to insoluble actives. Polyox water-soluble resins swell greatly when hydrated, and the resulting gel layer does not erode readily. The polymer, therefore, is an ideal vehicle for insoluble drugs in matrix tablets.
Figure 2.13 Effect of drug loading on in vitro release rate of caffeine from a matrix tablet with polyox WSR coagulant NF

5. Particle size

Particle size can play a role in matrix tablet performance by influencing the initial rate of hydration and gel layer formation. The smaller particles produce slower initial release compared to larger particles as it takes some longer time to hydrate. The data in Figure 2.14 were generated by selectively separating a standard polyox WSR sample into 5 different particle size fractions. Tablets were produced from each fraction and drug release rates were measured. The data indicate some variation in release rate as a function of particle size with the smaller particles producing slower initial release rates. Interestingly, extreme drug dumping is not seen even when using the very large particle size fraction due to the rapid swelling characteristics of polyox WSR.

Figure 2.14 Particle size effect on riboflavin release from matrix tablets using polyox water soluble resins
6. pH

When used in oral applications, polyox WSR systems do not show a strong pH response due to their nonionic nature. The data in Figure 2.15 show release profiles collected at different pH values for a theophylline matrix system. As expected, the release rate does not vary as a function of pH.

![Graph showing release profiles at different pH values](image)

**Figure 2.15** Effect of pH on release of theophylline from matrix tablets using polyox water soluble resins

2.1.4.2.6 Method of Manufacturing:

The material known as polyethylene glycol is in fact polyethylene oxide but has in addition hydroxyl groups at each end of molecule. The simple, water soluble, linear polymer can be modified by chemical interaction to form water-insoluble but water-swellable hydrogel retaining the desirable properties associated with the ethylene oxide part of structure.
2.1.4.3 Xanthan Gum

2.1.4.3.1 Introduction

Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug must diffuse. This property makes xanthan gum a useful ingredient for controlled and sustained release applications. Their compatibility with a wide variety of ingredients makes them particularly effective in these applications. Xanthan gum has been evaluated as a hydrophilic matrix for CR preparation, using different model drugs including theophylline (Fu Lu, et al., 1991), cephalaxin (Dhopeshwarkar, et al., 1994), prednisolone (Watanabe, and Yakou, 1992) indomethacin (Watanabe, and Yakou, 1993), and Diclofenac sodium (Yeole, et al., 2006).

**Non proprietary Names:** BP: Xanthan gum, PhEur: Xanthani gummi, USPNF: Xanthan gum

**Synonyms:** Corn sugar gum, Keltrol, polysaccharide 8-1459, Rhodigel, Vanzan NF, Xantural.

**Chemical Name:** Xanthan gum

**CAS Registry Number:** 11138-66-2

**Empirical Formula and Molecular Weight:** \((C_{35}H_{49}O_{29})\) and approximately \(2 \times 10^6\)

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

**Structural formula:**

Xanthan gum, an anionic polyelectrolyte is a high molecular weight heteropolysaccharide produced by viscous fermentation. Its unique functionality compared to other commercial polysaccharides is provided by the actual structure of the xanthan gum molecule. As shown in Figure 2.16, the polymer backbone is made up of \(\beta-1, 4\)-linked D-glucose residues and, therefore, is identical to the cellulose molecule. A trisaccharide side chain containing one glucuronic acid unit between two mannose units is linked to every second glucose unit at the number 3 position. This side chain consisting of \(\alpha\)-D-mannose, which contains an acetyl group, of \(\beta\)-D-glucuronic acid, and of a terminal \(\beta\)-D- mannose unit linked with a pyruvate group. The mannose closest to the backbone has an acetic acid ester on carbon 6, and the
mannose at the end of the trisaccharide is linked through carbons 6 and 4 to the second carbon of pyruvic acid. The negatively charged carboxyl groups on the side chains cause the molecules to form very viscous fluids when mixed with water. Approximately 60% of the terminal mannose units being pyruvylated and 90% of the proximal mannose units substituted at C6 with O-acetyl groups. It has side chains of side chains 2 mannose and 1 gluconic glucuronic acid group. It is not surprising that xanthans of different pyruvate levels (that is 1 to 6 %) display different rheological (flow) properties. Pyruvic acid attached to the terminal carbohydrate of the side chains adds another carboxylate group.

Figure 2.16 Structural unit of Xanthan gum

2.1.4.3.2 Typical properties

Appearance: Cream colored powder

Solubility in Cold Water: Dispersed hydrated to form pseudoplastic mixtures, high water solubility

Melting point: Chars at 270°C.

Viscosity: Viscosity of 1% aqueous solution ranges between 1200 to 1600 cps.

