PARTICLE COATING, TASTE MASKING & PELLETIZATION

PARTICLE COATING CONTENTS:-

- Introduction
- Applications
- Types of coating:-
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    - Dry particle coating
- Particle coating techniques:-

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    III. Bottom spray coating:-
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2. Solvent evaporation technique.
3. Coacervation and phase separation technique:-
    - By temperature change.
    - By incompatible polymer addition.
    - By non solvent addition
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    - By polymer polymer interaction
    - By solvent evaporation

4. Spray drying
5. Prilling or melt spraying
6. Centrifugation process
7. Interfacial polymerization.
8. Pan coating.
9. Melt dispersion technique.

b) VAPOR COATING OF POWDERS:-

- Fluidized bed chemical vapor coating

- DRY PARTICLE COATING EQUIPMENTS:-

1. Magnetically assisted impaction coating
2. Rotating fluidized bed coating
3. Hybridizer

- ✓ A NEW AND VERSATILE COATING METHOD OF PARTICLES AT ROOM TEMPERATURE

INTRODUCTION:-

Coating of particles is an important unit operation in the pharmaceutical industry. There are numerous applications of coating, including drug layering, modified release coating, physical and chemical protection, aesthetic purposes, taste masking, and enhanced identification of drugs

APPLICATIONS OF PARTICLE COATING:-

- **Particle coating are widely used in following industries:-**
  1) Pharmaceuticals, Powder
  2) Food
  3) Cosmetics
  4) Biochemical
  5) Dyestuff
  6) Toner
  7) Fertilizer
  8) Ceramics
  9) Electromaterials

Particle coating can change the properties of target particles:-

PHYSICAL PROPERTIES:-	**IMPORTANCE**:- (BASED ON DOSAGE FORMS)
1) Particle size distribution	POWDERS,TABLETS,CAPSULES,SUSPENSIONS
2) Shape/sphericity	POWDERS,TABLETS,CAPSULES,SUSPENSIONS
3) Solid phase reactivity	POWDERS
4) Hydrophilic/hydrophobic properties	SUSPENSIONS,SOLUTIONS
5) Wettability	SUSPENSIONS,SOLUTIONS
6) Dispersibility	SUSPENSIONS
7) Flowability	POWDERS,TABLETS,CAPSULES
8) Electrostatic/electric/magnetic/optical characteristics	POWDERS,CAPSULES,SUSPENSIONS,SOLUTIONS
ORGANOLEPTIC PROPERTIES:-	
1) Colouring	POWDERS,TABLETS,CAPSULES,SUSPENSIONS, SOLUTIONS SOLUTIONS
2) Flavour	POWDERS,TABLETS,CAPSULES,SUSPENSIONS,SOLUTIONS

TYPES OF COATING :-

- Wet particle coating
- Dry particle coating

- **WET PARTICLE COATING:-**

Involves use of either aqueous or non aqueous solution.

- Currently industrial standard for nanoparticle coating
  - Drawbacks
    - WPC solution may be volatile and toxic

- Requires post treatment and waste processing → increases cost

An innovative method to replace the wet coating process is to directly coat fine particles on target particles (dry particle coating) using strong mechanical forces.

- **DRY PARTICLE COATING:-**

Dry particle coating is used to create new-generation materials by combining different powders having different physical and chemical properties to form composites, which show new functionality or improve the characteristics of known materials. Materials with relatively large particle size (1–200 μm) form a core and these core (host) particles are mechanically coated with fine submicron (guest) particles; no liquid of any kind (solvents, binders or water) is required.

In this technology, powdered coating materials are directly coated onto solid dosage forms without using any solvent, and then heated and cured to form a coat. As a result, this technology can overcome such disadvantages caused by solvents in conventional liquid coating as serious air pollution, high time- and energy-consumption and expensive operation cost encountered by liquid coating.

Eg:- Improvement in the flow properties of a cohesive lactose powder by intensive mechanical dry coating.

