Chapter 1. INTRODUCTION AND LITERATURE REVIEW

Controlled drug delivery technique presents front line part of today’s developed technique, in this includes many scientific approaches, serving for individual care. The drug deliverance technique having abundant advantages than existing conventional type of dosage, it involves enhanced effectiveness, minimized poisoning, enhanced consumer conformity also ease.

This type of drug deliverance technique utilizes micro molecules, for caring drugs. As the varieties of forms for dosage are invented like microparticle as well as nanoparticles shown more significance. [Majeti N. V. Ravi Kumar et. al., 2000].

An ideal and advanced oral drug delivery system is that, which exactly controls speed, time as well as site of release of medicament separately of normal physiological variables such as gastrointestinal tract pH, digestive condition of the gastrointestinal tract, peristalsis movement and circadian rhythm. Advance in polymer science and technology outcome in pick up the pace research and developmental activity in the design of drug delivery devices.

Polymeric excipients are commonly worn for controlled release delivery systems, as a coating for drug particle by micro encapsulation technique and a matrix in which drug material can be embedded. There is an enormous selection of polymers accessible for use dosage forms. Starting from hydrophilic toward hydrophobic. Utilization of polymers in dosage forms is as miscellaneous as the polymers, in which can be natural, synthetic and semi synthetic types.

All the pharmaceuticals goods prepared for internally drug liberation by means of the orally through immediate or constant or proscribed liberate systems and the dosage forms in the form of firm dry or liquor suspension, should be manufactured under inherent uniqueness to Gastro Intestinal h to makeup, pharmacokinetics, pharmacodynamics. The dosage form design is important to success a systemic step towards the victorious expansion to orally admitted products.

The fundamental rational of proscribed drug liberation is to modify pharmacokinetic as well as pharmacodynamic property of drugs, by means of
novel drug delivery system and also altering physiological factor and molecular structure in the selected route of administration.

The duration of effect of drug becomes increases as dosing property of a rate controlled dosage form and decreases or not at all a possessions of the actives moieties.

The elective design of controlled release systems imposes thorough understanding of the pharmacodynamics and pharmacokinetics of the drugs. [Chien Y.W. 1992].

1.1. Underlying Principle of Sustained/Controlled Releasing System

Fundamental rational of proscribed drug deliverance technique is to modify the ADME and property of drugs, means using modern techniques of drug delivering systems, and with altering physiological factor and molecular structure in the selected route of administration. The duration of effect of drug becomes increases as dosing assets of proscribed drug deliverance techniques. [Chien Y.W. 1992].

1.1.1. Sustained Release System

- **Advantages**
  - Circumvent patient’s compliance problem due to reduced frequency of dosing.
  - Frequent administration of normal drug delivery system can be overcome by.
  - Make use of less total drug.
  - Reduce or eradicate local or systemic side effects.
  - Reduces drug accretion with chronic dosing.
  - Obtain less latent of reduction in drug activity with chronic use.
  - Better competence in treating patients.
  - Treat situation more quickly.
  - bio availability of some drugs Enhanced
  - Utilizing specific consequence. E.g. treatment of arthritis
  - cost-cutting measure
  - Overall, sustained release forms facilitated increased dependability of therapy. [Lachman Leon et.al.2000]

- **Disadvantages**
  - Abridged potential for dose titration.
  - Dose dumping may lead to toxicity.
- Enlarged potential for Hepatic Metabolism
- Constancy problems.
- Requirement of additional patient education.
- Recovery of drug is not possible in case of toxicity.
- Unpredictable in vitro- in vivo correlation.

[Bankers G.S. and Rhodes C.T. 1995]

### 1.2. Modified Release System

To minimize the potential problem related with normal dosage forms,
1.2.1. Delayed release system

Delayed release systems apply the principle repetitive intermittent dosage form.

Fig. 1.3. Amount of the Drug against time in SR system
Here

- Dotted line - Therapeutic level
- Solid line - Toxic level

- Sustained release system
- Controlled release system
- Prolonged release system

➢ Sustained release system

Sustained release systems attain sluggish discharge of drugs log time period and in this drug are originally made available in amount to cause the desired pharmacological effect in body.

![Fig. 1.4. Ideal Plasma Concentration Curves For Immediate Release, Zero Order Release, Sustained Release Drug Delivery System](image-url)
**Controlled release system** A best proscribed medicament releasing technique is that releases drugs for programmed speed, nearby or systemically for the programmed period.

![Diagram](image)

**Fig. 1.5.** Amount of drug at place of therapeutic effect after by conventional IV

- Thin line- conventional IV
- Bold line- temporal proscribed system
Fig. 1.6. Delivery of Drug by idyllic controlled liberate system.
Bold line- Amount of drug at place therapeutic action.-:
Thin line- Amount of drug at levels leads to toxicity

- **Prolonged release system**
  Prolonged release system, prolongs the time of action without maintaining a constant drug blood level. Thus maintain constant-drug leveling in blood or target tissue.

Fig. 1.7. Amount of drug against time in protracted releasing system
1.2.2. Site specific and receptor release system

The receptor release, site specific and targeted release refers to targets the drug straight towards a certain biological location. Thus, controlled release drug delivery systems are now most admired in the market over the conventional release drug delivery. [Brahmankar D. M. and Jaiswal S.B. 1995]

Fig. 1.8. Drug systemic concentration against time for controlled and conventional Drug Releasing Techniques
1.3. Principal of modified drug release
Following either of the two principles can modify drug release:

1.3.1. Barrier principal
In this technique the retardant material is forced between the drug and elusion medium. Drug discharge with diffusion from side to side barrier and/or erosion of the barrier or penetration of the barrier by moisture

Fig.1.9. Barrier mediated models of sustained release dosage form regimen. (A) Drug diffusion through the barrier, (B) Permeation of barrier by elution media followed by drug dissolution, (C) Erosion of barrier releasing drug and (D) Ruptures of permeation of elution media.
Fig. 1.10. Reservoir System Drug discharge

Fig. 1.11. Matrix System Drug discharge
1.3.2. Embedded matrix In this drug is entrenched in a matrix of retardant material that may be encapsulated in a particulate form or converted it into the tablet. Drug release occurs by penetration of water leaching removal of dispersal of drug through the surrounding polymeric area as well as erosion of polymer material.

Fig. 1.12. Embedded matrix concept as a mechanism of controlled released in sustained release dosage form design network model

(A) Drug is insoluble in the retardant material
(B) Drug is soluble in the retardant material.
1.4. Properties of drugs relevant to sustained release formulation

The drug properties that affect the integration of drug into a sustained release dosage form can be classified as-

- Physicochemical properties
- Biological properties

Physicochemical properties can be determined by in vitro experiments. Biological properties are results from typical pharmacokinetic studies of characteristics such as absorption, distribution, metabolism and elimination of drugs [Chang R.K., Robinson J.R., 2005].
1.5. Recent trends in sustained drug delivery system

S.R. dosage form categorized as:

- Single unit type
- Multiple unit type
- Mucoadhesive type

1.5.1. Single unit dosage form

These refers to diffusion system where the drug is consistently distributed all over the rigid polymer and the drug discharge managed by addition of hydrophilic polymer and some time with addition of hydrophobic polymer or with application of coatings of polymers. These systems can be classified as:

1.5.1.1. Monolithic system

The release rate is managed with addition of polymer with the matrix, is called as monolithic system. Where drug diffusion through the matrix is speed limited.

