1. **INTRODUCTION**

1.1 Drug Delivery Systems – An Overview

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action (Jain et al., 2003).

Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug may be incorporated into the device for preventing complications resulting from the device, it is regulated strictly as a device. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis.

1.2 Drug Delivery Routes
Drugs may be introduced into the human body by various anatomical routes. They may be intended for systemic effects or targeted to various organs and diseases. The choice of the route of administration depends on the disease, the effect desired, and the product available. Drugs may be administered directly to the organ affected by disease or given systemically and targeted to the diseased organ (Jain et al., 2003).

Classification of various methods of systemic drug delivery by anatomical routes:

A) Gastrointestinal system
   - Oral
   - Rectal

B) Parenteral
   - Subcutaneous injection
   - Intramuscular injection
   - Intravenous injection
   - Intra-arterial injection

C) Transmucosal: buccal and through mucosa lining the rest of gastrointestinal tract

D) Transnasal

E) Pulmonary Drug Delivery by inhalation

F) Transdermal Drug Delivery

G) Intra-osseous Infusion

Classification of Drug Delivery System that affect the release and availability of drugs:

a) Systemic versus localized drug delivery
b) General non-targeted delivery to all tissues

c) Targeted delivery to a system or organ

d) Controlled release delivery systems (systemic delivery)

e) Release on timescale
   ➢ Immediate release
   ➢ Programmed release at a defined time/pulsatile release
   ➢ Delayed, sustained, or prolonged release, long acting

f) Targeted release

g) Site-specific controlled release following delivery to a target organ

h) Release in response to requirements or feedback

i) Receptor-mediated targeted drug delivery

1.3 Oral Delivery Systems: Focus on Concepts of Rate Controlled Drug Delivery

Oral administration has been the traditionally preferred route of administration for most therapeutic agents and is, in general, the first avenue investigated in the discovery and development of new drug candidates and formulations. Drugs that are susceptible to acid hydrolysis or enzymatic degradation in the stomach require a delayed-release mechanism, most often accomplished with stable coatings that prevent drug release in the stomach and thereby postpone release until the formulation is in the more favorable environment of the small intestine. This technology commonly referred to as enteric coating. Although this approach has certainly proved effective for many drugs and has been utilized to prolong drug absorption or achieve a more stable pharmacodynamics response, the varying absorption rates and drug stability in different regions of the gastrointestinal (GI) tract has meant that a zero-
order release pattern will not necessarily achieve constant plasma drug levels (Lordi et al., 1991).

By definition, oral controlled-release products refer to those formulations in which a "controlling technology or component" is incorporated that is critical to modulating the drug-release pattern in a predictable fashion or that controls the timing, and subsequently the location, of drug release within the GI tract.

1.3.1 Definitions

- **Controlled-release dosage forms**: A class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower than normal manner.

- **Modified-release dosage form**: This refers, in general, to a dosage form for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

- **Extended-release dosage form**: This is a specific type of modified-release dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-(conventional-) release dosage form.

- **Delayed-release dosage form**: This is a specific type of modified-release dosage form that releases a drug at a time other than promptly after administration. An example is enteric-coated tablets.

1.3.2 Objectives and potential advantages of controlled release dosage forms:

- To reduce dosing frequency.
To provide more constant therapeutic drug levels.

To obtain more uniform pharmacological response, or in other words, less potentiation or reduction in drug activity with chronic use.

To reduce total amount of drug used.

To reduce inconvenience to the patient and increase compliance.

To avoid night-time dosing.

To reduce gastrointestinal irritation.

To reduce both local and systemic side effects.

To reduce fluctuations in circulating drug levels and minimization of drug accumulation in body tissues with chronic dosing.

To allow the use of drug with low therapeutic index.

Stabilization of medical condition (because of more uniform drug levels).

Improvement in bioavailability of some drugs because of spatial control.

Reduction in drug accumulation with chronic therapy.

Economical to the health care providers and the patient.

Illustration of innovative/technological leadership.

Product life-cycle extension.

Product differentiation.

Market expansion.

Patent extension.

1.3.3 Possible Disadvantages of Controlled Release Dosage Forms:

- Possibility of dose dumping.
- Reduced potential for accurate dose adjustment.
- Increased potentials for first pass metabolism.
- Possible reduction in systemic availability.
- Drug release profile restricted to residence time in gastrointestinal tract.
- Difficulty or impossibility of quick stoppage of pharmacological action of drugs, when serious poisoning or intolerance occurs.
- Little or no efficacy of pharmaceutical dosage forms if the drug is not absorbed by intestinal mucosa.
- Cost per unit dose is higher when compared with conventional doses.
- Greater dependence on GI residence time of dosage form.

1.3.4 Rationale for Controlled Release Dosage Forms

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. This is achieved by better control of plasma drug levels and less frequent dosing. In general the dosing interval may be increased either by modifying the drug molecule to decrease the rate of elimination or by modifying the release rate of a dosage form to decrease the rate of absorption. When attempting to extend the dosing interval by decreasing the rate of absorption, the formulator will be confronted with the physiological constraint of a finite resident time at absorption site.

