1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that causes irreversible destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. During the last decade, even though attempts were being made to eradicate HIV, it was found that eradication of HIV is highly unlikely, and effective antiretroviral therapy is required on a long-term basis to maintain viral suppression and reduce disease progression. Most of the antiretroviral drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for anti-HIV agents to reduce the dosing frequency, to increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, and to deliver them to the target cells selectively with minimal side effects (1).

1.1. HIV/AIDS (1-6)

Human immunodeficiency virus is a single-stranded RNA retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS), a condition in which individuals are at increased risk of developing certain infections and malignancies. The virus is found in two major forms: HIV-1, the most prevalent worldwide, and HIV-2, the most common in western Africa. HIV attacks the body’s immune system, specifically the CD4 cells (T cells), which help the immune system fight off infections. If left untreated, HIV reduces the number of CD4 cells (T cells) in the body, making the person more likely to get infections or infection-related cancers. Over time, HIV can destroy so many of these cells that the body can’t fight off infections and disease. These opportunistic infections or cancers take advantage of a very weak immune system and signal that the person has AIDS, the last state of HIV infection.

AIDS is the stage of infection that occurs when the immune system is badly damaged and it become vulnerable to opportunistic infections. When the number of CD4 cells falls below 200 cells per cubic millimeter of blood (200 cells/mm³), that condition considered to have progressed to AIDS. (Normal CD4 counts are between 500 and 1,600 cells/mm³.)

HIV and AIDS are not the same. Everyone who has AIDS has been infected with HIV, but everyone with HIV infection does not have AIDS.
Figure 1.1: Structure of the Human Immunodeficiency Virus (HIV)

Figure 1.2: Lifecycle of HIV and the sites of actions of currently available antiretroviral agents
1.2. TREATMENT: (1-7)

The success of antiretroviral treatment for someone living with HIV depends on:

- Starting treatment at the right time
- Choosing the right combination of antiretroviral drugs
- Monitoring the effectiveness of the treatment.

People who have a CD4 cell count higher than 350 cells/mm$^3$ are typically healthy and do not show any symptoms. Health professionals are concerned that people in this situation will feel complacent about adhering to taking treatment for a virus that is not yet making them ill. If the cells are less than 350 then we will be proceeding with antiretroviral therapy. There are currently more than 20 approved antiretroviral drugs in the US and Europe and much more in the expanded access programmes and trials.

Classification of ARVs:

- **Nucleoside reverse transcriptase inhibitors:**
  - Zidovudine (ZDV), Didanosine (ddI), Stavudine (d4T), Zalcitabine (DDC), Lamivudine (3TC), Abacavir (ABC), Tenofovir (TDF), Emtricitabine (FTC)

- **Non nucleoside reverse transcriptase inhibitors:**
  - Nevirapine (NVP), Efavirenz (EFV), Delavirdine, Rilpivirine, Etravirine

- **Protease inhibitors:**
  - Saquinavir (SQV), Indinavir (IDV), Ritonavir(RTV), Nelfinavir (NFV), Darunavir (DRV), Amprenavir (APV), Lopinariv (LPV/r), Atazanavir (ATV), Fosamprenavir (FPV), Tipranavir (TPV)

- **Fusion inhibitor:**
  - Enfuvirtide T-20

- **Integrase inhibitor:**
  - Raltegravir, Eltegravir, Dolutegravir

The multi drug regimen is commonly referred to as highly active antiretroviral therapy or HAART to provide effective treatment. For eg., A fixed-dose co formulation of Zidovudine + Lamivudine is available as COMBIVIR; a fixed-dose co formulation of Zidovudine + Lamivudine + Abacavir is available as TRIZIVIR; a fixed-dose co formulation of Abacavir with Lamivudine is available as EPZICOM; a fixed-dose co formulation of Tenofovir DF with Emtricitabine is available as TRUVADA.
1.3. DRAWBACKS OF CONVENTIONAL ARV DRUG THERAPY (8-11)

