CHAPTER II

LITERATURE ON CONTROLLED RELEASE

In recent years considerable attention has been focused on the development of new drug delivery systems known as controlled release drug delivery systems. Such interest is based largely on the fact that the controlled release products have established and retained a place in the market based on their uniqueness and their clinical advantages in the practices of medicine.

Controlled release drug delivery systems are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Drug release may be constant or cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled release drug delivery systems include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. The major types of controlled release systems include matrix tablets, coated beads, microcapsules and microspheres, mucoadhesive systems, ion – exchange resin complexes, cyclodextrin complexes, swellable tablets, floating tablets, osmotic pressure controlled systems, transdermal systems etc.

Advantages of controlled release systems:

They provide one or more of the following benefits or advantages.
1. Controlled administration of a therapeutic dose at a desirable delivery rate.


3. More consistent and prolonged therapeutic effect is observed.


5. Reduction of adverse side effects.

6. Minimization of the need for frequent dose intake.


**Disadvantages of controlled release dosage forms:**

1. Toxicity due to dose dumping occurs when more than usual fraction is being released.

2. Increased cost.

3. Poor *in vitro* – *in vivo* correlation.

4. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

**Characteristics of drugs suitable for controlled release:**

- Exhibit moderate rates of absorption and excretion.
- Uniform absorption through the gastrointestinal tract.
- Administration in relatively small doses.
- Possess good margin of safety.
- For the treatment of chronic therapy.

**Characteristics of drugs unsuitable for controlled release:**

- Short/long elimination half life
- Narrow therapeutic index
- Poor absorption
- Active absorption large doses
- Low aqueous solubility
- Extensive first pass metabolism

The ideal drug delivery system should be inert, bio compatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.
ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12-24 h period and that can be taken once or twice a day. Typically these products provide numerous benefits compared with immediate release products, greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug to the GI milieu.
Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

- Dissolution controlled release
  - Encapsulation dissolution control
  - Matrix dissolution control
- Diffusion controlled release
  - Reservoir devices
  - Matrix devices
- Diffusion and dissolution systems
- Ion-exchange resins
- Osmotically controlled release
- Gastroretentive systems
  - Altered density formulation
    - High density approach
    - Low density approach (Floating systems)
  - Swelling and expanding systems
  - Bioadhesive systems

**Dissolution controlled release:**

Dissolution controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness. The rate-limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the
stagnant-fluid diffusional boundary layer. Some examples of drugs with limited dissolution rate include digoxin, griseofulvin, salicylamide and nifedipine.

Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by encapsulation of a drug-polymer matrix with a relatively insoluble polymeric membrane. One of the most common approaches used to achieve sustained release is to incorporate a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, and ethyl cellulose; or a hydrophilic matrix such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and sodium carboxymethylcellulose. The rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. It depends on the porosity of the compressed structure.

**Diffusion controlled release:**

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution controlled systems, the drug is made available as a result of partitioning through the polymer. It is very common for diffusion controlled devices to exhibit a non-zero-order rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

Another configuration of diffusion controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. For instance, bupropion hydrochloride (Zyban®, Glaxo Wellcome) is formulated using carnuba wax and hydroxypropylmethyl cellulose.
Osmotically controlled release:

The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Therefore, the rate of drug delivered from the system is dependent on the osmotic pressure of the formulation.

OROS Push-Pull technology (ALZA Corporation) has proven to be very useful for delivering compounds of very high or low solubility such as oxybutynin chloride and nifedipine\textsuperscript{8}, respectively. OROS Push-Pull technology is capable of zero-order drug delivery for 24 h. OROS Push-Pull technology has been applied to several commercial products, including oxybutynin chloride (Ditropan XL\textsuperscript{®}), and nifedipine (Procardia XL\textsuperscript{®}), and isradipine (Dynacirc CR\textsuperscript{®}).

Ion exchange resins:

Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug-resin complex is formed by prolonged exposure of drug to the resin.

