CHAPTER 1

DRUG DELIVERY SYSTEMS

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1.1 Introduction

Most drugs used in primitive medicine were obtained from plants. These naturally occurring substances were employed in the form of infusion, decoction or poultices, and came in to medicines by the way of accident or by the herb doctors.

Drug used in 19^{th} century were naturally occurring substances extracted from plants, animals or minerals. The active principles were isolated and came in to medicine largely on an empirical basis. Although, these agents are still used today, they were first used in man without prior laboratory evaluation. The plants used as drugs were either relatively free from toxic effects or their lethal effects due to toxicity were known to herbal doctors and common people, these informations lacked proper documentation.

With the explosive development of new methods of organic chemistry in the last decades of the past century and the first decades of this century, it became possible to elucidate the structure of the pharmacologically active natural products and to synthesize either their active principles or a modified molecule of the parent substances. Subsequently, efforts were directed towards synthesis of molecules in which the pharmacological properties of the original natural products were preserved or present to a more enhanced degree, while the toxic side effects were reduced. This led to the synthesis of agents with novel structures, the pharmacologic effects of which were determined by study in laboratory animals. This approach proved very fruitful and led to development of thousands of new and potent synthetic dugs.

In addition to enormous development in science, the present century has made immense progress in the field of technology, which in natural course encroached in the pharmaceutical field too. This has made the emergence of more sophisticated dosage forms like tablets, capsules, parenteral products which superseded the dosage forms like infusion, decoction and others.

The curiosity and quest of human being have explored even his own physiological and anatomical network. In prevention and curing of diseases, as he has developed new medicines and newer dosage forms, he has also made the drug therapy more rational.

With better understanding of pharmacokinetic and pharmacodynamic parameters, the present day drug therapy is based on the delivery of adequate amount of drug in the body or

to the target organ to elicit the therapeutic responses and to maintain this level over a desired period of time.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve therapeutic action promptly and then maintain the desired drug concentration at the site of action for required period.

Maintenance of adequate drug concentration for an extended period of time at the site of action is one of the primary goals of the treatment. With the conventional dosage forms (CDF) this goal is fulfilled by multiple dosing of the drug formulation at an interval of predetermined period to compensate the drug loss from the body due to elimination and biotransformation as represented in Figure 1.1.

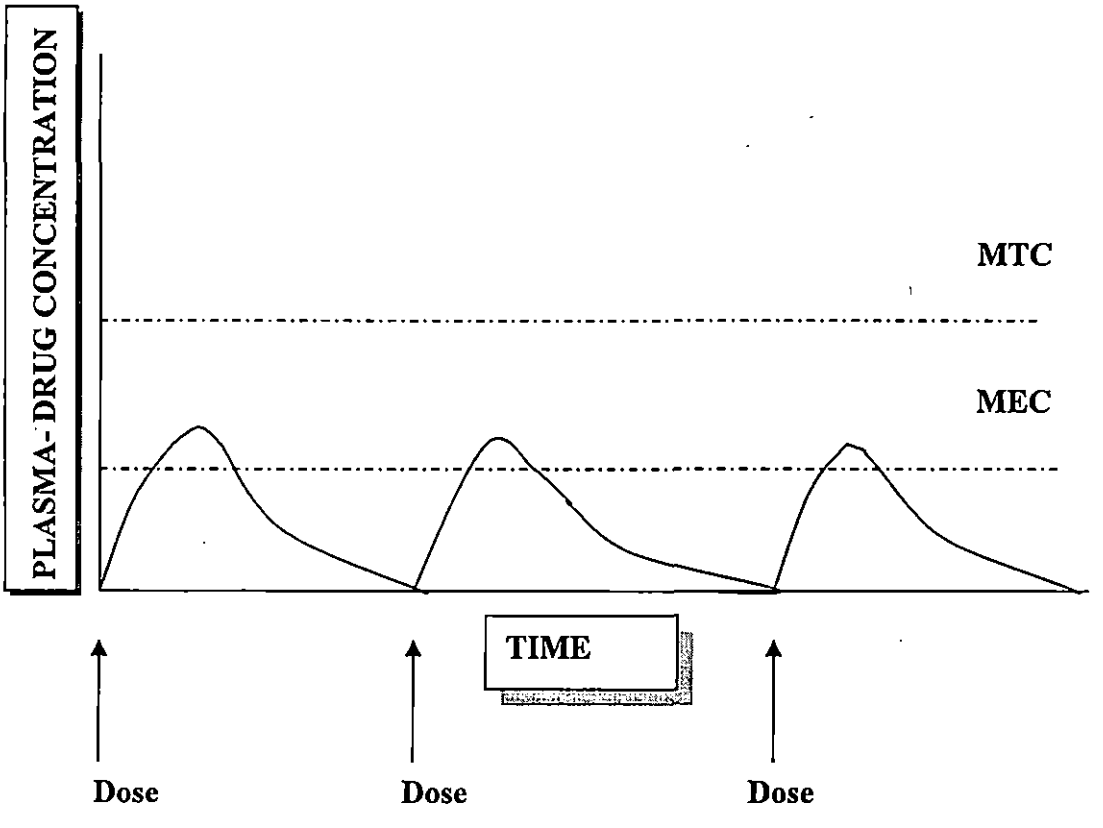

Figure 1.1 Plasma Concentration Vs Time curve following oral administration of equal doses of a drug at regular time interval which allows complete elimination of the previous dose

MTC- Minimum Toxic Concentration

MEC- Minimum Effective Concentration

The objective of the drug delivery system[1] should be based on two aspects, namely spatial placement and temporal delivery of the drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of delivery to the target tissue. So the drug formulation should be such that it will be capable to deliver a correct amount of drug in the right form, at the desired place, at proper rate, over the desired time, while the chemical integrity of the drug will be unaltered.
Thus, drug delivery system can be defined as a dosage form that releases one or more drugs systemically, topically or to a specified target organ.

Drug delivery systems can be broadly classified as:-

a) **Conventional Drug Delivery Systems (CDDS)**
b) **Controlled Release Drug Delivery Systems (CRDDS)**

1.2 Conventional Drug Delivery System

These kinds of drug delivery system consist of the active constituent and auxiliary biologically inert substance called excipients. An orally administered conventional dosage form releases the drug when it comes in contact with gastric fluid. Two main factors affecting drug release are as follows;

A. **Solubility of Drug**
B. **Dissolution rate of a Drug**

After release, the drug must pass through the various biological barriers in order to get absorbed. Absorption of hydrophobic drugs like Griseofulvin is dissolution rate-limited. Absorption of hydrophilic drugs like Cromolyn Sodium is permeation rate-limited.
About 90% of the drugs are absorbed by passive or non-ionic diffusion, where the main driving force is concentration or electrochemical gradient. Bioavailability is defined as the rate and extent of the drug that reaches the systemic circulation and is available at the site of action. After eliciting the desired pharmacological effect, the drug gets eliminated either as unchanged form or conjugated form through various rates of excretion.
The time required for elimination of half the plasma content of the drug by metabolism or excretion is called its biological half-life ($t_{1/2}$) and is of high interest for the dosage regimen

prescribed by the physician. Accurate dosage regimen is highly essential for chronic treatment and also for prolonged treatment when the plasma drug concentration is kept at a constant level for a prolonged period. The plasma drug concentration should lie between median lethal dose (LD_{50}) and the median effective dose (ED_{50}), the ratio of which (i.e. LD_{50} / ED_{50}) is called the therapeutic index and defines the safety margin of the drug.

