Chapter 4

General Introduction...
DRUG DELIVERY SYSTEM

Most drugs today are still prescribed in dosage forms that date back to the earliest records of practice of pharmacy: the pill (1500 BC); the coated pill (900 AD); the tablet (10th century); and the capsule (1983). Progress in pharmaceutical technology, since the inception of such a discipline (late 1800s and early 1900s), emphasized the development of high speed processing equipment. The functional characteristics of a dosage form attracted little attention until the unfolding of the 70s\(^1\).

The 20th century has witnessed great strides in the management of various pathological conditions with the discovery of increasingly sophistication and potent drug molecule such as antibiotics, steroids, peptides and proteins\(^2\). Significant advances in controlled drug delivery have been achieved and several products have enjoyed commercial success, past 25 years. And now, the concept of controlled release technology has entered the public's consciousness and reasonable resources have been committed to the field by both the pharmaceutical industry and government agencies.

All over the world, the novel Controlled Drug Delivery System (CDDS) is growing as one of the frontiers in pharmaceutical technology. Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of CDDS, greater attention has been focused on its development\(^3\).

4.2. DEFINITIONS

Attempts to control the time course and specificity of drugs within the body have led to the development of several drug modifications and dosage forms\(^4\). Different definitions/ terminologies have emerged in this new area of CDDS\(^4-6\).
Conventional Drug Delivery is a technique to deliver therapeutic agents into human body whereby therapeutic agent is immediately available for action and where no mechanism is incorporated in the system, which will modulate the release. This includes immediate release tablets, capsules, injectables, ointments and creams.

New Drug Delivery System(s) (NDDS) are techniques capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue.

Extended-Release Systems include drug delivery system such as sustained release, controlled release, time released, prolonged release that achieves prolonged therapeutic effect by continuous release of drug over an extended period of time after single administration. The release rate and site of delivery may be predefined in certain extended release system.

Controlled-Release System are drug delivery systems which provide some control, whether temporal or spatial nature or both, on drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells. If it is unsuccessful at this, but nevertheless prolongs therapeutic blood or tissue levels of the drug for an extended period of time, it is considered a Prolonged-Release System.

Delayed-Release Systems are those that use repetitive, intermittent dosing of drug from one or more immediate release units incorporated into single dosage form. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range, but, nonetheless, is more effective for patient compliance than conventional dosage forms.
Site Specific And Receptor Release refer to targeting a drug directly to a certain biological location. In the case of site specific release the target is adjacent to or in the diseased organ or tissue. For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

4.3. EXTENDED VS CONVENTIONAL DRUG DELIVERY

Consider a single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the

![Diagram: Optimum Drug Effectiveness vs Drug Delivery System]

Fig. 4.1. Requirement of drug delivery system.

drug, e.g., a solution, suspension, capsule, tablet, etc., probably will produce a drug blood level versus time profiles to that shown (fig. 4.2) It can be seen from this figure that administration of a drug by either intravenous injection or an extra route does not maintain drug levels within the therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If attempts are made to maintain drug blood levels in the
therapeutic range for longer periods by, for example, increasing the initial dose of an intravenous injection, as shown by the dotted line in the fig. 4.2. toxic levels may be produced at early times. This approach obviously is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval. This is shown in fig.4.3 for oral route. In this case, the drug blood level reached and the time required to reach that level, depends on the dose and the dosing interval. There are several potential problems inherent in multiple-dose therapy.

Fig. 4.2. Drug blood level versus time profile for intravenous (I. V.) and extra vascular (E.V.) route.

If the dosing interval is not appropriate for the biological half-life of the drug, large "peaks" and "valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.
- The drug blood level may not be within the therapeutic range at sufficiently early times, an important considerations for certain diseased states.
- Patient non-compliance with multiple dosing regimens can result in failure of this approach.

![Graph showing drug blood level versus time profile.](image)

**Fig. 4.3.** Drug blood level versus time profile from the multiple dose oral therapy.

Frequently, these problems are significant enough to make drug therapy with conventional dosage forms less desirable. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of extended release drug delivery systems.

Conventional dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.
The absorption pool represents solutions of the drug at the site of absorption and the terms $k_r$, $k_a$ and $k_{el}$ are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release from a conventional dosage form implies that $k_r \gg k_a$ or, alternatively that absorption of drug across a biological membrane such as the intestinal epithelium is the rate limiting step in delivery of the drug to its target area. For non-immediate release dosage forms $k_r \ll k_a$, i.e., release drug from the dosage form is the rate limiting step. This causes the above kinetic scheme to reduce to

Essentially, the absorption phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release drug delivery system must be directed altering the release rate by affecting the value of $k_r$. The ways in which this has been attempted are discussed later in this chapter.

4.4. RATIONALE OF EXTENDED RELEASE (ER) DRUG DELIVERY SYSTEM (DDS)

The basic rationale for extended drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties, by using novel drug delivery system by modifying the molecular structure and / are physiological parameters inherent in selected route of administration. It is desirable that the
duration of drug action becomes, more a design property of a rate controlled dosage form and less, are not at all a property of a drug molecule's inherent kinetic properties. Thus, optimal design of extended release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug.

The primary objective of extended drug delivery is to ensure safety and to improve efficacy of drug as well as patients' compliance. This is achieved by better control of plasma drug levels and less frequent dosing.

For conventional dosage form, only the Dose (D) and dosing Interval (T) only can be varied and for each drug, there exists a therapeutic window of plasma concentration, below which, therapeutic effect is insufficient and above which undesirable are toxic side effects are elicited. As an index of this window, the Therapeutic Index (TI) can be used. This is often defined as the ratio of median Lethal Dose ($LD_{50}$) to median Effective Dose ($ED_{50}$). Alternatively, it can be defined as the ratio of maximum drug concentration ($C_{\text{max}}$) in blood that can be tolerated to the minimum concentration ($C_{\text{min}}$) needed to produce an acceptable therapeutic response.

In general, the dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination ($k_e$) or by modifying the release rate of a dosage form to decrease the rate of absorption ($k_a$). Both approaches seek to decrease fluctuations in plasma levels during multiple dosing, allowing the dosing interval to increase without either overdosing or under dosing. When attempting to extend the dosing interval by decreasing the rate of absorption, the formulator will be confronted with the physiological constant of a finite residence time at the absorption site. For example, an effective absorption time for orally administered drugs is about 9-12 hour. If the rate of absorption decreases too much, some of the unabsorbed drug will pass into the large intestine, where absorption is slower and more variable.
and where bacterial degradation of the drug may occur. Thus, drugs with half-lives of 6 hour or less and possessing therapeutic indices less than 3 must be given not less frequently than every 12 hour⁸. Unless gastrointestinal transit can be lengthened, once daily orally dosing may prove to be difficult to achieve for drugs with such extremely short half lives⁹.

4.5. NEW DRUG DELIVERY SYSTEM

The term drug delivery covers a very broad range of techniques used to get therapeutic agents into the human body. In the recent years, several technical advancements have been made resulting in the development of New Drug Delivery Systems (NDDS). These techniques are capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue¹⁰. This is evidenced by general texts and review articles published in this subject¹¹⁻¹⁴.

New drug delivery systems have been a topic of great interest due to various possibilities:

- Possibility of patenting successful drug by applying the concepts and techniques of new drug delivery, eg. Ciprofloxacin OD.
- The enormous costs in bringing new drug entity successfully to the market have encouraged the development of NDDS.
- New systems are required to deliver novel, genetically engineered pharmaceuticals like peptides and proteins to the site of action; without incurring significant immunogenicity or biological inactivation.
- Treatment of enzyme deficient diseases and cancer can be improved by better targeting.
• Therapeutic efficacy and safety of the drugs administered by conventional methods can be enhanced by more, special and temporal placement with in the body, thereby reducing the strength and number of doses administered.

• NDDS is the phasing of the drug administered to the need of the conditions at hand so that an optimal amount of drug is used to cure or control the condition in minimum time.

• Research in new drug delivery during the last decade has resulted in an increase in the sophisticated means to sustain the delivery of drugs.

4.5.1. Possible Potential Advantages Of NDDS

Several authors have cited different reasons for attempting to modify action of drug. The potential advantages are as follows-

• Eliminate fluctuations in drug level, which are inevitable in conventional dosage forms where efficacy of drug is decreased which can be avoided with the use of NDDS.

• Patient acceptance of the product when compared to the conventional dosage form is increased due to decrease in frequency of administration, thus important patient compliance.

• In a multiple conventional dosage form, the dose of the drug being administered is too high which can be reduced by administration as NDDS.

• Nighttime dosing can be avoided without reducing the therapeutic efficacy, which is inevitable with conventional dosage forms, e.g. Diltiazem, Salbutamol.

• The severity or frequency of untoward effects sometimes may be reduced by administration of NDDS, e.g. Controlled release Ibuprofen.

• By minimizing the fluctuation of drug levels in the biological fluids a better management of diseases can be achieved.
3.2. Possible Limitations Of NDDS\textsuperscript{17}

Higher cost of production.

- Failure of systems: which may lead to accidental poisoning resulting in dose dumping or one where in no drug is released at the site of action.
- Size of dosage form may be big and hence may be a problem in case of geriatric patients (i.e., ability to swallow).
- Intra patient variation in absorption, distribution, metabolism and elimination of drug.
- NDDS cannot be administered when precision is required.
- Drugs whose biological half life ($t_{1/2}$) is long and self-prolonged and or blood levels of drugs with erratic patterns are not suitable for prolonged release formulation.

4.5.3. Different Avenues In NDDS

Current state of art is witnessing a revolution in new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the drug to specific tissue. These advancements led to the development of several novel drug delivery systems, which have been effectively applied to overcome the various drawbacks of conventional drug delivery.

The various avenues of NDDS include:

- Oral drug delivery and delivery systems.
- Mucosal drug delivery system, which encompasses the potential routes of non-invasive systemic administration.
- Nasal drug delivery systems.
- Ocular drug delivery systems.
- Transdermal drug delivery systems.
• Parenteral drug delivery systems.
• Vaginal drug delivery systems.
• Intrauterine drug delivery systems.
• Systemic delivery of peptide based pharmaceuticals.

4.6. THERAPEUTIC SYSTEMS

Heilmann coined a new term “Therapeutic System” to include a new route for drug administration and delivery to target organ. A therapeutic system\textsuperscript{18-19} is a drug containing preparation or dosage from that released one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Therapeutic systems may release the drug at a constant rate (zero order) or at a predictably constant declining rate (first order) for a certain period of time.

4.6.1. COMPONENT OF A THERAPEUTIC SYSTEM

A therapeutic system consists of four components (fig. 4.4)

A. The drug or drugs.
B. The drug delivery module.
C. The platform.
D. The therapeutic program.

4.6.1.A. DRUG

The drug is one of the several components in a therapeutic system. The choice of drug is with regard to its proven efficacy, pharmacokinetic behavior and its physicochemical characteristics.
Fig. 4.4. Therapeutic systems with open control loop.

4.6.1.B. DRUG DELIVERY MODULE

This is contained in the platform or carrying element. It is responsible for releasing the drug according to a predetermined therapeutic program. It consists of four elements:

(i) Drug Reservoir: A single or multi-chambered element that stores the compound in a stable form. Theoretically, the dimensions of reservoir may be of any size except the capacity of a target organ (such as conjunctival sac) imposes limitations on size.
(ii) Control Element: A control element is responsible for the programmed release pattern.

