CHAPTER 1

INTRODUCTION
1.1 INTRODUCTION TO MODIFIED RELEASE

1.1.1: INTRODUCTION:

The goal of any drug delivery system is to provide a therapeutic amount of drug at proper site(s) in the body to promptly achieve and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery namely, 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 the target tissue. These two factors should be kept in mind while designing a functional sustained release preparation. A lot of research has been directed at oral dosage forms that satisfy temporal aspect of drug delivery, since many drugs require constant 'drug blood levels' within therapeutic range for the required duration of action to be effective [1].

Conventional Drug Therapy:

Conventional dosage forms of a drug such as solutions, suspensions, capsules, suppositories, etc. release the active ingredients into the absorption pool immediately. The drug level time profile of such a system is as shown in Fig. 1.1.1

Fig. 1.1.1: Typical drug blood level versus time profiles for intravenous injections and an extravascular route of administration
As can be seen in the graph, administration of the conventional dosage form by intravenous injection or by extravascular route does not maintain the drug level in blood for an extended period of time. Here, the release of the drug is much faster than the absorption ($K_r \gg K_a$). The short duration of action is due to the inability of conventional dosage form to control temporal delivery. An attempt may be made to maintain drug blood levels in the therapeutic range for longer periods by increasing the intravenous dose but, this could prove toxic [2].

**Multiple Dose Therapy:**

Another approach in maintaining drug blood levels in the therapeutic range for longer periods is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. In this case the level of drug in the blood and the time required to reach that level depend on the dose and dosing interval. This results in a peak-through pattern as shown in Fig. 1.1.2.

![Typical drug blood level time profile following oral multiple dose therapy](image-url)

The potential problems associated with multiple dose therapy are:

1) If the dosing interval is not appropriate large 'peaks' and 'valleys' in the drug blood level may result. e.g. drugs with short half lives require frequent dosings to maintain therapeutic levels.
2) Patient non compliance with the multiple dosing regimen can result in failure of the approach.

In many instances, the problems associated with conventional drug therapy can be overcome by multiple dosing. However, the above mentioned problems are significant enough to necessitate drug therapy with non-immediate release drug delivery systems.

1.1.2: TERMINOLOGY IN MODIFIED RELEASE DOSAGE FORMS: [3,4]

In recent years there has been an accelerating interest in the development of modified release dosage formulations. Such interest is based largely on the fact that modified release drug products have established and retained a place in the market based on their uniqueness and their clinical advantages in the practice of medicine.

In order to treat a disease effectively, the drug dose regimen should be scheduled in such a way that, the plasma level does not decrease below the minimum effective concentration. However, frequent administration is a burden to a patient. Thus, ways to maintain an effective plasma level for a long period of time are often desired to increase patient compliance.

The absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage forms. Some dosage forms are designed for rapid and complete release of their medicament in the body, whereas other products are designed to release the drugs slowly to give sustained drug action. Products formulated for latter purpose have been referred to as sustained release, prolonged action, controlled release, extended release, timed release, depot and repository dosage forms. There are questionable and conflicting controversies regarding the true validation of these terms.
The Compendia describes all such dosage forms under one category as modified release dosage forms [3]. In other words all such drug delivery systems can be called as non-immediate release delivery systems [4].

Non-immediate release delivery systems may be divided into three categories [3]:

1) Delayed release
   a) Repeat action formulation
   b) Timed release formulation

2) Sustained release
   a) Controlled release
   b) Prolonged release

3) Site-specific and receptor release
   a) Organ targeting
   b) Cellular targeting
   c) Subcellular targeting

(1) DELAYED RELEASE

These are systems that utilize repetitive, intermittent dosings of a drug from one or more immediate release units incorporated into a single dosage forms. These include repeat action tablets and timed release tablets.

a] Repeat Action Formulations

Repeat action oral dosage form initially releases drug equivalent to a regular dose and then another single dose of the drug is released after some period of time. Here, smaller the release time between two units, smaller will be the oscillations in drug blood levels. More than four unit doses cannot be incorporated in this system as it is practically difficult from the manufacturer's view point.
b) Timed Release Formulations

Timed release formulations are generally the enteric coated tablets where the drug is released at the desired time and place in the body.

A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range as shown in Fig. 1.1.3 but nevertheless is more effective for patient compliance than the conventional dosage forms.