Rheology: The presence of anionic side chains on the Xanthan gum molecules enhances hydration and makes Xanthan gum soluble in cold water. In addition, the form and the rigidity of the macromolecules determine the rheology of the solutions. Rheological properties are mentioned in following diagram (SKW Boisystems).
2. Introduction and Review of Work Done

---

At rest  |  Low shear  |  High shear
Disordered structure  |  Semi-ordered structure  |  Ordered structure
with yield value  |  free flowing  |  flowing

**Figure 2.17** Schematic rheological behaviour of Xanthan gum—Shear dependent reversible flowing properties.

### 2.1.4.3.3 Application in pharmaceutical formulations and technology:

- Xanthan gum had been limited for use as thickening, suspending, and emulsifying agent for water-based systems.
- It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics (Tobyn et al., 1996; Sujja-areevath et al., 1998). In tablets xanthan gum can be used to create a retarded drug release effect. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug must diffuse. This property makes xanthan gum a useful ingredient for controlled and sustained release applications.
- It is an excellent stabilizer for pharmaceutical formulations. It uniformly suspends water insoluble ingredients, e.g. barium sulphate in X-ray contrast media and perfectly stabilizes all kinds of pharmaceutical emulsions.
- In lozenges, xanthan gum prolongs the contact time of the active ingredient. Their compatibility with a wide variety of ingredients makes them particularly effective in these applications.
2. Introduction and Review of Work Done

2.1.4.3.4 Method of manufacturing:

The polysaccharides for scientific and industrial applications are obtained more conveniently from microbial sources due to several factors. They can be produced under controlled conditions from selected species using renewable sources and are biocompatible and biodegradable. These factors have accelerated the use of microbial gums such as pullulan, curdlan, scleroglucan, dextran and xanthan. Microbial polysaccharides are composed of regular repeating units of simple sugars like glucose, mannose, fructose, etc. (Lachke, 2004).

Xanthan gum is a hydrophilic polymer, secreted from *Xanthomonas campestris* (a gram negative, yellow-pigmented bacterium). This polymer is studied for the fabrication of matrices with constant drug release characteristics (Tobyn et al., 1996; Sujja-areevath et al., 1998; Talukdar & Plaizier-Vercammen, 1993; Talukdar et al., 1998; Cox et al., 1999; Billa & Yuen, 2000; Munday & Cox, 2000). Xanthan is the only bacterial polysaccharide produced industrially on a large scale. It is a natural carbohydrate commercially produced by fermenting glucose with the appropriate micro-organisms. The percent composition of xanthan proposed for industrial use is as follows: Glucose 37, mannose 43.4, glucuronic acid 19.5, acetate 4.5 and pyruvate 4.4%.
2. Introduction and Review of Work Done

2.1.5 Hydrophilic swellable matrix (deelker, 1987, pitt et al., 1983, ranga Rao et al., 1988, Hogan, 1989 and Dow site (a))

A hydrophilic matrix tablet is a simple to formulate, yet effective sustained-release drug-delivery system in which a bio-active is uniformly distributed within a polymer matrix. The drug release mechanism is controlled by several variables in a dynamic process. The drug release into the physiological environment is extended over a much greater time than if the drug is used in its native form.

Hydrophilic and hydrophobic polymers are used in drug delivery systems. Very little information is available on hydrophobic polymers. Moreover, the temperature is to be critically controlled during fabrication of the dosage form especially when wax matrix is used.

The hydrophilic polymers can be arranged in to three broad groups:

1. Non-cellulose Natural or semi synthetic polymers: these are products of vegetable origin and are generally used as such. Agar, alginates, guar gum, chitosan, etc. are commonly used polymers.

2. Polymer of acrylic acid: these are arranged in the carbomer group and commercialized under the brand name of Carbopol\textsuperscript{R}. The major disadvantage of this type of polymers is its pH dependent gelling characteristic.

3. Cellulose ethers: the semi synthetic cellulose derivatives are the most widely used polymers. Non-ionics such as hypromellose (HPMC) of different viscosity grade are widely used. The methylcelluloses (MC), in contrast, have not proved especially useful in this field. In the last few years a number of interesting applications of the ionic sodium carboxymethyl cellulose (Na-CMC) have been found. Polyethylene oxide is non ionic hydrophilic matrixing agent available in various grades.

Manufactured by Dow chemicals under the trade name of POLYOX water soluble Resin NF for pharmaceutical application.

Hydrogels (hydro-colloids) are cross linked hydrophilic polymers capable of imbibing large volumes of water, yet insoluble in water but swellable when immersed. The water retention capacity of these materials is due to the presence of hydrophilic functional groups such as -OH, -COOH, -CONH\textsubscript{2}, -CONH, -SO\textsubscript{3}H along the polymer chains (Peppas and Mikos, 1986; Kudela, 1987; Saraydin et al., 1995). Hydrogels are known as good candidates for controlled release formulations for pharmaceutical applications mostly due to their high biocompatibility.
2. Introduction and Review of Work Done

(Korsmeyer and Peppas, 1983; Peppas, 1980). The hydrophilic gum swells and forms a gel layer and hence the drug release is controlled.