1.2.1 Limitations of Conventional Drug Delivery Systems

In case of conventional dosage forms, the drug is released rapidly by dissolution leading to a maximum high concentration, which then subsides exponentially due to first order absorption. This fact is characterized by saw-tooth pattern of drug concentration profile in stomach/intestine and also in plasma. This leads to alternating periods of over dosages and under dosages. Thus, the use of conventional dosage forms for maintaining therapeutic drug levels for a prolonged period is difficult and have the following drawbacks:

A. The typical peak-valley drug profile leads to insufficient efficacy of therapy provoking an excessive use of the drug. (Fig. 1.2)
B. Over dosage originating after dissolution of the drug may produce a high frequency of side effects leading to iatrogenic damage.
C. High frequency of administration of conventional dosage forms is limited by the reliability of patient compliance (omission, wrong frequency).
D. The peak-valley plasma concentration time profile makes the attainment of steady state condition highly difficult.

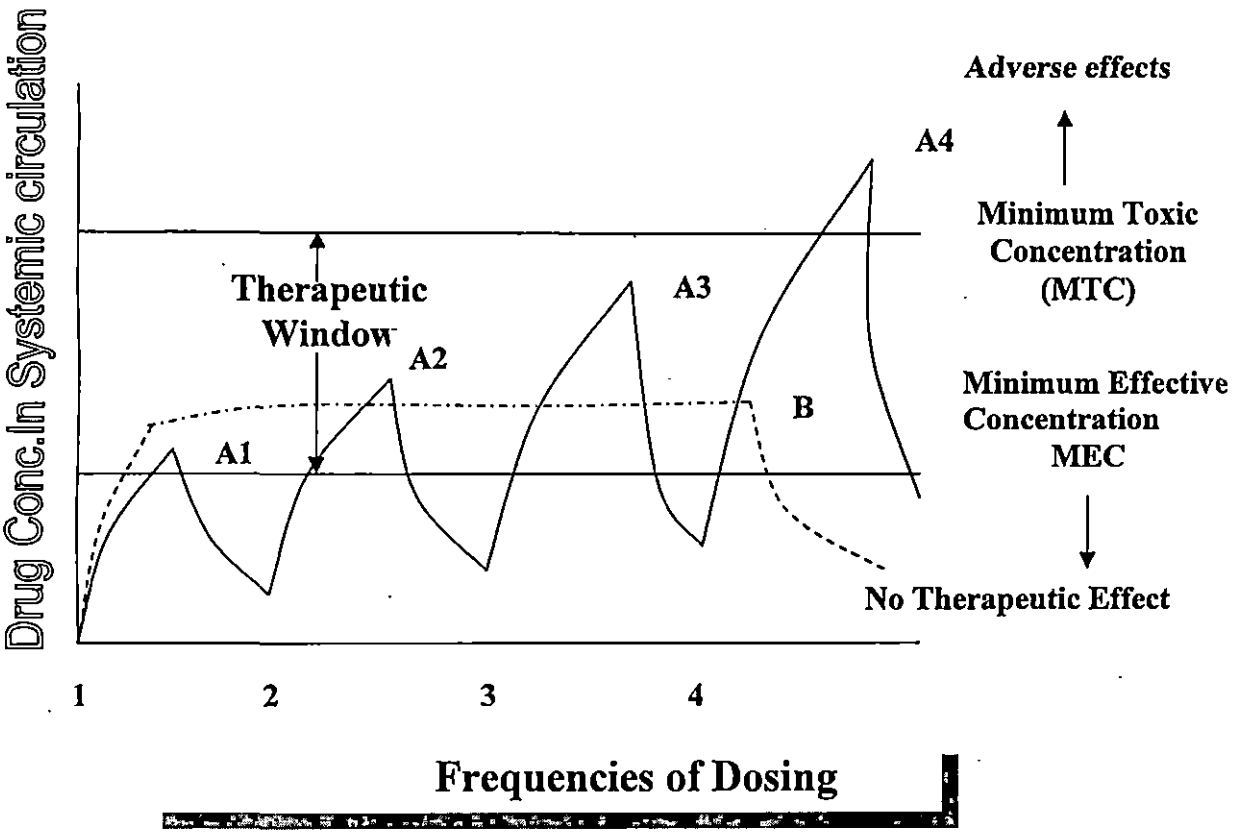

Figure 1.2 **Drug Concentration profile in systemic circulation following oral administration of conventional dosage form (A1, A2, A3, A4....) and ideal drug concentration in systemic circulation following oral administration of controlled release dosage form (B)**

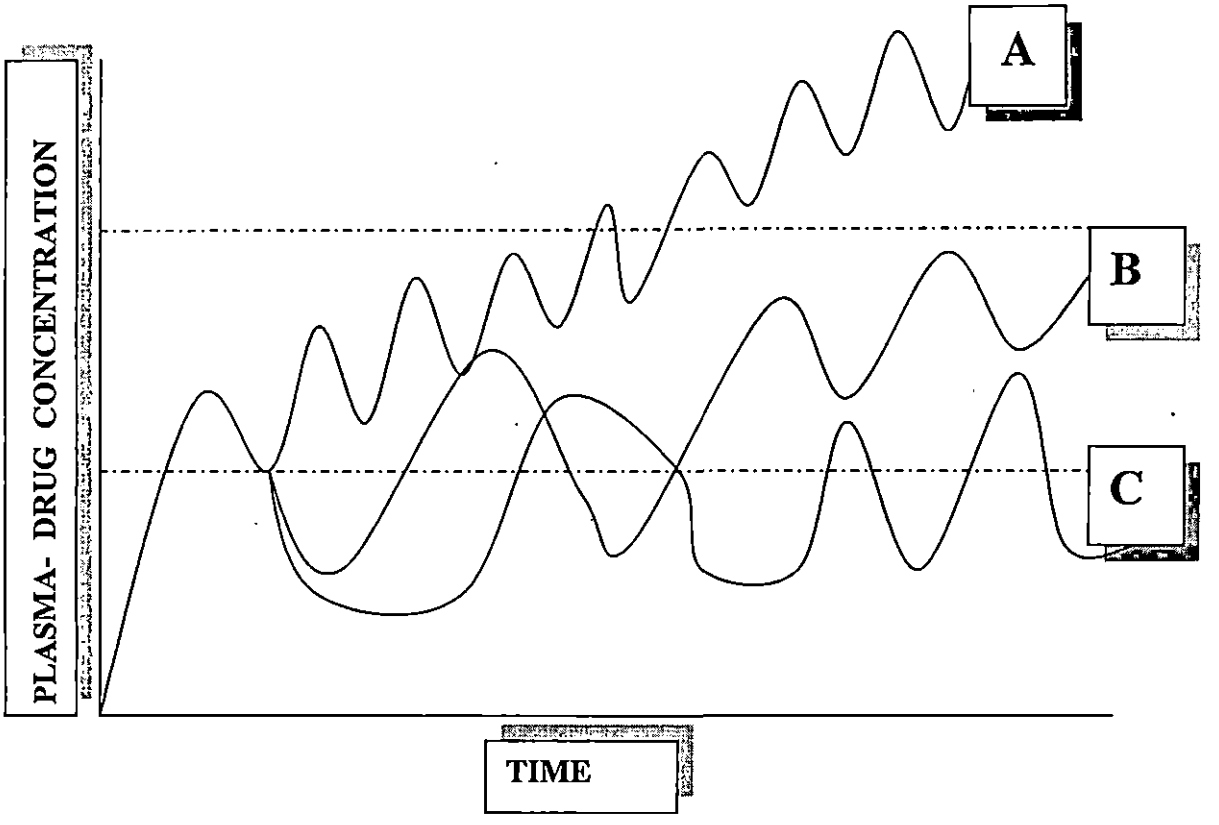

Figure 1.3 Effect of frequencies of Drug administration on plasma concentration

(A) Too Frequent (B) Uniform (C) Inadequate.