To establish a basis for discussion of drug property influencing the controlled release product design, it is worthwhile focusing attention on the two principal elements of the system:

- Behavior of the drug in its delivery system.
Behavior of the drug and its delivery system in the body.

The first of these two elements concerns itself with the way in which the drug properties can influence release characteristics from the drug delivery system. In a controlled release product one generally aims for release of drug from the dosage form as the rate-limiting step so that the availability of drug is controlled by the kinetics of drug release rather than absorption.

The second element, behaviour of the drug and its delivery system in the body, is an extremely complex picture, involving the rate of the drug during its transit to the target area as well as its fate while in the biophase. Availability of drug to its target area will depend on its pharmacokinetics as well as that of its carrier. The drug potentially interacts with a variety of substance leading to undesired drug loss as well as desired drug absorption.

1.3.5 Physicochemical properties of a Drug influencing the Drug Product Design and Performance

The performance of a drug in its release pattern from dosage form as well as in the body proper is a function of its properties. These properties at times prohibit placement of the drug in a prolonged release form, restrict the route of drug administration and significantly modify drug performance for one reason or another (Chein et al., 1992).

A. Aqueous Solubility

Since drugs must be in solution before they can be absorbed, compounds with a low solubility usually suffer oral bioavailability problems because of
limited gastrointestinal transit time of undissolved drug particles and limited solubility at absorption site. For many compounds the site of maximum absorption will also be in the area where drug is least soluble. Such drugs are poor candidates for sustained/controlled release systems, unless the system is capable of retaining the drug in the stomach and gradually releasing it to small intestine. Aqueous solubility also limits the loading efficiency of drugs into a variety of carriers such as liposomes, erythrocytes and microparticles. More water soluble drugs tend to leak out from such carriers readily.

**B. Partition Coefficient and Molecular Size**

Drugs with extremely high partition coefficient readily penetrate the membranes but are unable to proceed further, while drugs with excessive aqueous solubility i.e., low partition coefficient cannot penetrate the membranes. A balance in the partition coefficient is needed to give an optimum flux for permeation through the biological and rate controlling membranes. The ability of a drug to diffuse through membranes, it also called diffusivity is related to molecular size by following equation:

\[ \log D = -S_v \log V + K_v = -S_m \log V + K_m \]

Where D is diffusivity, m is molecular weight, V is molecular volume, and \( S_v \), \( S_m \), \( K_v \) and \( K_m \) are constants in particular medium.

**C. Drug Stability**

The stability of a drug in the environment to which it is exposed is another factor to be considered in the design of sustained/controlled release systems. Drugs that are unstable in stomach can be placed in a slowly soluble form or have their release delayed until they reach small intestine. To achieve a better
bioavailability and controlled release of drugs that are unstable in the small intestine, a different route of administration should be chosen. On the positive side, the presence of metabolizing enzymes at the site of administration or along the pathway to the target area can sometimes be utilized in controlled drug delivery.

D. Protein Binding

Many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. This drug-protein complex can serve as a depot for drug producing a prolonged release profile. Drugs bound to proteins may increase absorption, if bound drug act as a depot. However if degradation of the drug further down the GI tract occurs, then binding of drugs to proteins may result in reduction of free drug for absorption.

E. Drug pK\textsubscript{a} and Ionization at Physiologic pH

The pK\textsubscript{a} range for acidic drugs whose ionization is pH-sensitive is 3.0 to 7.5 and that for basic drug is 7.0 to 11.0. For optimum passive absorption, the drugs should be non-ionized at that site at least to an extent 0.1 to 5%. Drugs existing largely in ionized forms are poor candidates for controlled release systems. Thus from the knowledge of pK\textsubscript{a} of the drug and pH of the absorption site, the relative amount of ionized and unionized drug in the solution at a particular pH and the percent of drug ionized at this pH can be determined by Henderson-Hasselbach equation:
F. Biopharmaceutical Aspects of Route of Administration

(i) Oral Route: For a drug to be successful as oral controlled release formulation, it must get absorbed through the entire length of GIT. Since the main limitation of this route is the transit time, the duration of action can be extended for 12 to 24 hours. A drug whose absorption is pH dependent, destabilized by enzymes/GI fluids, undergoes pre-systemic metabolism, influenced by GUT motility, has an absorption window is an poor candidate for controlled release systems.

(ii) Intramuscular/Subcutaneous Routes: These routes are suitable when the duration of action is to be prolonged from 24 hours to 12 months. Only a small amount of drug, about 2ml or 2gms, can be administered by these routes.

1.3.6 Biological Factors Influencing the Drug Product Design
In drug delivery, pharmaceutical scientists generally are faced with an engineering problem i.e., develop a drug delivery systems that hit a desired target. The target in pharmacokinetics is generally a plasma/blood drug concentration that lies between the minimum effect concentration (MEC) and minimum toxic concentration (MTC). To be effective clinically but not toxic, the desired steady-state $C_p$ must be greater than the MEC and less than the MTC. This desired or target steady-state $C_p$ may be achieved by using a variety of dosage forms and delivery/dosage strategies (Carstensen et al., 1974).