The advantages of hydrogels are as follows:

i. They are biocompatible,

ii. The soft rubbery nature of hydrogels minimizes mechanical irritation,

iii. The drug release can be regulated by controlling water uptake and subsequent swelling,

iv. They can be used for both hydrophilic and hydrophobic drugs, and

v. Low hydrogel/water interfacial tension minimizes protein adsorption and cell adhesion.

Drug release from hydrogel matrices is dependent on factors such as swelling and dissolution of the polymer, giving rise to mass erosion of the system, concomitantly with dissolution and diffusion of drug. Initially the matrix thickness increases due to swelling of the polymer and then due to polymer dissolution as well as dissolution of drug and fillers, the matrix thickness decreases. The drug release is dependent on the relative magnitude of the rate of polymer swelling at the moving rubbery/glassy front and the rate of polymer erosion at the swollen polymer/dissolution medium front. It has been shown that it is necessary to attain synchronization of the velocities of the swelling front and the erosion front in order to achieve zero order release kinetics from hydrophilic matrices. The establishment of front synchronization is not commonly observed in pharmaceutical dosage forms because poorly water soluble polymers are employed for fabrication of dosage forms.
2.2 Review of work done

2.2.1 Review of work done on venlafaxine HCl

The matrix system based on swellable as well as non-swellable polymer for sustaining the release of venlafaxine HCl was developed (Makhija et al., 2005). Hydrophilic polymer such as Methocel K15M and Methocel K100M and a hydrophobic polymer Ethocel 100 were tried. The potential of Eudragit RSPO and cellulose acetate as release retarding agents was also investigated. The in vitro dissolution of developed formulation was compared with market product. Lag time was observed in marketed capsules containing pellets. The formulated product showed better bioavailability compared to the marketed formulation.

The press coated tablets of venlafaxine HCl were prepared to modify the drug release (Gohel et al., 2008). Hydroxypropylmethylcellulose K4M was used in core and hydroxypropylmethylcellulose K100M was used in coat in press coated tablet. They developed 12 h release profile with 16% drug release in first h and zero order drug release thereafter. Korsemeyer and Peppas model best explain the kinetic of drug release.

The investigators (Baldomero et al., 2005) studied effect of venlafaxine, on depressed patients in comparison with conventional antidepressant like paroxetine, sertraline, citalopram, etc. They concluded that extended release venlafaxine is more effective than the conventional antidepressants for the patients who do not tolerate or respond adequately to treatment with a conventional antidepressant.
2.2.2 Review of work done on dosage form and hypromellose

Once-daily sustained-release matrix tablets of nicorandil was developed (Reddy et al., 2003). The tablets were prepared by the wet granulation method. Ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinyl pyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose, and sodium alginate. They calculated theoretical release profile and according to that once daily formulation of nicorandil should release 5.92 mg drug in first hour followed by 3.21 every hour till 24 hrs. Amongst all composition tried, formulation containing drug-to-HPMC in 1:4 ratio and granulated with ethanolic solution of EC 4% w/v showed release comparable to calculated release profile.

The investigators (Bravo et al., 2002) developed uncoated hydroxypropyl methyl cellulose matrix tablets and evaluated the effect of different levels of microcrystalline cellulose and starch as release modulator and lactose as a soluble diluent. They concluded that each of these components was capable of interacting to some extent with each other to control the drug release. The developed formulation was stable, comparable to marketed diclofenac sodium sustained release tablets and has less gastrointestinal adverse effects.

The developers (Juarez, et al., 2001) studied the influence of admixing carboxymethylcellulose on release of 4-aminopyridine from hydroxypropyl methylcellulose matrix tablets. They prepared tablets with different proportions of HPMC as well as with different proportions of admixed carboxymethylcellulose in the range up to 35% of total polymer. They reported that by altering proportion of carboxymethylcellulose required zero order release was derived.

They (Yihong, et al., 2003) have prepared once daily controlled release dosage form of divalproex sodium with once daily administration and evaluated for in vitro and in vivo performance. The effect of different dissolution media and dissolution conditions was investigated. They identified the USP apparatus II at 100 RPM in 500 mL of 0.1 N HCl...
for 45 min followed by 900 mL 0.05 M Phosphate buffer containing 75 mM SLS and having PH 5.5 as the optimum conditions representing in vivo performance of divalproex sodium controlled release matrix system. The developed formulation showed nearly constant therapeutic plasma concentrations over 24 hr dosing interval.