1.5.2. Multiple unit dosage forms

It offers numerous advantages for releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are predictable with single type dosage form.

It is categorized as:

- Micro granules/Spheroids.
- Beads.
- Pellets.
- Microparticles (Microcapsule Microspheres)

1.6. Microparticles

These are particulate dispersed and or firm particles having diameter 01-1000 µm. The drug is embedded or covered in polymer or dissolved in polymer. The microspheres or microcapsules can be obtained it is depends on the method of preparation, In Microcapsules active constituent is restricted to a hollow cover of polymeric material. In microspheres drug is equally distributed [N.S. Dey et. al., 2008]. The procedure of preparation allows managing microparticle diameter. It is important for various applications [P. Burns et. al., 2002].
Chapter 1.

Introduction and Literature Review

Fig. 1.14. Classification of Microparticles

Fig. 1.15 Structure of Microparticle
Fig. 1.16. Different shapes of Microparticle
Fig. 1.17. Structure of microcapsule

Fig. 1.18. Structure of microsphere
Advantages
Microparticles proposes various important advantages
- Protects active constituents.
- Precisely control discharge of active constituents from hours – months.
- Ease of Use.
- Less unpredictability in GI transition cycle. as Microparticles system is less dependent on gastric empty ting,
- They are also better distributed and local irritation.
- improved bioavailability,
- No Chances of lethality of dose and GI tract annoyance.
- To hide bitterness of medicament.
- Protects core material against atmospheric effects.
- Trim downs hygroscopicity. [Juergen Siepmann et. al.2006].

Disadvantages
Microparticles comprise some disadvantages i.e.
- After administration of medication difficult to terminate the therapy.
- Immediate changes in drug need during therapy
- The prescriber have minimum flexibility for dose adjustment. [Abhay N. Padalkar et al., 2010]

1.6.1. Applications of Microsphere
- Controlled or Sustained release is probable.
- Taste covering in case of oral delivery.
- Fortification of drug or active component from moisture and/or oxygen and/or light.
- Allows grouping of incompatible constituents.
- Enhances flow properties of drug or active component.
- Simplicity of formulation
- Solid microsphere is broadly used in reflective traffic paint. [Lachman, L., Lieberman, H.A. Kanig 2000].
1.7. Methods of Preparation of Microparticles
1.7.1. Solvent evaporation

Generally coating material solubilised in volatile solvent and after that this polymeric solution is added to manufacturing liquid (Vehicle) in which the core and coat both are not soluble and by increasing temperature the volatile solvent is removed by means of evaporation.[Lachman L., Liberman H.A.1999].
Fig. 1.20. Schematic diagram of process of microspheres with various types of emulsion solvent evaporation techniques
1.7.2. Ionic gelation technique
Calvo and Janes discovered developed and examined Ionic gelation methodology for preparation of microspheres. The mechanism of microsphere formation is based on electrostatic reaction among polymeric amino group and negative charged polyanions. Using this methodology one can obtains desired particle size also free of adverse effects of organic solvents. The fundamental schematically described in fig bellow. Chemical interaction of sodium alginate as well as CaCl₂ used to develop microspheres. [Al-kassas RS 2007] and [Patil J.S.et.al 2010].
Fig. No. 1.22. Sodium alginate bead formation in CaCl₂ Solution
Fig. No. 1.23. Drops of alginate in CaCl₂ Solution

➢ Advantages
  • It does not affect Physical property and Pharmacological action of drugs.
  • It is having good product yield as well as encapsulation efficiency.
  • Insures reproducible quality and drug release.
  • No association or adherence of Microsphere.
  • At industrial scale usable methodology.
  • It is carried out without using organic solvents. It is a biggest.

1.7.3. Coaservation Phase Separation [Green B.K. et al., 1964].

Step I- Solubilize polymer which is to be used as coat in suitable solvent then to this solution incorporate active constituents as a core.

Step II- This stage involves the development of cover or coat on the core material. It is accomplished by just pouring the polymer solubilized solution
containing core material into another liquid medium in which Coating and core material in not having solubility and also for solvent in which coating polymer was solubilized.

The interfacial tension is minimizes and this energy act as the chemical driving force for ultimate microcapsule formation.

**Step III** -This stage involves hardening of the coat preferably by Temperature change, crosskicking otherwise desolation technique for obtaining microcapsules. Coacervation phase separation done by induced by many physical processes.

- **Alteration of Temperature technique:** While the temperature of the system existing as a single-phase homogenous solution is decreased, polymer which was in solution form use to separate out due to changes occurs in its solubility.

- **Addition of incompatible polymer:** Liquid separation of polymer occurs because when another incompatible polymer is added, it displaces previous polymer.

- **Addition of non-solvent:** When we add other nonsolvent to polymeric solution in which polymer is insoluble but solvent is miscible. Nonsolvent causes displacement of polymer ions from solvent and separation occurs.

- **Addition of salt:** When we add Soluble inorganic salt polymeric solution causes displacement of polymer ions from solvent and separation occurs.

- **Polymer to polymer interaction:** When we use to add oppositely charged polyelectrolyte to polymeric solution which binds to solubilized polymer and decreases the solubility of polymer hence separation occurs.

- **Solvent evaporation:** Generally coating material solubilized in volatile solvent and after that this polymeric solution is added to manufacturing liquid (Vehicle) in which the core and coat both are not soluble and by increasing temperature the volatile solvent is removed by means of evaporation. [Lachman L., Liberman H.A.1999].
Core material phase is dispersed in the solution of coating polymer, the solvent for polymer is vehicle the phase.

Deposition of polymer solution onto the core material.

Deposition of liquid polymer occurs when the polymer is adsorbed at the interface formed between the core material and liquid vehicle phase.

Rigidizing of coating material by thermal or cross linking technique.

Microcapsules are formed.

Fig. 1.24. Microencapsulation by phase separation coacervation process
Fig. 1.25. Schematic Representation of Microencapsulation by phase separation coacervation process
1.8. Drug properties suitable for sustained release

**Table No. 1.1. Drug properties suitable for sustained release**

<table>
<thead>
<tr>
<th>Physiochemical characters</th>
<th>Elucidation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Property</strong></td>
<td></td>
</tr>
<tr>
<td>Dose Size</td>
<td>If dose is greater than 500mg, it is not suitable drug because the product size will be exceptionally large.</td>
</tr>
<tr>
<td>Aqueous Solubility</td>
<td>Extreme in aqueous solubility will be undesirable, it’s very hard to add. Lowest value is 0.1mg/ml. pH dependent solubility will be another problem.</td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>Drugs that are highly soluble means limits in partition coefficient can result in less fluctuation in tissue or faster fluctuation follow buildup in the tissues. Any one case could be objectionable. The value of k at which optimum activity observed in 1000/1 in octanol/water.</td>
</tr>
<tr>
<td>Drug Stability</td>
<td>Extended release models fabricated to release their contents for span of GI, those drugs are uneven in intestine are not suitable for SR system.</td>
</tr>
</tbody>
</table>
Table No. 1.2. Drug properties suitable for sustained release

<table>
<thead>
<tr>
<th>Biological characters</th>
<th>Property</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Drugs which have slow absorption or with difficulties in absorption speed are not suitable for SR system. The 0.25/hr. absorption constant is lower limit on absorption rate.</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Drugs has higher apparent volume of distribution influences speed of removal, are not suitable for SR system.</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>As per the length of site, extent as well as rates of metabolism if already identified as well as speed constant is small, then successful sustained release system can be developed.</td>
<td></td>
</tr>
<tr>
<td>Period of action</td>
<td>The systemic t½ and time of action acting a major role. Drugs with biological half-life less than 2 hrs should not be used. Another thing a drug having t½ of greater than 8 hrs have inherently sustained action.</td>
<td></td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>Those Drugs having less t½ therapeutic range require precise control over the blood levels of drugs, placing a constant on sustained release dosage form.</td>
<td></td>
</tr>
</tbody>
</table>
1.9. Polymers
Polymers used to prepare microcapsules are classified in both synthetic and natural polymers. The majority of microcapsules developed using aqueous insoluble polymers which are related to temperature, nonaqueous solvent or high stirring which is not suitable for drug stabilization. Afterwards few techniques such as emulsion polymerization and solvent evaporation are complicated and require larger number of research steps that are more time and energy consuming.