Adv. of dry particle coating:-

- New particles may have completely different functionality or much improved properties
- Much reduced use of high-priced or rare materials
- Process is environmentally clean
- Water soluble powders can now be coated without compromising the sample.

- **PARTICLE COATING TECHNIQUES:-**
  - **MICROENCAPSULATION:-**

- Microencapsulation is a process of applying relatively thin coating to small particles of solids, droplets of liquids and dispersions, using various coating agents, such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnauba wax and shellac.
- It is a versatile & precise coating technique used to encapsulate individual particles.
- This proces results in individual particles of a drug substance being enveloped into a membrane.
- The type & level of membrane applied is determined by release rate requirements, organoleptic features & the dosage form application.
- Microencapsulation also increases the stability of the drug. It can be accomplished by a variety of methods, including
  - Air suspension coating.
  - Solvent evaporation technique.
  - Coacervation and phase separation technique.
  - By temperature change.
  - By incompatible polymer addition.
  - By non solvent addition
  - By salt addition
  - By polymer polymer interaction
  - By solvent evaporation
    - Spray drying and spray congealing
    - Centrifugation process
    - Interfacial polymerization.
    - Pan coating.

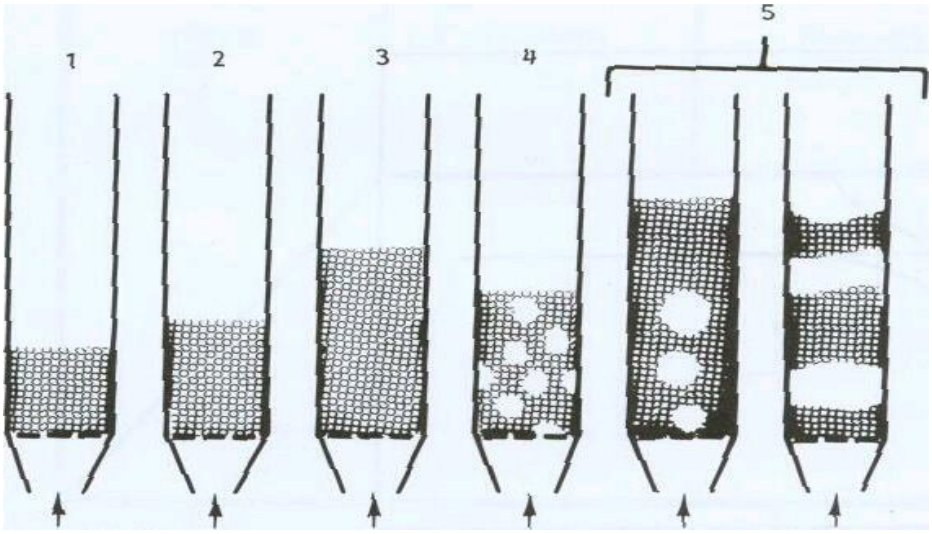
- Melt dispersion technique.

- **FLUIDIZED BED COATING:-**
  (AIR SUSPENSION COATER)

In fluidized bed powder coating, heated parts are either dipped directly into a container of fluidized powder or passed through an electrically charged cloud of powder, which is created above a container of fluidized powder.

Heating parts for use in a fluidized bed powder coating operation:-

conventional gas fire convection ovens are most common. However, electric and gas ir and other methods work fine as well, depending upon part dimensions. The main goal is to preheat the part above the melting point of the coating so the film thickness will build when submerged in the coater.induction heaters are used as well, especially on long, continuous parts.