The investigators (Samani, et al., 2003) evaluated the effect of polymer blends on the in vitro release profile of diclofenac sodium matrices. Different grades of hydroxypropyl methylcellulose and Carbopol 940 were tried alone as well as in combination. Hydroxypropyl methylcellulose (higher viscosity grade) was required in higher concentration, Carbopol 940 alone showed fluctuation in release. When both polymer were combined, the drug release became more uniform and its kinetic approached to zero order and release fluctuation were diminished. Additionally total amount of polymer was reduced to get the required drug release.

The effect of pH dependent solubility of weakly basic drug or salts thereof in the matrix tablets was studied (Streubel, et al. 2000). They studied two approaches: A) Use of enteric polymer like hydroxypropyl methylcellulose acetate succinate and B) Use of acidic substances like fumaric, succinic or adipic acid to create acidic microenvironment. The first approach failed to give pH independent release while the second approach worked well with verapamil HCl tablets containing combination of HPMC and ethylcellulose.

The hydration and matrix erosion of hydroxyethyl cellulose (HEC) and hydroxypropyl cellulose (HPC) and its effect on release of chlorpheniramine maleate was evaluated (Roy, and Rohera, 2002). They reported that HEC matrices followed non-fickian behavior and HPC matrices followed Higuchi diffusion-controlled matrix release. HEC matrix exhibite a faster liquid penetration rate and the matrix demonstrated 5-6 fold higher swelling and water uptake capability when compared with HPC matrix. High swelling index of HEC coupled with relatively higher rate of erosion (1.4 fold as compared to HPC) resulted in higher release rate. Higher release rate from HEC matrices compared to HPC matrices was due to relatively higher hydrophilicity of HEC.
The effect of hydrophilic (Hydroxypropyl methylcellulose (HPMC)) and hydrophobic (Hydrogenated Castor Oil (HCO)) polymers on the release rate of tramadol HCl was studied by the authors (Tiwari, et al., 2003). The HPMC tablets were prepared by wet granulation while melt granulation was used for preparing HCO tablets. The effect of ethyl cellulose in either of matrix tablet was evaluated to prolong the drug release. Amongst these two polymers, tablets containing HCO were found to be best suited for modulating the delivery of the highly water soluble drug, tramadol HCl. The burst release was controlled by coating the tablets with aqueous dispersion of ethyl cellulose. To further modulate the drug release, channel forming agent such as HPMC and lactose were tried.

The authors (Al-taani, and Tashtoush, 2003) evaluated the effect of microenvironment pH on release of diclofenac sodium from swellable and erodable buffered matrices. They prepared tablets using HPMC as swellable and pH independent polymer and Eudragit L100-55 as pH dependent polymer of different microenvironment pH ranging from 6.2 to 8.3. They concluded that the microenvironment pH can alter the release rate of diclofenac sodium. The drug release was found to be pH dependent. Both swelling and erosion controled the drug release and hence zero order release pattern was obtained.

Sustained release tablet of didanosine, anti HIV drug using combination of insoluble polymer like methacrylic resin (Eudragit RSPM) and ethylcellulose (Ethocel 100) was developed (Sanchez-Lafuente, et al., 2002). They found that with increase in amount of ethocel 100, drug release was decreased. They further evaluated the effect of percent of drug in the tablet and conclude that drug release increased with increase in drug percent in tablets.

They (Siahi, et al., 2005) used hydroxypropyl methylcellulose, tragacanth and acacia for making sustained release tablets of highly soluble drug verapamil HCl. They formulated one layer tablets as well as three layer tablets where middle layer contained the drug and polymer and the outer layers contained only polymer. They found that tragacanth and
H规程C yielded sustained release while acacia failed to prolong the drug release. The results also showed that the location of the polymers in the three layer tablets has a pronounced effect on the drug release.

Sustained released tablets of water soluble drug by direct compression using different grades of sodium alginate was developed by authors (Holte, et al., 2003). Amongst the four grades of sodium alginate investigated, no significant change in drug release was found. Drug release rate were not affected by tensile strength of tablets. Sustained release up to 16 hr was achieved using sodium alginate along with dibasic calcium phosphate.

The application of modeling system in the formulation of extended release hydrophilic matrices was studied by Levina, 2006. They used drugs of higher water solubility as well as of low water solubility, polymer of different viscosity grades in different levels as well as filler of different solubility. They concluded that drug solubility and drug to polymer ratio are the most important factors. Release rate is faster with more soluble drugs compared to low solubility drugs as well as soluble filler also increase release compared to insoluble fillers. They also verified the developed HyperStart model for Metformin HCl as high dose high solubility drug and nifedipine as low dose low solubility drug and found satisfactory results.