Fig. 1.1.3 : Typical drug blood level versus time profiles for delayed release drug delivery by a repeat action dosage form

(2) SUSTAINED RELEASE FORMULATIONS

Ideally, a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose into the gastrointestinal tract. This fraction (loading dose) is an amount of drug which will produce the desired pharmacological response as promptly as is consistent with the intrinsic availability of the drug for absorption from absorption sites. The remaining fraction of the total dose (maintenance dose) is then released at a controlled rate. The rate of drug absorption from the maintenance dose into the body should be equal to the rate of the drug removal from the body by all processes over the time for which the desired intensity of pharmacological response is required.
a) Controlled Release Formulations

The term 'controlled release' has become associated with those systems from which therapeutic agents may be automatically delivered at a predefined rate over a long period of time. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics. The period over which the drug is released may vary from days to months in case of injectable dosage forms. However, in case of oral controlled release drug delivery systems this period is in hours and it critically depends on the residence time of the dosage form in the gastrointestinal tract.

b) Prolonged Release Formulations

If the drug delivery system simply extends the duration of action of the drug over conventional drug delivery system but does not maintain uniform drug blood levels, it is called as the prolonged release drug delivery system. This is illustrated in Fig. 1.1.4.

![Fig. 1.1.4: Drug blood level versus time profiles showing the relationship between controlled release (A), prolonged release (B) and conventional release (C) drug delivery](image)

Fig. 1.1.4 : Drug blood level versus time profiles showing the relationship between controlled release (A), prolonged release (B) and conventional release (C) drug delivery

(3) SITE SPECIFIC AND RECEPTOR RELEASE [5]

It refers to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue, while
for receptor release, the target is a particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

1.1.3: OBJECTIVE OF SUSTAINED DRUG DELIVERY:

The conventional dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>drug</th>
<th>Absorption Pool</th>
<th>Absorption Area</th>
<th>Target elimination</th>
</tr>
</thead>
</table>

The absorption pool represents a solution of the drug at the site of absorption. The terms Kr, Ka and Ke are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release from a conventional dosage form implies that Kr >> Ka. Alternatively speaking, the absorption of drug across a biological membrane is the rate limiting step. For non-immediate release dosage forms, Kr << Ka, i.e. the release of drug from the dosage form is the rate limiting step. This causes the scheme to reduce as follows.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>drug</th>
<th>Target Area</th>
<th>Elimination</th>
</tr>
</thead>
</table>

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release delivery system must be directed primarily at altering the release rate.

The main objective in designing a sustained release system is to deliver the drug at a rate necessary to achieve and maintain a constant blood level.
This rate should be analogous to that achieved by continuous intravenous infusion where the drug is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release of a drug from the dosage form should follow zero-order kinetics, as shown by the following equation:

\[ K = \text{Rate In} = \text{Rate Out} = K_e \cdot C_d \cdot V_d \]

where,

\( K \) = Zero-order rate constant for drug release \(-\) Amount/time

\( K_e \) = First-order rate constant for overall drug elimination \(-\) time \(^{-1}\)

\( C_d \) = Desired drug level in the body \(-\) amount/volume, and

\( V_d \) = Volume space in which the drug is distributed \(-\) Liters.

The values of \( K_e, C_d \) and \( V_d \) needed to calculate \( K \) are obtained from appropriately designed single dose pharmacokinetic study.

It is important to recognize that while zero-order release may be desired theoretically, non zero-order release may be equivalent clinically to constant release in many cases.[4]

1.1.4 : DRUG PROPERTIES INFLUENCING DRUG RELEASE FROM FORMULATIONS : [2,6]

A) PHYSICO-CHEMICAL PROPERTIES

i) Aqueous solubility and \( pK_a \)

ii) Partition co-efficient

iii) Drug stability

iv) Protein binding

v) Molecular size and diffusivity
B) BIOLOGICAL PROPERTIES

i) Absorption

ii) Distribution

iii) Metabolism

iv) Elimination biological half-life

v) Side effects and margin of safety

vi) Dose size

In general, the characteristics that make a drug unsuitable for controlled release dosage forms are:

(i) Long elimination half-life,

(ii) Narrow therapeutic index,

(iii) Large doses,

(iv) Poor absorption,

(v) Active absorption,

(vi) Low or slow solubility,

(vii) Time course of circulating drug levels different to that of pharmacological effect and

(viii) Extensive First-pass clearance.

1.1.5 : DESIGN AND FABRICATION OF ORAL SUSTAINED RELEASE DOSAGE FORMS : [2,6,7]

The most acceptable technologies used to obtain sustained release oral products are:

i. Release from slow eroding solid matrices,

ii. Release from solid hydrophilic gel matrices,

iii. Release from porous inert solid matrices,

iv. Release from coated granules disintegrating at a controlled rate,

v. Release from granules coated with diffusion controlling membrane,
vi. Release from ion exchange resin complexes, and
vii. Release by reducing the solubilities of the drugs.

1.1.6 : ADVANTAGES OF SUSTAINED DRUG THERAPY :

i) Avoids problems of patient compliance

ii) Employ's less total dose
   a) minimizes or eliminates local side effects
   b) minimizes or eliminates systemic side effects
   c) minimizes drug accumulation

iii) Improves efficiency in treatment
   a) improves diseased condition by reducing fluctuations in drug blood level
   b) improves bioavailability of some drugs
   c) makes use of special effects, e.g. sustained release aspirin for relief of arthritis in morning by dosing before bedtime

iv) Economic
   Although initial unit cost of most sustained release drug delivery systems is usually greater than that of conventional drug delivery systems owing to the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may result from a decrease in nursing time, hospitalization, less lost work time etc. The most important reason for sustained drug therapy is improved efficacy in the treatment i.e. optimized therapy.