Pharmacokinetics and pharmacodynamics provide the time-course dynamics between drug concentration and desired target effect/outcome necessary in the development of optimal drug delivery strategies.

![Plasma concentration-time profile](image)

**Fig.1. Plasma concentration-time profile**

The frequently used acronym LADME, which stands for liberation, absorption, distribution, metabolism, and excretion, broadly describes the various biopharmaceutical processes influencing the pharmacokinetics of a drug.

A. Liberation
From a pharmacokinetics perspective, liberation encompasses all kinetic aspects related to the liberation of drug from its dosage form into its active or desired form. For example, free drug released from a tablet or polymeric matrix in the gut would be liberation. Although liberation is first in the LADME scheme, it does not need to occur first. Liberation kinetics can be altered by other physicochemical properties, such as drug solubility, melting point of vehicle (suppository), drug dissolution, gastrointestinal pH (Carstensen et al., 1968).

B. Absorption

Absorption is much more difficult to model accurately and precisely in pharmacokinetics. A great deal of work in this area by Wagner-Nelson and Loo-Riegelman (Wagner et al., 1961) reflects the complexities of using pharmacokinetics and diffusion models to describe the rate of drug absorption. Since most drugs are delivered via the oral route, the gastrointestinal (GI) tract is described briefly. In the GI tract, the source of these complexities lies in the changing environmental conditions surrounding the drug and delivery modality as it moves along the GI tract. Most drugs experience a mix of zero- and first-order kinetic absorption; this mixing of zero- and first-order input results in nonlinearities between dose and \( C_p \) (Loo et al., 1968).

AUC is closely and sometimes incorrectly associated with bioavailability. AUC is a measure of extent of absorption, not rate of absorption; true bioavailability is made up of both extent and rate of absorption. The rate of absorption tends to be more important in acute-use medications (e.g., pain management), and
the extent of absorption is a more important factor in chronic-use medications (Benet et al., 2001).

C. Distribution
Volume of distribution \( V_d \) has units of volume but is not an actual physiologically identifiable volume. Clinically, in general, the larger \( V_d \) is, the greater is the extent of drug partitioning and the greater is the amount of drug being removed from the site of measurement. Most drugs have a \( V_d \) of between 3.5 and 1000 L; there are cases where \( V_d \) is greater than 20,000 L (as in some antimalarial drugs).

D. Metabolism and Excretion

Systemic clearance \( Cl \) can be defined as the volume of blood/plasma completely cleared of drug per unit time (Thummel et al., 1997). Systemic clearance is calculated by dividing the amount of drug reaching the systemic circulation by the resulting AUC. At any given \( C_p \), the amount of drug lost per unit time can be determined easily by multiplying \( Cl \times C_p \).

\[
Cl = \frac{(F)(S) \text{dose}}{AUC}
\]

The first-order elimination rate constant \( K \) can be determined as shown in equation below and has units of 1/time. The larger the value of \( K \), the more rapidly elimination occurs. Once \( K \) has been determined, then calculating the half-life \( t_{1/2} \) is straightforward.

\[
K = \frac{Cl}{V_d}
\]
Clinically, the two pharmacokinetics parameters $t_{1/2}$ and systemic clearance (Cl) are very important when determining patient-specific dosing regimen. While $t_{1/2}$ is an important pharmacokinetics parameter when determining the dosing interval, the size of the dose is not based on $t_{1/2}$. Two other pharmacokinetics parameters, $V_d$ (volume of distribution) and Cl (systemic clearance), help to determine the size of the dose.

**E. Side-Effects**

For some drugs, the incidence of side effects, in addition to toxicity is believed to be related to their plasma concentration. A sustained release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and utilizing less total drug over the time course of therapy. The technique of controlled release has been more widely used to lower the incidence side effects and appears to be beneficial (Wagner et al., 1976).

**F. Margin of safety of the Drug**

For every potent drug whose therapeutic concentration range is narrow, the value of Therapeutic Index (TI) is small. In general, the larger the value of TI, the safer the drug. Drugs with very small values of TI are usually poor candidates for formulation into sustained/controlled release systems primarily because of technological limitations of precise control over release rates.

$\text{Therapeutic Index} = \frac{\text{Median toxic dose}}{\text{Median effective dose}}$

$= \frac{TD_{50}}{ED_{50}}$

In general larger is the ratio, the safer is the drug; in particular a drug is considered to be relatively safe if its therapeutic index exceeds 10.
1.3.7 Classification of Oral Controlled Release Systems

A) Oral Diffusion-Controlled Systems

Two basic types of controlled-delivery dosage forms have been designed in which diffusion is the rate-limiting step to generate temporal input profiles for drug delivery: matrix- and reservoir-type systems (Liu et al., 2006).

A matrix type system consists of a rate-controlling ingredient such as a polymer with drug uniformly dissolved or dispersed in it, and typically, a half order drug release corresponds to desorption from the preloaded matrix.

