Multiparticulate dds

- Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics.
- In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm
- Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits.
- To deliver the recommended total dose, these subunits are
- filled into a sachet and encapsulated or compressed into a tablet

Advantages

- Multiparticulates are less dependent on gastric emptying
- Less inter and intra-subject variability in gastrointestinal transit time
- Better distributed and less likely to cause local irritation
- Achieve unique release pattern
- Increased bioavailability
- Reduced risk of systemic toxicity
- Reproducible pharmacokinetic behaviour than conventional (monolithic) formulations
- No dose dumping

Disadvantages

- Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

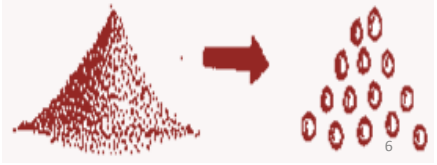
PELLETS

INTRODUCTION

WHAT ARE PELLETS?

In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment.

Historically, the term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment.



Advantages Of Pellets

High degree of flexibility in the design and development of oral dosage forms.

Offer technological advantages, such as better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing

They can be divided into desired dose strengths without formulation or process changes

Can be blended to deliver incompatible bioactive agents in the gastrointestinal (GI) tract.

In addition, pellets, taken orally, disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter- and intrapatient variability

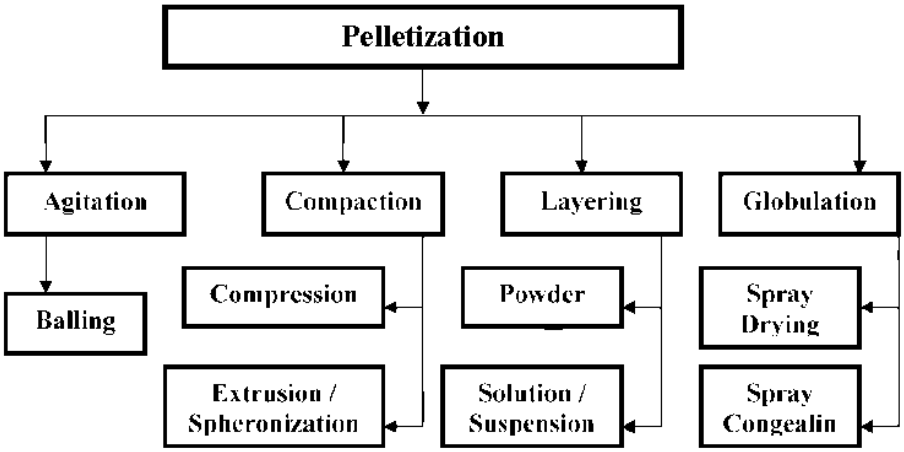
7

Disadvantages of pellets

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2mm.

8

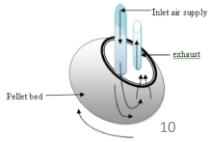
Techniques



9

POWDER LAYERING

- Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on preformed nuclei or cores with the help of a binding liquid.
- Powder layering involves the simultaneous application of the binding liquid and dry powder.
- The first equipment used to manufacture pellets on a commercial scale was the conventional coating pan, but it has significant limitations as pelletization equipment.
- The degree of mixing is very poor, and the drying process is not efficient.
- **Mixing** is a function of the **P**an shape, the **T**ilt angle, the **B**affle arrangement, and the **R**otational speed of the pan itself.



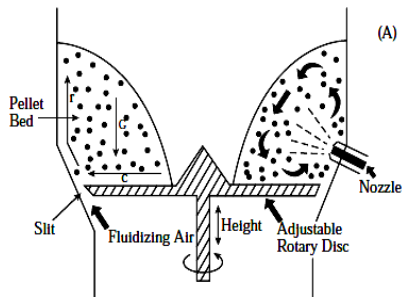
10

- Throughout the process, it is extremely important to deliver the powder accurately at a predetermined rate and in a manner that maintains equilibrium between the binder liquid application rate and the powder delivery rate.
- If the powder delivery rate is not maintained at predetermined equilibrium levels, over wetting or dust generation may occur, and neither the quality nor the yield of the product can be maximized.
- In an ideal process, no agglomeration occurs, and the particle population at the end of the process remains the same as that of the starter seeds or cores, with the only difference being an increase in the size of the pellets and thus in the total mass in the pan.

11

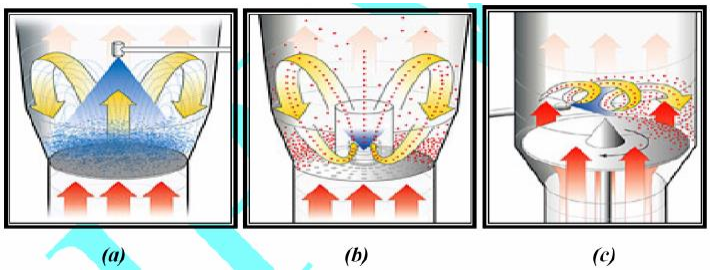
Other equipments used for powder layering process are:

- Tangential Spray granulator
- Centrifugal Fluid Bed granulator



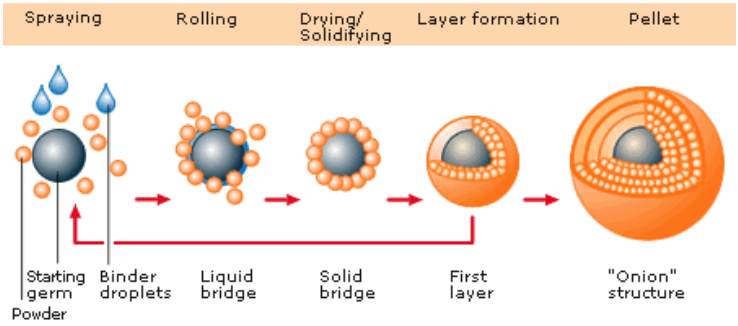
(A)Schematic representation of centrifugal fluid-bed equipment