(iii) Energy Source: An energy source for providing an impetus for the transport of the drug molecule from the reservoir to the biological medium that first receives the drug.

(iv) The drug must leave the system via the release opening or surface before it can arrive at the pre-selected target organ in the bio-system. The size and shape of the opening or surface may differ from system to system.

4.6.1.C. PLATFORM

All the elements of a therapeutic system are integrated into the platform (carrying element) to form the functional unit, which comes into contact with the bio-system.

4.6.1.D. THERAPEUTIC PROGRAM

The program contained in the therapeutic system is designed to meet a specific therapeutic need by maintaining optimal drug levels over a defined time period.

A therapeutic system provides for a release of a drug by use of a controlled source of energy. As an energy source, physicochemical energy (like diffusion, osmosis and dissolution / chemical reaction), mechanical energy (by the use of elastomers and pumps) and electrical or nuclear energy may be used.

4.6.2. CLASSIFICATION OF THERAPEUTIC SYSTEM

A therapeutic system may be accomplished through several routes of administration, e.g. oral, transdermal, nasal, ocular, rectal, subcutaneous implantation and intramuscular injection. Moreover, numerous technologies have been used
successfully to control the systemic delivery of drug. Therapeutic system can be classified into two major categories.

A. Non-biofeedback controlled drug delivery.
B. Bio-feedback controlled drug delivery.

4.6.2.A. NON-BIOFEEDBACK CONTROLLED DRUG DELIVERY SYSTEM

Non-biofeedback controlled therapeutic system has three components – (i) the drug or drugs, (ii) delivery module and (iii) the platform. A non-biofeedback controlled system releases the drug from the delivery systems in predictable manner either first order or zero order rate or can be designed to release the drug at specific rate or site. It can be passive preprogrammed or active preprogrammed. These drug delivery systems (DDS) are further classified depending on the release controlling mechanism.\textsuperscript{20-22}

4.6.2.A.i. Diffusion Controlled Drug Delivery System

In these systems, the release rate of drug is determined by its diffusion through a water insoluble or hydrophilic polymer. There are basically two types of diffusion devices: reservoir devices (fig. 4.5) in which a core of drug is surrounded by a polymeric membrane and matrix devices in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix.

4.6.2.A.i.a. Reservoir Systems\textsuperscript{23-25}

These dosage forms consists of a core of a drug surrounded by a polymeric membrane.
Fig. 4.5. Reservoir diffusion device representation. $C_{m(o)}$ and $C_{m(l)}$ represent concentrations of drug at the inside surfaces of the membrane and $C_{r(o)}$ and $C_{r(l)}$ represent concentrations in the adjacent regions.

The process of diffusion is described by a series of equation described by Fick. Basically, there are two laws: The Fick's First Law and the Fick's Second Law of Diffusion.

**Fick's First Law**

The amount of drug passing across a unit area is proportional to the concentration difference across that plane. The Fick's First Law equation is given as

$$ J = -D \frac{dc}{dx} \quad (4.1) $$

where

- $J$ = flux, given in units of (amount/area) x time
- $D$ = diffusion coefficient of drug in membrane in units of area/time (dependent on molecule's ability to diffuse, its size, concentration)
- $dc/dx$ = rate of change in concentration, "c" with respect to the distance "x" in membrane.
Fick’s Second Law

An equation for mass transfer that emphasizes the change in concentration with time at a definite location rather than the mass diffusion across a unit area of barrier in unit time is known as Fick’s Second Law. The Fick’s Second Law equation is given as

\[
dc/dt = D \cdot (d^2c/dx^2) \quad \text{(4.2)}
\]

(in one direction)

\[
dc/dt = D \cdot (d^2c/dx^2) + (d^2c/dy^2) + (d^2c/dz^2) \quad \text{(4.3)}
\]

(in three directions)

The Fick’s Second Law states that the change in concentration with time in a particular region is directly proportional to the change in the concentration gradient at that point in the system. If it is assumed that the drug on either side of the membrane is in equilibrium with the respective layer of the membrane surface can be related to the concentration in the adjacent region by the expressions

\[
K = \frac{C_{mm(o)}}{C_{(o)}} \quad \text{at} \quad x = 0 \quad \text{(4.4)}
\]

\[
K = \frac{C_{mm(l)}}{C_{(l)}} \quad \text{at} \quad x = l \quad \text{(4.5)}
\]

where \( K \) is the partition coefficient.

Assuming that \( D \) and \( K \) are constant, Eq. 4.1. can be integrated to give

\[
J = DK\Delta C / l \quad \text{(4.6)}
\]

where \( \Delta C \) is the concentration difference across the membrane.

If the activity of the drug inside the reservoir is maintained constant and the value of \( K \) is less than unity, zero-order release can be achieved. This is the case when the drug is present as a solid, i.e., its activity is unity. Depending on the device, the equation describing drug release will vary. Only the simplest geometry that of a rectangular slab or "sandwich", presented here.
For the slab geometry, the equation describing release is

\[ \frac{dM_t}{dt} = ADK\Delta C / l \]  \hspace{1cm} (4.7)

where \( dM_t \) is the mass of drug released after time \( t \), \( dM_t / dt \) is the steady state release rate time \( t \), \( A \) is the surface of the device and \( D, K \) and \( l \) are as defined previously.

Similar equations can be written for cylindrical or spherical devices. In order to obtain a constant drug release rate, it is necessary to maintain constant area, diffusion path length, concentration and diffusion coefficient. In other words, all of the terms on the right hand side of equation 4.6 are held constant. This is often not the case in actual practice because one or more of the above terms will change in the product, thus deviation from zero order release is frequently observed.

### 4.6.2.A.i.b. Matrix Devices\textsuperscript{27-39}

As the name implies, these consists of a drug dissolved or dispersed, and distributed uniformly in an inert polymeric matrix. In this model, drug in the outside layer, exposed to the bathing solution is dissolved first and then diffuses out of the matrix and continues with the interface between the bathing fluid and the solid drug moving towards the interior. Obliviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must reach faster than the diffusion rate of dissolved drug leaving the matrix. The equation presented below describes the rate of release of drugs dispersed in an inert matrix system and has been derived by Higuchi et al.

\[ Q = \left\{ \frac{D\varepsilon}{l} \left[ 2A - \varepsilon C_s \cdot l \right] \right\}^{1/4} \]  \hspace{1cm} (4.8)

where

- \( Q \) = amount of drug released per unit surface area at time “\( t \)”
- \( D \) = diffusion coefficient of the drug
\[ t \quad = \quad \text{time (hours)} \]
\[ \varepsilon \quad = \quad \text{porosity of the matrix} \]
\[ \tau \quad = \quad \text{tortuosity of the matrix} \]
\[ A \quad = \quad \text{total amount of drug in unit volume of the matrix} \]
\[ C_s \quad = \quad \text{solubility of the drug in release medium} \]

The above equation indicated that the amount of drug release is a function of square root of time.

4.6.2.A.ii. Dissolution Controlled Drug Delivery System\textsuperscript{40-41}

Certain drugs with a slow dissolution rate will yield an inherently sustained blood levels. In principle, then it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs, which are highly water-soluble. This can be done preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material or by incorporating it into a tablet with a slowly soluble carrier. These products are not truly sustaining in nature, but serve as useful function in direct release of the drug to a specific site. The same approach can be employed for drugs that are degraded by the harsh conditions of the gastric region.

The Noyes-Whitney equation describes the dissolution process at steady state

\[
\frac{dc}{dt} \quad = \quad K_d \cdot A \cdot (C_s - C) \tag{4.9}
\]

\[
\quad = \quad \frac{D}{h} \cdot A \cdot (C_s - C) \tag{4.10}
\]

where \( \frac{dc}{dt} \) = dissolution rate
\[ K_d \quad = \quad \text{dissolution rate constant} \]
\[ D \quad = \quad \text{diffusion coefficient} \]
\[ C_s \quad = \quad \text{saturation solubility of the solid} \]
\[ C \quad = \quad \text{concentration of solute in the bulk solution}. \]
Types of dissolution controlled systems:

4.6.2.A.ii.a. Encapsulated Dissolution Systems

Schematic representation of encapsulated dissolution systems is given in fig. 4.6 below.

Fig. 4.6. Schematic representation of dissolution governed system.

4.6.2.A.ii.b. Matrix Dissolution Systems

Schematic representation of matrix dissolution system (fig. 4.7).

Fig. 4.7. Schematic representation of matrix dissolution governed system.

In matrix formulation, drug release is determined by dissolution rate of a polymer. Matrix dissolution systems are prepared by compressing the drug with a slowly soluble polymer carrier. Congealing method can be used for wax mixed drug or they
can also be made by direct compression of a mixture of drug, polymer and excipients.

4.6.2.A.iii. Bioerodable and Diffusion / Dissolution Combined Drug Delivery System

Practically, a therapeutic system is rarely dependent only on dissolution or only on diffusion. The dominating mechanism for release will overshadow other processes sufficiently to allow classification as either "dissolution rate limited" or "diffusion controlled". Furthermore, these systems can combine diffusion and dissolution of both the matrix material and the drug. The inherent advantage of such a system is that the bioerodible property of the matrix does not result in a "ghost matrix", which requires removal when used as an implant, while limitation is of controlling release kinetics.

Another method of preparation of bioerodible systems is to attach the drug directly to the polymer by chemical bond, the release being dependent on hydrolysis or enzymatic reaction.

A third type utilizes combination of diffusion and dissolution and involves use of swelling controlled release matrix, the system minimizing burst effect since polymer swelling must occur before drug release.

4.6.2.A.iv. Osmotic Pressure Activated DDS

These systems depend on the osmotic pressure to activate the release of drug. The drug reservoir, which can be either a solution or solid formulation, is contained within a semi-permeable housing with controlled water permeability. The drug is activated to release in solution form, at a constant rate through a special delivery
orifice. The rate of drug release is modulated by controlling the osmotic pressure gradient. When such a device is exposed to water or any body fluid, ingress of water into the device will ensue.

The rate of flow, \( (dv/dt) \) is given as

\[
(dv / dt) = \frac{Ak}{h} (\Delta l - \Delta p)
\]  
(4.11)

where 
\( k \) = membrane permeability
\( A \) = area
\( H \) = thickness
\( \Delta l \) = osmotic pressure difference
\( \Delta p \) = hydrostatic pressure difference

Rate of drug release, \( (dm/dt) \) having the orifice is given by

\[
(dm / dt) = (dv / dt) C_s
\]  
(4.12)

where \( C_s \) is the concentration of the drug in solution.

### 4.6.2.A.v. Hydrodynamic Pressure Activated DDS

This type of system can be fabricated\(^{45-46}\) by enclosing a collapsible, impermeable container which contains a liquid drug collapsible, to form a drug reservoir compartment inside a rigid shape retaining housing. A composite laminate of an absorbent layer and a swellable, hydrophilic polymer layer is sandwiched between the reservoir compartment and the housing.

### 4.6.2.A.vi. Vapor Pressure Activated DDS

In this type\(^{47}\) the drug reservoir, which also exists as a solution, is contained inside the infusion compartment. It is physically pushed from the pumping compartment by a freely movable partition. The pumping compartment contains a fluorocarbon fluid
that vaporizes at body temperature from implantation site and creates a vapor pressure, which moves the partition upward, thereby forcing the drug solution to be delivered through a series of flow regulators and delivery cannulae.