On the contrary, polymer having solubility in aqueous media offer convenient and easy procedure devoid of the utilization of natural solvent as well as elevated rate of shear. Polymethacrylates occurs as synthetic anionic and cationic in nature.

More than a few dissimilar types also commercially obtainable also obtained in the dry powder form, like an organic solution as well as an aqueous suspension. Eudragit RS -100 is having a small particles size, white colored powder, an amine odor. It have more than or equivalent to 97% of dry polymer. [Tiyaboonchai W.2003].

1.10. Hydrophilic Gums
Hydrophilic gums and polymers are posses large in weight (molecular), generally not solubiliser in alcohols, gums could be solubilized in aqueous media to convert or prepare mucilage. Hydrophilic polymers are useful tools for the development of oral formulations.

Those drugs having aqueous solubility if not fabricated well and suppose administered orally may readily release the drug immediately to produce the toxic concentrations. Presently, majority of dosage forms are depends on natural, semi synthetic or synthesized polymers that differ in degree of eroding ability and swelling ability.

Gums utilized many dosage forms, e.g. Nanoparticles, Microcapsules, Hydrogels, and Parenteral Drug Delivery, the Osmotic Pump and Patches [Lawrence A.A 1973 and Zatz J.L., Berry J.J.1996].
1.10.1. Classification of Hydrophilic Gums and Polymers.
Gums are classified into four categories, on the basis of source of origin viz. Natural, biosynthetic, semi synthetic and synthetic.

- **Natural gums:**
  - **Plant origin gums**
    1) Gum Arabic- obtained from *Acacia Senegal* plant.
    2) Karaya Gum – obtained from Sterculia urens.
  - **Seaweed derived gums**
    1) Agar-agar obtained from *Sphaerococcus, Euchema* and *Gelidium*.
    2) Alginates- extracted from brown seaweed or kelp
    3) Carrageenans- obtained from red seaweeds *Rhodophyceae*.
  - **Animal Origin Gums**
    1) Gelatin- derived from collagen from animal connective tissues.

- **Biosynthetic Gums**
  These gums are obtained as a result of microbial fermentation.
  1) Gellan gum- derived from *Pseudomonas elodea* organism.
  2) Pulan gum- obtained from *Aureobasidium pullulans*.

- **Semisynthetic Gums**
  These gums are basically modified gums and are prepared by chemical reaction of materials of natural origin. They can be further classified as-
  - Chitosan –from *Crustaceans* ,
  - MethylCellulose (MC),
  - Microcrystalline cellulose (MCC),
  - Carboxymethylcellulose (CMC) and
  - Hydroxypropyl methyl cellulose (HPMC)

- **Synthetic Gums**
  These are the gums of synthetic origin -
  - Carbomer (Polyacrylic acid),
  - Polyvinyl pyrrolidone (PVP)
  - Poly vinyl alcohol (PVA)  [Lawrence A.A 1973]
1.10.2. Applications of Hydrophilic Gums and Polymers

- **Pharmaceutical Aid**-
  1) Binding agent,
  2) Disintegrating agent
  3) Suspending agent
  4) Emulsifying agent
  5) Gelling agent
  6) Viscosity builder etc.

- **Therapeutic Uses**-
  1) As a demulcent
  2) Antidiabetic agent
  3) Antiobesity agent
  4) Haemostatic
  5) Probiotics
  6) Antidote for heavy metal intoxication etc.

1.11. Methods of Enhancement of Dissolution
The pharmaceutical advances, which engage modification of formulation, manufacturing, procedure or the physicochemical characters of the drug without altering the chemical structure. The effort whether optimizing the manufacturing process, formulation or physicochemical characters of the drug, are mainly intended at improvement of dissolution rate, which plays important role in enhancing absorption of most drugs. There are a number of ways in which solubilization for drugs can be improved. Some of widely used techniques, nearly all of which are aimed at increasing the efficient surface of drugs [Takada et al., 2003].
- The Micronization
- Utilization of Surfactants
- Utilization of salt forms
- Employment of metastable Polymorphs
- Formation of Solute - Solvent complexation
- Deposition of Solvent
- Adsorption on Selective Insoluble Carriers
- Preparation of Solid solutions

1.11.1. Solid solutions
The three means by which the particle size of a drug can be reduced to sub micron level are-
- Utilization solid solutions
- Utilization of eutectic mixtures, and
- Utilization of solid dispersions.

1.11.2. Solid Dispersions
Oral solid dosage forms by their physical properties influences the rate and amount of absorption and bioavailability. The bioavailability is the main problem with hydrophobic drugs; particularly those posses solubility in water < 0.1 mg per ml when this type of water insoluble drugs shows incomplete or unpredictable absorption from gastrointestinal tract [David J.W et al., 2002].
To solve a problem of less bioavailability, related with hydrophobic drugs the first effort is to find a soluble active derivative. If that is not probable or not advantageous than technique such as complexation, solubilization, solid dispersion etc. To enhance the various factors such as low dissolution rates, poor solubility, researcher worked carried out for conversion of drugs in solid dispersion form.

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP)</td>
<td>Flufenamic acid</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose (HPMC)</td>
<td>Albendazole, Benidipine</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Urea</td>
<td>Ofloxacin</td>
</tr>
</tbody>
</table>

**Fig. 1.26. Examples of carriers and drugs**
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solid dispersion type</th>
<th>Matrix</th>
<th>Drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Eutectics</td>
<td>C</td>
<td>C</td>
<td>The first type of solid dispersion prepared</td>
</tr>
<tr>
<td>II.</td>
<td>Amorphous precipitation in the crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>Rarely encountered</td>
</tr>
<tr>
<td>III.</td>
<td>Solid solutions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td>Continuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Miscible at all compositions never prepared</td>
</tr>
<tr>
<td>b.</td>
<td>Discontinuous Solid solutions</td>
<td>C</td>
<td>M</td>
<td>Partially miscible, 2 phases even though drug is molecularly dispersed</td>
</tr>
<tr>
<td>c.</td>
<td>Substitution Solid solutions</td>
<td>C</td>
<td>M</td>
<td>Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case drug and matrix are substitution and can be continuous or discontinuous.</td>
</tr>
<tr>
<td>d.</td>
<td>Interstitial Solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility discontinues. e.g. Drug in helical interspaces of PEG.</td>
</tr>
<tr>
<td>e.</td>
<td>Glass suspension</td>
<td>A</td>
<td>C</td>
<td>Particle size of dispersed phase depends on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix.</td>
</tr>
<tr>
<td>f.</td>
<td>Glass suspension</td>
<td>A</td>
<td>A</td>
<td>Particle size of dispersed phase depends on cooling/evaporation rate. Many solid dispersions are of this type.</td>
</tr>
<tr>
<td>g.</td>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation.</td>
</tr>
</tbody>
</table>

Fig. No. 1.27. Classification of Solid Dispersions
Fig. No. 1.28. Eutectic mixture phase diagram

Fig. No. 1.29. Techniques in Solid Dispersions
Fig. No. 1.30. Schematic Representation of Solid Dispersion Process
## Solid Dispersion Applications

- Harmonized distribution in solid state of drug.
- Stabilization of unbalanced drug.
- Distribution in a solid dosage form of liquid or gaseous composites.
- In prolonged release dosage form it can be useful for primary dose immediate release.
- By adopting such carriers which are insoluble it can prolong the release of soluble drugs.