12



(a) Principle of Top spray, (b)Bottom spray, & (C) tangential spray coating

13



Principle of Powder layering process

14

2. Solution/Suspension layering

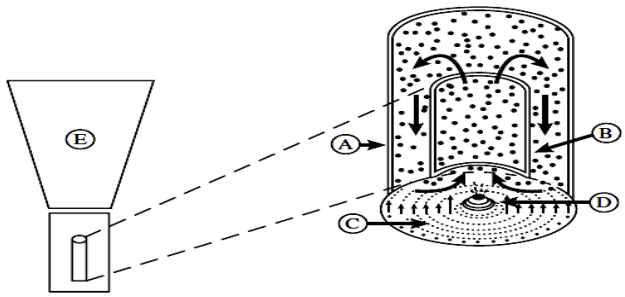
Solution/suspension layering involves the deposition of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug.

Wurster coating Process:

- This process is particularly suitable for a controlled release of active ingredients.
- In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed.
- By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently.

15

As the particles continue travelling upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.



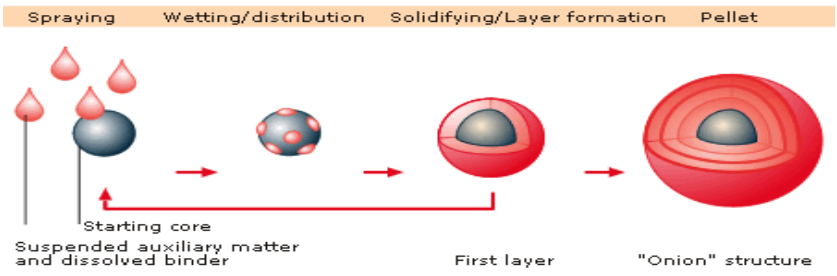
Schematic representation of the Wurster product chamber and process.
(A) product chamber, (B) partition, (C) orifice plate, (D) nozzle, and (E) expansion chamber.

16

- An important factor that needs to be considered when suspensions are used as opposed to solutions is the particle size of the drug.
- Micronized drug particles tend to provide pellets that are smooth in appearance, a property that is extremely desirable during subsequent film coating, particularly for controlled-release applications.
- If the particle size of the drug in the suspension is large, the amount of binder required to immobilize the particles onto the cores will be high, and, consequently, pellets of low potency are produced.
- The morphology of the finished pellets also tends to be rough and may adversely affect the coating process and the coated product.
- Moreover, because particles detach easily from the core they are being layered on owing to frictional forces, yield is usually low.

17

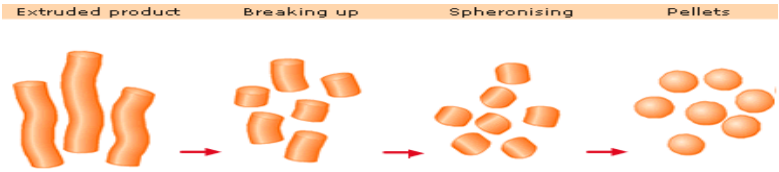
Principle of Solution layering process



18

3.EXTRUSION-SPHERONIZATION

- Extrusion–Spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening.



Variety of extruders:

- Screw-fed extruders,
- Gravity-fed extruders, and
- Ram extruders

19

➢**Screw-fed extruder:** The screw rotates along the horizontal axis and hence transports the material horizontally;

They may be of two types:

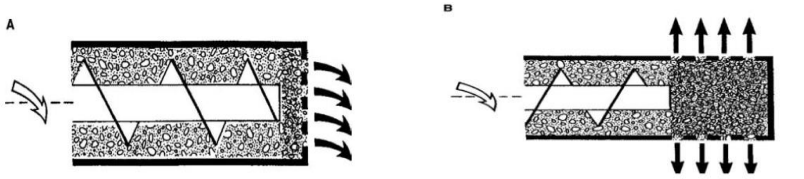
1. **A**xial screw extruders,
2. **R**adial screw extruders.

1. **Axial extruders**: These have a die plate that is positioned axially, consist of a feeding zone, a compression zone, and an extrusion zone.

2. **Radial extruders**: The transport zone is short, and the material is extruded radially through screens mounted around the horizontal axis of the screws.

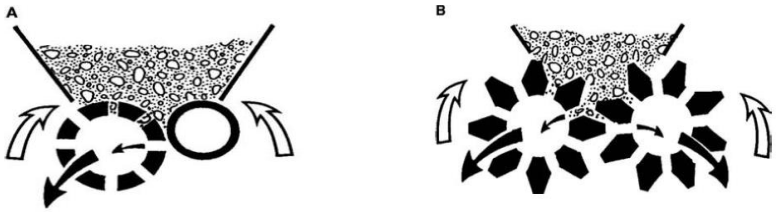
20

Screw-fed Extruders:



(A)Axial extruder (B)Radial screw extruder

Gravity-fed Extruders:



(A)Rotary-cylinder extruder (B) Rotary-gear extruder

21

➢**Gravity-fed extruder**s:

These are of two types , which differ primarily in the design of the two counter-rotating cylinders.

1. The Rotary Cylinder and
2. Rotary Gear Extruders

1. **Rotary Cylinder Extruder**: One of the two counter-rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller.