The investigators (Jamzad et al.,2005) studied the influence of water soluble and insoluble excipients on dynamics of hydration, front movement, erosion and drug release from hydrophilic matrix tablets containing water soluble drug. They concluded that matrices containing approximately 30% drug load and water soluble lactose demonstrated more pronounced swelling front movement and hence drug release relative to matrix tablets containing dicalcium phosphate dihydrate. They concluded that unlike in conventional dosage forms inclusion of excipients in hydrophilic controlled-release tablets containing water soluble drugs should be carefully analyzed as their various physico-chemical properties may have significant implications on swelling dynamics, front movement, drug release kinetics, and consequently in vivo performance.
The magnetic resonance imaging was used by the scientists (Tritt-Goc, and Pislewski, 2002) for study of hydration of hydroxypropyl methylcellulose samples. They performed measurement at two pH values, i.e. at pH 2 and pH 6. They concluded that change in the solvent pH value influences the diffusion and swelling properties of HPMC. At pH 2, anomalous behavior was observed while at pH 6, Fickian diffusion was observed. Hydroxypropyl methylcellulose hydrates more rapidly at pH 6 which leads to larger diffusion path length and hence slower drug release compared to that at pH 2.

The developers (Amaral, et al., 2001) evaluated the effect of concentration of hydrophilic (hydroxypropyl methylcellulose, HPMC) and hydrophobic (hydrogenated castor oil, HCO) excipients, fillers and buffers on release of naproxen. They concluded that increased amount of HPMC or HCO resulted in reduced drug release. The buffer modulated the drug release from the HPMC and HCO matrix. The presence of lactose did not show any change in release from HPMC matrix compared to dibasic calcium phosphate, while in HCO matrix, lactose significantly increased naproxen release.

The hydroxypropyl methylcellulose based matrix tablets of acetaminophen without filler as well as with soluble fillers like PEG 6000 and lactose was prepared by the authors (Sako et al., 2002). They found that there is no significant difference in vitro drug release even at high agitation speed while in vivo the significant difference was observed in area under the curve. The absorption profile of HPMC matrix with PEG 6000 was the fastest followed by the lactose and without filler. The dissolution test was modified to establish IVIVC.

The impact of formulation factors on the properties of 12 hour modified release formulation of verapamil HCl was investigated (Gohel, et al., 2003). The tablets containing 30% of Eudragit RS PO/RL PO as matrixing agent, 10% of HPMC K4M as auxiliary matrixing agent and 15% of PEG 4000 as channeling agent showed required release in acidic media. At higher pH the drug release was enhanced by the addition of succinic acid to create acidic micro environment around the tablet.
Rani, and Mishra (2004), prepared simple matrix tablet and osmotic matrix tablets. They compared the developed formulations with the market product of diclofenac sodium in vitro as well as in vivo. They concluded that better control of diclofenac sodium release was observed with HPMC compared to HPMC plus EC. The plastisizer type affected drug release. They concluded that all the developed formulations showed better AUC compared to market product.

The influence of fillers such as microcrystalline cellulose, spray dried lactose and partially pregelatinised maize starch (starch 1500) on chlorpheniramine maleate and theophylline release from hydroxypropyl methylcellulose matrix system was studied by the investigators (Levina, and Rajabi-Siahboomi, 2004). They concluded that starch 1500 significantly retarded the release of both the drugs compared to MCC and spray dried lactose. This effect may be imparted through synergistic interactions between starch 1500 and HPMC.

They (Colombo et al., 1999) developed matrix tablet of buflomedil pyridoxal, a water soluble drug. They concluded that in addition to erosion of hydroxypropyl methylcellulose matrix and drug diffusion, the dissolved drug in gel layer and polymer relaxation are the important factors affecting the kinetic of release.

The effect of microenvironment pH on release of weakly basic drug and their salts was studied by the investigators (Tatavarti et al., 2004). A drop in aqueous solubility at high pH conditions resulted in low and incomplete release of these drugs from sustained release formulations. The effect of Eudragit L 100-55 and Carbopol 71P was studied on release of papaverine HCl and verapamil HCl release from HPMC based matrix tablets. Both the acidic substances increased release of papaverine HCl. The verapamil HCl release was retarded in presence of Eudragit L 100-55 which may be due to interaction of drug and polymer. The verapamil HCl release was faster in presence of Carbopol 71P compared to conventional tablets containing HPMC without any acidic additives.
2. Introduction and Review of Work Done

They (Deshpande, et al., 1997) developed gastric retentive matrix tablets coated with permeable membrane. They used Carbopol as a gelling agent and carbonates as alkaline excipient. Additionally polyvinyl pyrrolidone XL was used to contribute swelling of tablets. Eudragit was used as permeable coating material.