### Fig. No. 1.31. Applications of Solid Dispersions

## Solid Dispersion Limitations

- Preparation methods are quite lengthy and costly.
- Physicochemical properties are lack in reproducibility.
- Manufacturing processes are difficult to Scale-up.
- Drug-carrier-vehicle stabilities are difficult to maintain.

### Fig. No. 1.32. Limitations of Solid Dispersions
1.12. Antihypertensive Drugs

Following drugs involved in the handling of hypertension can be divided according to site of action as follows:

I. Drug acting centrally
   - Alpha$_2$-adrenergic receptor stimulants e.g. Clonidine and Methyldopa.
   - Selective imidazole receptor (1- receptor) stimulatants. e.g. Moxonidine

II. Drugs acting on the autonomic ganglia
   - Trimethaphan Drug as Ganglion congesting agents

III. Drugs acting on the postganglionic sympathetic nerve endings
   - Adrenergic neuron blockers. e.g. Guanethidine, Bethanidine, Debrisoquine
   - Catecholamine depletors. e.g. Reserpine.

IV. Drugs acting on adrenergic receptors
   - e.g., Phentolamine, Phenoxybenzamine used as α$_2$- adrenergic choking agent
   - β -adrenergic blocking agents. e.g. Propranolol, Atenolol, Metoprolol
   - Both β and α adrenergic congesting agents e.g. Labetalol

V. Drug acting directly on vascular smooth muscle (vasodilators)
   - Arteriolar vasodilators.e.g., Hydralazine as a Calcium channel blockers
   - Arteriolar- e.g. Sodium nitroprusside as a Venular vasodilators

VI. Potassium channel activators
   - e.g. Nicorandil, Diazoxide, Minoxidil, Pinacidil

VII. Drugs which block rennin- angiotensin-aldosterone axis
   - Those which block rennin release. e.g. β - adrenergic blockers
   - Those which block the conversion of angiotension II by inhibiting the angiotensin ACE.
   - Those which competitively stop angiotensin II at the vascular receptor sites. e.g. losartan
   - Those which counteract the action of aldosterone. e.g.Sipronolactone.

VIII. Oral diuretics e.g. Thiazides

IX. Miscellaneous e.g. Metyrosine [Tripathi K. D. 2003].
1.13. DRUG PROFILE

2.1.1. Nifedipine

**Generic Name**: Nifedipine

**Chemical Name**: 3, 5 Pypidinecarboxylic Acid, 1,4-dihydro-2,6-dimethyl—4(2-3, 5 nitrophenyl), dimethyl ester,

![Nifedipine Structural Formula](image)

**Structure:**

**Description**: Yellow Crystals.

**Solubility**: Water insoluble, light alcohol soluble. Free solubility in chloroform as well as acetone.

**Melting point**: 172-174°C

**Molecular weight**: 346.3

**Dose:**
The recommended dose for the adult, orally initially 10mg 3 times a day to increased gradually to 20-30 mg, 2 or 4 times a day, if necessary (doses exceeding 180 mg a day, are not recommended sustained release. Initially 30
to 60 mg once a day, titrate to maximum (over 7-14 days period). [Goodman Gilman et al., 1996] and [Remington for pharmaceutical students et al., 1995].

**Dosage Forms:**
- In Capsules dosage form, **Dose** - 10 and 20 mg.
- In Sustained release tablets - **Dose** - 30, 60, and 90 mg

**Mechanism of Action:**
Nifedipine blocks channels of calcium. Such drugs stop Cl\(^+\) ions transportation in to the cells of soft tissues. In view of the fact that calcium is vital in muscle contraction and soothing coronary route. Nifedipine helpful to treat as well as avoiding chestach i.e. angina pectoris. [Tripathi K. D. 2003].

**Pharmacokinetic Parameters:**
Near about 90% of an oral drug is absorbed, but its bioavailability is 65 to 70%, there is momentous hepatic first pass metabolism > 90% drug is binds with protein. It is converted to active metabolites, possibly by the liver. Mainly (80%) of inactive metabolites, are excreted in urine, 15% are excreted in stool.
The decay or half – life is 2 – 6 hrs, sustained release dosage forms presents longer effective plasma levels.

**Therapeutic Use:**
The half – life is 2 – 6 hrs, sustained release dosage forms gives longer effective plasma levels. Nifedipine helpful to treat as well as, avoiding chestach i.e. angina pectoris. Nifedipine can be utilized as Anti hypertensive medicament.

**Drug Interactions:**
Particularly for β-blocking agents, quinidine, warfarin and calcium, Hyper tensing drugs. Keep away from any drugs that increase heart rate. These types of drugs are frequently found in over the counter - cold and - cough products. Evade eating grape fruit of drink grapefruit juice.
**Adverse Effects:**
Nifedipine may lead to cause dizziness and light headiness particularly in early stage of treatment. If seats as well as sleep on bed don’t getup false. Patients can have bloat like burning of heart, unclear eye site, nausea, muscular spasms, flush, sweat, headache, also unsleepness. All things could be disappears as patient adjust for treatment, indications of an allergic reaction involves, itching swelling, rash, trouble breathing and dizziness.

**Storage:** Avoid direct light and temperature, keep at room temperature.

**Contraindications:**
Nifedipine using patients
- Tight aortic stenosis
- Severe myocardial diffraction depression
- Clinical heart failure
- Unstable angina
- Pre-existing hypertension
1.13.2. Diltiazem Hydrochloride

Structure:

![Structure Diltiazem Hydrochloride](image)

**Fig. No. 1.34. Structure Diltiazem Hydrochloride**

Cis-d-3-Acetyloxy-5-(2-dimethyl amino ethyl)-2, 3-dihydro-2-(4-methoxy phenyl)-1, 5-benzothiazepin-4 (5 H)–one hydrochloride.

**Chemistry:**
- Mol. Formula: C_{22}H_{26}N_{2}O_{4}S. HCl
- Mol. Weight: 451.0 (414.5)
- Melting range: 214-218 °C
- pKa (> N-) : 7.7
- Description: Pallid with no odor bitter crystals in taste.
- Dose: Initially, 30 - 60 mg thrice in a day; maximum 480 mg.
- Solubility: Soluble- Methanol, Chloroform and Water.
  - Ssparingly Soluble- Formic acid and Ethanol.
  - Insoluble-Ether

**Storage:** store at light resistant, well closed container.

**Therapeutic Uses:**
- Stable and Unstable angina, MI, Coronary spasm, Hypertension, Cardiac Arrhythmias.
Pharmacology:
Diltiazem blocks channels of calcium. Such drugs stop Cl$^-$ ions transportation into the cells of soft tissues. In view of the fact that calcium is vital in muscle contraction and soothing coronary route. It is helpful to treat as well as avoiding chestach i.e. angina pectoris. (Tripathi K. D. 2003).