The desired therapeutic dose must attain plasma concentration which lies above the minimum effective concentration but below the minimum toxic concentration. The controlled release delivery systems should overcome the "Saw-Tooth" (Fig.1.3) pattern usually shown by conventional dosage forms.

1.3 Controlled Release Drug Delivery System

The goal of any delivery system is to provide a therapeutic amount of drug to the target site in the body and then maintain the desired drug concentration. Two aspects most important to drug delivery are spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to target tissue. An appropriately designed controlled release drug delivery system can be a major step towards solving these two problems. The

bulk of research has been directed towards oral dosage forms that satisfy the temporal aspect of drug delivery but newer approaches facilitating spatial placement are also under investigation. The term "Sustained Release"[2] is used to illustrate a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.[3] The term "Controlled Release" goes beyond the scope of sustained drug action. It also implies a predictability and reproducibility in the drug release kinetics.

1.3.1 Classification of Rate-Controlled Drug Delivery System

1) **Rate Programmed Drug Delivery System**

In this class of drug delivery system the release of drug molecules from the delivery systems has been programmed at specific rate profiles. This exhibited a whole new lacuna in the code of proof as a system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system.[2,50]

2) **Activation-Modulated Drug Delivery System**

In this group of controlled release drug delivery systems the release of drug molecules from the delivery system is activated by physical, chemical or biochemical processes and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

3) **Feed-back Regulated Drug Delivery System**

This group of controlled release system consists of a triggering agent that activates the release of drug molecules from the delivery system. The release is also regulated by the concentration of the triggering agent (a biochemical substance present in the body) via some feed-back mechanisms. The rate of drug release is then controlled by the concentration of the triggering agent detected by a sensor in the feedback-regulated mechanism.

4) **Site Targeting Drug Delivery System**

This delivery system is utilized for drug targeting to a certain organ or tissue. The drug can also be targeted to a particular receptor within an organ or tissue.

1.3.2 Rationale for Controlled Release Dosage Forms

The basic rationale for controlled release drug delivery is to alter 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.

The duration of action of the drug must be a designed property in case of controlled release dosage form and not at all the drug molecule's inherent kinetic properties. Thus the thorough knowledge of the pharmacokinetics and pharmacodynamics of the drug is necessary for optional design of the controlled release dosage form.

1.3.3 Objectives and Potential Advantages of Controlled Release Dosage Forms[1,4]

a) **To reduce dosage frequency.**
b) **To provide more constant therapeutic drug levels.**
c) **To obtain more uniform pharmacological response, or to minimize potentiation or reduction in drug activity in prolonged use.**
d) **To reduce total amount of dug used.**
e) **To reduce inconvenience to the patient and increase compliance.**
f) **To reduce gastrointestinal irritation.**
g) **To reduce both local and systemic side effects.**
h) **To allow the use of drugs with low therapeutic index.**
i) **To avoid night-time dosing.**
j) **To reduce fluctuations in circulating drug levels and minimization of drug *accumulation in body tissues with chronic dosing.***

1.3.4 Disadvantages of Controlled Release Dosage Forms

a) Possibilities of dose dumping.
b) Reduced potential for accurate dose adjustment.
c) Increased potential for first pass metabolism.
d) Possible reduction in systemic availability.
e) Drug release profile restricted to residence time in G.I.T.
f) Greater cost than conventional dosage forms.
g) Poor *in vitro-in vivo* correlation.
h) Difficulty of quick stoppage of pharmacological action of drugs when serious poisoning or intolerance occurs.

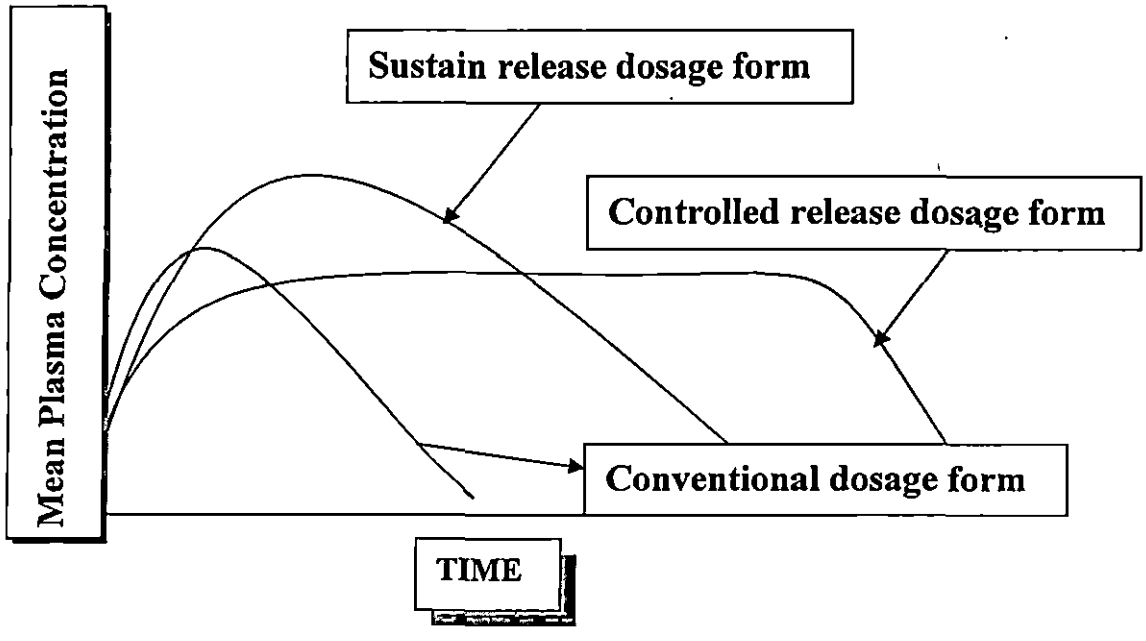

Figure 1.4 Comparative study of plasma concentration of drug with respect to time from the three different dosage form

1.3.5 Factors Influencing the Design and Performance of Sustained / Controlled Release Products

To establish criteria for the design of controlled release products, a number of variables are considered[51] which are explained below:

a) Drug Properties:

The physicochemical properties of drug like solubility, protein-binding propensity, partition coefficient etc play a dominant role in the design and performance of controlled release systems.

b) Route of Drug Delivery:

The area of the body in which drugs are applied can be restrictive on the basis of technological achievement of a suitable controlled release mechanism or device. Performance of a controlled release system may also be influenced by physiological constraints imposed by the particular route. e.g., First pass effect, G.I. motility etc.

c) Target Sites:

In order to minimize unwanted side effects it is desirable to maximize the fraction of the applied dose that reaches the systemic circulation. This can be done successively by local administration or by use of carriers.

d) Acute or Chronic Therapy:

During the design of controlled release systems, the expected length of the therapy and the intended duration of action of the dosage form, play an important role.

e) The Patient:

The condition of the patient like age, obesity, ambulatory or bedridden plays a vital role in designing of controlled release systems.

f) The Disease:

Pathological changes during the course of a disease can play a significant role in the design of a controlled release system. Sometimes one can take advantage of the unique manifestations of the disease state, e.g., the higher plasminogen activator levels in some tumor cells lead to preferential bioconversion of peptidyl prodrug in the cells.

1.3.6 Drug Properties Influencing the Design of Controlled Release Drug Delivery Systems

To establish a basis for discussion of drug property influencing the design of controlled release product, two factors are mainly highlighted.

1. **Behavior of the drug in the drug delivery system.**
2. **Behavior of the drug in the body.**

The first factor mainly deals with the influence of drug properties on the release characteristics of the drug.