Theoretically, this controlled delivery approach is relatively immune to the conditions of the GI tract because an ionic environment is required to displace the drug from the resin. Nicorette\textsuperscript{®} is a widely used product based on ion exchange technology as an adjunct to smoking cessation programs. It contains nicotinic acid absorbed to a carboxylic acid ion exchange resin (nicotine polacrilex) in a flavored chewing gum\textsuperscript{9}.
**Gastroretentive systems:**

Variability in GI transit time is a concern for oral controlled drug delivery systems\textsuperscript{10}. Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. If successful, gastroretentive controlled release formulations could offer a potential solution to problem by offering a prolonged gastric residence time\textsuperscript{11}. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach, e.g., antibiotic administration for *Haemophilus pylori* eradication in the treatment of peptic ulcer.

**Altered Density Systems:**

Several strategies have been employed to make the dosage forms float in the stomach. Hydrodynamically balanced system (HBS) was the formulation that used the floating property of a device with density lower than water\textsuperscript{12}. HBS is a capsule containing drug, gel-forming hydrophilic polymers (e.g. hydroxypropylcellulose), and some hydrophobic fatty materials (e.g. stearates)\textsuperscript{13}. In a different approach for gastric retention, ion exchange resin beads are loaded with bicarbonate, which, on contact with media containing hydrochloric acid, release carbon dioxide, causing the resin to float\textsuperscript{14}. Extension of the floating time is achieved by coating the bicarbonate-coated with beads with a semipermeable membrane.

**Swelling and Expanding Systems:**

Some hydrogels and superporous hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio\textsuperscript{10} of over 1000. Superporous hydrogels\textsuperscript{15} have unique superswelling properties combined with pore sizes in the range of few
hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min, which is an important requirement for gastric retention devices based on size.

**Bioadhesive systems:**

Bioadhesive can be defined as any substance that can adhere to a biological membrane and remain there for an extended period of time. If the membrane substrate is mucous membrane then the polymer is referred to as mucoadhesive\(^2\). The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane.
Matrix (monolithic) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as a dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network\textsuperscript{16} (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5 \% w/v) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10\% w/v), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost; such cavities fill with fluid from the environment increasing the rate of release of the drug.

It is common to add a plasticizer (e.g. a poly (ethylene glycol)), or surfactant, or adjuvant (i.e., an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticizer may be fugitive, and simply serve to aid film formation\textsuperscript{17} and, hence, decrease permeability - a property normally more desirable in polymer paint coatings). It was noted that the leaching of PEG acted to increase the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity; however, the films
retained their barrier properties, not permitting the transport of electrolyte\textsuperscript{18}. It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evidenced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50% w/w plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis; the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up.

Efentakis \textit{et al}\textsuperscript{19} investigated the effects of added surfactants on (hydrophobic) matrix devices. It was thought that surfactant may increase the drug release rate by three possible mechanisms namely (i) Increased solubilization, (ii) Improved 'wettability' to the dissolution media and (iii) Pore formation as a result of surfactant leaching.

For the system studied (Eudragit\textsuperscript{®} RL 100 and RS 100 plasticized by sorbitol, flurbiprofen as the drug, and a range of surfactants) it was concluded that improved wetting of the tablet led to only a partial improvement in drug release (implying that the release was diffusion, rather than dissolution, controlled), although the effect was greater for Eudragit\textsuperscript{®} RS than Eudragit\textsuperscript{®} RL, whilst the greatest influence on release was by those surfactants that were more soluble due to the formation of 'disruptions' in the matrix allowing the dissolution medium access to within the matrix. This is of obvious relevance
to a study of latex films which might be suitable for pharmaceutical coatings, due to the ease with which a polymer latex may be prepared with surfactant as opposed to surfactant-free. Differences were found between the two polymers - with only the Eudragit® RS showing interactions between the anionic/cationic surfactant and drug. This was ascribed to the differing levels of quaternary ammonium ions on the polymer.

Matrix properties of a new plant gum in controlled drug delivery were investigated by V. D. Kalu et al. A new plant gum, Okra (extracted from the pods of Hibiscus esculentus), has been evaluated as a controlled-release agent in modified release matrices, in comparison with sodium carboxymethyl cellulose (NaCMC) and hydroxypropylmethyl cellulose (HPMC), using paracetamol as a model drug. Okra gum matrices provided a controlled-release of paracetamol for more than 6 h and the release rates followed time-independent kinetics. The release rates were dependent on the concentration of the drug present in the matrix. The addition of tablet excipients, lactose and Avicel, altered the dissolution profile and the release kinetics. Okra gum compared favourably with NaCMC, and a combination of Okra gum and NaCMC or on further addition of HPMC resulted in near zero-order release of paracetamol from the matrix tablet.