The investigation was aimed at characterization of the mode of release from two different substitution types of HPMC and the effect of chemical structure of drugs using the QSPR technique (Gafourian, et al., 2007). They established the statistically significant relationship between release parameters and the structural descriptors like molecular mechanical parameters, quantum mechanical parameters, graph theoretical parameters, partition coefficient, the aqueous solubility of the drug etc. The concluded that the most important parameter determining the release profile from both HPMC K4M and HPMC E4M matrices were aqueous solubility of drug and the size of the drug molecule. The aqueous solubility have enhancing effect while the size of the drug molecule has reducing effect on the release profile for all the drug selected.

The significance of factors such as drug solubility, polymer molecular weight, drug loading dose, compression force, and hydrodynamic conditions on drug release from swellable hydrophilic delivery system was investigated by investigators (Kim et al., 1997). They found that mean dissolution time (MDT) for 50 and 80% drug release provided more accurate information on release behavior. The dominating effect of matrix composition over variations in drug solubilities in controlling drug release form the delivery system was observed. Hydrodynamic stress and intensity of fluid follow causes greater attrition at the swollen periphery and is responsible for dramatic increases in release rates.

The investigators (Gao, et al., 1996) characterized the effect of hydroxypropyl methylcellulose (HPMC)/lactose ratio and HPMC viscosity grade (molecular weight) on solute release and swelling of matrix tablets. They found that HPMC/lactose ratio modulate drug release rate by altering drug diffusivity, a function of gel composition. In contrast, HPMC viscosity grade has a critical impact upon both the matrix dissolution
and gel layer thickness development. This study further confirms that diffusion is the dominant release mechanism for water soluble drugs from polymer matrix tablets.

The investigator (El-nabarawi, 2005) prepared two layered device comprising of tenoxicam containing layer and a drug free membrane layer based on Geomatrix® Technology. The drug–hydroxypropyl methylcellulose (HPMC) layer was covered by drug free membrane layer composed of a mixture of different ratios of HPMC and ethyl cellulose (EC). The results indicate that, the release of drug from HPMC matrixes without the drug free membrane layer was fast and follows diffusion controlled mechanism. Few batches showed linear drug release with time (zero order) and extended for long time especially when thickness and the ratio of EC was increased in the drug free membrane layer. They concluded that, changing the geometry of drug layer by addition of drug free membrane layer and changing its composition and thickness plays an important role in determining whether the drug free membrane layer is rate-controlling or modulator membrane.
2. Introduction and Review of Work Done

2.2.3 Review of work done on polyethylene oxide

The author (Kim, 1995) evaluated drug release through powder mixture of poly (ethylene oxide), a drug and magnesium stearate. They studied effect of molecular weight, drug loading, drug solubility, pH of dissolution medium and stirring rate. The drug release from high molecular weight PEO was governed by swelling of polymer rather than erosion leading to anomalous release while from low molecular weight PEO it was governed by swelling/erosion resulting in synchronization and a constant release rate. Additionally they noticed that drug loading, drug solubility, pH of dissolution medium and stirring rate did not affect drug release regardless of the molecular weight of PEO.

The effect of molecular weight of poly (oxyethylene) on release of furosemide and captopril from controlled release hard gelatin capsules were studied (Efentakis, and Vlachou, 2005). Swelling experiments showed a high degree of swelling of these polymers in both gastric and buffer solution. These polymers can sustained the release of both water soluble and insoluble drugs from drug delivery systems. The low molecular weight polymer exhibited a less pronounced sustained effect compared to the high molecular weight polymers. An increase in content of polymer results in decrease in the release rate of the drug. Solubility of drug clearly influenced the release rate. The release kinetics was influenced by the molecular weight of polymer, the drug solubility and ratio of drug to polymer in capsule.

The developer (Fan, et al., 2001) observed synergistic swelling characteristics in simulated gastric fluid in tablets containing blends of poly(ethylene oxide) and certain cationic cellulosic polymers. Tablets containing the blend showed both faster initial rate of swelling and higher degree of swelling than those containing the parent polymer alone. Initial rate of swelling and degree of swelling increased with the molecular weight of any of the parent polymer as well as with increase in charged density of cationic polymer. Best swelling properties were observed at 40/10 weight ratio of poly(ethylene oxide)/Cationic cellulosic polymer. They also studied dissolution of caffeine and riboflavin from tablets containing these polymer blends and concluded that the drug
release closely resembled to their respective tablet containing high molecular weight poly(ethylene oxide) alone.

The release of verapamil HCl from tablets based on high molecular weight poly(ethylene oxide)(PEO) was studied by investigators (Dimitrov, and Lambov, 1999.). They concluded that release rate decreased with increase in molecular weight of PEO. The release was incomplete in alkaline media which may be due to poor solubility of drug. They included pH dependent polymers like Eudragit L, Eudragit hv and Carbopol 934 at concentration of 10 to 50% of total polymer and to improve drug release at alkaline pH.