- **Characterization of fluid beds:-**
- 

gas/liquid (low velocity) gas/liquid liquid gas gas gas

1. Fixed bed
2. Minimum fluidization
3. Smooth fluidization
4 .bubbling fluidization
5. Axial slugging
6. Flat slugging

There are different characteristics of fluid beds depending on the velocity of stream of air:-

- Initially bed remains static but as we pass air in the chamber it becomes fluidized in the air stream
- The point at which bed becomes just fluidized is known as incipient fluidization
- The velocity of particle in the bed under this condition is too low for efficient coating

- Increasing the air volume results in wider fluidization range known as bubbling fluidization , in which bed can be defined as containing 2 phases, a particulate phase, containing particles & air & a bubble phase ,which contains excess air.
- ***Can the fluidized bed process be used with both thermoset and thermoplastic powder coatings?***
  Yes. However, thermosets are rarely used and much more complicated due to the heat buildup in the fluid bed coater, which can cause the powder to cross-link in the coater. Thermoplastics are much more forgiving in this manner.
- ***Drawbacks associated with the fluidized bed process:-***
  color changes can be difficult. Where practical, one should use a dedicated bed for each color.
- ***Coating of fine particles are performed using MINI GLATT FLUIDIZED BED.***

  - **TOP SPRAY COATING:-**
- Most widely used in pharmaceutical industry
- With top spray coating in the fluid bed ,particles are fluidized in the flow of heated air which is introduced via base plate.coating liquid is sprayed into fluid bed from above against the air flow by means of a nozzle. Drying takes place as particles continue to move upwards in the air flow.small droplets & a low viscosity of the spray medium ensure uniform distribution.
- Coating in continuous fluid bed is particularly suitable for protective coatings/ colour coatings where product throughput rates are high.
- Depending on the application ,the system is sub-divided into pre-heating zones, spray zones & drying zones.
- The dry, coated particles are continuously extracted.

  - **ELECTROSTATIC FLUIDIZED BED COATING:-**

An electrostatic fluidized bed is essentially a fluidized bed with a high voltage dc grid installed above the porous plate to charge the finely divided particles. Once charged, the particles are repelled by the grid, and they repel each other, forming a cloud of powder above the grid. These electrostatically charged particles are attracted to and coat products that are at ground potential.
The advantages of electrostatic fluidized bed coating is that preheating of parts is generally not necessary and small products, can be coated uniformly and quickly. The disadvantages are that the product size is limited and inside corners have low film thickness owing to the well known faraday cage effect.

DIFFERENCE BETWEEN FBD & EFBD

Fbd:-with fluid bed coating, the part has to be preheated, immersed in the coating and then flowed out.
Efbd:- electrostatically assisted fluidized bed coating does not dip the part into the powder, it generates a cloud of charged particles (much like a conventional electrostatic gun) through which a heated or an unheated part passes. It generally applies a thin coat vs. The thicker coat from fluidized bed coating.

Does the pre-heating stage make fluidized bed a more expensive process than electrostatic spray?

Generally not. The overall thermal requirements for both coating methods are basically the same. Obviously, fluidized bed coating uses more heat prior to coating, and electrostatic spray uses more heat after coating, but these usually net out.

Some other benefits of fluidized bed powder coating:-

there is generally less waste since it's a 100% transfer efficient coating method. When compared to electrostatic spray, capital investment in equipment and ongoing maintenance is most always lower. It's basically a low-tech coating method, and once coating parameters are established, there are not that many things that can go wrong. It is by far the most efficient method of applying thick film coatings.

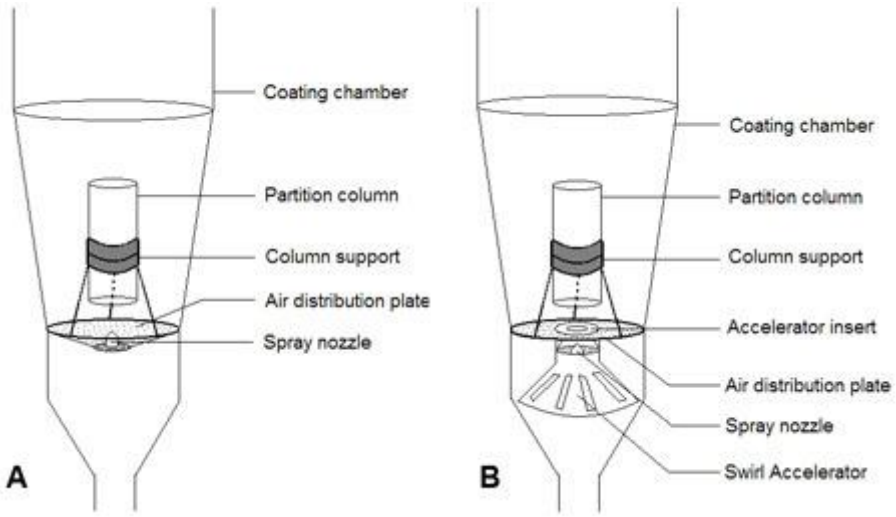
- **WURSTER COATER:-**
  (BOTTOM SPRAY COATING)