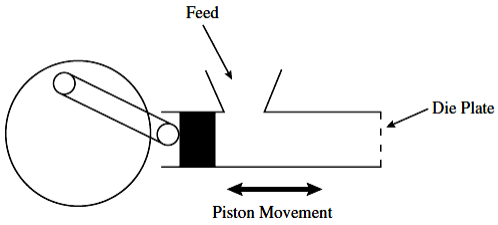
2. **Rotary-Gear Extruder:** There are two hollow counter-rotating gear cylinders with counterbored holes.

22

➢**Ram Extruders:**

1. The ram extruder is probably the oldest type of extruders; a piston displaces and forces the material through a die at the end.

2. These extruders are preferentially used in the development phase, because they can also measure the rheological properties of formulations.



Ram Extruder

23

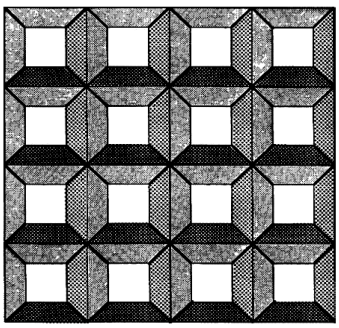
Marumeriser (spheroniser):

It consists of a two parts:

1. Static cylinder or stator and
2. Rotating friction plate.

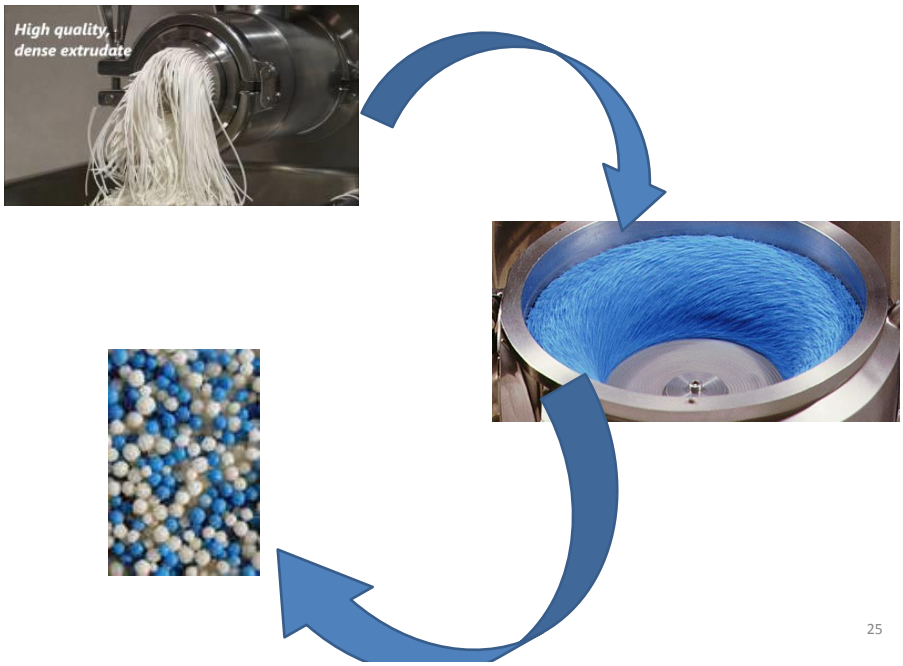
A typical friction plate has a crosshatch pattern, where the grooves intersect at a 90^0 angle.

The rotational speed of the friction plate is variable and ranges from 100 to 2000 rpm; depending on the diameter of the unit.



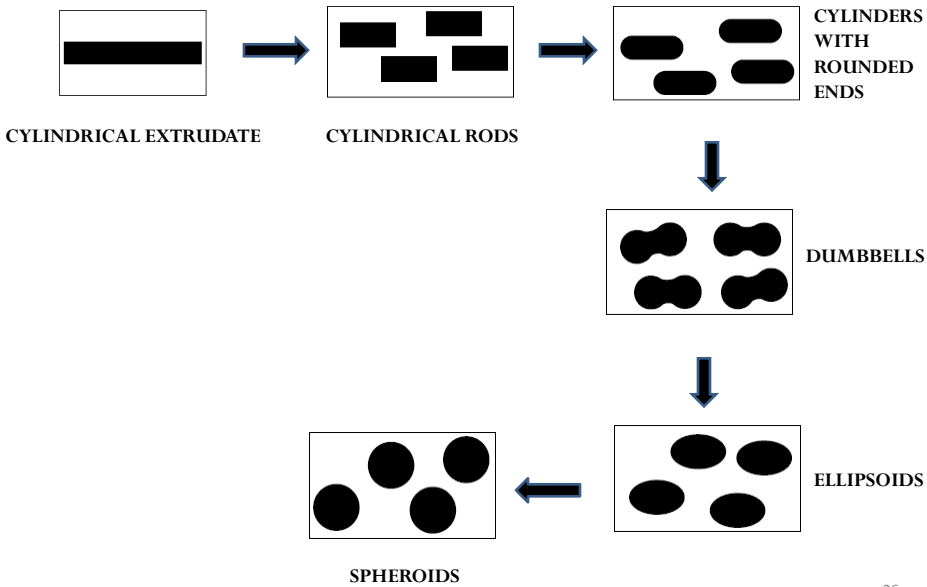
Spheronizer friction plate with a cross-hatch pattern.

24



25

Shape transitions during a Spheronization process



26

In an extrusion–spheronization process, formulation components such as fillers, lubricants, and pH modifiers play a critical role in producing pellets with the desired attributes.