They (Ozeki, et al., 1999) studied the complex formation between various molecular weight of poly(ethylene oxide) and carboxyvinyl polymer (Carbopol) and its effect on release profile of phenacetin. The complex formation was proved by X ray diffraction of individual polymer, physical mixture and solid dispersion of the same. The peak observed in the physical mixture disappeared in solid dispersion thereof. They concluded that maximum degree of complex formation was observed between PEO (molecular weight 35000) and Carbopol which resulted in the minimum drug release.

The Geomatrix tablets using HPMC K4M and K100M as well as PEO N60K and WSR 303 in core layer as well as in barrier layer were prepared by Maggi et al. (2000). They concluded that composition of barrier layer is playing more important role as compared to core composition. HPMC K100M in barrier layer showed maximum retardation in release of diltiazem HCl, a highly soluble drug. More over PEO forms weaker gel compared to HPMC of respective viscosity grade. Gel strength increased with increase in molecular weight of respective polymer. The active core and barrier layer design of Geomatrix technology allows a stronger control of the release kinetics and optimal dissolution profile can be easily achieved whether PEOs or HPMCs are used as polymer. The formulation was stable on storage.

The perfect linear chain structure of PEO and identical properties of CH₂ groups on the chain make this polymer ideal for radiation crosslinking purposes. It has been observed that
PEO-water can be easily crosslinked with \( \gamma \) rays at room temperature at various dose rates. The salicylic acid, phthalic acid and resorcinol were used as model substances. The active substance uptake capacity of Hydrogels was found to be lowest for phthalic acid and highest for resorcinol in the gel system obtained by irradiation both at low and high dose rate. The release was lowest both in rate and total amounts in Hydrogels containing phthalic acid, more in those with salicylic acid and highest in those with resorcinol. (Savas, 2001).

The investigator (Korner et al., 2005) developed bimodal polymer tablets, whose dissolution rates have been tuned by mixing low-molecular weight and high-molecular weight samples of polyethylene oxide in various proportions. They concluded that blending a high and low-molecular weight polymer is a good way to tune the dissolution rate of a polymer tablet. When the mixed tablet was dominated by the low molecular weight fraction, a faster dissolution was observed for the tablet mixed at the powder level due to small gel pieces were released from tablet during whole dissolution process. As long as no gel piece erosion was observed, it does not matter if the two polymer fractions are blended at molecular level or at the powder level, the steady state dissolution rate was same. Smooth, nearly linear release profiles are obtained at all mixing ratios.

They assessed the potential use of poly (ethylene oxide) (PEO) as matrix-forming material for tablets and extrudates (Pinto, et al., 2004). They found that release of the propranolol HCl occurred after swelling of the matrix and between 10% to 70% drug released, a quasi zero-order release for 10 mm tablets. They concluded that extrusion was possible for formulation with PEO only with amounts of water between 16% and 50%. The model drug release in same fashion as observed for the tablets. The study resulted that it was possible to produce tablets by direct compression and extrudates or pellets from those extrudates from different formulations with PEO.

They (Jin et al., 2008) study the effects of the formulation variables - POLYOX® molecular weight \( (X_1) \), the ratio of POLYOX®/Avicel® PH102 \( (X_2) \) and the amount of POLYOX® and Avicel® PH102 \( (X_3) \), hardness \( (X_4) \), HPMC amount \( (X_5) \), Eudragit®
L100 amount ($X_6$), and citric acid amount ($X_7$) — on the paroxetine HCl release from POLYOX® matrix tablet using the Plackett-Burman screening design. They found that POLYOX® molecular weight ($X_1$) and POLYOX®/Avicel® PH102 ratio ($X_2$) had significantly influence on the drug release mechanism and drug release rate as main effects. Hardness ($X_4$) had an insignificant effect on the drug release mechanism but a significant effect on the drug release rate. On the other hand, HPMCP, Eudragit® L100 and citric acid had an insignificant effect on the both responses.

They (Jamzad and Fassihii, 2006) develop a new monolithic matrix system to completely deliver glipizide, a Biopharmaceutics Classification System (BCS) Class II drug in a zero order manner over an extended time period. Glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. Linear and reproducible release similar to that of Glucotrol XL was achieved for optimized matrices ($f_2 > 50$) independent of hydrodynamic conditions. They found that HPMC matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to PEO matrices. They concluded that in the case of low dose/low soluble drug, total drug release in a zero order manner heavily depends on the synchronization of erosion and swelling fronts during the entire dissolution study.
2.2.4 Review of work done on xanthan gum

The researchers (Billa, N and Yuen, K., 2000) studied the processing variables at the laboratory and pilot scales that can affect hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. They found that granules from the pilot scale formulations were bulkier compared to their laboratory scale counterparts, resulting in more porous, softer tablets. Drug release was linear from xanthan gum matrices prepared at the laboratory scale and pilot scales; however, release was faster from the pilot scales. The data suggest that processing variables that affect the degree of wetness during granulation, such as increase in impeller speed and increase in amount of water used for granulation, also may affect the swelling index of xanthan gum matrices and therefore the rate of drug release.