At present, there are so many antiretroviral drugs that are commercially available in the market as solid oral dosage forms (tablets/capsules), liquid oral dosage forms (solutions/suspensions). The oral dosage forms have several advantages like convenience, oral delivery of drugs have some disadvantages also such as first pass effect, absorption variation and enzymatic degradation of the drug in the GI tract. For example, the first antiretroviral drug approved for HIV treatment such as zidovudine shows rapid elimination half-life of 1 hr and hepatic first pass metabolism and loses 40% of the administered drug. In the conventional dosage forms, the duration of the drug’s pharmacological action is very short and limited because the mean residence time of the drug depends on the elimination half-life and thereby the absorption of the drug. And also, many of the antiretroviral drugs show poor or low bioavailability due to various physicochemical factors such as dissolution, solubility, and permeability (didanosine).

The drug’s performance in in-vivo mainly depends on its physicochemical property such as drug stability and solubility. Research scientists today face so many formulation problems because of drug stability and GI tract liability. This can lead to the poor bioavailability and absorption.

In order to make the successive therapy in AIDS, it is required to maintain the drug at a constant and optimum concentration in the blood and also to the target tissue throughout the treatment.

Most of the antiretroviral drugs have a shorter biological half-life. However, because of their short biological half-life these drugs needed to administer frequently. Hence with do not maintain the drug concentrations constantly for a longer period of time. Due to the HIV’s virostatic nature, these drugs should be administered for the life of the patient. All most all antiretroviral drugs exhibit toxic effects such as hyperglycemia, hepatotoxicity, hyperlipidemia, lactic acidosis, lipodystrophy, osteonecrosis, osteoporosis, osteopenia, skin rashes, due to the higher blood concentration of the drugs. So the benefit and risk from the treatment are same with the use of these antiretroviral drugs but the treatment should be continued to increase the survival rate of the HIV-infected person. And also, with the continuation of the therapy resulted in frequent administration and thereby increased the Pill burden. These problems can be overcome by the design of novel drug delivery systems.
1.4. NEED FOR NOVEL & CONTROLLED DRUG DELIVERY OF ANTIRETROVIRALS (8-11)

To succeed in the HIV therapy for long-term treatment with the anti-HIV drugs, where the patients suffer from the problems associated with the plasma fluctuations, dose frequency; it is required to have an effective dosage form in the form of sustained and controlled release formulations to improve the therapeutic benefit and ideal therapy. With the help of the controlled and sustained drug delivery, effective plasma concentration was achieved without any fluctuations. It is also possible to avoid toxic plasma concentrations where it is a problem with conventional formulations and also possible to achieve effective therapy with a low dosage of the drug, and to avoid the frequency of the dose administration.

Advanced drug delivery technologies can potentiate a product's clinical and commercial value, it differentiates the product from its competitors. The oral route of drug administration is the most preferred mode of administering drugs for systemic effects for solid oral dosage forms. Pharmacologically, they improve the pharmacoeconomics of drugs by reducing adverse effects, improving therapy, safety, efficacy, convenience and compliance.

New drug delivery technologies make medicines more convenient to patients by simplifying the dosing regimen and improving oral administration with reducing dosing frequency. These improvements booster patient compliance and quality of life with reducing costs. Commercially, drug delivery technologies give new life to drugs with a new or improved therapeutic benefit and a competitive edge.

The drug's market value can be sustained by extending the product's lifecycle with a line extension by making new and effective drug delivery systems as to give a product a competitive edge and to enable or accelerate market entry.

1.5. INTRODUCTION TO DRUG DELIVERY SYSTEMS (12)

The manner by which a drug is delivered can have a significant effect on its efficacy. Drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases has demanded a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new
strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, and molecular biology.

Dosage forms are the means (or the form) by which drug molecules are delivered within the body. The need for dosage forms includes in order to optimize stability, safety and effectiveness of drug substances and to make them suitable for administration. According to the consistency, these dosage forms are classified as, solid, semisolid, liquid and gaseous dosage forms.

The path taken by the drug to get into the body is known as the route of drug administration. According to the route of administration, these dosage forms are classified as, enteral, parenteral, topical and inhalation dosage forms.