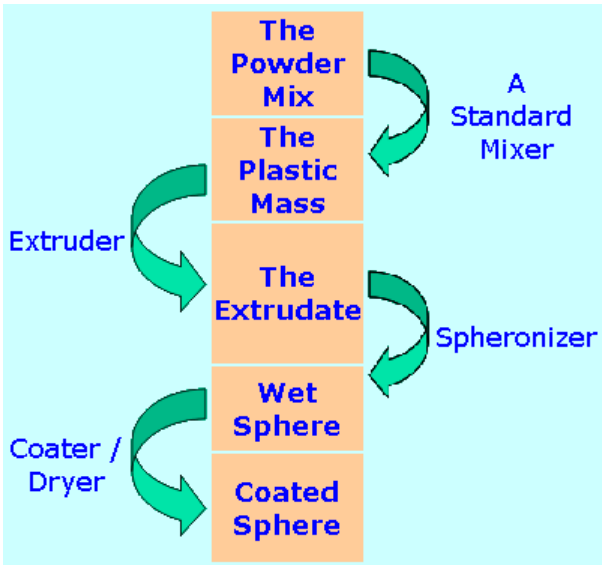
- **Binder**: Water and other Granulating media.
  Role: Binders are incorporated to get compact mass.

- Lubricants: Stearates and other lubricants
  Role: Lubricants are sometimes incorporated to improve processing.

- **Fillers**: Microcrystalline cellulose and lactose.
  Role: Regulating the water content and distribution in the granulation. In effect, it modifies the rheological properties of the formulation and imparts plasticity to the pellets.

- **pH modifiers**: Organic acids
  Role: Stabilize sensitive drug substances or modify the release characteristics, especially the solubility of the drug substance.

27



The extrusion-spheronization process

28

- **Product features**
  - Dust free
  - High spherocity
  - Free flowing
  - Compact structure
  - Low hygroscopicity
  - High bulk density
  - Low abrasion
  - Narrow particle size distribution
  - Smooth surface

29

4. SPHERICAL AGGLOMERATION

- **Spherical agglomeration**, or balling, is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, are converted to spherical particles by a continuous rolling or tumbling action.

- Spherical agglomeration can be divided into **two categories**—

1. **L**iquid-induced and

2. **M**elt-induced agglomerations.

30

Liquid-induced agglomeration

During liquid-induced agglomeration, liquid is added to the powder before or during the agitation step.

As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges.

These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase.

The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets.

At this point, coalescence is replaced by layering, whereby small particles adhere on much larger particles and increase the size of the latter until pelletization is completed.

If the surface moisture is not optimum, some particles may undergo nucleation and coalescence at different rates and form different sizes of nuclei admixed with the larger pellets.

As a result, spherical agglomeration tends to produce pellets with a wide particle size distribution.

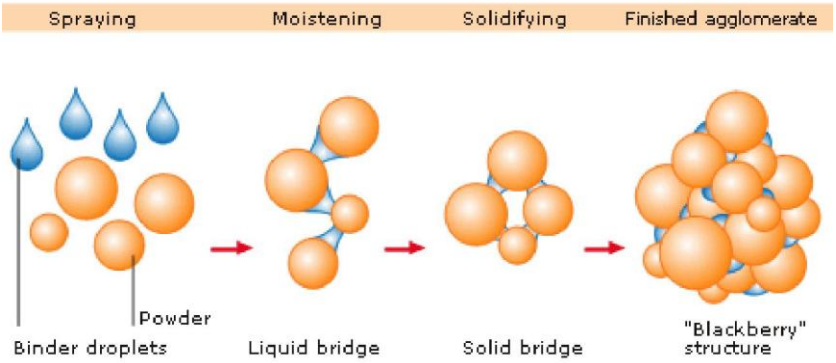
31

Melt-induced agglomeration

Melt-induced agglomeration processes are similar to liquid-induced processes except that the binding material is a melt.

Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges

32



Principle of spherical agglomeration (Balling)

33

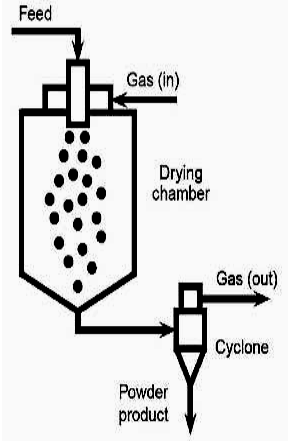
5.SPRAY DRYING AND SPRAY CONGEALING (Globulation)

- **Spray Drying** and **Spray Congealing**, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets.
- The droplet size in both processes is kept small to maximize the rate of evaporation or congealing, and consequently the particle size of the pellets produced is usually very small.

34

Spray Drying:

- The drug entities in solution or suspension are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles.
- As the atomized droplets come in contact with hot air, evaporation of the application medium is initiated.
- This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally, spray-dried pellets tend to be porous.

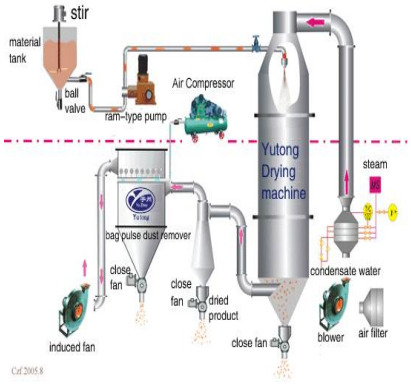


Spray Dryer

35

Process variables for spray drying

1. Feed material properties such as viscosity, uniformity, and conc. of core and coating material
2. Feed rate
3. Method of atomization
4. Drying rate controlled by inlet and outlet temp.
5. Air stream solvent conc