A reservoir-type system separates a drug compartment from a polymer membrane that presents a diffusional barrier to yield drug flux of either zero order (with infinite dose) or first order (by dose depletion).

Diffusion can be defined as a process by which molecules transfer spontaneously from one region to another in such a way as to equalize chemical potential or thermodynamic activity. The migrating molecules are termed diffusants (also called permeants or penetrants). The membrane or matrix in which the diffusant migrates is called the diffusional barrier. The external phase is called the medium. The concentration gradient or profile of the diffusant within the diffusional barrier is the driving force for diffusion.

MATRIX SYSTEMS

A matrix system consists of active and inactive ingredients that are homogeneously mixed in the dosage form. It is by far the most commonly
used oral CR technology, and the popularity of matrix systems can be attributed to several factors.

First, unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processing and equipment.

Second, development time and cost associated with a matrix system generally are viewed as favorable, and no additional capital investment is required.

Lastly, a matrix system is capable of accommodating both low and high drug load and active ingredients with a wide range of physical and chemical properties.

a) Hydrophobic matrix systems

The primary rate-controlling components of a hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethylcellulose and methacrylate copolymers. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into the formulation. The presence of insoluble ingredients in the formulations helps to maintain the physical dimension of a hydrophobic matrix during drug release. As such, diffusion of the active form from the system is the release mechanism, and the corresponding release characteristic can be described by the Higuchi equation. Very often, pores form within a hydrophobic matrix as a result of the release of the active ingredient.

\[ Q_t = \sqrt{C_s(2A - C_s)D_t} \]

b) Hydrophilic matrix systems
The primary rate-controlling ingredients of a hydrophilic matrix are polymers that would swell on contact with the aqueous solution and form a gel layer on the surface of the system. Robust swelling/gelling properties and straightforward manufacturing processes are to a large degree responsible for the versatility and performance of the system.

Hydroxypropyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer. Other polymers include high-molecular-weight polyethylene oxide (Polyox™), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), xantham gum, sodium alginate, and polyacrylic acid (Carbopol™).

Formulating hydrophilic matrices for active ingredients with extreme solubility profiles could be demanding. For very soluble compounds, diffusion of drug molecules is the dominant mechanism of release, and the role of polymer erosion is limited in modulating drug release. Thus, developing a hydrophilic matrix for highly soluble drugs that requires prolonged release (e.g., >12 h) can be challenging.

On the other hand, release of less soluble drugs from hydrophilic matrices is expected to be slow because both polymer dissolution and drug diffusion play key roles. This may not be a major problem as long as drug molecules dissolve before polymers erode from the dosage form. However, for highly insoluble compounds, drug particles may not dissolve completely after polymers have eroded.

**RESERVOIR SYSTEMS**
A typical reservoir system consists of a core (the reservoir) and a coating membrane (the diffusion barrier). The core contains the active ingredients and excipients, whereas the membrane is made primarily of rate-controlling polymer(s). The governing release mechanism is diffusion from the reservoir across the membrane to the bulk solution.

The most commonly used materials for constructing the membrane are ethylcellulose (Surelease™ or Aquacoat™) and acrylic copolymers (Eudragit™ RL30D, RS 30D, and NE 30D). Water-soluble polymers such as HPMC and polyethylene glycol (PEG) are employed as pore formers.

B) Oral Dissolution-Controlled Systems

The dissolution process includes two steps, initial detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. This process could be manipulated to design controlled release delivery systems with desired profiles and a desired rate (Wang et al., 2006).

In general, either matrix- or barrier/membrane-based controlled release systems are applied to slow down, delay, and control the delivery and release of drugs. In the former, drug is uniformly dispersed in a matrix consisting mainly of polymers or waxes, whereas the latter refers to coated systems. A combination of both (coated matrix) is also possible.

If the matrix or coated systems are made of water-soluble components, the rate-limiting step governing the release of drug from these systems will be dissolution. Unlike diffusion controlled release coated systems, release profiles from dissolution controlled release coated systems do not follow zero-
order kinetics but fall within the classification of delayed release systems, pulsatile or repeat-action systems.

**MATRIX SYSTEMS**

The delivery from these systems often follows a certain time course determined by the selection of the polymer and the geometry of the matrix. This type of delivery systems is suitable for reducing the frequency of drug administration, reducing toxicity for drugs with a small therapeutic window, and correcting poor pharmacokinetic behavior such as a short half-life.

**Surface erodible matrix systems:** The first system is a solid matrix that does not disintegrate nor swell during dissolution but dissolves from the surface that is exposed to a dissolution medium.

**Nonerodible systems:** In the second matrix system, the matrix does not change during dissolution (insoluble, no disintegration, and no swelling). Polymers that are hydrophobic or cross-linked polymers often are used for the matrix. The drug solid is dissolved inside the matrix and is released by diffusing out of the matrix. Both dissolution and diffusion contribute to the release profile of this type of matrix systems.