Pharmacokinetics:
Oral rout absorbs nearly 90% and before absorption metabolize 45-55%, Plasma half life range 3.5 ± 1.2 H, Volume of distribution systemic 5.1/kg Plasma protein binding 80-90%.

Adverse reactions:
Diltiazem may increase mortality for candidates having impaired left ventricle functions latter acute MI. Vasodilatation may be responsible for hypotension as well as facial flushing and pedal edema but these vasodilator properties rarely lead to serious unwanted actions.

Dosage forms:
Tablets : 30 and 60 mg.
Injection : 5 mg/ml.
Extended release capsules : 90, 120 and 180 mg.
1.13.3. Ofloxacin

**Generic Name**: Ofloxacin

**Chemical Name**: (RS)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo [7.3.1.0] trideca-5(13),6,8,11-tetraene-11-carboxylic acid

**Structural Formula**:

![Ofloxacin Structural Formula](image)

**Molecular Formula**: $C_{18}H_{20}FN_{3}O_{4}$

**Molecular Weight**: 361.368 g/mol

**Melting point**: 254 °C

**pKa (> N–)**: 7.7

**Half Life**: 5–6 hours

**Description**: Off-white to yellow crystals

**Solubility in water**: Insoluble

**Dose**: 200-600 mg twice daily
**Category**
- It is used as
  - Anti-Infectives, Anti-Bacterial Agents
  - Quinolones, Nucleic Acid Synthesis Inhibitors
  - Anti-Infective Agents, Urinary

**Dosage forms:**
- Tablet (With numerous strength),
- Solutions Orally-(250 mg/ml),
- Solutions-(numerous strength).
- Eye drops and Ear drops.

**Storage:** Store at room temperature, avoid light and temperature.

**Mechanism of Action:**
It is broad-spectrum antibiotic agent and is active against Gram-positive as well as Gram negative microbes. Inhibits gyrase of DNA, a type II & IV topoisomerase, that is an enzyme required to divide replicated DNA, by prohibiting bacterial cell separation.

**Pharmacokinetic Parameters:**
Climax blood intensity with 2.2μgpermL also with 3.6μgperml is expected at constant speed on multiple doses like 200-300 mg doses respectively. Near about 32percentage of the drug bounds to protein. It was detected in lung tissue, ovary, blister fluid, cervix, prostatic tissue, prostatic fluid, skin, and sputum. Ring of Pyridobenzoaxazine emerge to decline an amount of original composite metabolize. < 5% is removed through renal.

**Pharmacodynamic Parameters:**
when 65-80% administered orally shows 98% absorption liver metabolizes and within 48 removes by kidneys. 4-8 % excretes as unchanged via in the fecal.
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**Therapeutic Use:**
It is utilized in: Community-acquired pneumonia, Bronchitis, Skin infections, Urethra and cervix Mixed Infections, urethritis and cervicitis caused by Nongonococcal, Cystitis, Prostatitis, Urinary Tract Infections, Pelvic Inflammatory Disease, Urethral and Cervical gonorrhea.

**Drug Interactions:**
Absorption of ofloxacin may substantially decrease with administration of aluminum or magnesium antacids, sucralfate, calcium, iron or zinc. Ofloxacin hamper caffeine digestion, raise systemic theophylline improves warfarin activity. While undergoing fluoroquinolone therapy the use of NSAIDs not permitted because it leads to CNS ADR. Ofloxacin may enhance activity of Anisindione as well as cardiac toxicity arrives with barbiturate, Quinidine and Quinidine barbiturate.

**Adverse effects:**
Nerve, tendon harm, heart crisis, muscular killing, Liver crisis, Hematologic reactions and renal toxicities may happen after multiple doses.

**Contraindications:**
Ofloxacin is being contraindicated in STD treatment because of more chances of poor responses for antibiotics the fluoroquinolones in Southeast Asia. Also in the treatment of pediatrics, because of crisis to skeletal system [C.N. Nalini et.al.2011] and [Tripathi K. D. 2003].
1.14. Polymer Profile

1.13.1. Eudragit Rs-100

**Generic Name**: Eudragit Rs-100

**Chemical name**: Poly (ethylacrylate, methylmethacrylate, Hylammonioethyl methacrylate chloride) 1:2:0:1.

**Structural Formula**:

![Structural Formula of Eudragit Rs-100]

**Fig. No. 1.36. Chemical structure of Eudragit Rs-100**

- $R_1 = CH_3$,
- $R_2 = C_2H_5$
- $R_3 = CH_2CH_2N(CH_3)_3+Cl$.

**Functional Category**: Coating or Film forming agent also used as diluent and binder in tablet.

**Description**: Polymethacrylates are dimethylaminoethylmethacrylates as well as esters of methacrylic as well as methacrylic acid in different concentrations. Numerous different types also occur like dried fine particles, suspensions in water, nonaqueous solutions. Eudragit RS -100 occurred as fine powder, white colour as well as amine like odor. It composes $\geq 97\%$ of dry polymer.
Typical properties:

**Density: (bulk):** 0.390 gm/cm$^3$

**Density : (lapped):** -0.424 gm/cm$^3$

**Density: (true):** 0.816-0.836 gm/cm$^3$

**Solubility:**
Eudragit RS100 is freely soluble in alcohol, acetone, ethyl acetate and dichloromethane. Eudragit RS100 is insoluble in water, NaOH and petroleum ether.

**Stability and storage conditions:**
Dry powder form, secure at temperatures < 30°C. Beyond given temperature, it tends to create clumps and not affect value of substance as well as clumps could easily broken down and remains as it is minimum 3 yrs, in a air tight container at 30°C.

**Incompatibilities:**
Solid polymethacrylates incompatible with some drugs, but compatible with organic solutions, little bit with aqueous dispersions.

**Applications in pharmaceutical Area:**
Polymethacrylates utilized for Extended Release solid unit dosages forms (capsule tablet), filmformer and Transdermal Patches. [Y.W. Chein et al., 1992].

Structural formula:

![Molecular structure of PVP K 30](image)

Fig. No. 1.37. Molecular structure of PVP K 30

Nonproprietary Names: Povidone, polyvidonum

Synonyms: Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; Polyvidone; polyvinyl pyrrolidone;PVP; 1-vinyl 2-pyrrolidinone polymers.

Chemically known: 1-ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: (C6H9NO)ₙ

Molecular Weight: 2500-3000000

Functional Category: Tablet binder, Disintegrant; Suspending Agent, Dissolution aid.

Description:

It is odorless, free flowing whitish cream-whitish look, hygroscopic particles. Povidone have values of K either equal to 30 or < 30. Those are contrived through spray-drying are exist in free flowing spheres. Those Povidone having Kvalues nearly equal to 90 as well as more than 90 are contrived through drum-drying technique and exist in thin flex plates. [Raymond et. al., 2007]

Typical properties:

- pH=3- 7.
- bulk and tap Density : 0.409g/cm³ 0.508g/cm³
- Density(true): 1.180g/cm³
- Flow ability: 20g/s for povidone PVP K-30 16g/s
- Melting point: 150 °C
- Moisture content: potent hygroscopic, maximum amounts of wetness being engrossed at low RH.
Solubility:
In Acids, ethanol, chloroform, water ketones, and Methyl alcohol. Insoluble in, oil, hydrocarbons and ether.