The present study was aimed to formulate and evaluate matrix tablets of Tramadol HCl to achieve sustained drug release with reduced frequency of drug administration, side effects and improved patient compliance (Mishra et al., 2006). They used various polymers like hydroxypropyl methyl cellulose (HPMC), guar gum (GG) and xanthan gum (XG) alone and in combination in different proportions. Optional excipient, sodium carbonate and diluent lactose were also used. They found that matrix tablets having HPMC prolonged the rate and extent of drug release maximally followed by XG and GG. Increasing percentage of sodium carbonate in core further prolonged the rate and extent of drug release. Formulations with HPMC only followed almost zero order drug release whereas all other batches followed either Higuchi or super case II transport mechanism.

They (Patel et al., 2007) developed floating tablets of dipyridamole using xanthan gum and guar gum. The content of polymer blends (X1) and ratio of xanthan gum to guar gum (X2) were selected as independent variables. The diffusion exponent (n), release rate constant (k), percentage drug release at 1 hr (Q1) and 6 hr (Q6) were selected as dependent variables. They found that tablets of all batches had desired buoyancy characteristics. Multiple regression analysis with two way ANOVA revealed that both
the factors had statistically significant influence on the response studied \((p < 0.05)\). They conclude that the ratio of xanthan to gaur gum had equal or dominant role as controlling factor on kinetics of drug release compared to content of polymer blends.

Sustained release matrix tablets of diclofenac sodium, were developed by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28) (Yeole et al., 2006). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. Among different formulations, F1 showed sustained release of drug for 12 hours with 89.67% release. The kinetic treatment showed that the release of drug follows zero order kinetic \((R^2 = 0.9758)\). Korsmeyer and Peppas equation gave value of \(n = 0.9409\) which was close to one, indicating that the drug was released by zero order kinetic. Thus, Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium.

The researchers (Verhoeven and Remon, 2001) developed mini-matrices (multiple-unit dosage form) with release-sustaining by means of hot-melt extrusion using ibuprofen as the model drug and ethylcellulose as sustained-release agent. They used Xanthan gum, a hydrophilic polymer to the formulation to increase the drug release since ibuprofen release from the ibuprofen/ethylcellulose matrices (60/40, w/w) was too slow (20% in 24 h). They found that changing the xanthan gum concentration as well as its particle size modified the in vitro drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate. Regarding the effect of the xanthan gum particle size, no difference was observed for formulations containing 10% and 20% xanthan gum. However, using 30% xanthan gum, drug release was influenced by the particle size of the hydrophilic polymer due to the susceptibility of the coarser xanthan gum particles to erosion. Drug release from the mini-matrices was mainly diffusion controlled, but swelling played an important role to obtain complete drug release within 24 h.

Researchers (Talukdar and Kinget, 1997) conduct the study using three drugs with different solubility to know the differences observed between the matrix tablets of the two
polymers, xanthan gum and hydroxypropylmethyl cellulose. They found that under identical experimental conditions, the drug diffusivity in HPMC gel is higher than in XG gel. In view of salt effects, the diffusion through the hydrated XG matrices back up the release characteristics of water soluble drugs from XG matrix tablets, suggesting that the diffusion of drug molecules in the hydrated gel of a XG matrix tablet is the main mechanism of overall release for soluble drugs like caffeine and the sodium salt of indomethacin. On the contrary, no reflection of indomethacin diffusivity through XG gels was found in its release profiles from XG matrix tablets, suggesting that diffusion through the hydrated polymer mass is not the dominant factor for the release of an insoluble drug like indomethacin from a XG matrix tablet.

A comparative investigation has been undertaken by the authors (Talukdar et al., 1996) to assess the performance of xanthan gum (XG) and hydroxypropylmethyl cellulose (HPMC) as hydrophilic matrix-forming agents in respect of compaction characteristics and in vitro drug release behavior. They found that compaction characteristics are to be quite similar to each other and typical of polymer behavior. But the flow characteristics are different, i.e., XG is more readily flowable than HPMC. They concluded that the observed difference in drug release profiles between these two potential excipients is because of the difference in their hydrophilicity and subsequent hydration properties.
2.3 References


2. Introduction and Review of Work Done


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SKW Boisystems, Satiaxane-Xanthan gum for food applications, SKW Boisystems- Business unit texturant systems, France.


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