4.6.2.A.vii. Mechanically Activated DDS

The drug reservoir in a solution formulation is retained in a container equipped with a mechanically activated pumping system. A measured dose is reproducibly delivered into a body cavity, through the spray head upon manual activation of drug delivery pumping system.

4.6.2.A.viii. Magnetically Activated DDS

Here, the drug reservoir is a dispersion of peptide or protein powders in a polymer matrix from which macromolecular drug can be delivered only at a relatively slow rate. This slow rate can be improved by incorporating an electromagnetically triggered vibration mechanism into the polymeric delivery device combined with a hemispherical design\textsuperscript{48}.

4.6.2.A.ix. Sonophoresis Activated DDS

This utilizes ultrasonic energy to activate the delivery of drugs from a polymeric drug delivery system.

4.6.2.A.x. Iontophoresis Activated DDS

Here, electrical current is used to activate and to modulate the diffusion of a charged drug molecule across a biological membrane, like the skin.

4.6.2.A.xi. Hydration Activated DDS
Here, the delivery upon the hydration induced swelling process to activate release of drug.

4.6.2.A.xii. pH Activated DDS

This type permits targeting the delivery of a drug only in the region with a selected pH range. It is fabricated by coating the drug-containing core with a pH sensitive polymer combination\textsuperscript{45}.

4.6.2.A.xiii. Ion Activated DDS

Such a system\textsuperscript{45} is prepared by first complexing an ionic drug with an ion-exchange resin containing suitable counter ion, the granules of the drug-resin complex are first treated with an impregnating agent, to reduce the rate of swelling in an aqueous environment and then coated with a water-insoluble but water-permeable polymeric membrane which serves as a rate-controlling barrier to modulate the influx of ions as well as release of drug from the system.

Here, the drug bound to the resin is released by exchanging with appropriately charged ions.

\[
\text{Resin}^+ - \text{Drug}^- + X^- \rightarrow \text{Resin}^\cdot X^- + \text{Drug}^- 
\]

This system is advantageous for drugs that at highly susceptible to degradation by enzymatic process since it offers a protective mechanism, by temporarily altering the substrate.

4.6.2.A.xiv. Hydrolysis Activated DDS

This system depends upon the hydrolysis process to activate the release of drug molecules\textsuperscript{49}.
4.6.2.A.v.  Enzyme Activated DDS

The drug reservoir is either physically entrapped in microspheres or chemically bound to polymer chains from biopolymers. The release of the drug is activated by the enzymatic hydrolysis of biopolymers by the specific enzyme in target tissue\(^{50-51}\).

4.6.2.B.  FEEDBACK REGULATED DRUG DELIVERY SYSTEMS

In the feedback – regulated DDS, the release of drug molecules from these delivery systems is activated by a triggering agent such as biochemical substance in the body and also regulated by its concentration via some feedback mechanism. They have all the four elements of therapeutic system. These systems provides for release of a drug using controlled source of energy, which can be either physicochemical energy (like diffusion, osmosis and dissolution/ chemical reaction) or mechanical energy (by the use of elastomers and pumps and electrical or nuclear energy. These systems are further classified as:

a. Bioerosion regulated DDS
b. Bioresponsive DDS
c. Self-regulated DDS.

4.7.  FACTORS INFLUENCING THE DESIGN AND PERFORMANCE OF EXTENDED RELEASE PRODUCTS

To establish criteria for the design of extended release products, a number of variables must be considered.

4.7.1. Drug Properties

The physicochemical properties of a drug, including stability, solubility, partitioning characteristics, charge, and protein binding propensity, play a dominant role in the design and performance of controlled release systems\(^{52-53}\).
4.7.2. Route Of Drug Delivery

The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. At times, the drug delivery system, in certain routes of administration, can exert a negative influence on drug efficacy, particularly during chronic administration, and hence other routes of administration should be considered. Performance of the controlled release systems may also be influenced by physiological constraints imposed by the particular route, such as first pass metabolism, G/I mobility, blood supply and sequestration of small foreign particles by the liver and spleen.

4.7.3 Target Site

In order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by the use of carriers. However, the absorptive surfaces of most routes are impermeable to macromolecules or other targeted delivery systems, thereby necessitation either intra-vascular or intra-arterial administration.

4.7.4. Acute Or Chronic Therapy

Consideration of whether one expects to achieve cure or control or a condition and the expected length of drug therapy are important factors in designing controlled release systems. Attempts to generate a one year contraceptive implant presents significantly different problems in design than does an antibiotic for acute infection. Moreover, long-term toxicity of rate-controlled drug delivery system is usually different from that of conventional dosage forms.$^{54}$
4.7.5. Disease

Pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system. For example, in attempting to design an ocular controlled release product for an external inflammation, the time course of changes in protein content in ocular fluids and in the integrity of the ocular barriers would have to be taken into consideration. Sometimes one can take advantage of the unique manifestations of the disease state. For example, the higher plasminogen activator levels in some tumor cells can lead to preferential bioconversion of peptidyl prodrugs in these cells\textsuperscript{55-56}. Similarly, the higher tyrosinase level in melanoma cells has been demonstrated to allow targeting to and preferential bioconversion of 2,4-dihydroxyphenylalanine in them\textsuperscript{57}.

4.7.6. Patient

Whether the patient is ambulatory or bedridden, young or old, obese or gaunt, etc., can influence the design of a controlled release product. An implant or intra-muscular injection of a drug to a bedridden patient with little muscle movement may perform in a manner significantly different from that of an ambulatory patient. Some of these factors represent individual patient variation and cannot be controlled by the scientists while others must be considered. For example, single unit controlled release products are particularly prone to intra and inter subject variation because of variability’s in individual Gi motility\textsuperscript{58}.

To establish a basis for discussion of the influence of drug properties and the route of administration on sustained/controlled release product design, it is worthwhile focusing on:

(i). Behavior of the drug in its delivery system

(ii). Behavior of the drug and its delivery system in the body.
The first of these two elements is concerned with the ways in which drug properties can influence release characteristics from its delivery system. 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 1).

![Scheme 1](image)

In a sustained / controlled release product, one aims for release of drug from the dosage form as the rate limiting step instead. Thus, drug availability is controlled by kinetics of drug release rather than absorption. Consequently, the associated rate constants for drug release from the dosage form are smaller than the absorption rate constant and kinetically the process appears as shown (Scheme 2).

![Scheme 2](image)

To control drug release one can employ variety of approaches, such as dissolution, diffusion, swelling, osmotic pressure, complexation, ion-exchange, and application of magnetic field. The interplay between physicochemical properties of a drug and characteristics of its delivery system determines the temporal release pattern that is observed.

The second element, behavior of the drug and its delivery system in the body, is extremely complex, involving the fate of drug during transit to the target area as well
The second element, behavior of the drug and its delivery system in the body, is extremely complex, involving the fate of drug during transit to the target area as well as its fate while in the bio-phase. Availability of drug to its target will depend on its pharmacokinetics as well as that of its carrier. In the case of drug targeting, the carrier is used to alter the pharmacokinetics of drug in the body. The influence of physiological constraints on the fate of the delivery system in the body is usually negative, for example, oral absorption is usually limited by GI transit time of the delivery system.

From the previous discussion, it is clear that the formulation and performance of sustained/controlled release dosage forms have roots in the physicochemical properties of the drug and its carrier. The pharmacokinetics and pharmacodynamics, to a large extent, are derived functions of the intrinsic properties of the drug. Thus, development and assessment of sustained / controlled drug delivery system requires a rather complete knowledge of the intrinsic properties of a drug and the ways in which it can influence the design of sustained /controlled release systems. Often times, undesirable physicochemical and biological properties can be altered by suitable chemical modifications, by use of a carrier, or perhaps by administration via another route.

4.8. PHARMACOKINETIC MODELS FOR EXTENDED RELEASE DRUG DELIVERY SYSTEM

Objective of extended release dosage formulation is to give rapid blood concentrations of the drug sufficient to elicit the desired therapeutic effect; to maintain these concentrations at an essentially constant level for suitable period of time; to reduce the frequency of drug administration; to have more uniform biological response and reduced intensity and incidence of side effects.
To achieve these objectives, the interdependent parameters such as dosage form, drug release rate from dosage form, absorption, distribution and excretion of drug should be evaluated through the use of suitable pharmacokinetic model. These models help to formulate extended release dosage form having required blood levels with consideration also being made for calculation of initial dosage and maintenance dose.

Various pharmacokinetic models have been proposed for calculating dose and release profile of extended release dosage form. Nelson\textsuperscript{69} gave a method of deriving the maintenance dose of the drug from data based on its biological half-life. Weigand and Taylor\textsuperscript{60} presented a mathematical model and derived equation based on first order release rate of the drug from maintenance dose. Beckett\textsuperscript{61} presented a model for an ideal extended release form in which there is a constant rate of release of drug from maintenance dose. They have derived kinetic equations and their implication related to the model. Limitation of this model is that between the peak time for fast release component and sustain release component, the drug level tend to be higher producing a lump in the overall blood drug level versus time profile. Robinson and Eriksen\textsuperscript{62} have presented model, which provides analysis of kinetic relationship governing the rate of release of drugs from first order and zero order extended release dosage form. The model permit calculation of doses and of constant that will give a blood concentration versus time curve most closely approximately an idealized curves.
Following scheme 1 is used to describe Robinson and Eriksen model.

\[
\begin{align*}
D & \xrightarrow{k_r} C \xrightarrow{k_s} B \rightarrow U \\
B & \xrightarrow{k_e} E
\end{align*}
\]

**Scheme 1**

where \(D\) = concentration of drug remaining in dosage form

\(C\) = concentration of drug at the site of absorption

\(B\) = concentration of drug in the fluid of distribution (blood)

\(U\) = concentration of drug in the urine

\(E\) = concentration of drug metabolized

\(k_r\) = rate constant for release of drug from the dosage from,

where superscript 0 and 1 indicate the apparent order of release.

The stripped arrow is used to indicate the rate release is variable.

\(k_s\) = rate constant for absorption

\(k_e\) = rate constant for elimination via all other routes

For simplicity,

\[k_e + k_u = k_d\]  \hspace{1cm} (4.13)

In this model certain assumptions are made such as one compartment model is considered. The equilibria for each lie far to the right so that the reverse reactions are negligible. The drug is completely absorbed and that after release it is immediately available. The concentration of drug at the absorption site at time zero
is initial dose ($D_i$) and is equal to the fraction in the initial or in the immediately available dose ($F_i$) times the total dose given ($W$). The concentration of drug at time zero as maintenance dose ($D_m$) is that fraction of dose ($F_m$) required to maintain an optimum blood level for given length of times the total dose given ($W$).

According to the model in case of the release of drug by zero order kinetics, blood concentration at any time is function of $k_a$, $k_e$, and concentration of drug in the gut.

The concentration of drug in blood $B_i$, is given by following equation:

$$B_i = D_i \cdot k_a \left( e^{ka t} - e^{-ke t} \right) \div (k_a - k_e)$$

(4.14)

The time required 'Tp' to achieve peak concentration is given by

$$T_p = 2.3 \left( \log \left( \frac{k_d}{k_w} \right) \right) \div (k_a - k_w)$$

(4.15)

Total dose $W = D_i + D_m$

(4.16)

where 'DI' is initial dose and 'DM' is maintenance dose.

The maintenance dose 'DM', and time over which extended action (h) is desired is

$$D_m = k_r^0 \times h$$

(4.17)

$k_r^0$ can be roughly estimated as

$$k_r^0 = k_d \times B_d$$

(4.18)

where 'Bd' is desired blood level.