1.1.7 : DISADVANTAGES OF SUSTAINED DRUG THERAPY :

i. Administration of sustained release medication does not permit the prompt termination of therapy,

ii. The physician has less flexibility in adjusting the dosage regimens. This is fixed by the dosage form design,
iii. Sustained release dosage forms are designed for normal population i.e. on the basis of average drug biological half-life. Problems may be observed in diseased cases where the drugs disposition is altered. Similarly, if the liver and kidney functions are impaired then problems may be observed.

iv. Economic factors must also be assessed, since more costly processes and equipment are involved in manufacturing many sustained release forms.

1.1.8 : REGULATORY REQUIREMENTS FOR SUSTAINED RELEASE PRODUCTS [3]:

a) Requirements to Demonstrate Modified Release Nature of a Product

Over the past two decades significant advances in biopharmaceutics and analytical techniques, including analytical chemistry, have led to the recognition that assurance of reliable drug release from modified release dosage forms must be included in compendial standards.

The compendia established general standards involving three specific cases described below:

CASE 1: All articles that are subjected to specific dissolution requirements employing 900 ml of water and apparatus 1 at 100 RPM or apparatus 2 at 50 RPM, the portions of labelled drug dissolved should be:

1. At time equal to 0.25 D: 20-50% dissolved (Q=0.25)
2. At time equal to 0.5 D: 45-75% dissolved (Q=0.5)
3. Any time up until 1.0 D: not less than 75% dissolved (Q=1.0)

where, D=labelled usual dosing frequency or interval and

Q=Dissolution range

CASE 2: If the chemistry or the physical properties of the formulation do not allow compliance with case 1, and if no medically significant bioavailability problem is documented, then the monograph sets out details of a specific
dissolution test and a specification medium e.g. change of dissolution medium from water to any other medium.

CASE 3: If the chemical or physical properties of the formulations among a group of products from different manufacturers differ to such an extent that a single selection of dissolution test, its time and specifications are not acceptable, then each manufacturer of an article includes in the product labelling a graphic or tabular portrayal of either the release profile, using the procedure specified in the monograph, or the documented plasma level profile.

b) Requirements to Demonstrate Safety and Efficacy

   i) Controlled clinical studies and

   ii) Bioavailability data in lieu of clinical trials.

c) Dissolution Stability

   Dissolution stability (i.e. retention of the dissolution characteristics of a modified release dosage form from the time of manufacture up to its expiration date) is a critical parameter from the standpoint of quality control, regulatory compliance and impact on the bioavailability of the product. Significant changes in the in-vitro release profiles of a drug product during storage may alter its bioavailability.

   The factors that affect the dissolution stability of a modified release dosage form include:

   • Formulation components,
   • Processing factors,
   • Storage conditions and
   • Packaging

   As alteration in the in-vitro dissolution profiles has a major clinical significance, considering both legal and ethical responsibilities, strategies to avert and counteract such changes must be developed.
1.1.9: MICROSPHERES: [8]

1.1.9.1 Introduction

The microencapsulation processes were developed in the early 1950s by Barrett K. Green [9]. This first successful commercial development of a product using microcapsules was carbonless copy paper. The first pharmaceutical product using microcapsules was a controlled release aspirin tablet. In recent years, the technology has been used in many industries, such as food, food additives, cosmetics, adhesives, household products, agricultural materials as well as the aerospace industry. Microencapsulation has been used in the pharmaceutical industry for the conversion of liquids to solids, taste-masking of bitter drugs, prolonged or sustained release, separation of incompatibilities, reduced gastric irritation and environment protection of labile moieties. [10]

In oral sustained release drug delivery systems, the time of drug release critically depends on the residence time of a dosage form in the gastrointestinal tract, therapeutic concentration and pharmacokinetic characteristics of the drug. Different colloidal carrier systems are now a days widely used for obtaining target specificity and sustained action. These includes emulsions, microcapsules, polymeric microparticles, microspheres, nanoparticles, macromolecular complexes and liposomes. Being fluidized systems, colloidal carriers overcome the limitations of residence time due to gastric emptying.

The desirable attributes of a colloidal drug delivery system are:

a) It should bind the drug reversibly so as to carry it intact to the site of action
b) It should be compatible and/or biodegradable with nontoxic end products.
c) It should be pharmaceutically acceptable with respect to the ease of presentation as a dosage form, high drug loading and stability.