Preservation:
It is cast a shadow up to or excising temp 150 °c, along with loss aqua solubility. It is firm at 110-130 °C.

Incompatibilities:
It is stable into solutions containing inorganic salts, synthetic as well as natural resins and other chemicals. Povidone creates adduct with sulfathiazole, salicylic acid and additional amalgam.

Safety:
It’s nontoxic as well as unabsorbed through GIT and through membranes. It no causes any irritancy towards skin as well as without sensitization.

Application in pharmaceutical formulation or technology:
- The PVP K-30 solutions are used as binder in wet-granulation processes.
- PVP K-30 is utilized Solubilizer in parentral and oral formulation.
- It may also be utilized as coating agent.
- It is utilized as suspending agent, increases Viscosity in a number of External as well as oral suspension and solution.

Used as: carrier for drug (10-25%)  
Dispersing agent (5%)  
Eye drops (2-10%)  
Suspending agent (5%)
1.14.3. HPMC

Synonyms: Hydroxy Propyl MethylCellulose: E464, Hydroxypropyl Ethyl Cellulose, Hypermellose

Empirical Formula and Molecular Weight: \( C_{8}H_{15}O_{5}-(C_{6}H_{18}O_{6})_{8}-C_{8}H_{15}O_{5} \)

![Structural Formula of HPMC](image)

R -H, CH3CH (OH) CH2or CH3,

**Fig No. 1.38. Structural Formula of HPMC**

**Functional Category:**
Coat forming and film forming agent, sustains dissolution, used in suspension, binding excipient for tablet, thickness enhancer.

**Pharmaceutical Applications:**
It utilized binder for tablet, Coat forming agent, polymer in ER tablets.

**Description:**
HPMC is tasteless and an odorless, creamy-white or white granular or fibrous powder.
Typical Properties:

**Bulkiness Density:** 0.341 g/cm$^3$,

**Tappiness Density:** 0.557 g/cm$^3$

**Solubility:**
It is not soluble in ethanol (95%) as well as chloroform,
Solubilized in cold water as well as ether.

**Incompatibilities:**
It is not compatible with oxidizing ingredients will not form intricate through ionic organics leads to create insoluble impulsive.

**Regulatory Status:**
GRAS listed. In Europe acknowledged for foods, incorporated by FDA like an inactive element. (Capsules, ophthalmic preparations, tablet, as well as suspensions, and topical). Added in per oral medicine got permission at UK.
1.14.4. Xanthan Gum

It is a naturally occurred as well as biosynthesized, safe to eat and extra cellular polysaccharide obtained from \textit{Xanthomonas compestris}.

**Synonyms:**
Xantural, Vanzan NF; E415; Keltrol; Rhodigel; Corn sugar gum;

**Structure:**
\((C_{35}H_{49}O_{29})_n, 2 \times 10^6\)

\[\text{Fig. No. 1.39. Chemical structure of Xanthan Gum}\]

**Structural Formula:**
5 sugar residues: 2 mannose, 2 glucose, 1 glucuronic acid. \(4\beta\)-d-glucose connected to 1 & 4 stages in the polymer backbone.

**Functional Category:**
Suspending agent, Viscosity Enhancer, Stabilizing Agent

**Pharmaceutical Applications:**
Utilized in topical, oral formulations, food products, cosmetic preparations, a stabilizer and in suspension, Viscosity Enhancer and emulgent and rate
retarding matrix polymer in tablet.

**Description:**
Xanthan gum is odorless, free-flowing, fine powder white - or -cream colored.

**Typical Properties:**

**Melting point:** Chars at 270°C.

**Refractive index:** $n_{D}^{20} = 1.333$ for a 1% w/v solution.

**Solubility:**
In ethanol, ether not soluble free solubilized into warm and cold water.

**Viscosity:** 1% w/v aqueous solution at 25°C has 1200–1600 mPa s (1200–1600 cP).

**Incompatibilities:**
Is incompatible for polymers, surfactants (cationic) as well as preservatives leads to precipitin. The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the presence of some materials such as ceratonia, guar gum, and magnesium aluminum silicate.

**Regulatory Status:**
Accepted for use as a food additive at Europe. Included in the FDA Inactive constituents list, (solid, liquid dosage forms). Included in nonparenteral medicines and permitted at Canada and U.K.
1.14.5. Guar Gum

Synonyms : guar flour, jaguar gum and Galactosol,

Biological source : Its non-ionic poly-saccharide obtained by ground endosperms seeds belongs to Cyamopsis- tetragonolobus (Leguminosae).

Description : white to yellowish colour, odorless, amorphous, fine powder with characteristic odor and gummy taste. It swells rapidly in water with translucent suspension.

Solubility : In organic solvents practically insoluble. In hot and cold water go away and puff up almost instantly leads to a very viscous, solution.

Viscosity : 4860cps for 1%w/v dispersion at 25°C.

Functional category: It is used as emulsifying suspending agent, thickening agent.

Chemical structure:

![Chemical structure of guar gum]

Chemistry: It comprises of mannose galactose lateral branch and hence known as galactomannan gum.

Applications: Guar gum is used in food products, cosmetics and pharmaceutical products, sustained release matrix tablets, also use as a binder and disintegrants, to stabilize suspension and emulsion. [Rowe, R.C. & Sheskey].
1.14.6. Gelatin

**Synonym**: Gelatin

**Sources for gelatin**: Gelatin can be obtained with chemical treatment to collagen separated with very dilute acid from animal skin and bones. It is also obtained by extraction process from fish skins.

**Description**: white powder

**Solubility**: Water

**Viscosity**: is 0.69 dl/gm in water

**Chemical structure**: Composed with glycine mostly 1 into 3 remainders, prearranged each 3rd remainders, 4-hydroxyproline as well as proline remainders.

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![Chemical structure of Gelatin](image)

**Fig. No. 1.41. Gelatin Chemical structure**

**Chemistry**: Its blend of multi-stranded/single poly-peptides, enlarged left-hand proline helix structure, contains thousands of amino acids. The triple helix of type I collagen is contain Two α1 (I) and one α2 (I) chains.

**Use**: Gelling reagent, emulsifier in cream, foam stabilizer, surface films, at food industries and beverages. [Guy Matthew John Jones]
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1.15. Literature Review

- **Juergen Siepmann Florence Siepmann [et al., 2006]** Reviewed imperative approaches utilizing microparticle for enhancing medicament therapy, to get better the competence of various medical treatments. Particular importance given towards various methods of preparing microparticles.

- **Majeti N. V. Ravi Kumar [et al., 2000]** discovered the concept of microparticles, which are described spherical, hollow, spears. However, synonymously both the terms microcapsules and microspheres are used to all type of microparticles.

- **Wasfy M. Obeidat [et al., 2009]** Described and owed the different methods of preparation which are typically constructive for polymeric microparticles research in the area of microparticles.

- **Dey NS, MEB Rao [et al., 2010]** Reviewed drug delivery systems facilitate the addition of active constituents in microparticle. Therefore provided that plentiful curative and marketable benefits. Microparticle devices present vital benefits counting great suppleness and malleability of microparticles.

- **Ravi Kumar Reddy J. [et al., 2009]** Formulated and evaluated microparticles of Metronidazole and observed the delayed release of Metronidazole microparticles, by using CAP, HPMCP, EudragitL-100 and Eudragit S-100 as coating materials.