Among all these, oral administration of drugs is the most common and preferred route for delivery of therapeutic agents. The popularity of the oral route is due to patient compliance, ease of administration, accurate dosing and cost-effective manufacturing methods. Solid dosage forms, such as tablets, have many advantages over other types: greater stability, improved shelf-life of the product, less risk of chemical interaction between different medicaments, accurate dosage, and ease of production.

1.6. TABLETS \(^{13,14}\)

Tablets are solid unit dosage form of medicaments with or without suitable diluents and prepared either by molding or compression. They are a solid, flat or biconvex disc in shape. They vary greatly in shape, size and weight which depend upon the amount of medicament used and mode of administration. They also vary in hardness, thickness, disintegration and dissolution characteristics and in other aspects depending upon their intended use and method of manufacture. Tablets are the most widely used solid dosage form of the medicament. Because of their advantages, their popularity is continuously increasing day by day.

1.6.1. Properties of an ideal tablet

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in the proper format or over proper time. The tablet should be elegant, having its own identity and free from defects such as cracks, chips, contamination, discoloration etc. It should have the chemical and physical stability to maintain its physical integrity over time. It should be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
1.6.2. Types and Classes of tablets\(^{(14)}\)

1. Oral tablets for ingestion
   a. Compressed tablets
   b. Multiple compressed tablets
      i. Layered tablets
      ii. Compression coated tablets
   c. Chewable tablets
   d. Sugar & chocolate coated tablets
   e. Film-coated tablets
   f. Repeat action tablets
   g. Delayed action & enteric coated tablets
   h. Controlled release tablets

2. Tablets used in oral cavity
   a. Buccal and sublingual tablets
   b. Troches & lozenges
   c. Dental cones

3. Tablets administered by other routes
   a. Implantation tablets
   b. Vaginal tablets

4. Tablets used to prepare solutions
   a. Effervescent tablets
   b. Dispensing tablets
   c. Hypodermic tablets
   d. Tablet triturates

1.7. MODIFIED DRUG DELIVERY SYSTEMS RATIONAL\(^{(15)}\)

Modified Release Technology also known as Sustained-release (SR), extended-release (ER, XR, or XL) or controlled-release (CR) technology formulated to control the drug release over a period of time. Modified release (MR) dosage form is defined by USP as “The one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutically or convenience objectives not offered by conventional dosage forms”, whereas one class of MR dosage form is an extended-release (ER) dosage form defined as the one which allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance.
1.7.1. Different types of modified release dosage forms (16):

Modified release delivery systems may be divided conveniently into four categories.

(A) Delayed release

(B) Sustained release
   a. Controlled release
   b. Extended release

(C) Site specific targeting

(D) Receptor targeting

(A) Delayed release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action and enteric-coated tablets.

(B) Sustained release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

   a. Controlled release

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this is of a temporal or spatial nature, or both, of drugs, release in the body, or in other words, the system is successful at maintaining constant drug level in the target tissue or cells.

   b. Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

(C) Site specific targeting

These systems refer to the targeting of a drug directly to a certain biological location. In this case, the target is adjacent to or in the diseased organ or tissue.

(D) Receptor targeting

These systems refer to targeting of drug directly to a certain biological location. In this case, the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial of drug delivery and are also considered to be controlled drug delivery systems.
1.8. CONTROLLED RELEASE DRUG DELIVERY

In the mid to late 1960s, the term “controlled drug delivery” came into being to describe new concepts of dosage-form designing. These concepts usually involved controlling drug dissolution, but also had additional objectives. The primary objectives of a controlled-release system have been to enhance safety and extend the duration of action.

The first commercially developed oral controlled release formulation was the pellet-filled capsule called Spansules which was introduced in 1950 by Smith, Kline, and French. These were formulated by coating a drug with nonpareil sugar beads and further coating with glyceryl stearate and wax. Since then a number of strategies were developed to obtain controlled release of a drug in the body. These vary from simple matrix tablets or pellets to more technologically sophisticated controlled release systems which have been introduced into the marketplace.