There is a growing interest in the development of homogenous monolithic drug release systems for various routes of administration. One very attractive
type of such a dosage form is the formulations containing microspheres [11].
There has been a considerable interest in using polymer based microspheres
as drug carriers due to a variety of reasons;
• Flexibility in design and development
• Attractive in appearance
• Better patient compliance
• Microspheres improve the safety and efficacy of bioactive agents
• Desired release pattern can be engineered

Microspheres are solid, approximately spherical particles containing
dispersed drug in either solution or microcrystalline form. They are ranging in
size from 100 nm to 1000 μm. They are made of polymeric, waxy or other
protective materials such as biodegradable synthetic polymers or modified
natural products like starches, gums, proteins, fats and waxes.

The solvents used to dissolve the polymeric materials are chosen
according to the polymer and drug solubilities and stabilities, process safety
and economic considerations. Water-soluble and insoluble solids, water-
insoluble liquids, solutions and dispersions of solids in liquids can be
incorporated in the microspheres. The drug may be incorporated either in the
aqueous phase or in the organic phase depending on the solubility of the
drug. Typical classes of pharmaceutical core materials are listed in Table
1.1.1:
Table 1.1.1: Typical Class of drugs incorporated in Microspheres

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Antitussives</th>
<th>Minerals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthelminitics</td>
<td>Beta blockers</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>Antidotes</td>
<td>Calcium channel blockers</td>
<td>Nutrionals</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Cathartics</td>
<td>Sedatives</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Diagnostic aids</td>
<td>Stimulants</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Diuretics</td>
<td>Sympathomimetics</td>
</tr>
<tr>
<td>Antimalariaials</td>
<td>Effervescents</td>
<td>Thyroidals</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Enzymes</td>
<td>Tranquilizers</td>
</tr>
<tr>
<td>Antipyretics</td>
<td>Expectorants</td>
<td>Vitamins</td>
</tr>
<tr>
<td>Antiseptics</td>
<td>Hypnotics</td>
<td>Xanthines</td>
</tr>
<tr>
<td>Antituberculosis</td>
<td>Microorganisms</td>
<td>X-ray contrast agents</td>
</tr>
</tbody>
</table>

There are two types of microspheres as depicted in Fig. 1.1.5.
- Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall and
- Micromatrices, where the entrapped substance is dispersed throughout the polymer matrix.

Fig 1.1.5: (a) Microcapsule consisting of an encapsulated core particle
(b) Micromatrix consisting of homogeneous dispersion of active ingredients in particle
Microspheres are small in size and therefore have large surface to volume ratios. At the lower end of their size range they have colloidal properties [12]. The interfacial properties of microspheres are extremely important, often dictating their activity. In fact, the principle of microsphere manufacture depends on the creation of an interfacial area, involving a polymeric material which will form an interfacial boundary and a method of cross-linking the polymer in such a way that the microspheres possess a degree of permanency.

1.1.9.2 Methods of Preparation  [8, 13, 14, 15, 16]

Microspheres may be prepared by any one of the following techniques:

1. Solvent removal technique
   A) Emulsion solvent evaporation technique
      i) Oil in water (O/W) emulsion solvent evaporation
      ii) Water in oil(W/O) emulsion solvent evaporation
      iii) Water in oil in water(W/O/W) complex emulsion solvent evaporation
   B) Emulsion solvent extraction (precipitation)
   C) Emulsion solvent diffusion

2. Coacervation and phase separation technique or cross-linking
   (chemically / thermally)

3. Polymerization technique
   A) Vinyl polymerization
   B) Normal polymerization
   C) Interfacial polymerization

4. Spray drying and spray congealing

5. Freeze drying

6. Congealable disperse phase encapsulation technique.
In **emulsion solvent evaporation technique**, the polymer and drug should be soluble in an organic solvent. The solution containing the polymer and the drug may be dispersed in an aqueous/oily phase to form a droplet. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvent and leave the solid polymer-drug particles in the dispersion medium. The particles are finally filtered from the suspension. Oil in water emulsion solvent evaporation is used for hydrophobic polymers (e.g. polylactic acid, polylacticglycolic acid, ethylcellulose, Eudragit(RS, RL, S, L). Water in oil emulsion solvent evaporation technique is used for hydrophilic polymers.(e.g. casein, albumin, gelatin)

The **emulsion solvent extraction or precipitation technique** is same as above, except the emulsion consists of polar droplets dispersed in a nonpolar medium. Solvent may be removed from the droplets by the use of a cosolvent. The resulting increase in the polymer-drug concentration causes a precipitation forming a suspension. The particles are filtered from the suspension.

In **emulsion solvent diffusion method**, the alcoholic solution of drug and polymer is dispersed into aqueous/oily medium with constant stirring. During the process the solvent first diffuses out and then evaporates from the coacervate into the dispersion medium and forms the microspheres.

In **coacervation phase separation technique**, an aqueous solution of a polymer is emulsified in an organic phase. The polymer is then chemically cross-linked using suitable agents such as glutaraldehyde, formaldehyde, borax, glyoxal, epichlorhydrin, etc. or they are hardened by heat (thermally cross-linking).
In **polymerization technique**, vinyl monomers are polymerized. The microspheres are formed using techniques such as suspension, emulsion, soapless emulsion, dispersion, precipitation, seeding and support polymerization. Here the drug is incorporated within the monomers at the initial stage.