The initial dose is given as

$$D_i = D_b - (k_r^0 \times T_p)$$

(4.19)

where 'Db' is immediate dose to produce peak equal to desired blood level.
According to the model in case of the release of drug by first order kinetics, blood concentration at any time ‘t’ is function of ‘$K_a$’, ‘$K_e$’ and concentration of drug in the gut. The concentration of drug in blood ‘Bt’, is given by following equation:

$$B_t = \frac{D_m \ k_d \ k_e \ (e^{k_d t} - e^{k_e t})}{{(k_d - k_e)} \ + \ [D_i \ k_e - (D_m \ k_d \ k_e / k_d - k_e)]} + \frac{(e^{-k_d t} - e^{-k_e t})}{{(k_d - k_e)}}$$

(4.20)

Total dose ($W$) can be calculated as follows:

$$W = D_i + D_m$$

(4.21)

where $D_i = D_b - D_{(correction)}$

$$D_{(correction)} = D_m \ (k_e^{'} T_p)$$

(4.22)

Therefore,

$$D_i = (D_b - D_m) \ k_e^{'} T_p$$

(4.23)

$$D_m = (k_d - B_d) / \ [k_e^{'}^2 - (K_e^{'2})^{1/2}] \ = \ K_d \ B_d / k_e^{'}$$

(4.24)

Using above equation:

$$W = D_b - D_m \ k_e^{'} T_p + (K_d \ B_d / k_e^{'})$$

(4.25)

Dobrinska and Welling\(^63\)–\(^64\) have proposed model, which describes the pharmacokinetic behavior of extended release dosage forms. The schematic representation of the model is –

```
```

where
\( D_b \) = dose instantaneously available for absorption into the systemic circulation,

\( D_{ts} \) = maintenance dose to be released slowly at the absorption site,

\( S \) = total drug in solution and available for absorption from the absorption site,

\( A \) = amount of unchanged drug in the body,

\( U \) = cumulative amount of drug excreted unchanged in the urine,

\( M \) = cumulative amount of drug converted to metabolites or excreted by any process other than via the kidneys, i.e., in bile, sweat, saliva, etc. For brevity, this will be referred to in the text as metabolites.

\( k_0 \) = zero order rate constant for release of drug from \( D_{ts} \),

\( k_r \) = first order rate constant for release of drug from \( D_{ts} \),

\( k_{10} \) = first order rate constant for transfer of drug from the absorption site into the systemic circulation,

\( f_{u}k_{10} \) = first order rate constant for excretion of unchanged drug into urine

\( f_{m}k_{10} \) = first order rate constant for drug metabolism and all other routes of extra renal excretion (see 'M' above)

\( k_{10} \) = first order rate constant for overall elimination of drug from the body (= \( f_{u}k_{10} + f_{m}k_{10} \))

The curved arrow represents instantaneous release of drug from the dosage form to the absorption site. The simplifying assumptions embodied for the model are

(i) Absorption, metabolism and excretion are all first order processes;

(ii) Transfer from one compartment to another is irreversible;

(iii) All the drug which is released into the gastrointestinal tract or any other absorption site in the body is completely absorbed as intact drug;

(iv) Release of drug from the extended release portion is the rate-limiting step in the absorption process, and

(v) Drug distributes into one apparently homogeneous distribution volume in the body after absorption, i.e., simple-one compartment kinetics are operative.
Assumption (v) is reasonable on the basis that, for a drug obeying multi-compartment kinetics within the body, it would be difficult to define the microscopic distribution parameters when drug is introduced into the system at a slow rate. Even when a fast-release component is included in a drug formulation, the simple one compartment model is a reasonable compromise between pharmacokinetic accuracy, with accompanying mathematical complexity and practical utility.

4.8.1. CASE 1: Zero Order Drug Release From Dosage Form With No Instantaneous Release Component

In such system $D_n = 0$ and $D_{rs} = k_0 T$

where $T$ is the total time during which drug is release.

Drug release $D'_{rs} = D_{rs} - k_0 \cdot t$  \hspace{1cm} (4.26)

The above equation describes the quantity of drug in the formulation remaining to be released at any time $t$ after dosing; where $t$ varies from zero to $T$.

Drug at absorption site is given by the equation

$$ S = k_0 \left( 1 - e^{ks} \right) k_s \quad (0 \leq t \leq T) $$  \hspace{1cm} (4.27)

The above equation describes the time cause of amount of drug in solution at the absorption site.

Drug in the body is given by

$$ A = k_0 \left( 1 - e^{k_{10} t} \right) k_{10} $$  \hspace{1cm} (4.28)
4.8.2. CASE 2: ZERO ORDER DRUG RELEASE FROM DOSAGE FORM WITH INSTANTANEOUS RELEASE COMPONENT

In this model \( D_i \) is available for instantaneous absorption.

Drug release is given by equation:

\[
D'_{is} = D_i - k_0 \cdot t \quad (4.29)
\]

Integration of above equation gives:

\[
D'_{is} = D_i - e^{k_{at}} \quad (4.30)
\]

This equation describes mono exponential loss of the instantaneously available component from the absorption site, controlled by \( k_a \).

Drug at the absorption site at any time \( t \leq T \) is given by

\[
S = k_0 \left(1 - e^{-k_{at}}\right)/k_a + D_i e^{-k_{at}} \quad (4.31)
\]

Drug in the body at any time \( t \leq T \) is given by

\[
A = k_0 \left(1 - e^{-k_{10}}\right)/k_{10} + \left[\left(k_a D_i - k_0\right) \left(e^{k_{at}} - e^{-k_{10}}\right)\right] / (k_{10} - k_a) \quad (4.32)
\]

\( D_{fs} \) can be calculated from

\[
D_{fs} = \frac{1}{k_a} - \left(k_{10} - k_a\right) \left(1 - e^{-k_{10}}\right)/k_{10}k_a \left(e^{k_{at}} - e^{-k_{10}}\right) k_0 + \frac{A \left(k_{10} - k_a\right) / k_a \left(e^{k_{at}} - e^{-k_{10}}\right)}{k_a} \quad (4.33)
\]

Simplified form of above equation

\[
D_{fs} = k_0 / k_{10} \quad (4.34)
\]

4.8.3. CASE 3: First Order Drug Release From Dosage Form With No Instantaneous Release Component

For first order release model, with not instantaneous release \( (D_i = 0) \) drug release is given by the following equation:
\[ D_f' = D_f e^{-kt} \]  
\[ \text{Drug at absorption site} \]
\[ S = D_f k_r \left( e^{kt_0} - e^{kt} \right) / (k_a - k_r) \]  
\[ \text{Drug in the body is given as} \]
\[ A = D_f k_r \left( e^{kt_0} - e^{kt} \right) / (k_r - k_{10}) \]  
\[ \text{Drug in the body } A \text{ is given by} \]
\[ A = D_f k_a k_r \left( e^{kt} / k_{10} - k_a (k_r - k_{10}) e^{kt} / (k_a k_r) (k_{10} - k_r) + e^{kt} / (k_a - k_r) (k_r - k_{10}) \right) \]  
\[ \text{4.8.4. CASE 4: First Order Drug Release From Dosage Form} \]

\[ \text{With Instantaneous Release Component} \]

For first order release model, with instantaneous release, drug release is given by the following equation:
\[ D_f' = D_f e^{-kt} \]  
\[ \text{Drug at absorption site} \]
\[ S = D_f e^{kt} + D_f k_r \left( e^{kt} - e^{kt_0} \right) / (k_a - k_r) \]  
\[ \text{Drug in the body } A \text{ is given by} \]
\[ A = D_f k_a k_r \left( e^{kt} + (k_r - k_{10}) e^{kt} / (k_r - k_a) (k_{10} - k_{10}) + (k_r - k_a) \right) \]  
\[ \text{Total dose } D \text{ for this case contain loading dose } D_f \text{ required to reach the desired} \]
therapeutic level at its peak, minus the drug simultaneously released from } D_f \text{ up to time } t_{max} \text{ plus the } D_f \text{ required to maintain the level.}
\[ D_f = D_c' - D_{corr} \]
\[ D_c' = \text{initial dose to reach desired peak level.} \]
\[ D_{corr} \text{ is correction factor allowing for the contribution due to } D_f \text{ to time } t_{max}. \]
\[ \text{Total dose } D = D_c' - D_f - D_f k_r t_{max} + \left[ k_{10} A_{t_0} / k_r \right] \]  
\[ \text{- 103 -} \]
4.9. ORAL EXTENDED RELEASE DRUG DELIVERY SYSTEM 

PHYSICIO-CHEMICAL AND PHYSIOLOGICAL ASPECTS

Among all the routes of drug administration that have been explored for the development of extended release delivery system, the oral route has by far achieved the most attention and success. This is due, in part to the ease of administration as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.

An understanding of varied disciplines, such as GI physiology, pharmacokinetics, and formulation techniques, is essential in order to achieve a systematic approach to the design of oral ER products. The scientific framework required for development of a successful oral extended drug delivery dosage form consists of an understanding of two aspects of the system, namely

- Formulation characteristics
  - Physicochemical characteristics of the drug.
  - Dosage form characteristics.
- GI anatomical and physiological features.

4.9.A. FORMULATION CHARACTERISTICS

A number of formulation characteristics need to be considered in evaluating drug candidate, polymers and excipients for oral ER dosage forms. Some of these characteristics are discussed here.

4.9.A.i. Dose

A total dose of several grams may be administered orally as single or multiple units to obtain and maintain adequate drug levels. Nevertheless, for drug with elimination
half-life or less than 2 hour as well as those that are administered in large doses in CR dosage form may need to carry a prohibitively large quantity of drug.

4.9.A.ii. Biological Half Life\textsuperscript{39}

In general, drug with short half-lives (2-4 hours) make good candidate for ER systems.

Drugs with elimination half-lives of over 8 hours are commonly sufficiently extended in the body after a conventional oral dose to make extended release unnecessary.

4.9.A.iii. Therapeutic Range

Oral ER formulations are valuable for maintaining plasma levels within a narrow therapeutic range. In fact, a valid rationale for formulating drugs with half-lives of over 8 hours as ER formulations is to maintain plasma drug levels with a narrow range.

4.9.A.iv. GI Absorption\textsuperscript{65-72}

Efficient drug absorption from the GI tract is a prerequisite for a drug to be considered for use in an oral ER form. In general, the absorption rate for most drugs decreases as the dosage form moves beyond the jejunum. As long as the absorption rate remains above that of the release rate, this change does not affect plasma levels. However, once past the ileocecal junction, a variety of factors generally reduce the drug absorption rate to below acceptable values. This creates a time limit of about 6-9 hour during which the drug can be delivered in a predictable manner. For compounds that are absorbed via an active transport mechanism and for many others, an acceptable rate of absorption may exist only from a limited portion of the small intestine, which may further limit their suitability for ER systems.
4.9.A.v. Ionization, $pK_a$ And Aqueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the $pK_a$ of the compound and the absorptive environment. Considering that these dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release processes must be defined.

Compounds with very low solubility (less than 0.01 mg/ml) are inherently extended, since their release over the time course of a dosage form in the G/I tract will be limited by dissolution of the drug. ER formulations of low solubility drugs may be aimed at making their dissolution more uniform rather than reducing it.$^{73-77}$

4.9.A.vi. Stability Of Wide pH Range G/I Enzymes And Flora

Typically the drug must be stable in the pH range of 1 to 8. Unlike a conventional dosage form, an ER formulation is exposed to the entire range of G/I pH, enzymes and flora.

