1. INTRODUCTION

1.1 Sustained release drug therapy

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal.

Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of injectable dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities.¹

Controlled release systems also denotes systems which can provide some control whether this be of a temporal or spatial nature or both, of drug release in the body. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or
sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time.\(^2\)

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

**Advantages\(^1\)**

1. The frequency of drug administration is reduced

2. Patient compliance can be improved

3. Drug administration can be made more convenient

4. The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained
5. Better control of drug absorption can be attained, since the high blood level peak that may be observed after administration in an extended action form.

6. The characteristic blood level variations due to multiple dosing of conventional dosage form can be reduced.

7. The total amount of drug administration can be reduced, thus:
   a) Maximizing availability with minimum dose
   b) Minimize or eliminate local side effects
   c) Minimize or eliminate systemic side effects
   d) Minimize drug accumulation with chronic dosing

8. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

9. Improve efficacy in treatment:
   a) Cure or control condition more promptly
   b) Improve/ control i.e. reduce fluctuation in drug level.
   c) Improve bioavailability of some drugs
   d) Make use of special effect e.g. sustained release aspirin for morning relief of arthritis by dosing before bed time.

10. Economy
**Disadvantages**

1. Administration of sustained release medication does not permit prompt termination of therapy
2. Flexibility in adjustment in dosage regimen is limited
3. Controlled release forms are designed for normal population i.e., on the basis of average drug biological half lives.
4. Economy factors may also be assessed, since most costly process and equipment are involved in manufacturing so many controlled release dosage forms.

**Limitations**

1. If the active compound has a long half-life (over six hours), it is sustained on its own.
2. If the pharmacological activity of the active compound is not related to its blood levels, slow releasing then has no purpose.
3. If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
4. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.
5. Not effectively absorbed in lower small intestine
6. Large doses are required (more than 1 gm)
7. Drug with low therapeutic index
8. Precise dose to individuals is required

1.2 Design and Fabrication of oral systems

The majority of oral controlled release systems depend on dissolution, diffusion, or a combination of both mechanisms, to generate slow release of drugs into gastrointestinal milieu. The following techniques are employed in the design and fabrication of oral sustained release dosage forms.

1. Dissolution controlled release
   a) Encapsulation Dissolution control
   b) Matrix Dissolution control

2. Diffusion controlled release
   a) Reservoir devices
   b) Matrix devices

3. Diffusion and Dissolution controlled release systems

4. Ion Exchange resins

5. pH-Independent formulations

6. Osmotically controlled release

7. Altered Density Formulations
1.3 Microencapsulation

Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. It provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials.  

Size for microcapsules range from 5-500-µm and may be isolated as free flowing powders called as aggregates, or suspended directly in a vehicle for administration.

Microcapsules assume various shapes such as globular, spherical, bean like, rice grain like, flocculated masses. The thickness exceeds 10 µm with the walls having single layered or multilayered structures. Further microcapsules may contain 1 to thousands of core substances.

The capsule wall should be inert to the substance it contains, possess enough strength to allow for normal handling without rupture. The contents of capsule are contained within the wall until related by some means that serve to break, crush, melt, dissolve, rupture or remove the capsule shell or until the internal phase is caused to diffuse out through the capsule wall.
1.3.1 Fundamental considerations

For the microencapsulation to be successful, due attention must be given to the physical and chemical characteristics of the core material, nature and properties of the wall material (prior to and after encapsulation) and methods available for the encapsulation. The intended physical characters of the encapsulated product and the intended use of the final product must also be considered.

a) Characteristics of the core material/drug

The specific material to be coated is defined as the core material, can be either liquid or solid in nature. The composition of the core material can be varied as the liquid core can include dispersed and/or dissolved material. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators.

b) Characteristics of the wall material

The coating material should be capable of forming a film that is cohesive with the core material, be chemically compatible and non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability. The total thickness of the coatings achieved with microencapsulation techniques is microscopic in size.
c) **Physical character of the final product**

Microcapsule should have desirable physical properties like ability to flow, to be compacted or to be suspended and the capsule wall must be capable of resisting the pressure during compression etc.

d) **Intended route of administration of the drug**

Microcapsules intended for oral use may dissolve in the environment of the stomach or may be enteric coated. They may be designed to burst while being chewed or to release their ingredients on contact with saliva.