- **Abhay N. Padalkar and [et al., 2011]** Formulated and evaluated Microparticles to analyze use of various polymers for active moiety transportation, for increase curative advantages, and reduction of unwanted results.

- **Sachin E. Bhadke [et. al., 2006]** Formulated and evaluated of Repaglinide Microparticles by gelation methodology utilizing various polymer to extend the action of drug and studied various physicochemical parameters affect on microparticles characters.

- **Severine Jaspart [et. al., 2011]** Studied solid lipid microparticles composed of Salbutamol. Microparticle prepared with hot emulsion procedure and evaluated for various parameters.
Madhav N.V. [et. al. 2010] reviewed on aspects regarding microparticles, also technique of preparation. Also focused the various evaluation parameters.

Swarupananda Mukherjee [et. al., 2006] Prepared controlled release Nifedipine microparticulate system utilizing starch acetate as the rate controlling polymer. The prepared microparticles were subjected to standard evaluation.

Amal H. El-Kamel [et.al. 2005] Prepared captopril sustained release microparticles method involves evaporation of medium e.g. solvent and studied various factors affecting procedure. Like mol. weight of polymer, polymer content. Combination of drug and used polymer, on physiological characters of microparticle such as, flowing property, morphology, particle size and release characteristics of the drug.

Duane T. Birnbaum [et al., 2010] Prepared biologically degradable microspheres composed of luteinizing enzyme. and evaluated for such as, flowing property, morphology, particle size and release characteristics.

S. S. Bansode [et al., 2009] Reviewed the materials used in microencapsulation means for active moieties discharge from polymer methods of preparation and evolutionary parameters.

Yadav A.V. [et al., 2007] Formulated and evaluated microcapsules with enhanced drug transportation for intestinal area using ethyl cellulose rate retarding polymer.

Ofokans KC [et al., 2007] Formulated Microspheres of Cefuroxime. Reported that swellable microspheres based on admixtures of polymers are commonly utilized for dosage forms to obtain controlled delivery of active moieties and particular target for incorporated drug.

Simon Benita [et al., 2005] Found new and improved microencapsulation methodology for preparation of microcapsules, for the new discovered drug entities.

Li Dong Xun [et al., 2009] Formulated and evaluated Nifedipine microcapsule with gelatin and Eudragit acrylic resin polymer by help of a spray-drying method, the drug release of microcapsule were evaluated using rats against pure Nifedipine.
- **Sandile M. Khamanga [et al., 2002]** Prepared microcapsules of eudragit RS as well as RL-100 including verapamil as well as propranolol and evaluated mechanism of drug release as well as kinetics from prepared microcapsules.
- **Nokhodchi A. and Djavad Farid [2009]** prepared microcapsules of paracetamol using emulsion and solvent evaporation method as well as modified emulsion solvent evaporation method as well as emulsion nonsolvent addition (ENSA) method. Found that all methods given good results and reproducible parameters like, microcapsules size, drug content also drug release speed from dosage form. Major dissimilarity found in the applied procedures like time required to prepare microcapsules, percent drug, diameter of microcapsule, and drug discharge pattern.
- **Chowdary K.P.R. [et al., 2010]** prepared Nifedipine microspheres using olibanum resin and colophony as natural materials, and evaluated for various parameters.
- **MD. Sarfaraz [et al., 1996]** formulated and evaluated Rifampicin biodegradable microcapsules by emulsification-ionic gelation method for a novel controlled release product. Carbopol and Sodium alginate used as coating polymers in different ratios.
- **Chowdary KPR [et al., 2009]** Studied Microencapsulation of Nifedipine-MCC solvent deposited system for sustained release Nifedipine and its solvent deposited systems on Microcrystalline Cellulose polymer. After that microcapsules were prepared using cellulose acetate polymer using emulsification solvent evaporation technique and were studied for flowing property, surface characters, as well as size of particles and release phenomenon of drug.
- **Deore B.V. [et al., 2010]** Worked on solid dispersed Ketoprofen produced by a solvent diffusion methodology containing as core material and Aerosil dispersing carrier for enhancing water solubility of ketoprofen. After that prepared microspheres using polymer Eudragit RS100 for managing rate of discharge of drug.
- **Silva CM [et al., 2006]** protein, hemoglobin (Hb) containing microspheres were prepared using Chitosan and alginate by emulsification and internal gelation technique. Studied the effect of procedure related factors on...
emulsification stage, recovery of microsphere lastly products variables studied.

- **Angela Lopedota** [et al., 2010] Prepared a novel microparticulates based on mucoadhesioin property of polymers and find out utility of polymer Eudragit-RS 100 as well as cyclodextrins, Glutathione delivery.

- **Narender Reddy M.** [et al., 2000] Microcapsules containing Diltiazem Hcl with rosin by an emulsion solvent evaporation methodology, Using different drug and polymer concentrations to obtain sustained release drug.

- **Regina M.** [et al., 2010,] prepared microspheres containing suspended drug and PHB produced by solvent evaporation methodology. The matrix evaluated for vitro as well as invivo studies.

- **Tae Gwan Park** [et al., 2001] study represents that constant release can be done through microencapsulating reversibly dissociable protein comprehensive inside biodegradable polymers.

- **Udupa N.** [et. al., 1994] Developed three different implantable formulations, containing Flubiprofen with three biodegradable aliphatic polyesters, hydrophilic polymers e.g. Alginates and HPMC using ionotropic gelation methodology, the three dosage forms are polymeric form, microspheres and pellets. Studied the effect of different formulations polymers property.

- **Kakkar A. P.** [1995] Developed and evaluated Ibuprofen loaded microcapsules using calcium chloride as well as sodium alginate with ionotropie gelation technique. Microspheres were smooth surfaced Spherical. The preparation of microsphere was based on concentration of sodium alginate-Ibuprofen matrix in liquid paraffin followed by coating process by calcium chloride.

- **Guzman M.** [et.al. 1996] Designed and studied ketoprofen microspheres using poly-e-caprolactone and hydroxyl propyl methyl cellulose phthalate. Studied the effects of various process parameters on microspheres.

- **Cuna M.** [et. al., 1997] Prepared Cefuroxime Axetil microspheres. The CAT other hydroxyl propyl methyl cellulose phthalate and HPMCP-50-55 by solvent extraction procedure. Studied constancy, % of drug discharge.
Cilurzo F. and Mangetti P. [et. al. 2002] The HPMC is used as solubility enhancer by solid dispersion technique. Hence the required concentration of nifedipine can be achieved in blood.

Arias M. J. [et. al 2002] Studied disbanding possessions and invivo performance of triamterene in solid dispersions with poyethelyne glycol. The prepared solid dispersions were studied for various parameters.

Ganza A. Gonzalcz [et. al., 1999] Reported the preparation of chitosan and chondroitin microspheres of metoclopramide by using solvent evaporation technique and evaluated for various parameters.

Chikwa H. Z. [et. al., 1997] produced the prolonged releasing microcapsules containing Diclofenac sodium by solvent evaporation methodology and analyzed effects relevant to various polymers concentration upon Diclofenac sodium release pattern.

Agar Ali [et. al., 1998] prepared the Sustained release microparticles of Nifedipine by using polyvinyl acetate as rate retarding polymer and evaluated for various parameters.

Gopte [et. al., 2004] Prepared and Evaluated paclitaxed S-fu and palitaxel +5 FU PLGA microspheres using modified evaporation technique. analyzed the efficiency of materials to microencapsulate the drug.