**Soluble matrix systems:** The third matrix system is based on hydrophilic polymers that are soluble in water. For these types of matrix systems, water-soluble hydrophilic polymers are mixed with drugs and other excipients and compressed into tablets. On contact with aqueous solutions, water will penetrate toward the inside of the matrix, converting the hydrated polymer from a glassy state (or crystalline phase) to a rubbery state. The hydrated layer will swell and form a gel, and the drug in the gel layer will dissolve and
diffuse out of the matrix. At the same time, the polymer matrix also will dissolve by slow disentanglement of the polymer chains. This occurs only for un-cross-linked hydrophilic polymer matrices. In these systems three fronts are formed during dissolution:

- The **erosion front** between the dissolution medium and the erosion (or dissolving) surface.
- The **diffusion front** between the dissolved and undissolved drug in the gel (or swelled) phase.
- The **swelling front** between the gel phase and the glassy (or semicrystalline) phase of the matrix.

When such a system is in contact with an aqueous solution, at the early stage of release, the swelling of the matrix causes the erosion front to move outward and the swelling front inward. At the same time, the diffusion front is also receding owing to dissolution of the drug solid in the gel phase and diffusion of the dissolved drug out of the matrix.

**1.3.8 Polymer Microspheres for Controlled Drug Release**

Microencapsulation is one of the most intriguing fields in the area of drug delivery systems. It is an interdisciplinary field that requires knowledge of the field of pure polymer science, familiarity with emulsion technology, and an in-depth understanding of drug and polymer stabilization (Freiberg et al., 2004). Biocompatibility can be achieved by the use of natural polymers such as cellulose, chitin, and chitosan or by the employment of polymers made from naturally occurring monomers such as lactic and glycolic acids. Polymers derived from synthetic monomers also show excellent delivery properties.
a) Classification of Microencapsulation Techniques

Microencapsulation is a technology devoted to entrapping solids, liquids, or gases inside one or more polymeric coatings. Different types of microencapsulation methods: (Candau et al., 1985)

- Interfacial polymerization
- Complex coacervation
- Coacervation
- Thermal denaturation
- Salting-out
- Solvent evaporation
- Hot melt
- Solvent removal
- Spray-drying
- Phase separation

Interfacial polymerization involves the condensation of two monomers at the interface of the organic and aqueous phases. Polyamide capsules are a great example of this system.

Dispersion polymerization results in particle sizes in the range of 0.5–10 µm and all of the reagents including monomer, initiator, and stabilizer (often an organic polymer consisting of hydrophobic and hydrophilic parts) are dissolved in an organic medium (Strover et al., 1996). Since the initiator is soluble inside the monomer, polymerization takes place inside the monomer droplets. The polymer beads, insoluble in the organic solvent, precipitate, and the stabilizer prevents bead flocculation.
Suspension polymerizations are typically employed for micron-sized particles (50–500 µm). In suspension polymerization the monomer is dispersed in a water phase with a stabilizer; the initiator is soluble in the monomer phase where polymerization occurs. Sizes obtained from various bead-forming techniques

<table>
<thead>
<tr>
<th>Method of preparation</th>
<th>Size range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion polymerization</td>
<td>0.01–1(µm)</td>
</tr>
<tr>
<td>Dispersion polymerization</td>
<td>0.5–10(µm)</td>
</tr>
<tr>
<td>Suspension polymerization</td>
<td>50–500(µm)</td>
</tr>
<tr>
<td>Sedimentation polymerization</td>
<td>mm sizes</td>
</tr>
</tbody>
</table>

Complex coacervation encapsulation processes use the interaction of two oppositely charged polyelectrolyte in water to form a polymer-rich coating solution called a coacervate. This solution (or coacervate) engulfs the liquid or solid being encapsulated, thereby forming an embryo capsule. Cooling the system causes the coacervate (or coating solution) to gel via network formation. Gelatin is a primary component of most complex coacervation systems.

The precipitation and/or gelation processes listed in Table 1 cover many techniques. One example is the precipitation of water-soluble polymers such as gelatin with water-miscible solvents such as isopropanol. The objective is to precipitate a preformed polymer around the core (sometimes a multiparticulate core) to cause encapsulation.
**Salting-out** also listed in Table 1, involves the addition of salt to an aqueous polymer solution ultimately causing the polymer to phase separate from solution.

**Solvent evaporation** is the most popular way to accomplish encapsulation. A core material and capsule wall material are briefly dissolved in water immiscible, volatile organic solvent and the resulting solution is emulsified in an aqueous solution. The solvent is allowed to evaporate, thereby producing solid microcapsules or microparticles.

**Hot melt encapsulation** was developed to avoid the use of solvents throughout the process. Solvent removal was developed as a modification of the solvent evaporation technique, using organic solvents as the extracting medium.

In **spray-drying**, the evaporation of the solvent is achieved in a special, temperature-controlled cyclone. And finally, phase separation is a new method in which a one-step precipitation of two polymers or more produces double-walled microspheres.