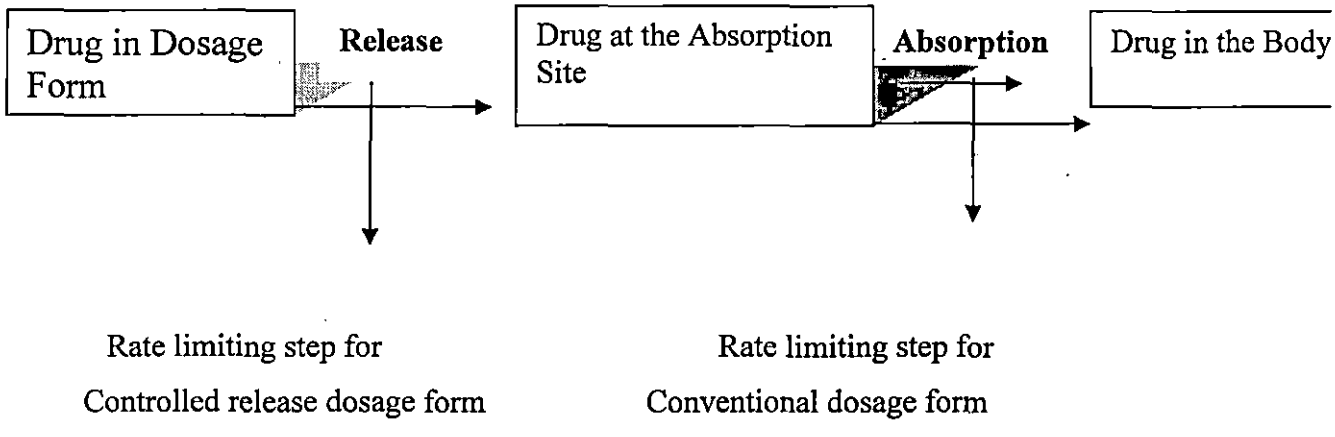

Figure 1.5 Schematic Diagram of the Dosage form after Administration

The second factor i.e. the behavior of drug in the body is a very complex scenario. This includes the rate of drug release during its passage to the target area as well as its fate while in the bio phase. The drug interacts with a variety of substances leading to undesired drug loss as well as desired drug absorption. This drug loss unintentionally as well as the useful absorption is a function of the structure and hence properties of the drug as well as the type of the delivery system in which the drug is housed.

1.3.7 Physico-Chemical Properties of a Drug Influencing the Drug Product Design and Performance

i. Dose Size:

Erikson[3] has stated that drugs with a single oral-dose more than 0.5 gm are poor candidates for oral controlled release products. Since the absorption mechanism will in most cases generate a substantial volume of the product depending on the density of the drug, duration of intended prolongation and type of sustaining mechanism. However, compromise between dose size and efficacy should always be sought.

ii. Aqueous Solubility:

Extremes in aqueous solubility are undesired in the preparation of controlled released products. The main motto behind this restriction revolves around the dissolution rate of the drug. Aqueous solubility monitors absorption in two ways:-

1. Aqueous solubility influences the dissolution rate of a compound, which in turn determines the drug concentration in solution. The drug concentration in solution serves as the driving force for tissue permeation.
2. The aqueous solubility of the drug could be used as the first approximation to its dissolution rate.

Drugs[8] with water solubility less than 0.1 mg/ml have reduced bioavailability in conventional oral dosage forms whereas on the other hand highly soluble drugs are difficult to design in a sustained release form.[2]

The choice of mechanisms for oral sustained/controlled release system is limited by aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion; the aqueous concentration will be low. Such drugs can be effectively incorporated into matrix systems.

iii. Partition Coefficient:[9]

It has been shown hat a parabolic relationship exists between partition coefficient and membrane permeation extremes. Drugs with extremely high partition coefficients (extremely oil-soluble) readily penetrate the membranes but are unable to proceed further

while drugs with low partition coefficient (extremely water soluble) cannot penetrate membranes. A balance in the partition coefficient is needed to give an optimum flux and to prevent drug accumulation in the tissues.

iv. Drug Stability:[12]

The extent of drug loss through hydrolysis or biodegradation in the stomach and intestine is proportional to the residence time in these organs and their apparent rate of degradation. Drugs unstable in stomach can be remodeled into slowly soluble form or have their release sustained until they reach the small intestine. For drugs having stability problems is intestine a different route of administration should be chosen. E.g. controlled release of nitroglycerine by the transdermal route.

v. Protein Binding:

If a drug undergoes high degree of protein binding, the bound drug can serve as a depot for drug resulting in a prolonged release profile. However various drug protein interactions have a negative influence on the therapeutic efficacy of many drugs and may even lead to toxic manifestations.

vi. pKa[24,51]:

The pH partition hypothesis states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. For optimum passive absorption, the drugs should be nonionized at that target site at least to an extent of 0.1 to 5%. A sustained release product should be programmed in accordance with pH variation in GIT so that the amount of unchanged drug and the plasma level of the drug would be approximately constant through out the time course of the drug.

vii. Molecular Size:

The ability of a drug to diffuse through membranes depends on molecular size of the drug. The diffusivity of the drug can be related to the molecular size by the following equation.

$$LogD = -S_v LogV + K_v = -S_m Log\, M + K_m \qquad (1.1)$$

D = diffusivity. **M** = Molecular Weight **V** = Molecular Volume

$\mathbf{K_v}$ **and** $\mathbf{K_m}$ = coefficient of molecular volume and molecular weight, respectively,

$\mathbf{S_v}$ **and** $\mathbf{S_m}$ = specific molecular volume and molecular weight, respectively.

Molecular size is an important parameter when rate controlling polymeric membranes serves as a controlled release weapon.

1.3.8 Biological Factors of a Drug Influencing the Drug Product Design and Performance

The design of controlled release system requires a vivid description of the drug disposition. Every pharmacokinetic property and biological response parameter has a useful range for the design of controlled release products, outside of which controlled release product design becomes difficult or impossible.

- **Absorption:**

Drugs[24] that are slowly absorbed or absorbed with a variable absorption rate are poor candidates for a sustained release system. For oral dosage forms, the lower limit of the absorption rate constant is in the range of $0.25h^{-1}$ (assuming a GI Transit time of 10-12 hr).

- **Distribution:**

The knowledge of the apparent volume of distribution of a drug is highly essential for its fabrication into a sustained release forms. The apparent volume of distribution influences the plasma drug concentration as well as the drug concentration in the target tissues. Apparent volume of distribution of the drug also influences the elimination kinetics of the drug. Thus the drugs with high apparent volume of distribution are poor candidates for controlled release systems.

- **Metabolism:**

Metabolism of a drug will be reflected in the elimination constant of a drug or by the appearance of metabolite. It is possible to incorporate this pharmacokinetic property into the design of a controlled release product provided that the rate and extent of metabolism are predictable and the rate constant for the process is not too large. Complex metabolic pattern

hinders the fabrication of sustained release products particularly when the therapeutic activity of the drug is wholly or partly due to a metabolite.

- **Biological Half-Life:**

The rate of elimination of a drug is quantitatively described by its biological half-life ($t_{1/2}$). The half-life of a drug is related to its apparent volume of distribution (V_d) and its Systemic Clearance (Cls).

$$t_{½} = 0.693\ V_d / Cl_s = 0.693\ V_d\ AUC / Dose. \qquad (1.2)$$

The systemic clearance is equal to the ratio of an intravenously administered dose to the total area under the drug blood level versus time curve, Area Under Curve (AUC). A drug with a short half-life requires frequent dosing and is a desirable candidate for sustained release system whereas, drugs with larger half-lives are more suitable for conventional dosage forms. The exact limits of half-lives of drugs that is best suited for sustained release action is not clearly defined. Generally, drugs with half-life less than 2 hrs are not suitable for sustained release systems due to their faster release rates and large dose size. On the other hand drugs with half-life greater than 8 hr are better approached as conventional dosage unit.