Gibaud J. [et. al., 1997] Prepared and Evaluated diaminopymmidine microparticles by using PCL with solvent evaporation technique. all the microparticles were studied for evaluation parameters ,

Anand Eldin Hassan [et. al., 1997] Prepared ketoprofen extended releasing lipid micron pellets by emulsion congealing. Analyzed the efficiency of materials to microencapsulate the drug.

Guyout M. and Fawaz J. [et. al., 1998] Prepared and Evaluated the Nifedipine loaded polymeric microspheres all the microparticles were studied for evaluation parameters.

Hideki Z. Chikawd [et. al., 1997] Formulated the 100 μm sized Microcapsules with prolonged release by using western process.

Khan A. [et. al., 1997] Prepared and Evaluated Polymethylacrytate Based insulin microparticulates for oral delivery and studied for the invitro dissolution stability in presence of enzyme inhibition.
o Alf T. [et. al., 2005] Formulated the 5 FW loaded Eudragit P. 413 of microsphere by oil in water emulsion solvent evaporation methodology, therapy of colon cancer.

o Gripeg K. [et. al., 1997] Prepared and evaluated solid dispersions griseofulvin and carriers polyvinyl pyrotdione and polyethylene glycol. Reported the pharmaceutical application of same.

o Mankala S. K. et. al. [2011] – Prepared Gliclazide microspheres with sodium alginate using gum kondagogu, gum guar and xanthan gum as polymer material by orifice-ionic gelation and emulsification ionic gelation techniques. Prepared microspheres with spherical and free flowing with a size range 400-600μm. % drug content and encapsulation efficiency found in the range of 55%-68% and, 86.23%-94.46% respectively. Drug release studies showed that compared to other gums guar gum potentiality to retard the drug release with slow following zero order release kinetics with non-fickian release mechanism means release was associated to polymer and drug concentration as well as methodology.

o Rasala T. M. et. al. [2010] Microcapsules containing Diclofenac sodium and Diltiazem Hydrochloride were prepared via mucoadhesive material such Carbopol 934 as as well as HPMCK 15 in grouping with sodium alginate by orifice-ionic gelation methodology. Quality control parameters lied inside satisfactory levels. Though, trapping competence originated for diclofenac sodium (69%) as well as diltiazem HCl (15%). slow and sustained discharge achieved, discharge of drug shown depended on the concentration of coat material. It could conclude orifice-ionic gelation process is appropriate for entrapping slowly soluble drug than liberally soluble drugs.

o Ashok K. A. et. al. [2011] Prepared and evaluated microcapsule of Metformin Hcl alginate and karaya gum with gelation technique. The evaluated parameter lies within the satisfactory limits. Microcapsules appeared free flowing. Metformin discharge from microsphere was slowly independent on concentration.

method. F5 batch among the six formulations showed satisfactory results. Microspheres shown good trap efficiency as well as % yield values. The no Drug-Polymer interaction assured in Infrared spectroscopy. Batch (F5) shown In-vitro release of 92 % drug release up to 12 hour.

- **Sivanarayana P. et. al. [2011]** Prepared and evaluated microspheres of Diltiazem HCL using gelation procedure with Sodium alginate NaCMC and HPMC. The quality control constraints were within the satisfactory limits with of 99.48± 0.32% encapsulation efficiency. The cross linking agents release rate observed with following order Aluminum chloride < Barium chloride< Calcium chloride. With different cross-linking agents it can conclude that drug release is depends upon the valence and size of the cations of the respective cross-linking agent. The release rate followed zero order kinetics as well as by peppas model. The microspheres prepared with, HPMC, sodium alginate and calcium chloride exhibited a satisfactory sustained release profile for 12 hours.

- **Sambathkumar R. et. al. [2010]** Prepared and evaluated Rifabutin beads by ionotropic gelation in acidic medium. With gas-generating agent, to produce an extremely porous internal structure. Prepared Beads shown excellent buoyancy up to 18 hrs. Rifabutin release was dependent on Ca++ concentration. In this study results obtained confirmed that floating beads bearing rifabutin were able for stomach specific delivery of drug for longer period with amplified bioavailability compared to non-floating beads.

- **Patel H. et. al. [2010]** Prepared and evaluated pellets of Verapamill HCL by technique of ionotropic gelation with, HPMC and Hydroxy Propyl Cellulose in sodium alginate solution. Prepared micropellets tested in favor of dissolution study flowing property, drug trapping efficiency, and SEM. nine formulations batches the F3, F6 and F9 were shown satisfactory results, following Non-Fickian diffusion. It can accomplished that, using gelation micropellets protracted release of Verapamill HCL made possible.

- **Chakraborty A. et. al. [2011]**. Prepared and evaluated Salbutamol sulphate (SS) loaded alginate microspheres by ionotropic gelation method using different calcium chloride, magnesium aluminum silicate, barium chloride and aluminum sulphate. The size of the hot air oven dried and simple air dried microspheres obtained within range. Microspheres
followed Higuchi kinetics. The accelerated stability showed satisfactory results.

- **Umamahesh B. et al [2012]**. In the present study author prepared the Diclofenac Sodium microspheres through phase separation Co-acervation method using change in temperature technique, with different drug, gelatin and HPMC ratios. All batches of microspheres shown good results.

- **Suja C. Jayan et. al. [2009]**. Microspheres of Salbutamol sulphate developed by coacervation using temperature change technique with gelatin as a polymer. The prepared microspheres characterized for various evaluation parameters. Here author used glutaraldehyde as crosslinking agent and checked its effect. Microspheres obtained in diameter range 5.6 m- 22.4 m, spherical in shape. The loading capacity found up to 80% also the sustaining action found up to 8.5 hrs.

- **Surendiran. N. S.et. al. [2010]**. Formulated the Ibuprofen Micro spheres by using phase separation Co-acervation method using change in temperature technique with gelatine-carbopol as polymers for improvement of the bioavailability of ibuprofen. Also evaluated micromeritic properties, morphology and percent drug release. Microspheres found in size range between 60.8μm-78.5μm. In microspheres drug release study (F1) batch with less amount of gelatin shown 85.0% upto 8 hrs. and with high amount of gelatin Batch (F3) shown 66.3% drug release.

- **Roy S. et al. [2009]**. Prepared the mefenamic acid microspheres by thermal method and glutaraldehyde cross linking method with chitosan as a polymer. The prepared microspheres characterized for various evaluation parameters. Those batch prepared by using glutaraldehyde cross linking method shown fast release of drug.

- **Arunachalam A. et. al. [2010]** Found impact of process variables on diameter of Ofloxacin microspheres, prepared with different ratios of gelatin and HPMC by Co-acervation phase separation method, using temperature change technique. The obtained microspheres diameter found 42-45μm with spherical shape, e Ofloxacin entrapment found in the range of 78-90 % and also the sustaining action found up to 8.5 hrs.
Vidhyaa Kumari et.al. [2012] Prepared the Ofloxacin microspheres using natural matrix sodium alginate, Chitosan, Gelatin by non-ionic cross linking technique. The microspheres prepared in five different formulations with different concentrations of Ofloxacin and polymers. Microspheres checked for entrapment efficiency, entrapment, in-vitro release, and surface morphology characteristics. Cumulative release data were fitted into kinetic models. Also studied the effect of addition of these polymers on various characters. In the stability study of Ofloxacin microspheres 93% of drug content observed and no observable changes were occurred.