Formulation of sustain release matrix systems of highly water soluble drugs was investigated by S. Siddique et al. Matrix systems are of favor because of their simplicity, patient compliance etc., than traditional drug delivery which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral sustained release matrix tablets for highly water soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymer has
become material of choice as an important ingredient for formulating sustained release formulations of highly water soluble drugs. Drug release to matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like metoprolol tartrate, diltiazem, primodol; ranitidine has been formulated as sustained release matrix tablets.
<table>
<thead>
<tr>
<th>Matrix characteristics</th>
<th>Material</th>
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<tbody>
<tr>
<td>Insoluble, inert</td>
<td>Poly ethylene</td>
</tr>
<tr>
<td></td>
<td>Poly vinyl chloride</td>
</tr>
<tr>
<td></td>
<td>Methyl acrylate – methacrylate copolymers</td>
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<tr>
<td></td>
<td>Ethyl cellulose</td>
</tr>
<tr>
<td>Insoluble, erodible</td>
<td>Carnauba wax</td>
</tr>
<tr>
<td></td>
<td>Stearyl alcohol</td>
</tr>
<tr>
<td></td>
<td>Stearic acid</td>
</tr>
<tr>
<td></td>
<td>Poly ethylene glycol</td>
</tr>
<tr>
<td></td>
<td>Castor wax</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
</tr>
<tr>
<td>Hydrophilic, swellable</td>
<td>Methyl cellulose(400cps, 4000 cps)</td>
</tr>
<tr>
<td></td>
<td>Hydroxyl ethyl cellulose</td>
</tr>
<tr>
<td></td>
<td>Hydroxyl propyl methyl cellulose</td>
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<tr>
<td></td>
<td>Sodium carboxy methyl cellulose</td>
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<tr>
<td></td>
<td>Galactomannose</td>
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<tr>
<td></td>
<td>Sodium alginates</td>
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</table>
In case of insoluble and inert polymers, the rate limiting step in controlling release from these formulations is liquid penetration into the matrix, unless channeling (wetting) agents are included to promote permeation of the polymer matrix by water, which allows drug dissolution and diffusion from the channels created in the matrix. Drug bioavailability critically dependent upon on the drug, polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in low – milligram – potency formulations.

In case of insoluble, erodible polymers, release is more effectively controlled by the addition of surfactants or wicking agents. Mechanism of release is both diffusion and erosion simultaneously.

Methods used to disperse drug and additive in the retardant base are,

1. **Solvent evaporation technique**: In which a solution or dispersion of drug and additives incorporated into the molten wax phase. Then the solvent is removed by evaporation.

2. **Dry blending**: Dry blending of ingredients slugged and granulated.

3. **Fusion techniques**: In which drug and additives are blended into the molten wax matrix at temperature slightly above the melting point. Then molten material may be spray congealed, solidified and milled.

In case of hydrophilic and swellable polymers, drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen matrix.
Drug release from matrix device:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and solid drug moving toward the interior. Obviously, for this system to be diffusion-controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

![Diagram](image)

**Fig. 2.1. Drug Delivery from a Typical Matrix Drug Delivery System**

The equations, which describe the rate of release of drugs dispersed in an inert matrix system have been derived in an inert matrix system have been derived by Higuchi\textsuperscript{22}. The following equation can be written

\[
\frac{dM}{dh} = dC_0 dh - C_s/2 \quad (1)
\]

Where \(dM\) = change in the amount of drug released per unit area.

\(dh\) = change in the thickness of the zone of matrix that has been depleted of drug.

\(C_0\) = total amount of drug in a unit volume of the matrix.

\(C_s\) = saturated concentration of the drug within the matrix.
From the diffusion theory:

\[ dM = \left( \frac{D_m C_s}{h} \right) dt \]  \hspace{1cm} \text{(2)}

Where \( D_m \) is the diffusion coefficient in the matrix.