- **Side Effects:**

The occurrence of side effects of many drugs is believed to be a function of its plasma concentration. Thus the fabrication of a controlled release system minimizes the side effects by monitoring the plasma concentration and utilizing less total drug over the time course of therapy.

- **Margin of Safety of The Drug:**

It is best described by the therapeutic index of the drug.

Therapeutic Index (TI) = Mean Lethal Dose/ Mean Effective Dose = LD_{50} / ED_{50} (1.3)

Generally, higher the therapeutic index, the safer is the drug. A drug is considered relatively safe when the therapeutic index crosses 10.

Drugs with small values of TI are poor candidates for formulation into sustained release products primarily because of technological limitations of precise control over release rates.

1.3.9 Techniques of Obtaining Controlled Release Systems

Methods of formulating controlled release systems can be classified under three broad categories.

A. Biological Methods:

This method has limited applications and is mostly a physician's weapon. This approach consists of co-administration of two drugs in order to modify the biological fate of one of them. The therapeutic effect of rapidly excretable oral penicillin can be prolonged by the co-administration of probencid which prevents the rapid excretion of penicillin.

B. Chemical Methods:

The chemical method of preparing controlled release system is based on the promise of programmed release of the drug at the target site. Two approaches[24] are used to serve this purpose.

I. Analog Approach

The synthesis of analogs, which may alter the solubility pattern, partitioning characteristics, increase of efficacy and decrease of toxicity etc. However, this method is rarely implemented for the formulation of controlled release products.

II. Pro-drug Approach

The Pro-drug Approach involves use of a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound. Many sustained release steroids generate the active molecule through *in vivo* hydrolysis of their esters or ethers.

C. Pharmaceutical Methods:

These are based on providing a slow release of active ingredient from the dosage form itself. These methods involve dissolution and/or diffusion of the drug through the matrix delivery system, ion exchange resins etc.

1.3.10 Classification of Controlled Release System:

This classification is based on the mechanism that controls the release of the incorporated drug.[10,11]

A. Monolithic Devices:

In the field of controlled drug delivery, the term "monolithic device" refers to a rate controlling polymer matrix throughout which the drug is dissolved or dispersed. Although the drug releases from matrix systems do not proceed by zero-order kinetics it is the simplest and most convenient approach towards acquiring prolong release effect of the drug. These devices can be easily prepared by simple polymer fabrication techniques followed by compression moulding, injection moulding, extrusion, calendaring or solvent casting.

B. Reservoir Devices:

The reservoir devices consist of a drug core that is surrounded by a rate controlling membrane. Transport of the material from the core through the surrounding nonporous, homogenous polymer film occurs by dissolution at one interface of the membrane and then diffusion down a gradient in the thermodynamic activity. The thermodynamic activity of the active agent in the reservoir remains constant if there is no change in the rate limiting membrane characteristics and if infinite sink conditions are maintained at the downstream side of the membrane. Thus the release of the active agent will be constant and can be predictable from knowledge of membrane permeability and device configuration.

 # Example of the Devices:

1. **Membrane.**[21]
2. **Capsules.**[17]
3. **Microcapsules.** [15,16,17]
4. **Liposomes** [19].
5. **Hollow Fires** [20].

Although reservoir device may require more complex fabrication procedures than monolithic devices, they are capable of releasing drug for long term, nearly zero-order kinetics and thus are considered having commercial importance.

- **Solvent Controlled Devices:**

Solvent controlled devices release agents as a consequence of controlled penetration of a solvent into the device. Water is of main importance in controlled release products for human application though non-aqueous solvents are used. Based on two general mechanisms, osmosis and swelling, there are two types of devices.

- **Osmotically Controlled Device:**

In this device, an osmotic agent is contained within a rigid housing and is separated from an active agent compartment by a movable partition. One wall of the rigid housing is a semi permeable membrane so that when pup is exposed to aqueous environment water will be driven osmotically across the membrane; the increased volume within the osmotic compartment will force the active agent of the device through the delivery orifice.

- **Swelling Controlled Devices:**

In swelling controlled release systems an active agent is homogenously dispersed in a glassy polymer. Because glassy polymers are essentially impermeable, the drug is immobilized in the matrix and no diffusion through the solid polymer phase takes place.

When such a monolithic device is placed in an aqueous environment, water begins to penetrate the matrix and swelling takes place. Due to swelling, chain relaxation takes place and the incorporated active agent begins to diffuse from the swollen layer.

- **Chemically Controlled Devices:**

In chemically controlled device, rate of drug release from the polymer is controlled by a chemical reaction that can be hydrolytic or enzymatic cleavage of a labile bond, ionization or protonation.

1.3.11 Oral Controlled Release Drug Delivery Systems:

Oral controlled release drug delivery is thus a drug delivery system that provides the continuous oral delivery of drugs at a predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit. The several novel drug delivery systems for oral controlled release drug administration are as follows.[50]

- **Osmotic Pressure-Controlled Gastrointestinal Delivery Systems:**

There are systems fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or combination of osmotically inactive agent with an osmotically active salt. e.g., NaCl.) within a semi permeable membrane made from biocompatible polymer e.g., cellulose acetate. A delivery orifice with a controlled diameter is drilled, using a laser beam.

- **Hydrodynamic Pressure-Controlled Gastrointestinal Delivery System:**

This system can be fabricated by enclosing a collapsible drug compartment inside a rigid shape-retaining housing. The space between the drug compartment and the external housing contains a laminate of swellable, hydrophilic cross-linked polymer e.g. polyhydroxy alkyl methacrylate, which absorbs G.I. fluid. Thus the laminate swells up, generates hydrodynamic pressure in the system and forces the drug compartment to reduce in volume causing the drug to move out through the delivery orifice.

- **Membrane Permeation-Controlled Gastrointestinal Delivery System:**

These polymer membrane permeation-controlled drug delivery systems are known to use a prefabricated micro porous or nonporous membrane to meter the release of therapeutic agents. This type of system can be categorized in two types.

i) Microporous Membrane Permeation-Controlled Gastrointestinal Delivery Device.
ii) Gastric Fluid-Resistant Intestine Targeted Controlled Release Gastrointestinal Delivery Device.

❖ Gel Diffusion-Controlled Gastrointestinal Delivery System:

This type of system is fabricated by dispersing the drug in layers of water-soluble polymer, sandwiching the drug-loaded polymer between layers of a cross-linked water insoluble polymer. These polymer layers are further compressed to form a multilaminate device, which is then further coated with a polymer to convert it into a gastrointestinal delivery device.

❖ pH- Controlled Gastrointestinal Delivery Systems:

This type of gastrointestinal delivery system is designed for the controlled release of acidic (or basic) drugs in the GIT at a rate of GIT p^H. It is prepared by blending the drug with one or more buffering agents and then granulated with appropriate pharmaceutical excipients to form small granules. These granules are further coated with GIT fluid permeable film-forming polymer e.g., cellulose derivatives.

❖ Ion Exchange-Controlled Gastrointestinal Delivery System:

These systems are fabricated by first absorbing an ionized drug onto the ion-exchange resin granules. After filtration the drug-resin complex granules were coated with a water permeable polymer and then spray dried to yield the polymer-coated drug resin preparation.

❖ Altered Density Formulations:

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site till its entire drug content is released, it would have limited utility. Altered density formulations are used to prolong the residence time of drug delivery system in the GIT. These are mainly of two types.

i. High-density approach -------- where the density of the formulation is increased to at least 1.4 times that of normal stomach content.

ii. Low-density approach ---------- where the formulation density is lower than that of normal stomach content.