4.9.A.vii. First-pass Metabolism$^{78-79}$

Saturable hepatic metabolism may render a drug unsuitable for oral CR. This is because systemic availability for such drugs is highly reduced when the input rate is small.

4.9.A.viii. ER Polymer Properties$^{80-95}$

Understanding polymer properties is must, since in most of the extended release system drug release mechanism are based on diffusion through polymer, erosion of polymers and other characteristics such as osmotic and ion exchange properties.
The polymer properties that influence drug release are:

(i). Molecular weight and molecular weight distribution.
(ii). Material characteristic time.
(iii). Polymer microstructure.
(iv). Glass transition temperature.
(v). Solubility parameter.
(vi). Diffusibility.

The details are in Chapter 5.

4.9.B. EFFECT OF DOSAGE FROM SHAPE ON DRUG RELEASE

The release of drug from planar device was first proposed by Higuchi\textsuperscript{79} who used a pseudo steady state approximation approach to simplify complex boundary problem and is illustrated in fig. 4.8.

\[ Q_t = AD_m \frac{dc}{dx} \]  

(4.43)

where \( Q_t \) = rate of diffusion
\( A \) = cross section area available for diffusion
\( D_m \) = diffusion coefficient
\( c \) = concentration of drug
\( x \) = distance measure from the solvent matrix interface.

4.9.B.i. Slab Geometry

Consider following boundary condition

\[ C = C_b \text{ at } x = 0 \text{ and } \]

\[ C = C_e \text{ at } x = 0X_{(0)} \]

where

\( C_b \) = drug concentration in the bulk, which is constant over the period of release
Fig. 4.8. Co-ordinate system to study drug release kinetics from planar cylindrical and spherical geometry.

\[ C_m = \text{drug solubility in the matrix} \]
\[ K = \text{matrix to bulk partition coefficient} \]
\[ x(l) = \text{receding boundary length is function of time} \]

On application of above condition, integrating the equation, applying mass balance equation in diffusion region gives following equation:

\[
\frac{dM_t}{dt} = Q_t = A \cdot \left[ D_m (C_m - C_b K) 2C_T - C_m - C_b K \right]^{1/2} (4.44)
\]

where

- \( M_t \) = amount of drug released at time \( t \)
- \( C_T \) = drug loading dose in matrix.
It can be clearly seen from above equation that the release rate in slab is inversely proportional to square root of time.

Cumulative drug release and receding boundary length is directly proportional to square root of time.

4.9.B.ii. Cylindrical Geometry

For cylindrical geometry (fig. 4.8), Qt = rate of diffusion is given by the equation

\[ Q_t = 2 \pi r L D_m \frac{dc}{dr} \]  \hspace{1cm} (4.45)

Consider following boundary condition:

\[ C = C_b \text{ at } r = R_0 \]

\[ C = C_m \text{ at } r = R_0 \]

Integrating above equation and making appropriate mass balance equation gives following implicit equation

\[ \frac{dM}{dt} = Q_t \]

\[ = 2 \pi L D_m (C_m - C_b K) \ln \left( \frac{R_0}{R_0 t} \right) \]  \hspace{1cm} (4.46)

\[ [R^2(t)/2. C_n . R(t)/R_0] + \frac{1}{4} [R_0^2 - R^2(t)] = D_m (C_m - C_b K) t / C_t \]

\[ (4.47) \]

4.9.B.iii. Spherical Geometry

For spherical device (fig. 4.8), Qt = rate of diffusion is given by the equation

\[ Q_t = -4 \pi r^2 D_m \frac{dc}{dr} \]  \hspace{1cm} (4.48)

at \( C = C_b \text{ at } r = R_0 \)

\[ C = C_m \text{ at } r = R_0 \]

\[ Q_t = - [4 \pi D_m (C_m - C_b K)] \ln \left( \frac{1}{R_0 t} - \frac{1}{R_0} \right) \]  \hspace{1cm} (4.49)

Thus, like cylindrical geometry, spherical geometry shows concentration profile for pseudo state assumption is no longer linear with radius. The rates and fraction for three geometrics when plotted against time t does not give zero order release. The release behavior is inherently first order in nature which is due to increase in
diffusional resistance and decrease in effective area at diffusional front as drug release proceeds. Methods of altering kinetics of drug release from the inherent first order behavior, to achieve constant rate of drug release from matrix device have involved use of geometry factor, erosion/dissolution, swelling control, uniform drug loading and matrix membrane combination.

4.9.C. DRUG RELEASE FROM SWELLING CONTROLLED SYSTEMS

It is reviewed in detail in Chapter 5.

4.9.D. GENERAL POLYMER TOXICOLOGICAL CONSIDERATIONS

The potential adverse effects of polymers must be known or evaluated prior to using in drug delivery system for humans. Potential adverse effects may result from contact with the polymer or from leachables such as residual monomers, reactive agents, or processing additives. The effects of polymers or extracts will be dependent on unique chemical characteristic and the amount (or dose) of polymer/extract administered. There should be an evaluation of whether the polymer is in direct or indirect contact with the drug-containing component of the system or with tissues of the patient. These evaluations will assist in the determination of the types of safety assessments that may be required during the various stages of the development process. To assist in selection of materials, a review of the manufacture's and published scientific literature should be conducted to gather clinical and non-clinical safety information. If necessary, in vivo and in vitro tests are used to evaluate the incompatibility of the polymer and/or extract acid of the drug delivery system, thereby ensuring the safety of the system. In vitro studies should be conducted prior to initiating in vivo studies. Cytotoxicity tests are simple and rapid in vitro procedures that can provide predictive information on in vivo biocompatibility of polymeric materials96. If polymer is not absorbed or data indicate that blood levels
are acceptable based on historical exposure or existing toxicological data, then it may be sufficient to conduct toxicological studies with the final drug delivery formulation with a written review and justification of the use of the polymer.

If the polymer is an NCE (new chemical entity), a series of in vitro and in vivo (animal) genotoxicity studies should be conducted. These mutagenicity and clastogenicity studies determine if the polymer harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of the polymer should be halted. If no genotoxic activity is present, the next step is to quantify exposure. If the polymer is absorbed from the GI tract, a full toxicology program consisting of acute, chronic, reproduction and carcinogenicity testing is likely to be required. If the polymer is not absorbed, studies up to 6 months may be required with an evaluation of any proliferative changes. If proliferative changes occur, a carcinogenicity study might be indicated. Whether or not the polymer is absorbed or not, additional toxicology studies need to be conducted with the final formulation at multiple doses.

4.9.E. GASTRO INTESTINAL ANATOMY AND PHYSIOLOGY

Insight into the biological aspects of oral delivery is more important for CR systems than it is for conventional dosage forms. Listed below are some of the factors that influence delivery of drugs to the GI tract. GI mobility and transit time, blood flow, environment of GI tract which includes luminal contents and pH, mucus, ileo-cecal junction, gut flora, gut immunology.

4.9.E.I. GI Anatomy

Fig. 4.9. is the schematic representation of the route of oral drug delivery and Table 4.1 lists some of the characteristics of GI tract that are relevant to drug delivery system.
4.9.E.ii. **Gastro Intestinal Motility**

An important consideration when contemplating use of CR dosage forms in the GI tract is the continuous motility of this organ. The pattern and force of the motility vary depending on whether the animal is in a fed or a fasted state\textsuperscript{97-98}. It is now well documented that there are two modes of GI motility patterns in humans and animals.

---

**Fig. 4.9.** Schematic representation of gastrointestinal tract.
Table 4.1. Characteristics of the GI tract.

<table>
<thead>
<tr>
<th>Section</th>
<th>Area (m²)</th>
<th>Fluid secretion (l/d)</th>
<th>Reaction (pH)</th>
<th>Important Constituents</th>
<th>Food Transit Time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>~0.05</td>
<td>0.5–2</td>
<td>5.2–6.8</td>
<td>Amylase, Ptyalin, Mucins</td>
<td>Short</td>
</tr>
<tr>
<td>Esophagus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Very short</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.1–0.2</td>
<td>2–4</td>
<td>1.2–3.5</td>
<td>Lipase, Cathepsin, HCl, Pepsin, Lipase, Intrinsic Factor</td>
<td>0.25–3</td>
</tr>
<tr>
<td>Duodenum</td>
<td>~0.04</td>
<td>1–2</td>
<td>4.6–6.0</td>
<td>Amylase, Lipase, Bile acids, Glucohydrolase, Galactohydrolase, Trypsin, Chymotrypsin</td>
<td>1–2</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>4500*</td>
<td>0.2</td>
<td>4.7–6.5</td>
<td>Like in duodenum</td>
<td>1–10</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>0.5–1</td>
<td>About 0.2</td>
<td>7.5–8.0</td>
<td>Mucus, Bacterium</td>
<td>4–20</td>
</tr>
</tbody>
</table>

*Taking intestinal microvilli area into account; without them, ~100m².

4.9.E.ii.a. GI Transit

The single most limiting biological factor in the development of once daily oral ER systems is the transit time of a dosage form through the GI tract.
4.9.E ii.b.  Fasted State Transit Behavior

The process of disintegration and dissolution starts in the stomach. Transit of liquids already present in the stomach and administered with the dosage form can play an important role in the process. A dosage form given with a small volume of liquid can stay in contact with that liquid in the fasted state up to 60 min\(^70\). A solid dosage form stay in a fasted stomach for any duration up to 120 min\(^78\). Thus, manipulation of density and shape of solids does not seem to be a viable approach, although some studies have claimed otherwise. The only possibility may be to increase the size of the dosage form to a degree that it cannot pass through the pylorus until degraded or perhaps convert the stomach to a fed state.

For multiunit dosage forms, once the particles have left the stomach, there is, if any further spreading of particles in the intestine. Since particles usually leave the stomach as a bolus during the fasted state, multiunit dosage forms may not serve their intended claim of dispersion\(^100\).

4.9.E ii.c.  Fed State Transit Behavior

In general, solids are not empties in the fed state unless they have been ground to a particle size of 2mm or less. Multiunit dosage forms however will disperse and empty with food and thus achieve a better degree of distribution than tablets. Total time for gastric emptying varies from about 2 to 6 hr.


The presence of food in the GI tract can often have a marked and sometimes variable effect on drug absorption. Food can increase or decrease the rate or extent of absorption of a drug, or delay the onset of absorption\(^100-102\).
In general, food prolongs the gastric residence time of non-digestible solids for up to 6 hour. For formulations designed to release drug independent of pH, gastric residence time does not affect drug release and subsequent absorption, unless the drug is unstable in an acid environment. For such formulations, food generally improves the bioavailability. Food can have a marked influence on the GI distribution of multiunit dosage forms provided they are 2 mm or smaller\textsuperscript{65,101}.

4.10. ORAL EXTENDED RELEASE DRUG DELIVERY SYSTEMS: FORMULATION ASPECTS\textsuperscript{103-111}

The thrust of oral extended release efforts has been focused mostly on the dosage forms with 'well-defined' CR profiles. Almost all the oral solid ER products in today's market are based on the designs of matrix, membrane controlled, and osmotic systems (Table 4.2). The mechanisms of these CR dosage forms generally involve drug diffusion through a viscous gel layer, tortuous channels or a barrier, drug dissolution via system erosion: and drug solution or suspension forces out of the device by osmotic pressure. In this section, the more common methods that used to achieve extended release of orally administered drugs are discussed\textsuperscript{112}.