Today, we also have controlled-release systems designed to produce more reliable absorption and to improve bioavailability and efficiency of drug delivery. Usually conventional dosage forms produce wide-ranging fluctuation in drug concentration in the bloodstream and tissue with consequent undesirable toxicity and poor efficiency. This factor, as well as factors such as repetitive dosing and unpredictable absorption, led to the concept of controlled drug delivery system. The goal in designing sustained or controlled delivery system is to reduce the frequency of the dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, the controlled release dosage form is a dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

1.8.1. Problems with conventional drug therapy:

- If the dosing interval is not appropriate for the biological half-life of the drug, large peaks, and troughs in drug blood level may results.
- The drug blood level may not be within therapeutic range
- Patient non-compliance with multiple dosing regimens.

1.8.2. Potential advantages of controlled drug delivery:

- Reduction in frequency of drug administration
- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Stabilization of medical condition because of more uniform drug levels
- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient
- Product life-cycle extension

1.8.3. **Immediate release versus Controlled release formulations:**

Compared with immediate release formulations, controlled release formulations can decrease the frequency of administration required to maintain therapeutically effective plasma drug levels. In addition to producing more constant blood levels, such formulations can reduce the large changes in plasma levels observed between doses. With controlled release formulations, the time to peak plasma concentration is extended because the amount of drug released at once is not as high as it with immediate release formulation.

![Figure 1.3: A hypothetical plasma drug concentration – time profile from conventional multiple dosing and an ideal controlled delivery formulation](image-url)
1.8.4. Factors governing the design of CRDDS \(^{(18,19)}\)

Table 1.1: Factors in the design of CRDDS

<table>
<thead>
<tr>
<th>Properties of Candidate Drug</th>
<th>Desired Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Biopharmaceutical properties</strong></td>
<td></td>
</tr>
<tr>
<td>1. Molecular size</td>
<td>Less than 600 Daltons</td>
</tr>
<tr>
<td>2. Aqueous solubility</td>
<td>More than 0.1 mg/ml</td>
</tr>
<tr>
<td>3. Partition coefficient (k_{o/w})</td>
<td>1 - 2</td>
</tr>
<tr>
<td>4. Dissociation constant (pK_a)</td>
<td>Acidic drugs, &gt; 2.5; Basic drugs, &lt; 11</td>
</tr>
<tr>
<td>5. Ionization at physiological pH</td>
<td>Not more than 95%</td>
</tr>
<tr>
<td>6. Stability in GI milieu</td>
<td>Stable at both gastric and intestinal pH</td>
</tr>
<tr>
<td>7. Absorption mechanism</td>
<td>Passive, but not through a window</td>
</tr>
<tr>
<td><strong>(B) Pharmacokinetic properties</strong></td>
<td></td>
</tr>
<tr>
<td>1. Absorption rate constant (K_a)</td>
<td>High</td>
</tr>
<tr>
<td>2. Elimination half-life (t_{1/2})</td>
<td>2 – 6 hours</td>
</tr>
<tr>
<td>3. Metabolism rate</td>
<td>Not too high</td>
</tr>
<tr>
<td>4. Dosage form index</td>
<td>One</td>
</tr>
<tr>
<td><strong>(C) Pharmacodynamic properties</strong></td>
<td></td>
</tr>
<tr>
<td>1. Dose</td>
<td>Maximum 1 g</td>
</tr>
<tr>
<td>2. Therapeutic range</td>
<td>Wide</td>
</tr>
<tr>
<td>3. Therapeutic index</td>
<td>Wide</td>
</tr>
<tr>
<td>4. PK/PD relationship</td>
<td>Good</td>
</tr>
</tbody>
</table>