- **Complexation:**

The preparation of complexes or salt of active drugs that are slightly soluble in the GI fluids gives sustained action, for e.g. therapeutic active amine drugs forms insoluble complexes with tannic acid.

1.3.12 Newer approaches in obtaining Controlled Release Drug Delivery System:

Several new approaches have been introduced to overcome the problems associated with oral drug administration.

1. Development of a viable drug delivery system, which is capable of administering a therapeutic agent at a programmed rate for duration, required for an optimal efficacy.
2. To develop preventive measures for drugs which undergo extensive hepatic "first-pass elimination". Some measures taken in this regard.
    a) **Physical approaches.**
    b) **Chemical approaches.**
    c) **Buccal & Sublingual drug administration.**
    d) ***Transmucosal* sustained release Traches.**
    e) **Oral sustained release Microcapsules.**
    f) **Rectal drug administration.**
    g) **Transdermal drug delivery system.**

3. Prolongation of gastrointestinal residence time so that the drug can reside at the absorption window for sufficiently long period of time to deliver the entire drug-loading close.[50] The steps taken to extend G.I. transit time are:
    a) **Intra-gastric floating drug delivery device.**
    b) **Gastro-inflatable drug delivery system.**
    c) **Intra-gastric osmotic-controlled drug delivery systems.**
    d) **Intra-lumen controlled release drug delivery device.**
    e) **Bio-adhesive oral drug delivery device.**

1.3.13 Pharmacokinetic Consideration for Controlled Release:

A basic pharmacokinetic understanding of disposition of a given drug in the body is essential for development of controlled release systems not just intended for delayed or prolonged release of drug but are to be formulated to achieve the desired target concentration in the blood/plasma or at pre-selective site or organ[18, 25]. Drug disposition is a complex process with a cascade of sequentially and simultaneously occurring events described by LADMER (Liberation, Absorption, Distribution, Metabolism, and Elimination & Response) System.[29]

In case of controlled release formulation the drug release is the rate-limiting step for the absorption process. Controlled release systems are in-built multiple dose systems designed to achieve a steady state concentration Css. The magnitude of Css depends on the dose rate $\mathbf{R_o}$ (amount of drug release per unit time) and the total clearance (elimination of drug from the total volume of distribution per unit time) of the drug. For the calculation of desired release rate (DR) and desired dose (DD), controlled release products are usually compared with constant rate IV infusions. An infusion provides specific amounts of drug in relatively short dosing intervals "τ". If an infusion pump delivers drug at constant rate τ becomes infinitely small and the delivery rate $\mathbf{R_o}$ is described as $\mathbf{R_o = D / \tau}$

The desired rate (DR) for controlled release is analogous to R_o as such provides a constant desired target steady state concentration Css. In case when drug's elimination follows a first order process and the drug release from the system follows zero-order process, the rate of drug release ($\mathbf{R_o}$) must be equal to the elimination rate of drug ($\mathbf{R_e}$)

$$\mathbf{R_o = R_e} \qquad \textbf{(1.4)}$$

The rate of drug elimination ($\mathbf{R_e}$) is the product of maintenance dose (**MD**) and the elimination rate constant.

$$\mathbf{R_e = MD \times K_e} \qquad \textbf{(1.5)}$$

Where $\mathbf{K_e = 0.693 / t_{1/2}}$ and $\mathbf{t_{1/2}}$ = biological half-life of the drug.

$$\text{Therefore, } \mathbf{R_e = MD \times 0.693 / t_{1/2}} \qquad \textbf{(1.6)}$$

Because amount of drug is equal to the product of concentration and Volume of Distribution (V_d).

Therefore R_e can be expressed as

$$R_e = C_{ss} \times Vd \times 0.693 / t_{1/2} \qquad (1.7)$$

Substituting this in equation (1.4)

$$R_o = C_{ss} \times V_d \times 0.693 / t_{1/2} \qquad (1.8)$$

However, whole of the incorporated drug is not released by the system and additionally presystemic drug loss may take place, therefore delivery rate (R_o) must be corrected for the absolute bioavailability (F)

$$R_o = F \times MD / \tau \qquad (1.9)$$

1.3.14 Maintenance Dose Calculation:

Maintenance dose (MD) or the dose size for the controlled release systems can be calculated from equation (1.9)[18,25]

$$R_o = F \times MD / \tau$$

or, $$MD = R_o \times \tau / F$$

$$= C_{ss} \times V_d \times 0.693 \times \tau / F \times t_{1/2} \qquad (2.0)$$

Many controlled release systems contain two or more dose compounds a loading dose which is an immediately available dose D_i that results in a blood level with a fast peak and one or more controlled release doses D_{cr}, which gives a flat plateau. The total dose D_T is

$$D_T = D_i + D_{cr} \qquad (2.1)$$

D_i = loading dose = amount of drug used in conventional dosage form.

D_{cr} = Maintenance dose = $(Css_{ss} \times V_d \times 0.693 \times \tau) / F \times t_{1/2}$

1.4 Micro encapsulation Technology

Micro encapsulation is a highly proliferating field, which has made enormous progress in the recent years.[30] By definition it means applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Usually microcapsules have a particle size range between 1 and 2000 μm.

- **Rationality for Micro Encapsulation:**

Drugs are micro encapsulated due to various pharmacological reasons; some important applications of micro encapsulations are listed below in Table 1.1.

Table 1.1 Benefits of Microencapsulation with few examples

Benefits	Examples Of Drugs
Sustained Release Properties	Nitrofurantoin, Aspirin, Glyceryl trinitrate.
Environmental Protection	Citric Acid, Ferrous Citrate, Vit-C, Levodopa.
Gastric Irritation Reduction	Indomethacin, Paracetamol, Phenyl butazone.
Liquid-Solid Conversion	Castor oil, Clofibrate, Cod-liver oil.
Odour-Masking	Castor oil, Cod-liver oil.
Separation Of Incompatibilities	Beclamide, Chloramphenicol, Propoxyphen.
Taste-Masking	Aminophylline, Ampicillin etc.

There are several other reasons for micro encapsulation. A liquid such as eprazinone [26] may be converted to a pseudo solid by micro encapsulation to aid handling or storage. Toxic chemicals such as insecticides may be encapsulated to reduce hazard to operators.[28]

Ampicillin trihydrate has been micro encapsulated to reduce the possibility of sensitization of factory personnel.[27] The hygroscopic properties of many core materials such as sodium chloride may be reduced by micro encapsulation.[30]

Considerable interest has been shown in the immobilization of various enzymes in acrylic polymers and co-polymers. Nilson et al [34] used a suspension polymerization technique to immobilize trypsin. Later on, Johansson and Mosbach [23]successully immobilized other enzymes such as ribonuclease, β-glucosides, urease etc. Using entrapment or covalent bonding to acrylic polymers and co-polymers [23] in bead form.

- **Pharmacological and Physico-Chemical Consideration:**

Micro encapsulated products consist of numerous micro capsules having variable release rates because of the composition or the amount of the coating applied. The main function of micro encapsulation is to establish the drug level within therapeutic range which is then maintained over an extended period by the progressive drug release from various micro capsules fractions present. Due to combination of micro capsules of different release rates in one dosage-form, a pseudo-zero order or steady state release of the drug can be achieved for a prolonged period. This results in better disease management with the use of less amount of drug and also minimizes side effects. The aim of these products is to make the rate-limiting step the drug release from the dosage regimen rather than its rate of absorption.

The multiparticulate sustained release systems are usually preferred over single unit dosage forms because of less chance of dose dumping, less chance of inter subject variation in plasma concentration and more predictable transmit time in G.I.T.

- **Preparation Methodology for Micro Capsules:**

Several procedures for Micro encapsulation have been developed with the goal of achieving controlled release effects. Several coating methods for non-pharmaceuticals are also used for the encapsulation of drugs.