<table>
<thead>
<tr>
<th>Matrix Systems</th>
<th>Reservoir Systems</th>
<th>Osmotic Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Swellable.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Swellable &amp; erodible.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrophobic matrix:</td>
<td></td>
<td>Push-stick system.</td>
</tr>
<tr>
<td>• Homogeneous (non porous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Heterogeneous (porous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Inert (monolithic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Erodible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Degradable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2. Common oral extended release polymeric systems feasible for commercial development.
4.10.1. **Matrix Controlled Drug Delivery System**

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. Plastic matrices include methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene. Hydrophilic polymers include methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose and carbopol. Fatty compounds include various waxes such as carnauba wax and glyceryl tristearate.

The most common method of preparation is to mix the drug with the matrix material and then compress the mixture into tablets. In the case of wax matrices, the drug is generally dispersed in molten wax, which is then congealed, granulated and compressed into cores. In any extended release system, it is desirable to release a portion of drug immediately as a priming dose, and the remainder to be release in an extended fashion. This can be accomplished in a matrix tablet by placing the priming dose in a coat of the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating. Table 4.3 gives some matrix diffusion controlled products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fero-Gradurnet</td>
<td>Ferrous Sulphate</td>
<td>Abbott</td>
</tr>
<tr>
<td>Desoxyr</td>
<td>Methamphetamine HCl</td>
<td>Abbott</td>
</tr>
<tr>
<td>Procan SR Tablets</td>
<td>Procainamide</td>
<td>Parke-Davis</td>
</tr>
</tbody>
</table>
Matrix dissolution devices are prepared by compressing the drug with a slowly soluble polymer carrier into a tablet. There are two general methods of preparing drug-matrix particles: congealing and aqueous dispersion methods. In the congealing method, drug is mixed with a wax material and either spray congealed or congealed and screened. In the aqueous dispersion method, the drug wax mixture simply is sprayed or agitated in water and the resulting particles are collected. Matrix tablets also are made by direct compression of a mixture of drug, polymer and excipients. Some marketed preparations are mentioned in Table 4.4.

Table 4.4 Matrix dissolution products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimetane</td>
<td>Brompheniramine</td>
<td>Robins</td>
</tr>
<tr>
<td>Mestinon</td>
<td>Prridostigmine bromide</td>
<td>Roche</td>
</tr>
<tr>
<td>Nicobid</td>
<td>Nicotinic acid</td>
<td>Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td>Demazin</td>
<td>Chlorpheniramine maleate phenylephrine HCl</td>
<td>Schering</td>
</tr>
</tbody>
</table>

4.10.2 Reservoir Controlled Drug Delivery System

In developing reservoir polymeric systems, commonly used methods include micro-encapsulation of drug particles, coating of tablets or multi-particulates, and press coating of tablets. A polymeric membrane offers a predetermined resistance to drug diffusion from the reservoir to the sink. The driving force of such systems is the concentration gradient of active molecules between reservoir and sink. The resistance provided by the membrane is a function of film thickness and characteristics of both the film and the migrating species in a given environment. The mechanisms of the drug release from the film-coated dosage forms may be categorized into (a) transport of the drug through a network of capillaries filled with dissolution media; (b) transport of the drug through the homogeneous film barrier by
diffusion; (c) transport of the drug through a hydrated swollen film; and (d) transport of the drug through flaws, cracks and imperfections within the coating matrix.

Some materials used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl or ethylcellulose, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate, various waxes and silicone elastomers.

Some reservoir diffusion controlled products available in the market are given in Table 4.5.

Table 4.5. Matrix reservoir controlled products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nico-400 Capsules</td>
<td>Nicotinic acid</td>
<td>Jones</td>
</tr>
<tr>
<td>Nitro-Bid</td>
<td>Nitroglycerin</td>
<td>Marion</td>
</tr>
<tr>
<td>Cerespan</td>
<td>Papaverine HCl</td>
<td>Rhone Poulenc Rorer</td>
</tr>
<tr>
<td>Bronkodyl SR Capsules</td>
<td>Theophylline</td>
<td>Sanofi - Winthrop</td>
</tr>
</tbody>
</table>

Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thickness of slowly soluble polymers or by micro-encapsulation. Microencapsulating can be accomplished by suing phase separation, interfacial polymerization, heat-fusion or the solvent evaporation method. The coating materials may be selected from a wide variety of natural and synthetic polymers, depending on the drug to be coated and the release characteristics desired. The most commonly used coating materials include gelatin, carnauba wax, shellac, ethylcellulose, celluloseacetate phthalate or cellulose acetate butyrate. Drug release from micro-capsules, is a mass transport phenomenon; can be controlled by adjusting the size of microcapsules, thickness or coating materials and the diffusivity of core materials. The coating thickness of microcapsules is normally very less, and
for a given coat-core ratio, it decreases rapidly as the microcapsule size decreases. The thickness can be varied from less than 1 μm to 200 μm by changing the amount of coating material from 3 to 30% of the total weight. If only a few different thicknesses is used, usually three or four, drugs will be released at different, predetermined times to give a delayed release effect, i.e., repeat action. If a spectrum of different thickness is employed, a more uniform blood level of the drug can be obtained. Microcapsules commonly are filled into capsules and rarely are tabletted as their coatings tend to disrupt during compression. Some marketed preparations are mentioned in Table 4.6.

Table 4.6. Encapsulated dissolution products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredient(s)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexedrine Capsules</td>
<td>Dextro amphetamine</td>
<td>Smithkline Beechem</td>
</tr>
<tr>
<td>Thorazine</td>
<td>Chlorgylin HCl</td>
<td>Smithkline Beechem</td>
</tr>
<tr>
<td>Diamox</td>
<td>Acetazolamide</td>
<td>Lederle</td>
</tr>
<tr>
<td>Ferro-sequels</td>
<td>Ferrous fumarate docusate sodium</td>
<td>Lederle</td>
</tr>
</tbody>
</table>

4.10.3. Osmotic Controlled Drug Delivery System

Osmotic pressure can be employed as the driving force to generate a constant release of drug provided a constant osmotic pressure is maintained and few other features of the physical system are constrained. Consider a tablet consisting of a core of an osmotically active drug, or core of an osmotically inactive drug, in combination with an osmotically active salt surrounded by a semi-permeable membrane containing a small orifice. The membrane will allow free diffusion of water, but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet due to osmotic pressure difference.
Fig. 4.10. Schematic representation of a two-compartment osmotic pressure controlled drug delivery system.

Several modifications of the osmotic pressure controlled drug delivery system have been developed. A layer of bio-erodible polymer can be applied to the external surface of the semi-permeable membrane. A system consists of two compartments separated by a movable portion (fig. 4.10). For a system that does not have an orifice, pressure is built up until the wall ruptures and the contents are released to the environment.

The advantage of the osmotic system is that it requires only osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH change through the GI tract. Some materials used as the semi-permeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride. Drugs that have demonstrated successful release rates are potassium chloride and acetazolamide.
4.10.4. Controlled Drug Delivery System Using Ion-Exchange Resins

Ion-exchange resins are water-insoluble cross-linked polymers generally as powders or beads, containing salt forming groups in repeat positions on the polymer chain. Drug is bound to the resin by exposure of the resin to the drug in a column, or by contact of the resin with the drug solution. The drug resin then is washed to remove free, unbounded and contaminating ions and dried to form particles or beads. Drug release from the drug resin complex depends on the ionic environment, i.e., pH and electrolyte concentration within the GI tract as well as properties of the resin.

Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract followed by diffusion of the free drug molecule out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional path-lengths and extend of cross-linking in the resin. A modification of the release rate can be made, by coating the drug with resin complex. Further improvement of this ion exchange type drug delivery system is called the Penn Kinetic system. In this system, the drug containing resin granules first treated with an impregnating polymer such as PEG 4000 to retard the rate of swelling in water and further coated with water insoluble polymer such as ethylcellulose, to serve as a rate limiting barrier to control the drug release.

Most ion exchange resins employed in extended release products contain sulfonic acid groups that exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl butylamine (phenetermine), phenyltoloxamine and hydrocodone.
4.10.5. **Gastro Retentive Drug Delivery System**

Variability in GI transit time is a concern for oral controlled drug delivery systems. Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both availability and times to achieve peak plasma levels. In successful, gastro retentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time. A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach. For example, antibiotic administration for Haemophilus pylori eradication in the treatment of peptic ulcer.

Researchers in the area have attempted to achieve prolonged gastric retention by several means, including altering the density of the formulations and bio-adhesion in the stomach lining. Several strategies have been employed to make the dosage forms float in the stomach. Hydro-dynamically balanced system (HBS) was the first formulation that uses the floating property of a device with density lower than water. HBS is a capsule-containing drug, gel-forming hydrophilic polymers (e.g., hydroxypropylcellulose), and some hydrophobic fatty materials (e.g. stearates). 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. Extension of the floating time is achieved by coating the bicarbonate-coated beads with a semi-permeable membrane. Recently, a multiple-unit floating dosage form has been prepared from freeze-dried calcium alginate. In fed subjects, these floating units were retained in the stomach for 8.5 - 9 hours.
Some hydrogels and super-porous hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio of over 1000\textsuperscript{113}. They can be made by cross-linking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Super-porous hydrogels\textsuperscript{119} have unique super-swelling 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 important requirement for gastric retention devices.

4.10.6. Pulsative or Timed-Release Drug Delivery System

Maintaining constant blood levels of a drug may not always be a desirable option for all types of diseases or ailments. Several circumstances exist in which varied blood levels of the drug during the course of therapy is preferred. For example, hypertension, diabetes mellitus, cardiac arrhythmia, and certain infections require varied concentrations of drug in blood according to the intensity of the disease and the physiological parameter being controlled. Thus, delivering drugs in a pulsatile fashion for certain clinical conditions is beneficial.

4.10.7. Targeted or Site-Specific Drug Delivery System

Delivering drugs to the desired site of action has several advantages, including reduced bio-burden and toxicity. Colonic drug delivery is gaining interest as one of the important targeted drug delivery systems. The objective of colonic drug delivery is not treat local diseases of the colon, but also to deliver certain drugs such as proteins and peptides. Most colon-targeted systems are coated systems because of their wide acceptance, technological developments, and design flexibility.
4.10.8. Prodrug Drug Delivery System
A prodrug is a compound formed by chemical modification of a biological active compound, which will liberate the active compound \textit{in vivo} by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as GI irritation. Prodrugs can be used to increase the strategies for extended release and, in a limited sense, can be sustaining in their own right.\textsuperscript{120-122}

4.11. RELEASE CONTROLLING POLYMER AVAILABLE IN MARKET\textsuperscript{95}
Materials used for controlling drug release from oral tablets and capsules include polymers from natural products, chemically modified natural products and synthetic products. Some of the common materials that have regulatory clearance are discussed briefly based on their applications in different types of controlled release systems.

4.11.1. Materials Used For Matrix System
The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (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.

Hydroxypropyl methylcellulose is nonionic water-soluble cellulose ether made by Dow Chemical under the brand name of 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 Methocel of ultrafine particle size for controlled release formulations include K100LV, K4M, K100M, E4M and E100M. When dissolved at a concentration of 2% in water, the viscosity ranges from 100 to 100,000 cps. Similar grades of HPMC (Metolose SR) are also available from ShinEtsu, Japan.