36

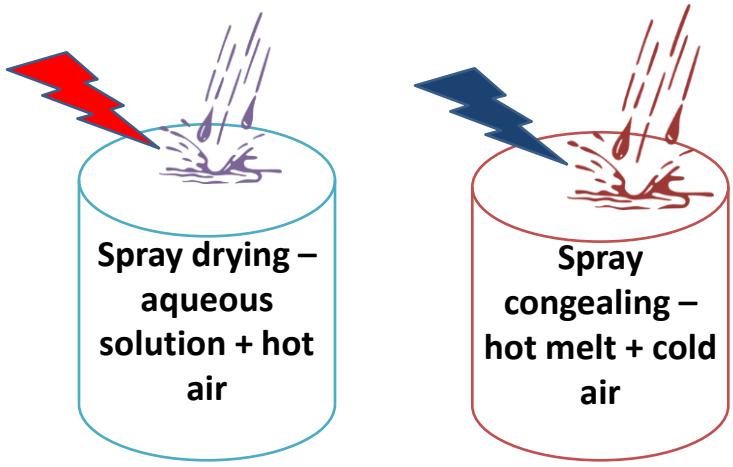
Spray Congealing

This process consists of suspending the particles in a molten coating material and pumping the resultant slurry into a spray dryer in which cold air is circulated.

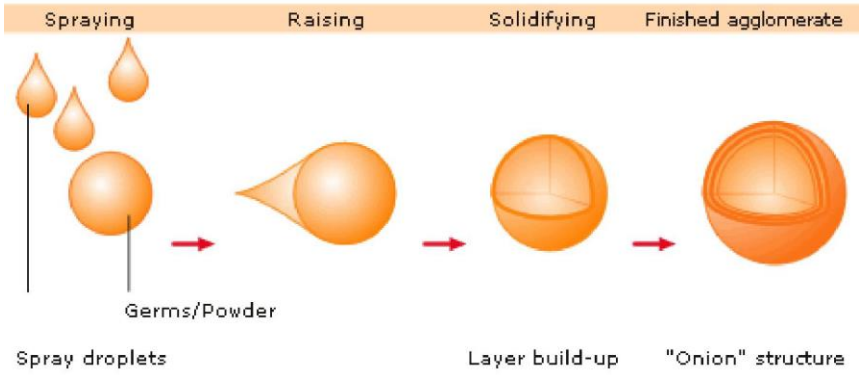
The slurry droplets congeal on contact with the air. The coating agents normally employed are low melting materials such as waxes.

The congealing process require higher ratio of coating agents to active material than does the spray drying, because only the molten coating agent constitutes the liquid phase.

37



38



Principle of Spray Granulation (Globulation)

39

6.MELT SPHERONIZATION

Melt Spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets.

The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature.

The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter.

The segments are spheronized in a jacketed Spheronizer to generate uniformly sized pellets.

40

Advantages

- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature

41

Disadvantages

- Requires high energy input.
- The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates

42

- Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinyl acetate (PVA) co-polymers.

- Based on this technology, two controlled release systems Implanon® and Nuvaring® have been developed.

- A melt extrusion process for manufacturing matrix drug delivery system was reported by Sprockel and co-workers. In 1994 Follonier and co-workers investigated hot-melt extrusion technology to produce sustained-release pellets.

43

Process and Equipment:

- Hot-melt extrusion equipment consists of an extruder, auxiliary equipment for the extruder, down stream processing equipment, and other monitoring tools used for performance and product quality evaluation.

- The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw– driving unit

44

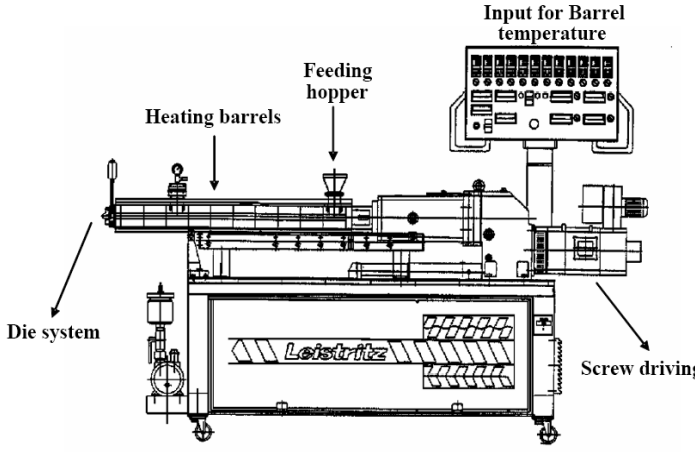


Figure: Micro-18 Twin screw co-rotating Leistritz extruder

45

- The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product and a solvent delivery pump.

- The monitoring devices on the equipment include temperature gauges, a screw-speed controller, an extrusion torque monitor and pressure gauges.

46

The theoretical approach to understanding the melt extrusion process is therefore, generally presented by dividing the process of flow into four sections:

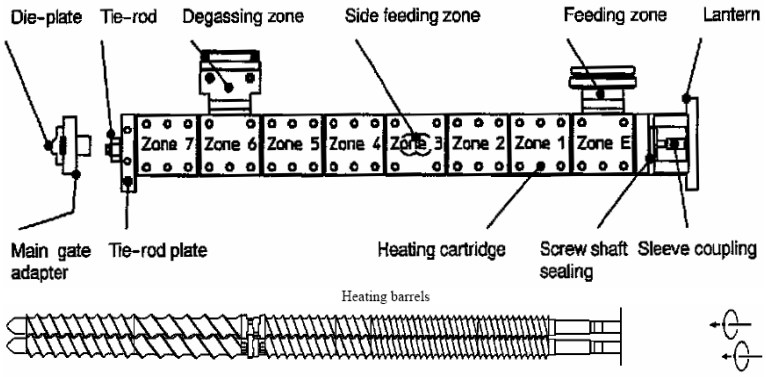
1) Feeding of the extruder.