Equating equations (1) and (2), integrating and solving for \( h \) gives

\[ M = \left[ C_s D_m (2C_0 - C_s) \right] \frac{1}{2} \]  \hspace{1cm} \text{(3)}

when the amount of drug is in excess of the saturation concentration, that is \( C_0 >> C_s \)

\[ M = \left( 2C_s D_m C_0 t \right) \frac{1}{2} \]  \hspace{1cm} \text{(4)}

which indicates that the amount of drug released is a function of the square root of time.

In a similar manner, the drug release from a porous or granular matrix can be described by

\[ M = \left[ D_s C_a p/T \left( 2C_0 - p C_a \right) t \right] \frac{1}{2} \]  \hspace{1cm} \text{(5)}

Where

- \( p \) = porosity of the matrix
- \( T \) = tortuosity
- \( C_a \) = solubility of the drug in the release medium.
- \( D_s \) = diffusion coefficient in the release medium.

This system is slightly different from the previous matrix system. In that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly.
For purposes of data treatment, equation (4) or (5) can be reduced to

\[ M = Kt^{1/2} \]

where \( K \) is a constant.

So that a plot of amount of drug release versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying\(^{23-27}\) initial concentration of drug in the matrix, porosity, tortuosity, polymer system forming the matrix and solubility of the drug.
POLYMERS IN CONTROLLED DRUG DELIVERY

Polymers play a vital role in controlling drug release from controlled drug delivery systems. Different natural and synthetic polymers, silicon elastomers and poly peptides can be used in the formulation of sustained and controlled release products. In general synthetic polymers offer greater advantages than natural materials, in that they can be tailored to give a wider range of properties and more predictable lot-to-lot uniformity. Also they represent a reliable source of raw materials, free from concerns of immunogenicity.

Different cellulose derivatives like hydroxypropylmethyl cellulose, methyl cellulose, polyvinyl pyrrolidone, dextran and other swellable polymers can be used as matrix system for controlled drug release with zero order kinetics. Many of these materials are designed to degrade within the body.

**Characteristics of ideal polymer system**:28,29:

- It should have good mechanical strength.
- It should be chemically inert and free from leachable impurities.
- It should be non – toxic and compatible with body environment.
- It should be easy and inexpensive to fabricate.
- It should be easily sterilizable.

**Types of polymers:**

Polymers have been broadly classified as natural and synthetic polymers.

- **Natural polymers:** These include nucleic acids, proteins, polysaccharides and complexes of proteins and polysaccharides.
b. **Synthetic polymers:** They include polyesters, polyurethanes, polyamides, polycarbonates, polysiloxanes, polyvinyl compounds and acryllics.

**Classification of Polymers:**

**Non-biodegradable hydrophobic polymers:**

These are inert in the environment of use are eliminated or extracted intact from the site of administration and serve essentially as rate limiting barriers to the transport and release of drug form the device.

**E.g.** Polyethylene vinyl acetate (EVA), polydimethyl siloxane (PDS), polyur-ethane (PEU), ethyl cellulose (EC), cellulose acetate (CA), polyethylene (PE) and polyvinyl chloride (PVC) etc.

**Hydrogels:**

These swell but do not dissolve when brought in contact with water. They are inert removed intact from the site of administration and function by forming a rate limiting barrier to the transport and release of drugs.

**E.g.** Polyhydroxyethyl methacrylate (p-HEMA), cross-linked polyvinyl alcohol (PVA), cross-linked polyvinyl pyrrolidone, polyacrylamide and dextran etc.

**Soluble polymers:**

These are moderate polymers without cross links that dissolve in water. These materials can be used alone or in combination with other hydrophobic polymers to provide devices that slowly erode over time.

**E.g.** Polyethylene glycol (PEG), uncross-linked polyvinyl alcohol, polyvinyl pyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), copolymers of methacrylicacid and acrylic acid methyl ester (Eudragit L) etc.
Biodegradable polymers:

They slowly disappear from the site of administration, however this disappearance occurs in response to a chemical reaction such as hydrolysis.

E.g. Polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), several generic classes such as the polyanhydrides and polyorthoesters.

Mucoadhesive polymers:

Certain polymers become adhesive on hydration and exhibit the property of bioadhesion, i.e. adhesion to a biological tissue or membrane by interfacial forces. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used.