Hydroxypropylcellulose and hydroxyethylcellulose are nonionic water-soluble cellulose ethers made by the Aqualon division of Hercules Inc. under the brand names Klucel and Natrosol, respectively. For controlled release applications they are available in high- and low-viscosity grades, such as Klucel HXF, EXF and Natrosol 250 CHX.

Xanthan gum is a water-soluble polysaccharide gum produced by the Kelco division of Monsanto Co. under the brand name of Keltrol. It is composed of D-glucosyl, D-mannosyl, and D-glucosyluronic acid residues and differing proportions of D-acetyl and pyruvic acid acetal. The primary structure consists of a cellulose backbone with trisaccharide side chains.

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

Poly(ethylene oxide) polymer is a nonionic water-soluble resins made by Union Carbide under the brand name Polyox. Its common structure is -(OCH₂CH₂)ₙ - OH. For controlled release applications 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 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, 974 P and 934 NF are specifically designed for preparing hydrogel and mucoadhesive controlled release systems.

Hydrophobic and monolithic polymer matrix systems usually use waxes and water-insoluble polymers in their formulation. Many waxes are long chain wax esters, glycerides, and fatty acids. Natural and synthetic waxes of differing melting points have been used as controlled release matrix materials. Examples include carnauba wax, bees wax, candelilla wax, microcrystalline wax, ozokerite wax, paraffin waxes, and low molecular weight polyethylene, to name a few. Insoluble polymers used in preparing controlled release matrices include fine powders of ammoniometeracrylate copolymers (Eudragit RL 100, PO, RS 100, 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).

4.11.2. Materials Used For Reservoir System

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 dispersion that form films by a process of coalescence of sub-micrometer polymer particles. Ammoniometeracrylate copolymers (Eudragit RL 30D, RS 30D) are water-permeable and swellable film formers based on neutral methacrylic esters with a small portion of trimethylammonioethyl methacrylate.
chloride. Methacrylate ester copolymers (Eudragit NE30D) is a neutral ester without any functional groups. They are supplied by Rohm America as 30% aqueous dispersions without the need of plasticizers unless improved film flexibility is desired. Ethylcellulose for film coating is available as an aqueous polymeric dispersion containing plasticizers under the brand name of Surelease (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), hydroxypropylmethylcellulose phthalate (HPMCP), Methacrylic acid and Methacrylic esters (Eudragit L and S). Enteric polymers and pH-dependent polymers. At high pH (e.g., > 5.5), the polymer dissolves whereas at low pH, the polymer is impermeable and insoluble.

4.11.3. Polymers Used For Osmotic System

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

4.12. EXTENDED RELEASE DEVELOPMENT TECHNOLOGIES

Almost all oral extended release systems are in the forms of tablets and capsules. Development technologies for these dosage forms include tableting, pelletization, and film coating of single unit or multi-particulate.
4.12.1. **Tableting**

Extended release tablet dosage forms are usually manufactured using conventional processes of granulation such as wet granulation, dry granulation or direct compression. Granules prepared by wet granulation or dry granulation are sifted, lubricated and compressed into tablets while in case of direct compression the steps are blending and compression. The tablets may be further coated with functional membrane for controlling the release, stability or aesthetic purpose. Tablets can be compressed as multiple-layer for achieving specific release.

4.12.2. **Pelletization**

Controlled release pellets, beads, or spheres may offer certain advantages over single unit dosage forms in that they minimize the risk of unexpected drug release (e.g., dose dumping), which may occur when a single-unit device is defective\textsuperscript{124}. In addition, multi-particulate dosage forms can be designed to provide customized release profiles by combining beads with different release rates or to deliver incompatible drugs in the same dosage unit\textsuperscript{125}.

The basic methods for pellet or bead production include

(i) microencapsulation,
(ii) spray congealing,
(iii) formation of particles from a plastic mass, and
(iv) agglomeration.

Most microencapsulation techniques are based on processes by which coatings of natural or synthetic polymers are applied to solid or liquid agent via coacervation or polymerization\textsuperscript{126-127}. The spray-congealing process consists of embedding the active drug in an excipient such as wax or plastic. Formulation of particles from a
plastic mass is achieved using a machine known as marumerizer or a spheronizer. The spheronization process in the marumerizer involves partial shaping of pellets followed by utilization of friction and surface forces to form spheres. Powdered raw materials are converted into a plastic mass using water or solvents in conjunction with binding agents. This mass is extruded under pressure through a perforated screen or die. Spinning in the marumerizer the breaks down the cylindrical, spagnetti-like extrudates until the length is equal to the diameter. The process continues until they are rolled into spheres by centrifugal and frictional forces. To produce solid spheres, the extrudate must break into short segments and short cylinders must be sufficiently plastic to be rounded by spheronization. The materials that break into short cylinders without sufficient plastic properties do not yield a spherical product. Microcrystalline cellulose is found to exhibit the elasticity required for extrusion and spheronization. Thus, it is an excipient most commonly used for pelletization / spheronization.

Agglomeration is one of the oldest process for manufacturing spherical particles. It is based on the layering technology derived from sugar coating in a coating pan. Traditionally, these spheronization processes involving surface forces can be divided into two stages: nucleation (seed growth) and sphere growth (bead preparation). With the layering technique, the active drug or other ingredients in the form of either a dry powder or solution / dispersion are agglomerated to form seeds. They are commercially available nonparell seeds containing active drugs. This process can be performed in a coating pan, a rotary granulator, or a fluidized bed.

4.12.3. Coating Technologies

In the pharmaceutical industry, significant advances have been achieved in polymer coating of solid dosage forms over the last two decades. Polymer coating involves
deposition of a uniform membrane of polymer ration onto the surface of the substrates, such as tablets, spheres, or pellets and drug particles. Coating techniques that are used in developing controlled release reservoir or osmotic systems include

(i) film coating,
(ii) layering coating and
(iii) compression coating.

Coating formulations as well as processing variables influence the properties of the resulting functional coating.

The film coating process is performed in a coating pan, a fluidized bed or a rotary granulator. Ethylcellulose, methacrylic ester copolymers, methacryl ester copolymers, cellulose acetate etc. are widely used either alone or in combination with water-soluble polymers for the preparation of controlled release films. Since, the integrity of the film and the absence of flaws or cracks are important factors in controlling the drug release from such preparation, it is imperative that the film formulation be optimized. Plasticizers are often added to such films to increase the film flexibility and minimize the incidence of flaws. Often factors affecting film coating and drug release include additives (e.g. pigment, plasticizer, solvent) and process variables (e.g., equipment, batch scale, airflow, spray rate, temperature).

The layering coating process is often performed in a coating pan or a fluidized bed coater. This type of coating process is not continuous. For example, in coating beads, the seeds may first be coated with one layer of active drug layer. The process is repeated until multiple layers are completed to meet the predetermined requirement. In some cases, the active drug may be dissolved or dispersed with the
coating materials. Factors affecting coating quality and performance of the final product are similar to those discussed in the film coating process.

The compression coating process is performed using a tablet press to make a compress coat surrounding a tablet core (tablet-in-tablet). The compress coat may function as a barrier to drug release or as a part of formulation to provide biphasic release. The process involves initial compression or the core formulation to produce a relatively soft tablet followed by transferring to a larger die for final compression of the compress:coat layer. This process can be used to develop a controlled release product with unique release profiles or to formulate two incompatible drugs by incorporating one in the core and the other in the compress coat layer.

4.13. PRODUCT EVALUATION FOR DRUG AVAILABILITY

4.13.1. In Vitro Measurement Of Drug Availability

It is not possible to simulate in a single in vitro test system the range of variables that affect drug release during the passage of extended release medication through GI tract. Properly designed in vitro tests for drug release serve two important functions however. First, data from such tests are required as a guide to formulation during the development stage prior to clinical testing. Second, in vitro testing is necessary to ensure batch-to-batch uniformity in the production of a proven dosage form. Different methods are usually required by these two distinctly different testing situations.

Tests developed for the purpose of quality control are generally limited to USP dissolution testing methods using the rotating basket (Apparatus 1), the paddle (Apparatus 2), or the modified disintegration testing apparatus (Apparatus 3). In many instances in which USP test procedures are followed, upper and lower limits are specified for drug release in simulated gastric and/or intestinal fluid.
Measurements are made at specified time intervals appropriate to the specific product. Procedures are determined by nature of the dosage form (e.g., disintegrating or non-disintegrating), and the maintenance period. The methods used to measure drug release profiles should have the following characteristics. As far as possible the analytical technique should be automated so that the complete drug release profiles can be directly recorded. Allowance should be made for changing the release media from simulated gastric to simulated intestinal fluid at variable programmed time intervals, to establish the effect of retention of the dosage form is likely to encounter in vivo. In addition, the hydrodynamic state in the dissolution vessel should be controllable and capable of variation.

Besides, the USP dissolution testing apparatus, testing equipment used for extended action formulation have included the rotating bottle, stationary basket/rotating filter, Sartorius absorption and solubility simulator, and column type flow through assembly. The rotating bottle method was developed for evaluation of extended release formulations. Samples are tested in 90 ml bottles containing 60 ml of fluid, which are rotated end over end in a 37 °C bath at 40 rpm. However, the method is not adaptable to automated analysis, or to easy manipulation of the dissolution media. The Sartorius device includes an artificial lipid membrane, which separates the 'dissolution' chamber from a simulated plasma compartment in which drug concentration are measured. Alternatively, a dialysis type membrane may be used. Systems of this type are advantageous in measuring release profiles of disintegrating dosage units and suspension, granular, and powdered material, if the permeability of the membrane is properly defined. The column flow through apparatus possesses similar advantages since drug release is confined to a relatively small chamber by highly permeable membrane filters. This apparatus is flexible, well defines, and meets all the necessary requirements for measurement of drug release profiles from extended release dosage forms. It can also be adapted to measurements under
near sink conditions if the release medium is passed only once through the dissolution chamber, directly measuring the rate of release. Alternatively the dissolution fluid might be recirculated continuously from the reservoir, allowing measurement of the cumulative release profile. The composition of the release media as well as the flow rate can readily be altered.

The time of testing may vary from 6 to 12 hours, depending on the design specifications of the dosage form. If formulations contain retardants whose function depends on the action of normal constituents of the GI fluids (e.g., bile salts, pancreatin and pepsin), then the appropriate materials must be included in the simulated release media. Apparatus of the Sartorius type would be advantageous in these circumstances if the analytical procedure for the drug would be adversely affected by the presence of these substances. Otherwise, the simulated fluids consisting of pH 1.2 and pH 7.2 buffers, as well as intermediate pH values, which represent the transition between gastric and intestinal pH would suffice at 37°C. Drug release information are processed mathematically and graphically to understand the release kinetics. Confidence limits for the kinetic parameters can be calculated allowing establishment of limits for the percentage of released drug under limited testing conditions established for purpose of quality control. Comparison of results obtained with the same product using different testing methods as well as comparisons between multiple runs, different lots, and different products can be made more readily.

4.13.2. *In Vivo* Measurement Of Drug Availability

Validation of extended release product design can be achieved only by *in vitro* testing. The basic objective is to establish the bioequivalence of the product for which a controlled release claim is to be made with conventional dosage forms of the
formulated drug\textsuperscript{134}. Since no necessary human testing should be done, animal models, such as dogs, should be used initially during the product development stage to tune the formulation to the desired specifications. It is necessary to verify that dumping or insufficient drug availability are not observed \textit{in vivo}. Tests in both animal and subsequent human trials should include periodic blood levels determinations, comparisons of urinary excretions patterns, serial radiophotographs (in human) to follow the course of the dosage form in the GI tract, and sequential observations of pharmacologic activity. In some instances (e.g., with insoluble core tablets), ingested dosage forms should be recovered and assayed for drug content. If drug levels cannot be measured in biologic fluids, then the pharmacologic effect must be observed as a function of time, or clinical trials must be designed, to establish the effectiveness of the drug product.