1.4.1 Micro encapsulation methods can be classified as:

1. **PHASE SEPARATION.**
2. **INTERFACIAL POLYMERIZATION.**
3. **PAN COATING.**
4. **AIR SUSPENSION COATING.**
5. **SPRAY DRYING & SPRAY CONGEALING.**
6. **SPRAY EMBEDDING.**
7. **SPRAY POLYCONDENSATION.**
8. **POLYMERIZATION procedure for non-biodegradable micro and nanocapsules and particles.**
    i. **BULK-POLYMERISATION.**
    ii. **SUSPENSION-POLYMERISATION.**
    iii. **EMULSION POLYMERISATION.**
    iv. **MICELLE POLYMERISATION.**
9. **POLYMERISATION PROCEDURES for biodegradable micro and nanocapsules and particles.**
10. **ION EXCHANGE RESINS.**
11. **CONGEALABLE DISPERSED PHASE ENCAPSULATION.**
12. **MULTI-ORIFICE CENTRIFUGAL METHOD.**
13. **ELECTROSTATIC METHODS.**
14. **DIP COATING.**
15. **LIPOSOMES.**

16. SPHERONIZATION.

17. MOLECULAR SCALE ENTRAPMENT.

18. SOLVENT EVAPORATION TECHNIQUE.

1.4.2 Micropelletization Technology:

Micro pellets (microspheres) differ from the microcapsules because they consist of a solid matrix throughout which the drug is distributed.

Akbuga[32] prepared microspheres of furosemide a potent diuretic using various acrylic co-polymers (Eudragit, Rohm Pharma) as the microspheres matrix. Microspheres formed had a diameter of 250-280μm and contained 75% to 80% by weight of furosemide. The results of dissolution experiments showed that the drug release followed the Higuchi Matrix [31,33] model.

Gupta[40] and associates investigated the effects of Albumin microspheres on the release rate of entrapped Adriamycin, a broad-spectrum antineoplastic agent.

Spenlehauer [39] *et al* developed poly-(D, L-lactide) microspheres by solvent evaporation process. Cisplatin was dispersed in methylene chloride before polymer addition. The organic phase was emulsified and the pH adjusted to 2 with HCL. Evaporation of organic solvent methylene chloride was effected by mechanical stirring of the dispersion.

Leuceta [43] designed ophthalmic drug delivery of pilocarpine using albumin or gelatin microspheres. Microspheres prolonged the residence time of the drug in the age and showed improved bioavailability.

Bodmeier and McGinity [41] evaluated the incorporation of various ionized and non-ionised drugs in poly-(D, L-lactide) or PLA microspheres and studied their glass transition temperatures as well as various methods of solvent selection.

Margel Hirsh [42] developed polymercaptal microspheres, which served as antidote for mercury poisoning.[44,45]

Morimoto, Natsume *et.al* formulated biodegradable albumin microspheres of Mitomycin-C for chemoembolization against liver tumors in rats.

1.4.3 Advantages of Micropelletization over Micro Encapsulation:

1. Unlike Micropelletization, Micro encapsulation process is highly sensitive and largely depended on the process variables and formulation factors.
2. Incomplete encapsulation of the core during formulation sometimes hampers the controlled release characteristics whereas in micropelletization the drug is uniformly dispersed in the solid matrix enabling the drug release at the desired rate.
3. Micro encapsulation process is a more time-consuming process than micropelletization.

1.4.4 Emulsion-Solvent Evaporation Technique for Micropelletization:

The emulsion-solvent evaporation technique, also termed as emulsion hardening has been widely used to prepare microspheres for controlled drug release.[53].

This technique involves dispersion of drug in an organic polymer solution, followed by the emulsification of the polymer solution in the water. After continuous stirring, the solvent evaporates and drug containing rigid microspheres are formed. The stirring is performed by the help of a homogenizer or a submicron dispenser.[52]

- **Disadvantages of the Conventional Methods in Producing Controlled Release Drug Delivery Systems:**

The conventional methods of controlled release drug delivery systems utilized organic solvents and synthetic polymers and possessed several disadvantages.

a) **Organic solvents were highly inflammable.**
b) **Some Organic solvents also produced toxicity e.g., chloroform produces high incidence of hepatoxicity.**
c) **Cost of Organic solvents has increased along the time.**
d) **Organic Solvents and Synthetic polymers produced environmental pollution and health hazards to operators. Regulatory organisations like OSHA & EPA have banned the use of chlorinated hydrocarbon due to its pollutive effect.**

e) **When controlled release system fails to disintegrate *in vivo*, it must be removed surgically. Therefore, synthetic polymers having biodegradable features are preferred.**

These hazards are minimized by the improvement in the equipment and technology or by using aqueous solution or lattices.

1.5 Ionotropic Gelation Technique for Micropelletization:

Ionotropic Gelation Technique was used for the preparation of microspheres by dispersing the needed quantity of drug in aqueous solution of sodium alginate with or without other aqueous polymeric dispersion. This suspension was extruded through disposable needles onto a gently agitated calcium chloride solution. The gelled micropellets were instantly formed, separated and washed with distilled water and dried at 60°C for 5 hrs in hot air oven.

Ionotropic Gelation Technique yielded microspheres of various drugs like Propanolol, Griseofulvin Tolbutamide, Sulphadiazine, Theophylline etc. Even erythrocytes were encapsulated by this novel method. Process parameters like Nozzle diameter [37,49], pumping rate[46], falling height[46], concentration of calcium chloride[47], curing time[46] etc. has been studied by researchers to improve the characteristics of the microspheres formed.

Circular Dichroism and Nuclear Magnetic Resonance studies have elucidated the reason why alginates with different M/G ratio have different gelling characteristics. It is due to the fact they contain different properties of block structures i.e. Mannuronic acid blocks (M), Glucoronic acid blocks (G) and alternating blocks (MG). G blocks aggregate readily and excess calcium causes syneresis whereas M locks require high calcium levels to aggregate.

X-ray[48]diffraction studies show a buckled two-fold conformation for poly-L-guluronic acid, which appears to persist in all of the salt forms, studied. In this favored two-fold conformation, poly-guluronate chains display a regular array of electronegative cavities whose size and geometry appear to be compatible with chelation of calcium.

The interaction between calcium ion and poly-guluronate chain is mainly due to favorable orientation of carboxylate groups in this chain. The specific interchain linkage of G chain by calcium ion results in the formation of gel-network structure in the alginate.

1.5.1 Advantages of Ionotropic Gelation Technique:

1. **The technique is based on aqueous system. It utilizes water as the only solvent, which is the cheapest among all solvents, non-toxic, and non-inflammable, readily available and does not cause health hazards to operators.**
2. **This process does not require sophisticated instrumentation.**
3. **This process is least affected by process variables.**
4. **This is a fast and cheaper process of micropelletization.**
5. **The process is less sensitive to formulation and process variables.**

The author adopted ionotropic gelation technique as one of the methods for the preparation of calcium alginate micro pellets containing Frusemide, a potent diuretic, as the model drug.

1.6 Objective and Aim of the Research Work

The main objective of this research work was to develop microparticulate drug delivery system (MDDS) with natural polymers using a novel and effective method quite different from the conventional one. To achieve this, ionotropic gelation method was selected in the project work. Several literatures suggest that micropellets are generally prepared by emulsion – solvent evaporation method involving large volume of organic solvents. Further research was done to modify the method but failed to eliminate the use of organic solvents completely. The aim of this research work was to produce sustained release micropellets in a completely non-toxic, aqueous environment devoid of the use of any organic solvents. The method would be highly beneficial ecologically and economically to the pharmaceutical industry. Further, a potent loop diuretic, Frusemide was selected as the model drug for the designing of the microparticulate dosage form. No sustained release preparations of the drug are available in the market. The drug, though popularly prescribed for peripheral edema, ascites in congestive heart failure and also in the management of hypertension, is not free from adverse reactions. Excessive micturation within a short span of time leads to loss of electrolytes, muscular cramps, hypokalemia etc. leading to incompliance with the patient. Sustaining and extending the release of the drug would bring down these adverse reactions significantly alongwith reducing the dosage frequency and thereby delivering optimum therapeutic effect with patient compliance.