E.g. Methylcellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, caromers, chitosan, poly (acrylic acid co acrylamide) co polymers, carrageenan, sodium alginate, guar gum polyanhydrides and polylactic acid.

Drug release mechanisms for polymeric drug delivery:

Two broad categories of polymer systems have been studied. The reservoir device involves the encapsulation of a drug within a polymer shell, while the matrix device describes a system in which a drug is physically entrapped within a polymer network. The drug will be released over time either by diffusion out of the polymer matrix or by erosion (due to degradation) of the polymer or by a combination of two mechanisms.

Polymers used in oral controlled release technologies are summarized in Table 2.2.
<table>
<thead>
<tr>
<th>Method of achieving controlled release</th>
<th>Polymer used</th>
<th>Examples of dosage forms</th>
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</thead>
<tbody>
<tr>
<td><strong>Matrix or Embedding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Hydrophilic Carriers</td>
<td>Methyl Cellulose, Sodium CMC(^{31}), Carboxymethyl cellulose, Polyacrylic acid, HPMC(^{32,33}), Hydroxyethyl cellulose, Methacrylate Hydrogels(^{34}), Polyethylene Glycols, Galactose Mannate, Sodium Alginate</td>
<td>Multilayer tablets with slow releasing cores, Compression-coated tablets</td>
</tr>
<tr>
<td>(b) Hydrophobic Carriers</td>
<td></td>
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<tr>
<td>(i) Soluble Carrier</td>
<td>Glycerides, waxes, fatty alcohols, fatty acids</td>
<td>Matrix tablets</td>
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<tr>
<td>(digestible base)</td>
<td></td>
<td></td>
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<tr>
<td>(ii) Insoluble carrier</td>
<td>Polyethylene, polyvinyl chloride, polyvinyl acetate, waxes(^{35}), calcium sulfate</td>
<td>Reservoir Type</td>
</tr>
<tr>
<td>(nondigestible base)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reservoir Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Coating with insoluble membrane</td>
<td>Ethyl cellulose(^{32,33})</td>
<td>Granules, pellets, tablets</td>
</tr>
<tr>
<td><strong>Osmotic Systems</strong></td>
<td>Vapor permeable walls(^{36})</td>
<td>Vapor permeable capsules</td>
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<tr>
<td></td>
<td>- Tenite 808A polyethylene</td>
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<td></td>
<td>- Kynar 460 polyvinylidene</td>
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<td></td>
<td>Fluoride</td>
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<td></td>
<td>Hydroxypropylmethyl cellulose</td>
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<td></td>
<td>Hydroxypropyl cellulose</td>
<td>Single and bilayer tablets</td>
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Sodium carboxymethylcellulose
Ethyl cellulose

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<tr>
<th>Ion-exchange Resins</th>
<th>Dowex® 50, 1, 2</th>
<th>Controlled release capsules</th>
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<tbody>
<tr>
<td>Amberlite® IRC 50</td>
<td></td>
<td></td>
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<tr>
<td>With polystyrene-based polymeric backbone</td>
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<td>Chewable tablets</td>
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<tr>
<td></td>
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<td>Chewable gums</td>
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<td></td>
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<td>Liquid suspension</td>
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<tr>
<th>Gastric retention Systems</th>
<th>Hydroxypropylmethyl cellulose(^{37})</th>
<th>Compressed tablets</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Agar, Carrageenan,</td>
<td>Gelatin capsules</td>
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<tr>
<td></td>
<td>Alginic acid(^{37}),</td>
<td></td>
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<tr>
<td></td>
<td>Oils,</td>
<td></td>
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<tr>
<td></td>
<td>Porous calcium silicate(^{37})</td>
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<td></td>
<td>Superporous hydrogels(^{39})</td>
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<tr>
<td></td>
<td>Ion-exchange resin beads coated with</td>
<td></td>
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<tr>
<td></td>
<td>bicarbonate(^{38,39})</td>
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<tr>
<td></td>
<td>Ethyl cellulose for coatings</td>
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</tbody>
</table>

**Materials used for matrix systems:**

The materials used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), xanthan gum, sodium alginate, poly (ethylene oxide), and crosslinked
homopolymers and copolymers of acrylic acid. They are usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface.