It can be seen that when the decision is made to microencapsulate particular material, it is imperative to have the necessary knowledge of the core material, the available coat material, the nature of the final wall, and the available methods for microencapsulation.
1.3.2 Coating materials

A number of different substances both biodegradable and non biodegradable have been investigated for the preparation of microcapsules. These materials include the polymers of natural and synthetic origin and also modified natural substances. Some of the polymers used in the preparation of microcapsules are classified and listed below.

**Synthetic polymers**

- **Non biodegradable**
  
  PMMA, Acrolein, Glycidyl methacrylate, Epoxy polymers

- **Biodegradable**
  
  Lactides and glycolides and their copolymers, Polyalkyl cyanoacrylates, Polyanhydrides, Carbopol

**Natural Materials**

Proteins such as albumin, gelatin, collagen
Carbohydrates like starch, agarose
Carragenin, Chitosan
Chemically modified carbohydrates such as DEAE cellulose, Polyacryl dextran, Polyacryl starch

**Ideal properties of coating materials**

The materials utilized for the preparation of micro particulates should ideally fulfill the following prerequisites:

- Longer duration of action
✓ Control of content release
✓ Increase in therapeutic efficiency
✓ Protection of drug
✓ Reduction of toxicity
✓ Biocompatibility
✓ Sterilizability
✓ Relative stability
✓ Water solubility or dispersibility
✓ Bioresorbibility
✓ Targetability
✓ Polyvalent

1.3.3 Methods of Microencapsulation\textsuperscript{6,7}

Preparation of microcapsules as prolonged action dosage form can be achieved by various techniques under following headings

1 Coacervation phase separation

A) By temperature change
B) By incompatibility polymer addition
C) By non solvent addition
D) By salt addition
E) By polymer-polymer interaction
F) By solvent evaporation

2. Physical Methods

2. Multi orifice centrifugal process
3. Pan coating

4. Air suspension coating

5. Spray drying and spray congealing

6. Melt dispersion technique

3. Chemical Methods

1. Interfacial polymerization
2. In-situ polymerization
3. Matrix polymerization

1.3.4 Applications of microencapsulation\textsuperscript{8, 9}

1. To mask the taste of bitter drugs
2. To provide protection to the core material against atmospheric effects
3. In the design of controlled and sustained release dosage form
4. To reduce gastric and other GI tract irritation
5. To decrease the volatility
6. To reduce toxic hazards
7. To reduce hygroscopicity
8. To increase flow properties
9. For the separation of incompatible substance
10. For liquid–solid conversions
11. Biomedical
12. As artificial cell: to remove or convert unwanted metabolites or toxins from the body; for the treatment of chronic renal failure and congenital enzyme deficiency.

13. Liposome: entrapment of enzyme within concentric layers of lipids used for enzyme and drug targeting.


1.3.5 Characterization of Microcapsules

The parameters that are generally evaluated for characterization of microcapsules are:

1. Particle size and shape

The most widely used procedure is conventional light microscopy and scanning electron microscopy (SEM). Both techniques can be used to determine the shape and other structure of microcapsule. SEM provides higher resolution in contrast to the light microscopy. It allows investigation of the microsphere surfaces and after particles are cross sectioned, it can also be used for the investigation of double walled systems. Confocal laser scanning microscopy is applied as a nondestructive visualization technique, which allows characterization of structures not only on surface but also inside particle.

2 Size analysis of microcapsules

Different sizes in a batch are separated by sieving using a range of standard sieves 12/16, 16/20, 20/30, 30/40 and amounts retained
on different sieves were weighed. Studies were carried out in triplicate. The average size of the microcapsules were calculated by using equation

\[ \text{Dave} = \frac{\sum X_i f_i}{f_i} \]  

Where, \( X_i \) is the mean size of range and \( f_i \) is the percent material retained on the smaller sieve.

3. Angle of repose

Angle of repose was employed to assess the flowability. Angle of repose, \( \theta \), was determined by fixed funnel method and calculated as

\[ \theta = \tan^{-1}(h/r) \]

4. Fourier transform- Infrared spectroscopy

FTIR is used to determine the degradation of polymeric matrix of the carrier system, and also interaction between drug and polymer system if present.