In **interfacial polycondensation method**, two complementary monomers are taken in a two phase system and one of the phases is dispersed as droplets in an another phase. The drug is incorporated in any one phase and microspheres are obtained when condensation of monomers takes place at the interface.

In **spray drying** the core substance is dispersed in a solution of the coating material, which is then atomized and the solvent is evaporated using heated air. Spray congealing is same as spray drying except that no solvent is used for the coating material. The polymer has the property of melting at elevated temperatures and congealing when the droplets meet cool air in a spray drier.

In **freeze drying technique**, the freezing of the emulsion is done. The relative freezing points of continuous and dispersed phases are important. The continuous phase solvent is usually organic and is removed by sublimation at low temperature and pressure. Finally, the dispersed phase solvent of the droplets is removed by sublimation, leaving polymer drug particles.

In **congealable disperse phase encapsulation procedure**, the fine particles of drug at high temperature are dispersed in a hydrophilic or hydrophobic liquid vehicle that will solidify when cooled to normal ambient
temperature. Suitable hydrophilic vehicles include gelatin, agar and starch. Suitable hydrophobic vehicles include waxes [17]. The factors which affect the release of drugs from monolithic particles are listed below:

**Drug**
- Position in the microsphere
- Molecular weight.
- Physicochemical properties
- Concentration
- Interaction between the drug and the matrix.

**Microsphere**
- Type and amount of matrix material
- Method of manufacture
- Size and density of the spheres
- Extent and nature of cross-linking or polymerization
- Presence of adjuvants.

**Environment**
- pH
- Polarity
- Presence of enzymes

**Miscellaneous**
- Inclusion of plasticizers and fillers
- Thickness of the polymer
- Permeability of drug in polymer

1.1.9.3 Characterization of Microspheres [8, 18]

1. Polymer characterization
   a) Molecular weight.
   b) Purity
   c) Miscellaneous
2. Microsphere characterization
   a) Particle size and size distribution
   b) Surface characterization
   c) Surface charge analysis
   d) Hydrophobicity
   e) Density
   f) Surface area
   g) Porosity
   h) Flow properties
   i) Drug content
   j) Drug release profiles

1.1.9.4 Applications of Microspheres [8, 18, 19]

The potential use of microspheres in the pharmaceutical industry has been considered since the 1960s [20-22].

1. In sustained and controlled release [23-26]

The microspheres can be designed to release their ingredients at a specific rate. Drugs such as theophylline, indomethacin, aspirin, diclofenac sodium, riboflavin, antimicrobial agent (nitrofurantoin) and steroids like progesterone, testosterone etc. can be incorporated in microspheres to control their release.

2. In enteric release dosage form

Drugs which are irritant to the stomach and exhibit other side effects e.g. aspirin, erythromycin and salbutamol sulphate can be incorporated in microspheres for their selective release in the intestine.

3. To protect reactive materials against the environment

It is useful for drugs like vitamins and aspirin which are sensitive to oxygen and water.
4. **To mask the bitter or unpleasant taste of the drug**

It is used to mask offensive taste of drugs such as quinidine, nitrofurantoin, paracetamol, prednisolone, metronidazole, fish oils, sulpha drugs, clofibrate, alkaloids and its salts.

5. **For drug targeting**

Casein and gelatin microspheres containing adriamycin and interferons respectively were magnetically delivered to tumor site. Albumin microspheres were used for anti-inflammatory agents for directing to knee joint.

6. **To alter the residence time and to improve the bioavailability.**

Albumin and gelatin microspheres containing pilocarpine nitrate (ophthalmic drug delivery) for delivery to the eye increase residence time of drug in the eye and provide improved bioavailability. Also the delivery of poorly absorbed drugs by the mechanism of transcellular passage across the gastrointestinal tract, alter the gastrointestinal transit time of a drug through their mucoadhesive properties.

7. **As a topical drug delivery system**

Microspheres of benzoyl peroxide were used as a topical drug delivery system for their bactericidal activity against acne.

8. **As drug carriers**

Albumin has been used to protect/target enzymes within the body. By using it, different enzymes are protected against proteolytic digestion, immunologically tolerated or remain in the circulation for long times.
9. **As an antidote in the poisoning of heavy metals**
Polymercaptal microspheres have been used as an antidote against mercury poisoning.

10. **As antigen carriers**
Poly(lactic acid) and poly(lactic glycolic acid) microspheres of varying composition have been used to improve the ability of the antigens to provoke a mucosal immune response.

11. **For liver cell immobilization**
Microspheres have been investigated as artificial cells as a means to immobilize live cells such as liver, kidney and red blood cell substitutes and can be targeted to the site.