2) Conveying of mass (mixing and reduction of particle size).

3) Flow through the die.

4) Exit from the die and down-stream processing.

47



Heating barrels and co-rotating screws for hot-melt extruder

48

7. CRYOPELLETIZATION

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium.

The technology, which was initially developed for lyophilization of viscous bacterial suspensions, can be used to produce drug-loaded pellets in liquid nitrogen at -160^{0}C.

The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen.

The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed.

49

The equipment consists of a container equipped with:

- Perforated Plates
- A Reservoir
- Conveyor belt with Transport baffles
- Storage Container

The perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen below.

The frozen pellets are transported out of the nitrogen bath into a storage container at -60^{0}C before drying.

50

Desirable properties of pellets

- **Uncoated pellets:**
  - Uniform spherical shape,
  - Uniform size,
  - Good flow properties,
  - Reproducible packing,
  - High strength,
  - Low friability, Low dust,
  - Smooth surface,
  - Ease of coating.
- **Coated pellets:**
  - Maintain all of the above properties,
  - Have desired drug release characteristics.

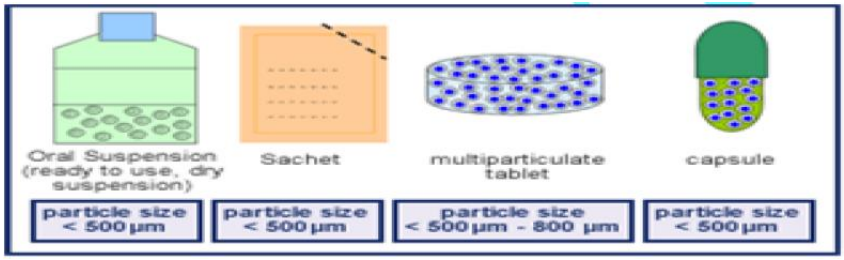
51

Formulation aids

- Fillers
- Binders
- Lubricants
- Separating agents
- Disintegrants
- pH adjusters
- Surfactants
- Spheronization enhancers
- Glidants

- Sweetening agents
- Flavouring agents
- Colouring agents
- Release modifiers
- Polymer

52



Flexibility of pellets in development of dosage form.

53

IN VITRO EVALUATION

54

Characterisation of pellets

- Particle size
- Surface area
- Porosity
- Density
- Hardness
- Friability
- Content uniformity
- Disintegration
- In vitro drug release

55

Sieve analysis

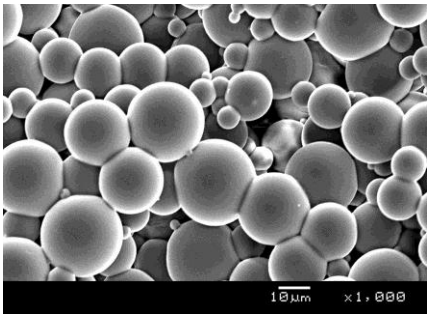
- Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker (Sieving machine, Retsch, Germany).
- A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size.
- Five grams of drug loaded microspheres are placed on the upper-most sieve.
- The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed

56

Morphology

- Done by:

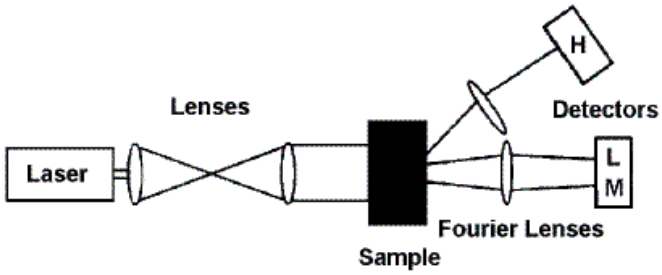
1. Scanning electron microscopy
2. Atomic force microscopy



57

Particle size determination

- Laser diffractometer



58

Bulk density

- The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder.
- The cylinder is tapped until the microsphere bed volume is stabilised.
- The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.

59

Strength

- Measurement of pellet strength is estimation of attractive forces seeking to hold the pellets together
- Strength can be measure by placing the pellets between two anvils (flat face) and force required to break the granules is measured.

60

Drug release

- Beaker method
  - The dosage form in this method is introduced in the beaker containing the medium and stirred uniformly using over head stirrer.
  - Volume of the medium used in the literature for the studies varies from 50- 500 ml
  - Stirrer speed from 60-300 rpm

61

- Dissolution apparatus

<u>Type of release:</u>

- Triggered release – Release occurs due to a change in environment, such as pH, temperature, moisture, pressure, electromagnetic. This is used to achieve immediate, delayed or pulsatile release profiles.
- Sustained release
- Burst release
- Combination release

62

Product	Company
Bontril SR	Carnick laboratories, Inc.
Brexin L.A	Savage Laboratories, Bangalore.
Catazyme S	Organon pharmaceuticals, USA.
Compazine	Smith & French, MUMBAI.
Dilgard XL 180	Smith kline & French, MUMBAI.
Elixophyline	CIPLA Ltd, Ahmedabad.
Fastin	Berlex Laboratories, USA.
Hispril	Berlex Laboratories, USA.
Ibugesic S.R 300	CIPLA Ltd, Ahmedabad.
Indocrin S.R	Merk Sharp, MUMBAI.
Nicobid T.S	U.S Vitamin, USA.
Ornade	Smith kline.