1.8.5. Polymers used in CRDDS \(^{(20,21)}\):

- **Hydrogels**: Polyhydroxyethylmethacrylate, Cross-linked polyvinyl alcohol, Cross-linked polyvinyl pyrrolidone, Polyethylene oxide, Polyacrylamide.
- **Soluble polymers**: Polyethylene glycol, Polyvinyl alcohol, HPMC, PVP
- **Biodegradable polymers**: Polylactic acid, Polyanhydrides, Polyorthoesters.
- **Non-biodegradable polymers**: Polyethylene vinyl acetate, Polydimethylsiloxane, Polyether urethane, Polyvinyl chloride, Cellulose acetate, Ethyl cellulose.
- **Mucoadhesive polymers**: Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
- **Natural gums**: Xanthan gum, Guar gum, Karaya gum, Locust bean gum.
1.8.6. **ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS** (22, 23)

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of oral controlled release systems rely on dissolution, diffusion, or a combination of both mechanisms to generate slow release of drug to the gastrointestinal milieu.

1.8.6.1. **Dissolution controlled release**

Sustained release oral products employing dissolution as the rate-limiting step are in principle the simplest to prepare.

**a) Encapsulation dissolution control**

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in Spacetabs or placed in capsules as in the Spansule Products. Since the time required for dissolution of the coat is a function of its thickness and aqueous solubility, one can obtain repeat or sustained action by employing a narrow or a wide spectrum of coated particles of varying thicknesses respectively.

**b) Matrix dissolution control**

An alternative approach is to compress the drug with a slowly dissolving carrier of some sort into a tablet form. Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This, in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particles surface.

1.8.6.2. **Diffusion controlled release**

There are basically two types of diffusion controlled systems which have been developed over the past two decades, reservoir devices and matrix devices.

**a) Reservoir devices**

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the membrane, diffuse to the periphery, and exchange with the surrounding media.

**b) Matrix devices**

In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution.
1.8.6.3. Diffusion and Dissolution controlled systems

The main feature of this system is that the drug core is enclosed with a partially soluble membrane. Dissolution of part of the membrane allows for diffusion of the contained drug through pores in the polymer coat.

1.8.6.4. Ion-exchange resins

Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. The drug-charged resin is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatographic column or by keeping the resin in contact with the drug solution for extended periods of time. The drug-resin is then washed to remove contaminant ions and dried to form particles or beads. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecule is exchanged and diffuses out of the resin to the bulk solution.

1.8.6.5 pH – independent formulations

The granules are designed for the oral controlled release of basic or acidic drugs at a rate that is independent of the pH in the GI tract. They are prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients, and finally, coating with a gastrointestinal fluid permeable film-forming polymer. When the GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH, thereby rendering a constant rate of drug release.

1.8.6.6. Osmotically controlled release

In this type of drug delivery systems, osmotic pressure is the driving force that generates constant drug release. This system is fabricated by applying a semipermeable membrane around a core of an osmotically active drug or a core of an osmotically inactive drug in combination with an osmotically active salt. A delivery orifice is drilled in each system by laser or by a high – speed mechanical drill.

1.8.6.7. Altered density formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. One such approach is the bioadhesion approach, which is based on the adherence of bioadhesive polymers to the mucin / epithelial surface of the GI tract. The other approach is to alter the formulation’s density by using either high or low density pellets.
1.9. DRUG RELEASE KINETICS \(^{(24)}\)

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug \((Q)\) is a function of the test time, \(t\) or \(Q = f(t)\). Some analytical definitions of the \(Q(t)\) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas models.

1.9.1. Zero order kinetics:

\[ Q_t = Q_0 + K_0 t \]

Where \(Q_t\) is the amount of drug dissolved in time \(t\), \(Q_0\) is the initial amount of drug in the solution (most times, \(Q_0=0\)) and \(K_0\) is the zero order release constant.

\[ f_t = 1 - \left(\frac{W_t}{W_0}\right) \]

Where \(f_t = 1-(W_t/W_0)\) and \(f_t\) represents the fraction of drug dissolved in time \(t\) and \(K_0\) the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

**Use:** This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by a unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

1.9.2. First order kinetics:

Kinetic equation for the first order release is as follows

\[ \log Q_t = \log Q_0 + K_1 t/2.303 \]