12. **As an absorption promoting systems**
Degradable starch microspheres have been used for increasing the drug or peptide absorption across the nasal epithelium.

13. **To separate incompatible substances**
The stability of incompatible drugs such as aspirin and chlorpheniramine maleate can be increased by separately microencapsulating them.

14. **For administration in solid state and dry handling**
Liquids such as eprazine can be converted to a pseudo-solid by microspheres as an aid to handling and storage.
15. **To facilitate handling of toxic materials**

Microspheres have been used to decrease potential danger in handling toxic substances like pesticides, fertilizers and certain pharmaceuticals.

16. **To reduce gastric irritation**

A unique feature of the microsphere is the smallness of the particles and their use and adaptation to a wide variety of dosage forms. Because of the smallness of the particles, drugs can be widely distributed throughout the gastrointestinal tract, thus ensuring more reproducible drug absorption with less local irritation. Table 1.1.2 shows the number of particles available per gram of microcapsules at various diameters.

**Table 1.1.2 : Microcapsule Diameter and Number of Microcapsules per Gram of material**

<table>
<thead>
<tr>
<th>Diameter (nm)</th>
<th>Microcapsules /gm of material</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>15,279,000,000</td>
</tr>
<tr>
<td>50</td>
<td>15,279,000</td>
</tr>
<tr>
<td>100</td>
<td>1,909,800</td>
</tr>
<tr>
<td>200</td>
<td>238,730</td>
</tr>
<tr>
<td>400</td>
<td>29,841</td>
</tr>
<tr>
<td>600</td>
<td>8,842</td>
</tr>
<tr>
<td>800</td>
<td>3,730</td>
</tr>
<tr>
<td>1000</td>
<td>1,900</td>
</tr>
</tbody>
</table>
17. **For encapsulation of artificial cells**

Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins and hormones. The encapsulation prevents unwanted immunological reactions that would lead to inactivation or rejection. [27,28]

18. **In biotechnology**

The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of these products. Containment of the products within microspheres significantly enhances the efficiency of the process. [29]

19. **Miscellaneous applications**

Microspheres can be used as a carrier for vaccines, as a diagnostic tool and for drug follicular targeting.

### 1.1.9.5 Controlled Release from Microspheres

The rate of drug release from microspheres dictates their therapeutic action. Drug release is governed by the molecular structure of the drug and the polymer, the resistance of the polymer degradation, and the surface area and porosity of the microspheres [30-32]. The mechanisms for release of a drug at a controlled rate from microspheres include diffusion of drug through a polymeric excipient, diffusion of trapped drug as the polymer erodes, or release of drug through pores in the polymeric excipient.

If the drug is released by diffusion through the polymeric excipient without significant erosion, the release depends on the surface area of the microspheres and the path length of the drug in transit to the surrounding environment. Thus, increasing the surface area, by reducing particle size may result in an increased release rate. The path length of travel for the drug
in the matrix can be controlled by manipulating the microspheres loading. Microspheres with a high drug content release the active ingredient more rapidly than those with a low load. Physicochemical properties of the drug and excipient such as permeability of one in the other, identity of polymer, degree of crystallinity, inclusion of plasticizers, fillers and surfactants influence the drug release rate.
1.2 INTRODUCTION TO DICLOFENAC SODIUM

Diclofenac sodium is a phenyl acetic acid derivative and is a potent synthetic nonsteroidal anti-inflammatory drug (NSAID). It has mainly analgesic, antipyretic and anti-inflammatory action.

1.2.1 DESCRIPTION: [33]

(a) Generic Name : Diclofenac Sodium
(b) Synonyms : Voltaren, Voltarol, Voldal, Voveran, Orthophen
(c) Chemical Name : 2-[(2,6-dichlorophenyl)amino] benzene acetic acid monosodium salt

\[ \text{Sodium [o-} (2,6\text{-dichloroaniline)phenyl] amino-} \text{phenyl acetate.} \]

\[ \text{Sodium [o-} (2,6\text{-dichlorophenyl}) \text{amino} \text{phenyl acetate} \]

(d) Empirical Formulae : C\textsubscript{14} H\textsubscript{10} Cl\textsubscript{2} N O\textsubscript{2} Na
(e) Structural Formula

(f) Molecular Weight : 318.13

(g) Element Composition :
- C - 52.85 %
- H - 3.17 %
- Cl - 22.29 %
- Na - 7.27 %
- N - 4.40 %
- O - 10.06 %

(h) Appearance : It is white to off white in color, odourless, crystalline and slightly hygroscopic in nature.