COMMERCIALY AVAILABLE MARKETED PELLET PRODUCTS

63

MICROSPHERES

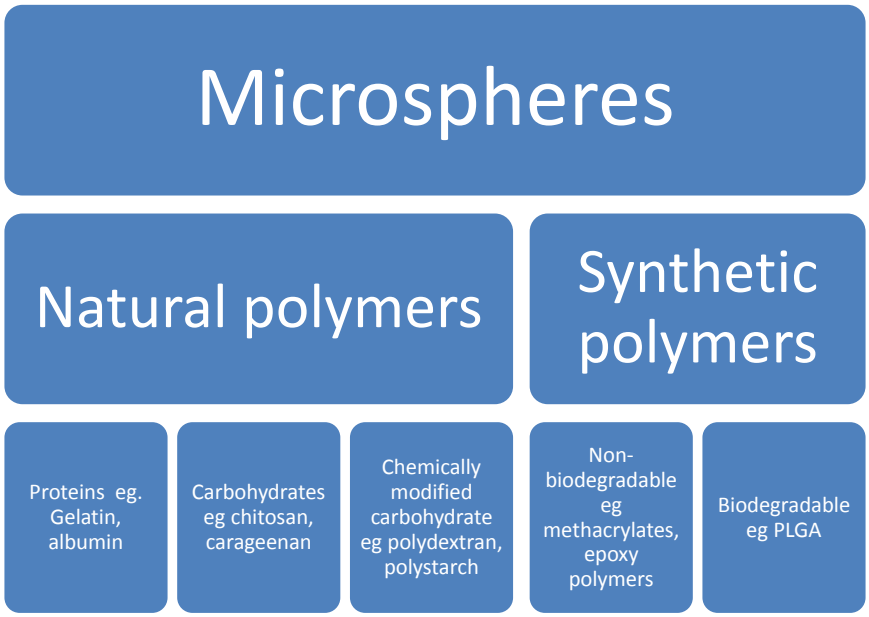
- **Microsphere**s are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm).
- Microspheres are sometimes referred to as microparticles
- Various microspheres available are made up of:
  - Glass, polymer, ceramic, hollow microspheres etc

Advantages

- Provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release

Disadvantages

- Differences in the release rate from one dose to another.
- Dosage forms of this kind should not be crushed or chewed



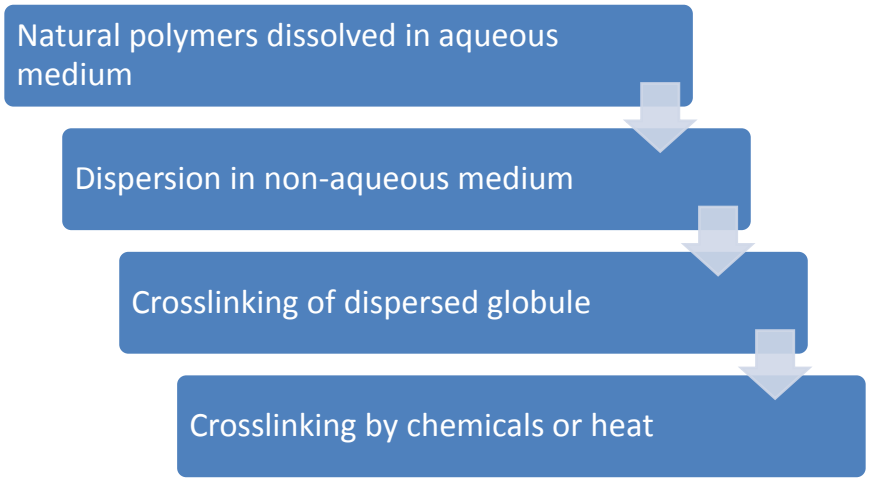
Method of preparation

- Preparation of microspheres should satisfy certain criteria:

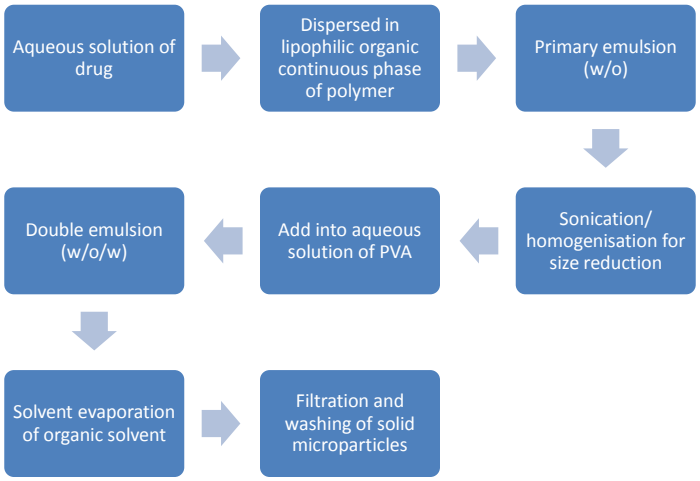
1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

1. Single emulsion technique
2. Double emulsion technique
3. Polymerisation technique
    1. Normal polymerisation
    2. Interfacial polymerisation
4. Phase separation coacervation technique
5. Spray drying and spray congealing
6. Solvent extraction
7. Emulsion Solvent Evaporation
8. Emulsion solvent diffusion technique

Single emulsion technique



Double emulsion technique



Normal polymerisation – 3 types

Bulk

- A monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization
- Formation of pure polymers