1.7 REFERENCES

1. *Remington's Pharmaceutical Science*, 17th Ed, A.R.Gennaro eds., Mack Pub.Co., Pennsylvania, 1985, 1645-50.
2. B.Ballard, *Sustained and Controlled Released Drug Delivery System*, Marcel Dekker, **3,** 1978, 76-106.
3. M.Robinson, in *The Theory & Practice of Industrial Pharmacy*, L.Lachman, H.A.Liberman and J.L.Kanig, Eds. Lea & Febiger, Philadelphia, 1970, 408-437.
4. P.G.Welling, *Drug Dev. Ind. Pharm.*, 1983, 1185.
5. T.salsa, F.Veiga and M.E.Pina, *Drug Dev. Ind. Pharm.*, **25(9)**, 1997, 929-938.
6. J.M.Vergnaud, *Controlled Drug Released of Oral Dosage Forms*, Ellis Horwood, England, 1993.
7. Zaffaroni, *A new Approach to Drug Administration*, 31st International Congress of Pharmaceutical Science, Washington D.C., 1971, 19.
8. J.H.Fincher, *J.Pharm. Science*, **57**, 1968, 1825.
9. J.Fujita, J.Iwasa and C.Hawsch, *J.Amer. Chem. Soc.*, **85,** 1964, 5175.
10. R.Langer, *Chem.Eng. Common*, **6**, 1980, 1.
11. R.Langer and J.Folkman, *Nature,* **262**, 1976, 797.
12. B. Beerman, K.Halstrom and A.Rosen, *Clin. Pharmacol.Ter.*, **13**,1972, 212.
13. H.Beechgaard and O.Antonsin, *F.I.P. Abstracts*, 37th International Congress of Pharmaceutical Science, The Hague, 1977, 69.
14. B.Beechgaard and K. Ladefogedl, *J.Pharm. Pharmacol.*, **30**,1978, 690.
15. T.M.S.Chang in *Artificial Cells*, C.C.Thomas Eds., Springfield, Illinois, 1972.
16. J.E.Vendegare, *Microcapsulation Process & Application*, Plenum Press, New York, 1974.
17. Dr.R.Paul, in *Controlled Release of Polymeric Formulations*, Dr.Paul and F.W.Harris, Eds., American Chemical Society, Washington, 1976, 1.
18. S.P.Vyas and R.K.Khar, *Controlled Drug Delivery, Concept & Advances*, 1st Edition, Vallabh Prakashan, 2002, 6-9.
19. E.Theis, *Polymer Plast . Technol Eng.*, 5, 1975, 1.
20. J.M.Goodson, A.Hoffajee and S.S.Soeransky, *J.Clin. Peridontology*, **6**, 1979, 83.
21. R.W.Baker and H.K.Lonsdale, in *Advances in Experimental Biology & Medicine*, A.C.Tanquary and R.E.Lacey, Eds., Plenum Press, New York, **Vol. 47**, 1974, 15.
22. J.M.Hinton, J.E.Lennard Jones and A.C.Young, *Gut*, **10**, 1969, 842.

23. *Micro encapsulation of Pharmaceuticals & Related Materials*, The National Cash Registrar Co., Dayton, Ohio, 1966.
24. D.M.Brahmankar and Sunil Jaiswal, *Biopharmaceutics and Pharmacokinetics*, Vallabh Prakashan, 1st edition, 2001.
25. M.Gibaldi and D.Perrier, *Pharmacokinetics*, Mercel Dekker Inc., 1975, 27-37.
26. Si Nang, P.F.Carlier, P.Delort, J.Gaggola and D.Lafont, *J.Pharm.Sciences*, **62**, 1973, 452.
27. H.Seager, *U.S. Patent 4*, **16**, 1977, 254.
28. E.S.Raum and R.D.Jackson, *J.Econ. Entomol*, 1966, 620.
29. N.A.Ritschel, *Handbook of Basic Pharmacokinetics*, 3rd Edition, Drug Intelligence Publications. Hamilton, **Vol.II** 1986, 18.
30. J.A.Bakon, *Food Technology*, **27**, 1973, 34.
31. T.Higuchi, *J.Pharm. Sciences*, **52**, 1963, 1145.
32. J.Akbuga, *Int J. Pharm.*, **53**, 1989, 99.
33. R.W.Baker and H.K.Lonsdole, in *Controlled Release of Biologically Active Agent*, A.C.Tanquary and R.E.Lacey, Eds., Plenum Press, New York, 1974, 15-71.
34. H.Nilsson, R.Mosbach and K.Mosbach, *Biochem. Biophy. Acta.*, **268**, 1972, 253.
35. L.A.Luggi, M.A.Zoglio and H.V.Moulding, *J.Pharm. Sciences*, **59**, 1970, 338.
36. Y.Raghunathan, L.Amsl, O.Hinsvark and W.Bryant, *J.Pharm. Sciences*, **70**, 1981, 379.
37. F. Lim, A. M. Sum, *Science*, **210**, 1980, 908-910.
38. J.M.Gallo, C.T.Hung and D.C.Perrier, *Int. J.Pharm.Sciences*, **22**, 1984, 63.
39. G.Splenlehamer, M.Veillard and J.P.Benoit, *J.Pharm. Sciences*, **75**, 1989, 750.
40. P.K.Gupta, F.C.Lam and C.T.Hung, *Int. J.Pharm. Sciences*, **51**, 1989, 253.
41. R. Bodmeier and J.W.McGrinity, *Pharm. Res.*, **4**, 1987, 495.
42. S.Margel and J.Hirsh, *J.Pharm. Sciences*, **71**, 1982, 130.
43. S.E.Leucuta, *Int. J.Pharm. Sciences*, **54**, 1989, 71.
44. H.Natsume, K.Sugibayashi, K.Juni, Y,Morimoto, T.Shibata and S.Fugimoto, *Int. J. Pharm. Sciences*, **58**,1990, 79.
45. H.Natsume, K.Sugibayashi, Y.Moromoto and S.Fugimoto, *Int. J. Pharm. Sciences*, **54**, 1989, 27.
46. R. Bodmeier and O. Paeratakul, *J.Pharm.Sciences*, **78(11)**, (1989), 964-967.
47. R.Bodmeier and J.Wanf, *J.Pharm. Sciences*, **78**, 1993, 191-194.
48. D.Thom, G.T.Grant, E.R.Morris and D.A.Rees, *Carbohyd. Res.*, 1982, 29-41.

49. T. Yotsuyanagi, T. Ohkubo, T. Ohhashi and K. Ikeda, *Chem. Pharm. Bull.*, **35 (4)**, 1987, 1555 – 1563.

50. Yie W. Chien, *Novel Drug Delivery System,* 2nd Edition.

51. J. R.Robinson and Vincent H.L.Lee, *Controlled Drug Delivery,* 2nd Edition.

52. W.C.Gunsel and J.L.Kanig in *Pharmaceuticals Dosage Form: Tablets*, L.Lachman, H.A.Liberman and Schwarty, Eds., **Vol. 3**, 2nd Edition, 1996, 321-358.

53. R.K. Chang, J.C. Price and C.W.Whitworth, *Drug Dev. Ind. Pharm.*, 1987, 1119-1135.