<table>
<thead>
<tr>
<th>Process</th>
<th>Coating material</th>
<th>Suspended medium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process</td>
<td>Coat Material</td>
<td>Solvent Used</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Interfacial polymerization</td>
<td>Water-soluble and insoluble monomers</td>
<td>Aqueous/organic solvent</td>
</tr>
<tr>
<td>Complex Coacervation</td>
<td>Water-soluble polyelectrolyte</td>
<td>Water</td>
</tr>
<tr>
<td>Coacervation</td>
<td>Hydrophobic polymers</td>
<td>Organic solvent</td>
</tr>
<tr>
<td>Thermal Denaturation</td>
<td>Proteins</td>
<td>Organic</td>
</tr>
<tr>
<td>Salting-out</td>
<td>Water-soluble polymer</td>
<td>Water</td>
</tr>
<tr>
<td>Solvent evaporation</td>
<td>Hydrophilic or hydrophobic polymers</td>
<td>Organic or water</td>
</tr>
<tr>
<td>Hot melt</td>
<td>Hydrophilic or hydrophobic polymers</td>
<td>Aqueous/organic solvent</td>
</tr>
<tr>
<td>Solvent removal</td>
<td>Hydrophilic or hydrophobic polymers</td>
<td>Organic solvents</td>
</tr>
<tr>
<td>Spray-drying</td>
<td>Hydrophilic or hydrophobic polymers</td>
<td>Air, nitrogen</td>
</tr>
<tr>
<td>Phase separation</td>
<td>Hydrophilic or hydrophobic polymers</td>
<td>Aqueous/organic</td>
</tr>
</tbody>
</table>

**Table 1: Summary of processes, coating materials and solvents used in microencapsulation**
In general, microspheres offer a number of advantages with respect to other delivery systems: (Strover et al., 1996).

- Their physicochemical characteristics remain unaltered for long periods allowing long-term storage.
- Depending on their composition, they can be administered by different routes.
- They protect encapsulated drug from enzymatic-or pH-dependant degradation, oral, oral mucosal, intramuscular, or subcutaneous.
- They are suitable for industrial production.
- Microsphere-based formulations can be formulated to provide a constant drug concentration in the blood or to target drugs to specific cells or organs.
- Microspheres can also be used to treat diseases that require a sustained concentration of the drug at a particular anatomical site, e.g., the periodontal pocket.

c) Polymers Commonly Used For Fabrication of Controlled Release Systems (Piirma et al., 1985)

HYDROPHILIC POLYMERS

- Cellulosic
  - Methylcellulose
  - Hypromellose (Hydroxypropylmethylcellulose, HPMC)
  - Hydroxypropylcellulose (HPC)
  - Hydroxyethylcellulose (HEC)
  - Sodium carboxymethylcellulose (Na-CMC)
- Noncellulosic: gums/polysaccharides
• Sodium alginate
• Xanthan gum
• Carrageenan
• Ceratonia (locust bean gum)
• Chitosan
• Guar gum
• Pectin
• Cross-linked high amylose starch

- **Noncellulosic: others**
  • Polyethylene oxide
  • Homopolymers and copolymers of acrylic acid

**WATER-INSOLUBLE AND HYDROPHOBIC POLYMERS**

- Ethylcellulose
- Hypromellose acetate succinate
- Cellulose acetate
- Cellulose acetate propionate
- Methacrylic acid copolymers
- Poly (vinyl acetate)

**FATTY ACIDS/ALCOHOLS/WAXES**

- Bees’ wax
- Carnauba wax
- Candelilla wax
- Paraffin waxes
- Cetyl alcohol
- Stearyl alcohol
- Glyceryl behenate
- Glyceryl monooleate, monostearate, palmitostearate
- Hydrogenated vegetable oil
  - Hydrogenated palm oil
  - Hydrogenated cottonseed oils
  - Hydrogenated castor oil
  - Hydrogenated soybean oil

d) Focus on Solvent Evaporation Method

For insoluble or poorly water-soluble drugs, the Oil-in-Water (O/W) Method is frequently used. This method is the simplest and the other methods derive from this one. It consists of four major steps (Berkland et al., 2002):

- Dissolution of the hydrophobic drug in an organic solvent containing the polymer;
- Emulsification of this organic phase, called dispersed phase, in an aqueous phase called continuous phase;
- Extraction of the solvent from the dispersed phase by the continuous phase, accompanied by solvent evaporation, transforming droplets of dispersed phase into solid particles; and
- Recovery and drying of microspheres to eliminate the residual solvent.
The aforementioned method is not suitable for the encapsulation of high hydrophilic drugs. There are two main reasons:

- The hydrophilic drug may not be dissolved in the organic solvent;
- The drug will diffuse into the continuous phase during emulsion, leading to a great loss of drug.

Four other alternative methods have been proposed and therefore make it possible to encapsulate the hydrophilic drugs.

- **The W/O/W Double Emulsion Method:** the aqueous solution of hydrophilic drug is emulsified with organic phase (w/o emulsion) this emulsion is then dispersed into a second aqueous solution forming a second emulsion (w/o/w double emulsion);
- **The O/W Co-Solvent Method**: when the drug is not soluble in the main organic solvent, a second solvent called co-solvent is necessary to dissolve the drug;

- **The O/W Dispersion Method**: the drug is dispersed in form of solid powder in the solution of polymer and organic solvent;

- **The O/O Non-Aqueous Solvent Evaporation Method**: the aqueous phase is replaced by oil (such as mineral oil).