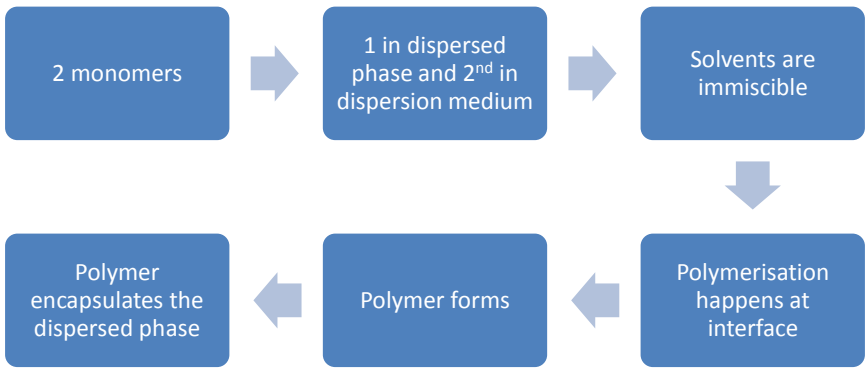
Suspension

- Referred as bead or pearl polymerization
- Carried out by heating the monomer or mixture of monomers along with the initiator or catalyst as droplets dispersion in a continuous aqueous phase

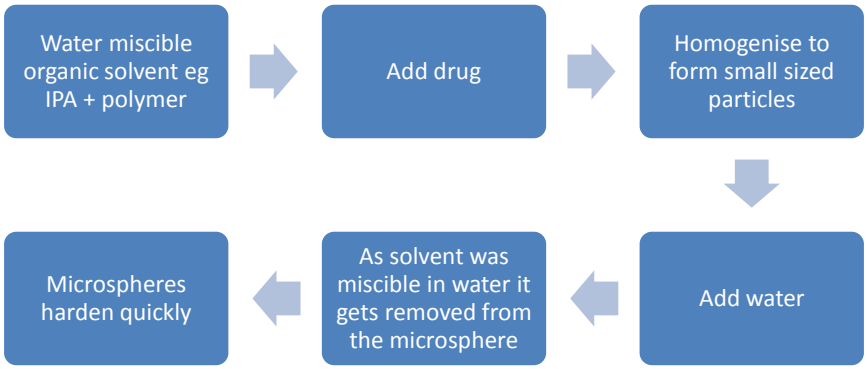
Emulsion

- Presence initiator in the aqueous phase, which later on diffuses to the surface of micelles

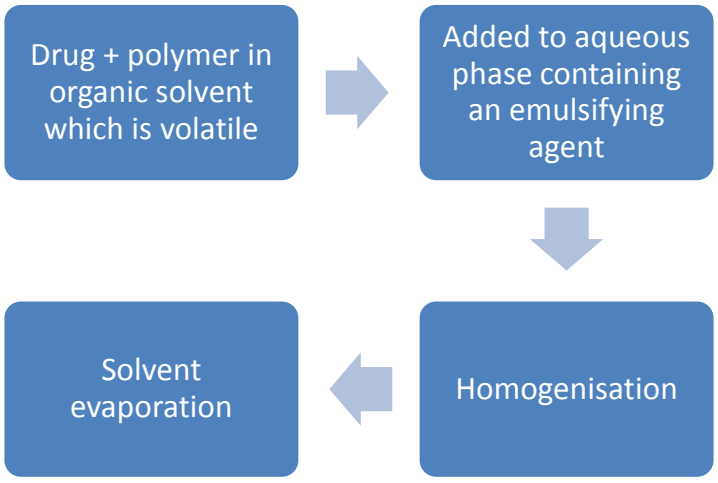
Interfacial polymerisation



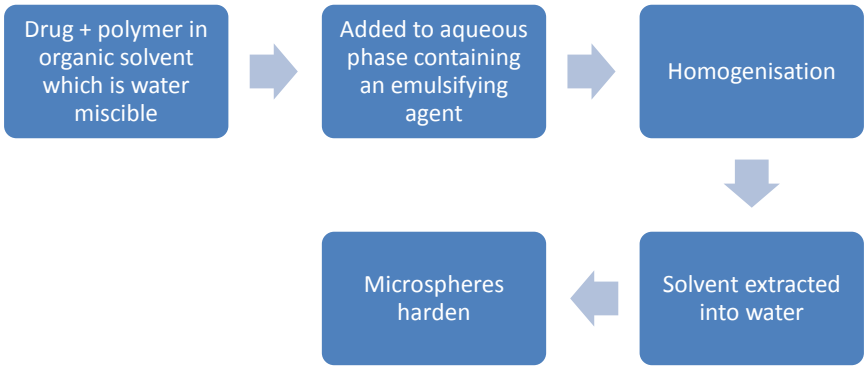
Solvent extraction



Emulsion Solvent Evaporation



Emulsion solvent diffusion technique



Evaluation

- Particle size and shape – electron microscopy
- Capture efficiency – assay

$$\%\ entrapment = \frac{actual\ content}{theoritical\ content} X100$$

- Release studies
- Permeation studies

Applications – based on route/ target

1. Ophthalmic drug delivery
2. Gene delivery
3. Tumor targeting
4. Oral drug delivery
5. Nasal drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Peroral drug delivery
9. Vaginal drug delivery
10. Transdermal drug delivery
11. Colonic drug delivery
12. Multiparticulate delivery system

Applications – type of microspheres

Type of microsphere	Application
Bioadhesive microsphere	Buccal, oral, ocular, nasal, colonic drug delivery Nasal - Gentamicin, Insulin , GI - Glipizide Colonic – Insulin, Ocular - Methyl prednisolone
Magnetic microsphere	Targetting drugs to tumour sites(Doxorubicin)
Floating microspheres	Carriers for drugs like antiviral, antifungal and antibiotic agents(so called absorption windows), non-steroidal anti inflammatory drugs, Prednisolone, Lansoprazole
Radioactive microspheres	For diagnostic purpose For therapeutic purpose - Radioembolization of liver and spleen tumours
Polymeric microspheres	Vaccine delivery, gene delivery, controlled release of proteins and peptides