Where \(Q_t\) is the amount of drug released at time \(t\), \(Q_0\) is the initial amount of drug in the solution and \(K_1\) is the first order release constant. In this way, a graphic of the decimal logarithm of the released amount of drug versus time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by a unit of time diminishes.
1.9.3. **Higuchi model:**

\[ f_t = K_H t^{1/2} \]

Where \( K_H \) is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based on the Fick’s law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

1.9.4. **Hixson–Crowell model:**

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

\[ W_0^{1/3} - W_t^{1/3} = K_s t \]

Where \( W_0 \) is the initial amount of drug in the pharmaceutical dosage form, \( W_t \) is the remaining amount of drug in the pharmaceutical dosage form at time \( t \) and \( K_s \) is constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time.

1.9.5. **Korsemeyer – Peppas model:**

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behavior of polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.

\[ \log \left( \frac{M_t}{M_\infty} \right) = \log K_{KP} + n \log t \]

Where, \( M_t \) is the amount of drug release at time \( t \), \( M_\infty \) is the amount of drug release after infinite time; \( K_{KP} \) is a release rate constant incorporating structural and geometrical characteristics of the tablet, and \( n \) is the release exponent indicative of the mechanism of drug release.
1.10. DOSAGE FORMS SELECTED IN THE PRESENT STUDY

1.10.1. Single unit system (matrix tablets) by Embedment technique (25, 26)

Controlled drug delivery technology is fast growing because of its many potential advantages like minimum fluctuations in plasma drug concentration and a reduced frequency of dosing when compared to the conventional dosage forms. Many newer technologies are also emerging for designing controlling drug delivery systems with improved efficiency and embedment is one such novel technique. The release rate retarding material or polymer is the major component of these systems and its concentration influences the release rate.

Matrix drug delivery systems consist of a polymer, drug, and other excipients distributed throughout the matrix. This system is dependent on polymer wetting, polymer hydration, and polymer dissolution for the controlled release of the drug. At the same time, other soluble excipients or drug substances comprising the tablet will also become wet, dissolve, and diffuse out of the matrix, while insoluble excipients or drug substances will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

1.10.2. Compression coated tablets (27)

Compression coating, or press-coating, has been introduced during the period 1950-1960 (Windheuser and Cooper, 1956) to formulate incompatible drugs. This coating became interesting in the last two decades owing to the advantages over liquid coating since the process does not need the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet. Nowadays, pharmaceutical aspects of compression-coated tablets in dosage form development are: to protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs; to separate incompatible drugs from each other and achieve sustained release; and to modify drug release pattern. However, some drawbacks of compression coating technique include the requirement of reliable and reproducible central positioning of the core tablet within the compression-coated tablet, the need for a multiple-step process or a special tableting machine.

A compression-coated tablet consists of a core tablet which is coated by compression with a solid barrier. The barrier could contain polymeric material, diluents. Compression coated tablets could be modulated to provide different release patterns depending on the drug distribution and plus with different type of controlling polymer used in core and coat.
1.10.3. Microcapsules assisted bilayered tablets

1.10.3.1. Microparticles (28-31):

These are particles with size more than 1 µm, containing the polymer. At present, there is no universally accepted size range that particles must have in order to be classified as microparticles. However, many workers classify the particles smaller than 1 µm, as nanoparticles and those more than 100 µm, as macroparticles.

Microparticles are classified into two groups.

- **Microcapsules**
  - Microcapsules are small particles that contain an active pharmaceutical ingredient or core material surrounded by a coating or shell.

- **Microspheres**
  - Microspheres
    - (Reservoir system)
  - Microspheres
    - (Matrix system)

**Microcapsules**: Microcapsules are small particles that contain an active pharmaceutical ingredient or core material surrounded by a coating or shell.

1.10.3.2. Bilayered tablets (32):

Bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form and two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the polymers into a porous/viscous gel that serves as a barrier between the drug and the surrounding fluid. Depend on the polymer, the mechanism varies and results in the release of drug in a controlled manner. Again both immediate-release and controlled-release combinations of the two drugs are feasible.