The main factors influencing the properties of the microspheres are summarized in Fig. 3.

---

**Fig.3. Schematic overview of the factors influencing properties of microspheres**
**DISPERSED PHASE**

I) POLYMER

The biodegradability or biocompatibility is an essential property for the polymer used for pharmaceutical applications. ‘Biodegradability’ means that the components are degraded into harmless components which are either metabolized or excreted. ‘Biocompatibility’ means that the component should be physiologically tolerable and should not cause an adverse local or systemic response after administration (Li et al., 2008). Polymers and copolymers of lactic and glycolic acids are the most commonly used to develop drug delivery systems due to their safe and FDA (Food and Drug Administration) approved applications in humans. They can ultimately degrade by hydrolysis of their constituents, which are usual metabolic products. Non-biodegradable polymers with good biocompatibility are also used as drug carriers, such as ethyl cellulose (degradable but no biodegradable) and polymethyl methacrylate (biocompatible but non-degradable).

II) SOLVENT

For the technique of microencapsulation by solvent evaporation, a suitable solvent should meet the following criteria:

- Being able to dissolve the chosen polymer;
- Being poorly soluble in the continuous phase;
- Having a high volatility and a low boiling point;
- Having low toxicity.
Chloroform was frequently used before, but due to its toxicity and low vapour pressure, it is gradually replaced by methylene chloride (Herrmann et al., 1998). Methylene chloride is the most common solvent for the encapsulation using solvent evaporation technique because of its high volatility, low boiling point and high immiscibility with water. Its high saturated vapour pressure compared to other solvents (at least two times higher) promises a high solvent evaporation rate, which shortens the duration of fabrication of microspheres.

III) ALTERNATIVE COMPONENTS

In certain cases, other constituents are added in the dispersed phase such as co-solvent and porosity generator. **Co-solvent** is used to dissolve the drug that is not totally soluble in the solvent in the dispersed phase (Luan et al., 2006). Organic solvents miscible with water such as methanol and ethanol are the common choices.
CONTINUOUS PHASE

I) SURFACTANT

The surfactant, also called tensioactive agent, is frequently employed for the dispersion of one phase in another immiscible phase and for the stabilization of obtained emulsion. It reduces the surface tension of continuous phase, avoids the coalescence and agglomeration of drops and stabilizes the emulsion. For the most used emulsion of methylene chloride/water, typical stabilizers include:

Non-Ionic: Partially hydrolyzed PVA (polyvinyl alcohol) methylcellulose, tween (Yang et al., 2000a) and span.

Anionic: Sodium dodecyl sulphate (SDS);

Cationic: Cetyltrimethyl ammonium bromide (CTAB).

f) Mechanism of Formation of Microspheres

Mathematical models have been built to analyze the formation of microspheres by solvent evaporation under atmospheric pressure in an open vessel.

As shown in Fig. 4, there are two main mass flows (Wang et al., 1999):

1. The solvent diffuses from drops of the dispersed phase to the continuous phase (solvent diffusion rate F1);

2. The solvent diffuses into the continuous phase and evaporates into the air (solvent evaporation rate F2). Accompanied by the solvent
evaporation, the drops of the dispersed phase become rich in polymer
due to solvent removal and they begin to solidify.

**Stage A:** At the beginning, when the dispersed phase is rich in solvent, the
solvent diffusion rate $F_1$ into the continuous phase is greater than the solvent
evaporation rate $F_2$. So the continuous phase becomes rapidly saturated with
solvent. Consequently the concentration of solvent inside the continuous
phase $C_s$ reaches the solubility (maximum concentration). This stage is very
short with duration of several seconds. Therefore, it can be neglected.

**Stage B:** The quantity of solvent evaporated is compensated with solvent
diffused into the continuous phase and $C_s$ remains constant. The duration of
this stage depends on the initial quantities of the dispersed phase and of the
continuous phase.

**Stage C:** The diffusivity of solvent in the dispersed phase decreases with an
increase in polymer concentration. $F_1$ becomes smaller than $F_2$ so $C_s$ begins
to decrease. The moment that occurs the transition between stage B and
stage C is the critical time $t_c$.

![Fig.4. Schematic overview of solvent diffusion and evaporation steps.](image-url)
During the solidification of the drop of the dispersed phase into solid microsphere, two mass transfers take place: the solvent diffusion inside drop and the solvent diffusion at the boundary of the dispersed phase into the continuous phase. In both cases, there is liquid diffusion inside the drop and convection at the boundary of the drop.

**Fig.5. Two approaches for evolution of drop size during solidification:**

(A) formation of crust and size decrease stopped; (B) formation of crust accompanied by continuous size decrease.

1.4 Tablets

The oral route of administration is the most important method of administrating drugs for systemic effects. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the effect by the oral route.
Tablets and capsules of the two oral solid dosage forms commonly employed in this country, the tablet has a number of advantages.