The FDA has promulgated the general bioavailability and bioequivalence requirements for drug products\textsuperscript{135}. These are made to ensure that the new drug formulation meets its controlled release claims, that no dose dumping occurs, that performance is consistent between individual dosage units, and that steady state drug levels obtained with the product are equivalent to currently marketed products with approved new drug applications (NDAs). Reference materials can include the pure drug substance in solution or suspension as well as conventional dosage forms administered according to their usual dosage schedules or according to the dosage schedule of the controlled release product. Bioavailability studies are ordinarily single dose comparisons of tested drug products in normal adults in a fasting state. A crossover design in which all subjects receive both the product and reference material on different days is preferred.

Guidelines for clinical testing have been published for multiple dose steady state studies as well as for single dose studies. Correlation of pharmacologic activity or
clinical evidence or therapeutic effective with bioavailability may be necessary to validate the clinical significance of controlled release claims.

While single dose studies are usually sufficient to establish the validity of extended release dosage form designs, multiple-dose studies are required to establish the optimum-dosing regimen. They are also required when differences may exist in the rate but not the extent of absorption, when there is excessive subject-to-subject variation or when the observed blood levels after a single dose are too low to be measured accurately. A sufficient number of doses must be administered to attain steady state blood levels.

4.13.3. In Vitro In Vivo Correlation

Attempts to correlate in vivo performance with in vitro availability tests generally have been based on 'single point' measurements. For example, AUC values, peak blood levels or peak times might be correlated with the time required for 50% of drug to be released in vitro. The best that can be expected from this approach is a rank order correlation. Significantly bioavailability difference between formulations might be masked by improper in vitro methods, or drug release studies might indicate a greater difference than is actually seen in vivo.

Two general approaches interrelating in vivo and in vitro measurements of drug release have been suggested. In one approach, an in vitro release profile is transformed into a predicted in vivo response. A weighting function characterizing a reference product is determined between the release profile and the average in vivo response, which is measured in a panel of human subjects by the mathematical operation of deconvolution. The in vivo response, predicted in vitro, of the dosage form undergoing testing is obtained by convolution of the observed release profile and the weighting function.
The technique is computationally complex but maximizes the amount of information derived from in vitro dissolution testing\textsuperscript{137}. Alternatively, a reference blood level profile is used as the input to a feedback controlled dissolution testing apparatus, which is subsequently forced to yield a release profile close to the standard by dynamically changing release media and flow rates. The conditions established using the reference product is used for testing other formulations. Applications of these techniques to extended release products require a similar formulation as the reference.

In the second approach, the apparent in vivo drug release profile is computed from smoothed blood level or urinary excretion data\textsuperscript{138}. This technique requires knowledge of the pharmacokinetic model of the drug. The in vivo data are used as input to a computer simulation of the pharmacokinetic model; the output represents the amount of drug released at the absorption site as a function of time. Beckett, in applying this method to a extended release form of phendimetrazine, found that measured in vitro release rate were significantly faster than computed in vivo release rates\textsuperscript{138}.

In vivo testing involves a number of simplifying assumptions regarding the uniformity of the absorption process and suitability of using average data points to represent the population. Since the formulator has no control over physiologic variables, it is essential that clinical studies be based on sufficiently large cross sections of the population to provide meaningful results. Both in vivo and in vitro testing methods play a major part in validating the effectiveness of extended release formulations.
14. STABILITY STUDIES

As with all pharmaceutical dosage forms, stability testing is an important aspect of the development stage. The same standards that apply to conventional dosage forms with respect to stability of active ingredient and dosage form integrity should be used. The stability-testing program includes storage of the formulation under both normal (shelf) and exaggerated temperatures and other conditions, so that appropriate extrapolations for long term stability can be made. The stability of the release profile in addition to that of the active ingredient must be assessed.

Most ER formulations are complex. They may be formulated with ingredients that often present special problems regarding their physical stability upon storage. Further, more accelerated stability testing may induce changes in some systems. (e.g., polymorphic or amorphous to crystalline transitions); these changes would not be observed under normal shelf storage conditions. In additions, observed release profiles measured after storage at elevated temperatures reflect loss of drug due to degradation. Consequently, predictions of long term release profile stability based on accelerated tests could lead to erroneous conclusions. The stability-testing program for an ER product cannot be outlined specifically. It depends on the dosage form and its composition.

4.15. REGULATORY CONSIDERATIONS IN EXTENDED RELEASE DRUG DELIVERY SYSTEMS

The regulatory requirements related to controlled release dosage forms, appeared first in the regulation that was published thirty years ago by the US FDA. It defined the conditions under which drugs delivered to patients in a controlled release formulation over a prolonged period would be regarded as new drugs. As with new drugs in conventional dosage forms, the regulatory approval for a controlled release
pharmaceutical product (or drug delivery system) requires submission of scientific documents to pharmaceutical firms to substantiate the clinical safety and efficacy of the controlled release drug delivery system and to demonstrate its controlled release characteristics\textsuperscript{139}.

To demonstrate the safety and efficacy of a controlled-release formulation (or drug delivery system) controlled clinical studies may be required to be done along with the standard with regard to effectiveness and side effects. Without appropriate clinical studies, the label cannot be modified. Bioavailability studies are required to be performed under steady-state conditions to demonstrate approved comparatively to an approved immediate-release drug product.

The firms are also called to furnish information regarding the following point:

- The product meets the controlled release claims made for it.
- The bioavailability profile established for the product rules out the occurrence or dose dumping.
- The product's steady-state performance is equivalent to that of currently marketed non-controlled release pharmaceutical products that contain the same active ingredient.
- The product's formulation provides consistent pharmacokinetic performance between individual dosage units.

For comparative studies, the following preparations are generally used.

- A solution or suspension of the same active drug ingredient.
- An approved non-controlled release pharmaceutical product containing the same active drug moiety.
• An approved controlled release formulation containing the same active ingredient in the same concentration and same form (e.g. Tablet, Capsules, etc.).

To demonstrate the controlled release characteristics of drug(s) delivered from an ER pharmaceutical product, the information is required to be submitted includes:

• *In vitro* drug release data highlighting reproducibility of method, proper choice of medium, maintenance of perfect sink conditions and good control of solution hydrodynamics. Also, a meaningful *in vitro* *in vivo* correlation should have been established.

• *In vivo* bioavailability data highlighting the pharmacokinetic profiles, data comparable to already marketed preparations and supporting the label claims and reproducibility of *in vivo* performance.

In addition to safety and efficacy, considerations of such new drug delivery systems, biopharmaceutics and pharmacokinetics issues need to be addressed by the manufactures. The key elements that need to be established are as follows:

• Reproducibility of drug release kinetics.

• A defined bioavailability profile that rules out the possibility of dose dumping.

• Demonstration of reasonably good absorption relative to an appropriate standard.

• A well-defined pharmacokinetic profile that supports drug labeling.
16. POST APPROVAL CHANGES

Following the successful launch of a new product, it is not uncommon for development scientist to make continuous effort to improve its quality or to reduce its manufacture cost. The modifications typically involve changes in the formulation components or compositions, the site of manufacturing, scale-up or scale-down of the manufacturing process and/or equipment. The issues involved in these changes of controlled release products are different and usually more complex than their IR counterparts. Thus, the FDA issued a separate guidance on the scale-up and post approval changes (SUPAC) for modified-release solid dosage forms in Sept. 1997. Based on fundamental pharmaceutical principles and the scientific database, acceptable ranges of these changes are defined and categorized into three different levels on their likelihood of having significant impact on the product quality and performance.

Additional in process and finished product control parameters are also specified for used in supporting these changes. Formulation and process changes discussed in this section are mostly based on SUPAC Guidance for modified-release solid oral dosage forms published by the Center for Drug Evaluation Research, Food and Drug Administration.

4.16.1. Formulation Changes

For modified-release solid dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release.

4.16.1.a. Non-Release Controlling Excipient

Three levels of changes for non-release controlling excipients are defined as follows:
• Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

• Level 2 changes are those that could have a significant impact on formulation quality and performance.

• Level 3 changes are those that are likely to have a detectable impact on formulation quality and performance.

4.16.1.b. Release Controlling Excipient

The changes for the release-controlling excipient are categorized into three levels similar to the non-release controlling excipients:

• Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

• Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for level 2 changes would vary depending on whether the product could be considered to have a narrow therapeutic range.

• Level 3 changes are those that are likely to have a detectable impact on formulation quality and performance affecting all therapeutic ranges of the drug.

4.16.2. Process Changes

If the manufacturing process that is not identical to the original manufacturing process used in the approved application is to be used, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process. For oral controlled release dosage forms, consideration should be given to
whether or not the change in manufacturing process is critical to drug release. Three levels of process changes are defined as follows:

- **Level 1 Changes:** This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds within original approved application ranges affecting the non-release-controlling and/or release-controlling excipient(s).

- **Level 2 Changes:** This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds outside the original approved application ranges.

- **Level 3 Changes:** This category includes changes in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

4.17. EXTENDED (SUSTAINED/CONTROLLED) DRUG DELIVERY — TODAY AND TOMORROW\textsuperscript{141-146}

There is a little doubt that newer drugs, including gene therapy, are intended to treat the cause of a disease rather than the symptoms. These newer drugs have inherent disadvantages of size, usually sufficiently large to slow or inhibit membrane permeability, sensitivity in dose and dosing regimen, commonly potent drugs needing short exposure time to target receptor, and then being quite unstable to external environment. One can develop a short list of needed technologies. Carriers to assist membrane permeability. The carriers can be tissue friendly, classic penetration enhancers, or preferably modeled after the physiologically based chaperones, e.g. macromolecules.

**Biocompatible – Bioerodible Injectable Polymers:** A sizable number of non-toxic, erodible polymers possessing a range of physicochemical properties are
needed to embrace the diverse properties of new and emerging drugs. These drugs include microencapsulation and transplantation of endocrine tissue.

**Stimuli-Sensitive Polymers:** These polymers respond to pH, temperature and electrochemical stimuli as well as to more subtle specific biochemical triggers. Such intelligent polymers are necessary for feedback controlled drug delivery systems.

**Kinetic- And Equilibrium-Modulated Polymers:** The need for cycling in release rate is essential for many drugs. Such flexibility in polymers is currently at a primitive stage.

**Platforms For Tissue Engineering:** There is need for biocompatible casing for all transplants, polymer composites for patching wounds, scaffolds that guide and encourage cells to form tissue bioreactors for large-scale production of therapeutic cells. From this list, a number of issues become instantly apparent. First, drug delivery is a multidisciplinary activity involving polymer scientist, pharmaceutical scientists, chemical engineers and a variety of biologically oriented scientists. Second, the trend to produce polymers possessing multiple properties, depending on the environment, highly specialized function is apparent. Third, the driving force for most of these changes is an expanding understanding of biology as it pertains to drug delivery systems. If last two decades represent the period to define what is needed in controlled drug delivery and understand, even at an organ level, disposition tissues for the various routes of administration, next two decades will represent the true biomedical polymer period. Of course, success of this period is dependent on continued economic success of drug delivery systems and the willingness of certain companies or entrepreneurs to invest in this future.
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