1.2.2 : PHYSICAL PROPERTIES : [33]

(a) Solubility [34] : It is soluble in water, alcohol, acetone and phosphate buffer. It is insoluble in acids, cyclohexane, acetonitrile and chloroform. Table 1.2.1 shows the solubility of diclofenac sodium in different solvents
Table 1.2.1: Solubility of Diclofenac Sodium

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature</th>
<th>Solubility mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deionized water (pH 5.2)</td>
<td>RT</td>
<td>&gt; 9</td>
</tr>
<tr>
<td>Methanol</td>
<td>RT</td>
<td>&gt; 24</td>
</tr>
<tr>
<td>Acetone</td>
<td>RT</td>
<td>6</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>RT</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>RT</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>pH 1.1 (HCl)</td>
<td>RT</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>pH 7.2 (Phosphate Buffer)</td>
<td>RT</td>
<td>6</td>
</tr>
</tbody>
</table>

(b) Melting Point: 283-285°C

(c) Stability: It can be frozen for at least two weeks without degradation in biological fluid (serum). Diclofenac sodium is also stable at 130°C for 8 hr.

(d) Dissociation Constant: The pKa is 4.2 in aqueous solution at 30°C

(e) Partition Co-efficient [34]: The octanol-water partition coefficient at 25°C is reported as 4 to 4.17.

1.2.3: PHARMACOLOGY:

(a) Properties [35,36]: Diclofenac sodium is a potent non-steroidal anti-inflammatory drug with pronounced analgesic, antipyretic and anti-inflammatory properties. Its potency is much greater than that of indomethacin, naproxen, and phenylbutazone. Diclofenac sodium appears
to reduce intra-cellular concentration of free arachidonate in leukocytes by altering the release or uptake of the fatty acids.

(b) **Mechanism of Action** [36]: Diclofenac sodium inhibits cyclo-oxygenase enzyme. It inhibits the conversion of arachidonic acid to unstable endoperoxide intermediate, prostaglandin E1, a reaction catalyzed by cyclo-oxygenase. Thus it inhibits the production of prostaglandin content of human serum, urine and synovial fluid of arthritic knee joint, thereby acting as a potent anti-inflammatory agent.

(c) **Pharmacokinetics and Metabolism** [35-39]:

(i) Absorption:

Absorption of diclofenac sodium is almost complete from solutions by oral and intramuscular route. Absorption may vary according to the specific dosage forms used. Food delays but does not reduce absorption after administration of enteric coated tablets but this effect is of no clinical significance during long term treatment.

Peak plasma concentration ($C_{\text{max}}$) and area under plasma concentration-time curve (AUC) are dose related in the range of 25 to 150 mg. Slow release tablets may take upto 17 hours to dissolve. First pass metabolism reduces oral bioavailability to 50-60%. There is no accumulation during multiple dosing.

<table>
<thead>
<tr>
<th>Type of dosage form</th>
<th>$C_{\text{max}}$ (mg/ml)</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Uncoated tablet-50 mg</td>
<td>1.00</td>
<td>10-30 min</td>
</tr>
<tr>
<td>2. Enteric coated tablet</td>
<td>1.50</td>
<td>1.5-2.5 hr</td>
</tr>
</tbody>
</table>
The drug accumulates in synovial fluid after oral administration, which may explain its considerably longer duration of action than the plasma life.

<table>
<thead>
<tr>
<th>Site</th>
<th>Mean concentration at 2 hr (µg/ml)</th>
<th>Mean concentration at 7 hr (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Plasma</td>
<td>300</td>
<td>52</td>
</tr>
<tr>
<td>2. Synovial fluid</td>
<td>200</td>
<td>205</td>
</tr>
</tbody>
</table>

(ii) Protein Binding and Distribution:

At therapeutic concentration, the drug is extensively bound to plasma protein (albumin 99.7%). Apart from liver, bile and kidney, highest levels of diclofenac is found in blood, heart and lung. Diclofenac crosses the placenta in animals but human data are not available.

(iii) Metabolism:

Diclofenac sodium is metabolised in the liver. The principle metabolite is 4' hydroxy diclofenac which has about 0.033 to 0.025 activity of diclofenac.

(iv) Excretion:

Diclofenac sodium and its metabolites are excreted through bile (33%) and urine (67%). The concentration of unchanged drug in urine is about 0.7%. The clearance rate is reported as 4.2 ± 0.9 ml/min. kg., and elimination rate as 1.2 to 1.8 hr. The volume of distribution (Vd) is reported as 0.17 ± 0.11 L/kg.

(v) Biological Half Life:

It is reported as 4 hr.
(d) ADVERSE EFFECTS [35-37]: The most common adverse effects occurring with diclofenac sodium are gastrointestinal irritation, peptic ulceration and gastrointestinal bleeding due to inhibition of cyclooxygenase enzyme. In acute toxicity studies diclofenac sodium was found to cause gastric lesions in lower dose (12 mg/kg). Elevation of hepatic transaminase activities in plasma occurs in about 15% of patients. The elevations in transaminases are usually reversible and are only rarely associated with clinical evidence of hepatic disease. Transaminase activities should be evaluated during the first 8 weeks of therapy and the drug should be discontinued if abnormal values persist or if other signs or symptoms develop. Other untoward responses of diclofenac include central nervous system effects, skin rashes, allergic reaction, edema, headache and drowsiness. Hypertensive reactions, abnormality of liver function tests, impairment of renal function, agranulocitosis and thrombocytopenia are rarely observed.