Hydroxypropylmethyl cellulose is a non-ionic water-soluble cellulose ether made by Dow chemical under the brand name Methocel. Methocel is available in four different chemistries (E, F, J, and K series) based on varying degrees of hydroxypropyl and methyl substitution. The specially produced HPMC of ultrafine particle size for controlled release formulations include K 100LV, K4M, K15M, K100M, E4M, and E10M. When dissolved at a concentration of 2% in water, the viscosity ranges from 100 to 100,000 cps.

Both HPC and HEC are also nonionic water-soluble cellulose ethers made by the Aqualon division of Hercules Inc. under the brand names Klucel and Natrosol, respectively. For controlled release application, they are available in high- and low-viscosity grades, such as Klucel HXF, EXF, and Natrosol 250HX.

Xanthan gum is a water soluble polysaccharide gum and is composed of D-glucosyl, D-mannosyl and D-glucosyluronic acid residues and differing proportions of O-acetyl and pyruvic acid acetal.

Sodium alginate is a water-soluble gelling polysaccharide made by Kelco under the brand name Keltone. Keltone HVCR and LVCR are forms that are used in controlled release products.

Poly (ethylene oxide) polymer is a nonionic water-soluble resin made by Union Carbide under the brand name of Polyox. For controlled release application it is available in a variety of viscosity grades. Examples include Polyox WSR N-12K, WSR N-60K,
WSR-301, WSR-coagulant, WSR-303, WSR -308 with molecular weights ranging from 100,000 to 8 million.

Crosslinked homopolymers and copolymers of acrylic acid are water-swellable, but insoluble, resins made by the B. F. Goodrich Company under the brand name Carbopol. Carbopol 971P NF, 974P, and 934P NF are specifically designed for preparing hydrogel controlled release systems.

Hydrophobic and monolithic polymer matrix systems usually use waxes and water-insoluble polymers in their formulation. Natural and synthetic waxes of differing melting points have been used as controlled release matrix materials. Examples include carnauba wax, beeswax, candelilla wax, microcrystalline wax, ozokerite wax, paraffin waxes, and polyethylene, to name a few. Insoluble polymers used in preparing controlled release matrices include fine powders of Ammoniomethacrylate copolymers (Eudragit RL 100, PO, RS100, PO) by Rohm America, Inc., ethylcellulose (Ethocel FP7, FP10, FP100) by Dow Chemical Co., cellulose acetate (CA-398-10), cellulose acetate butyrate (CAB-381-20), cellulose acetate propionate (CAP-482-20) by Eastman Chemical Co., and latex dispersion of methacrylic ester copolymers (Eudragit NE30D).

**Materials used for reservoir systems:**

The most common materials to form a drug release barrier surrounding a core tablet, drug particles, beads, or pellets for diffusion-controlled reservoir systems include water-insoluble acrylic copolymers and ethylcellulose. These film-coating polymers have historically been used in an organic solution. In recent years, they have been mostly applied as aqueous dispersions that form films by a process of coalescence of submicrometer polymer particles.
Ammoniomethacrylate copolymers (Eudragit RL 30D, RS 30D) are water permeable and swellable film formers based on neutral methacrylic esters with a small proportion of trimethylammonioethyl methacrylate chloride. Methacrylic ester copolymer (Eudragit, NE30D) is neutral ester without any functional groups. Ethyl cellulose for film coating is available as an aqueous polymeric dispersion containing the plasticizers under the brand name of Surelase (Colorcon) and as pseudolatex dispersion, Aquacoat ECD (FMC), which requires addition of plasticizers to facilitate film formation during coating.

Enteric polymers may also be incorporated into the coating film to modify release rate, such as cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), methacrylic acid and methacrylic esters (Eudragit L and S).

**Polymers used for osmotic pump systems:**

Cellulose acetate comprising a certain percentage of acetyl content can be used together with other pH-dependent and pH-independent soluble cellulose derivatives to form a semipermeable film. Other polymers including polyurethane, ethyl cellulose, poly(ethylene oxide) polymers, PVC, and PVA may be used in the osmotic pump systems.
REFERENCES