**Advantages of Tablets:**

- They are a unit dosage form, and they offer the greatest capabilities of all oral dosage forms for the all oral dosage precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- In general they are the easiest and cheapest to package and ship of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed.
- They may provide the greatest ease of swallowing with the least tendency for “hang-up” above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as extended or delayed release product.
- They may better suit to large scale production than other unit dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability of all oral forms.

The main disadvantages of tablets are the bioavailability of poorly water-soluble drugs or poorly absorbed drugs, and the local irritation of the GI mucosa that some drugs may cause.

**1.4.1 Immediate Release Tablet**
Recently, immediate release drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Immediate release tablet can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, and sublimation. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging.

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under Moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. Immediate release delivery 1 In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving performance, convenience and compliance.
**Needs of Immediate release Tablet?**

The need for non-invasive delivery systems continues due to patients' poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety (decreasing gastrointestinal side effects), improve efficacy for organ targeting, and improved compliance via sustained release or easy to swallow dosage forms.

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies to survive. This applies to all pharmaceutical companies, regardless of their size. In his book, Jurgen Drews has emphasized that the pharmaceutical industry must accomplish more than it has to date with more modest financial resources.

Pharmaceutical marketing is another reason for the increase in available fast-dissolving/disintegrating products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, immediate release tablet formulations are similar to many sustained release formulations that are now commonly available. An
extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

1.4.2 Characteristics of Immediate release Tablets

It as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug. Current methods of taste masking in immediate release tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the immediate release technologies incorporate unique forms of excipients as a sweetener.

Immediate release delivery technology offers:

- Improved compliance/added convenience
- No or Less water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled/sustained release actives
• Allows high drug loading.

• Ability to provide advantages of liquid medication in the form of solid preparation.

• Adaptable and amenable to existing processing and packaging machinery

• Cost-effective
1.5 Hypertension

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension (Maestrelli et al., 2008).

Hypertension can be classified as either essential (primary) or secondary. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure and represents about 90-95% of hypertension cases. Secondary Hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney diseases or tumours.

1.5.1 Classification of Hypertension

A recent classification recommends blood pressure criteria for defining normal blood pressure, pre-hypertension, hypertension (stages I and II), and Isolated systolic hypertension, which is a common occurrence among the elderly.

In individuals older than 50 years, hypertension is considered to be present when a person's blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures over 130/80 mmHg along with Type I or Type 2 diabetes or kidney disease require further treatment (Barry et al., 1996).
<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>kPa</td>
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<td>Normal</td>
<td>90–119</td>
<td>12–15.9</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>16.0–18.5</td>
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<td>Stage 1</td>
<td>140–159</td>
<td>18.7–21.2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160</td>
<td>≥21.3</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>≥18.7</td>
</tr>
</tbody>
</table>

*Source: American Heart Association (2003).*

**Table 2: Classification of hypertension**

### 1.5.2 Signs and symptoms
Mild to moderate essential hypertension is usually asymptomatic. Accelerated hypertension is associated with headache, somnolence, confusion, visual disturbances, and nausea and vomiting are affected with narrowing of arterial diameter to less than 50% of venous diameter, copper or silver wire appearance, exudates, hemorrhages.
1.5.3 Prevention

The process of managing hypertension according the guidelines of the British Hypertension Society suggest that non-pharmacological options should be explored in all patients who are hypertensive or pre-hypertensive. These measures include:

- Weight reduction and regular aerobic exercise (e.g., walking) are recommended as the first steps in treating mild to moderate hypertension. Regular exercise improves blood flow and helps to reduce resting heart rate and blood pressure. Reducing dietary sugar intake.

- Reducing sodium (salt) in the diet may be effective: It decreases blood pressure in about 33% of people (see above). Many people use a salt substitute to reduce their salt intake.

- Reducing stress, for example with relaxation therapy, such as meditation and other mind body relaxation techniques, by reducing environmental stress, device-guided paced breathing.

1.5.4 Treatment

There are many classes of medications for treating hypertension, together called anti hypertensive, which by varying means act by lowering blood pressure.

Classification of anti-hypertensive agents:

- Diuretics
- Adrenergic receptor antagonists
- Adrenergic receptor agonists
- Calcium channel blockers
• ACE inhibitors

• Angiotensin II receptor antagonists

• Aldosterone antagonists

• Vasodilators

Commonly used drugs include the typical groups of:

• **ACE inhibitors** such as captopril, enalapril, fosinopril (Monopril), lisinopril (Zestril), quinapril, ramipril (Altace).

• **Angiotensin II receptor antagonists** may be used where ACE inhibitors are not tolerated: eg, telmisartan (Micardis, Pritor), irbesartan (Avapro), losartan (Cozaar), valsartan (Diovan), candesartan (Amias), olmesartan (Benicar, Olmetec).

• **Calcium channel blockers** such as nifedipine (Adalat), amlodipine (Norvasc), diltiazem, verapamil.

• **Diuretics** eg, bendroflumethiazide, chlorthalidone, hydrochlorothiazide (also called HCTZ).