(e) CONTRAINDICATIONS [35]: Diclofenac sodium should not be used by children, nursing mothers or pregnant women. It is also contraindicated in individuals with ulcerative lesions or renal disease.

(f) THERAPEUTIC USES [35,36]: Diclofenac sodium is mainly used for the long term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also used for short term treatment of acute musculoskeletal injury, acute painful shoulder, acute renal colic, post operative pain and dysmenorrhea.
(g) **DOSE**

For adults:
- Oral: 75 to 150 mg daily in divided dose.
- Intramuscular: 75 mg once / twice daily
- Rectally: 100 mg

For children:
- Orally or rectally: 1-3 mg/Kg body weight daily in divided doses.

It is used intramuscularly in renal colic at a dose of 75 mg repeated once after 30 minutes if necessary. For children, the suggested oral or rectal dose for juvenile chronic arthritis is 1 to 3 mg/kg of body weight in divided doses.

(h) **DOSAGE FORMS**

It is available as enteric coated tablets, sustained release tablets, suppositories, intramuscular injection, eye drops and gels.
### 1.2.4 PROPRIETARY PREPARATIONS

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Preparation</th>
<th>Name of Company</th>
<th>Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol</td>
<td>Geigy, U.K.</td>
<td>25 / 50</td>
</tr>
<tr>
<td>2</td>
<td>Voveran</td>
<td>Ciba Geigy, Bombay</td>
<td>25 / 50</td>
</tr>
<tr>
<td>3</td>
<td>Diclofen</td>
<td>P&amp;B Lab, Bombay</td>
<td>25 / 50</td>
</tr>
<tr>
<td>4</td>
<td>Relaxyi</td>
<td>Franco India, Bombay</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Diclofen</td>
<td>P&amp;B Lab, Bombay</td>
<td>25 / 50</td>
</tr>
<tr>
<td>(B) Sustained Release Tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol Retard</td>
<td>Geigy, U.K.</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Voltaren</td>
<td>Spain, Italy</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Voveran SR</td>
<td>Ciba Geigy, Bombay</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Diclofen</td>
<td>Lupin</td>
<td>100</td>
</tr>
<tr>
<td>(C) Suppositories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Modified Release</td>
<td>Japan</td>
<td>25</td>
</tr>
<tr>
<td>(D) Gels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol Emugel</td>
<td>Geigy</td>
<td>1%</td>
</tr>
</tbody>
</table>
1.2.5 : METHODS OF ANALYSIS :

[A] Ultraviolet spectrophotometric determination [33] :
This method is based on the measurement of absorption of appropriately diluted diclofenac sodium solution in ultra violet light in a 1 cm matched quartz tube. Beer's law is obeyed in the concentration range of 3 to 30 μg/ml of diclofenac sodium.

[B] Colorimetric determination [41] :
This is a sensitive method based on the reaction of diclofenac sodium with potassium ferricyanide (1% w/v) in basic medium. The yellow color developed after addition of sodium hydroxide (6% w/v) shows maximum absorbance at 450 nm. The Beer's curve shows linear relation in the concentration range of 2 to 10 μg/ml of diclofenac sodium.

[C] Determination of diclofenac sodium through the formation of charge transfer complex with chloranil :
A colorimetric method based on formation of a colored charge transfer complex between the drug and chloranil. The complex formed in ethanol shows maximum absorbance at 545 nm. The beer's law is observed in concentration of 0.08 μg/ml.

[D] Gas liquid chromatography [33] :
This method was used to analyze diclofenac sodium and its metabolites using electron capture detector. Before injecting into the column, diclofenac or its metabolites are derivatized into the indolones or the methyl esters. The various columns used are coated with barium carbonate and satirically coated with Carbowax 40M; 3%OV-17 Gas-Chrom Q on 80-120 mesh glass beads ; 3% JXR (methyl silicone) on Gas-Chrom Q ; 1.5% Silicone OV-17 on Shimalite W AW DMCS, 80-100 mesh.
[E] High performance liquid chromatography [42]:

Diclofenac was chromatographed on C-18 reverse phase columns using mobile phase consisting of methanol, acetic acid and water and detected at 254 nm. The recovery was 98.73-102.11% and relative standard deviation was 0.2737-0.4266%.

[F] Nuclear Magnetic resonance [33]:

Proton magnetic method to quantify diclofenac sodium in tablet form has been described. Diclofenac has a well defined sharp peak (at 3.62 ppm) which was chosen for quantitative measurement. Internal standard used was anhydrous sodium acetate (1.85 ppm). The amount of diclofenac sodium can be calculated by comparing the peak ratio of diclofenac to that of the internal standard.