5. Encapsulation efficiency

The encapsulation efficiency of microcapsules or the percent drug entrapment can be determined by allowing washed microcapsules to lyse. The lysate is subjected to the determination of active constituents as per monograph. The percent encapsulation efficiency is calculated using following equation,
Amount of drug in the microcapsules

\[
\text{% Drug loading} = \frac{\text{Amount of drug in the microcapsules}}{\text{Mass of microcapsules}} \times 100
\]

6. **In vitro release studies**

Release studies for microcapsules can be carried out in different pH conditions like pH 1.2 and pH 7.4 using USP rotating basket or paddle apparatus. The samples are taken at specific time intervals and are replaced by same amount of fresh medium. The samples withdrawn are analyzed as per the monograph requirement and release profile is determined using the plot of amount released as a function of time.

**Kinetics of drug release**

The release of active constituent is an important consideration in case of microcapsules. Many theoretically possible mechanisms may be considered for the release of the drug from the microcapsules.

1. Liberation due to polymer erosion or degradation
2. Self diffusion through the pore
3. Release from the surface of the polymer
4. Pulsed delivery initiated by the application of an oscillating or sonic field

In most of the cases, a combination of more than one mechanism for drug release may operate, so the distinction amongst
the mechanisms is not always trivial. The release profile from the microcapsules depends on the nature of the polymer used in the preparation as well as on the nature of the active drug.

Attempts to model drug release from microcapsule have been reported and in the treatment of their data, it was assumed that drug release was confined to any of the order such as zero order or first order processes. One indication of mechanism can be obtained using a plot of log of cumulative percentage of drug remaining in the matrix against time.

First order release\(^{12}\) would be linear as predicted by following equation

\[
\log C = \log C_0 - \frac{Kt}{2.303}
\]

Where,

\(C\) = Amount of drug left in the matrix

\(C_0\) = Initial amount of drug in the matrix

\(K\) = First order rate constant (time\(^{-1}\))

\(t\) = time in hours

The in vitro drug release data obtained from selected batch of microcapsules was treated according to equation (1) by plotting log of cumulative % of drug remaining against time.
Next, an attempt was made to see whether the drug release is by diffusion or erosion. For system, which will release the drug by diffusion, was proposed by Higuchi.

\[ Q = \frac{D\varepsilon}{T(2A-\varepsilon Cs)Cs t^{1/2}} \] ……………………(2)

Where,

- \( Q \) = Weight in grams of drug released per unit surface area of matrix (g/cm²)
- \( D \) = Diffusion coefficient of drug in the release medium (cm²/min)
- \( \varepsilon \) = Porosity of microcapsules
- \( Cs \) = Solubility of drug in the microcapsule (gm/ml)
- \( A \) = Total amount of drug in microcapsules.
- \( T \) = Tortuosity of capillary system
- \( t \) = Time (min)

The assumptions made in the deriving equation (2) is as follows:

- A pseudo steady state is maintained during the release
- \( A >> Cs \) i.e., excess solute present
- \( C=0 \) solution at all times (perfect sink)
- The diffusion coefficient remains constant
- No interaction between the drug and the matrix occurs

For the purpose of data treatment, equation is usually reduced to,
Q=Kt^{1/2} \ldots \ldots \ldots (3)

Therefore a plot of amount of drug released vs the square root of time should be linear if the drug release from the matrix is diffusion controlled.

Precisely, to know the mechanism of drug release, whether it is by diffusion or with combination of diffusion and erosion control, the data has also been plotted according to equation suggested by Korsmeyer, they used a simple empirical equation to describe the general solute release behavior from control release polymer matrices.

\[ \frac{M_t}{M_\infty} = K_p t^n \ldots \ldots (4) \]

Where

\[ \frac{M_t}{M_\infty} \] is the fraction of drug released

\( t \) = release time at time

\( K_p \) is Kinetic rate constant and

\( n \) is the diffusional exponent for drug release

The value of ‘n’ gives an indication of the release mechanism. For non-Fickian release, the value of ‘n’ falls between 0.5 and 1.0, while in the case of Fickian diffusion, \( n \leq 0.5 \), for zero order release (case II transport), \( n=1 \) and for super case II transport, \( n>1 \). The in vitro drug release data obtained from microcapsules was treated according to equation (4) by plotting log cumulative % of drug release vs log time.
In the present study, the release obtained was plotted according to the above equation. These graphs are shown in results section.