Wurster coaters are bottom spray fluid bed coaters that have been extensively used in the pharmaceutical industry for coating of small particulates. They offer excellent heat and mass transfer within the product bed and are able to form uniform coats. however, their use has been limited by the propensity of the particles to agglomerate during the coating the precision coater**(B)** is similar to the wurster coater **(A)**except for its mode of air distribution.

The air distribution plate in the precision coater consists of a perforated plate connected to the swirl accelerator. The swirl accelerator functions to swirl and accelerate the inlet air to impart spin and high velocity to the particles as they transit through the partition column where coating takes place. This process can change the fluid dynamics of the particles.
In bottom spray fluid bed processes, the area of the air distribution plate directly under the partition column has more perforated area than the periphery region of the air distribution plate, resulting in a higher central air velocity through the partition column. This creates a region of lower pressure that draws in particles by the venturi's effect and lifts particles up the partition column (up-bed zone) according to Bernoulli's law. As such, particles from the product bed enter the partition column (horizontal transport zone) and decelerate in the expansion chamber (deceleration zone)—falling outwards freely in an inverted u-shape trajectory back onto the product bed staging area (down-bed zone).

The particles then reenter the partition column though the partition gap and repeat the fountain-like cyclic flow. Particles receive coating droplets during the passage through the spray zone within the partition column, and this cycle is repeated until the desired coating level is achieved.

Fluid dynamics was found to be important in controlling product quality and productivity in bottom spray fluid bed coaters.



- **TANGENTIALLY/ROTATING FLUIDIZED BED COATING:-**

- Ideal for coatings with high solid content.
- The product is set into spiral motion by means of rotating base plate ,which has air fed into the powder bed at its edge.
- Spray nozzle is arranged tangentially to the rotor disc @ sprays concurrently into the powder bed.
- Very thick film layers can be applied by means of rotor method.

- **NOVEL ROTATING FLUIDIZED BED COATER:-**

Fine particle coating has been conducted by using a novel rotating fluidized bed coater. The coater consists of a plenum chamber and a horizontal porous cylindrical air distributor, which rotates around its axis of symmetry inside the plenum chamber. Cohesive fine cornstarch was used as core particle and an aqueous solution of hydroxypropylcellulose (hpc-l) was sprayed onto the cornstarch to generate a film coating. Fine particle coating was conducted under various coating levels (wt.% hpc-l) and the particle size distribution of the coated particles, release rate of an aqueous pigment (food blue no. 1), which had been pre-coated onto the initial cornstarch, and the degree of agglomeration were investigated. The relationship between the coating level and the physical properties of the coated particles was analyzed. The results indicated that coating of cohesive fine cornstarch with hpc-l could be achieved, producing a favorable prolonged release property with almost maintaining the individual single particle.

- **COACERVATION PHASE SEPARATION:-**

  The general outline of the processes consists of three steps carried out under continuous agitation.

  1. Formation of three immiscible chemical phases.
  2. Disposition of the coating, and
  3. Rigidization of the coating

a. *By thermal change*: phase separation of the dissolved polymer occurs in the form of immiscible liquid droplets, and if a core material is present in the system, under proper polymer concentration, temperature and agitation conditions, the liquid polymer droplets coalesce around the dispersed core

material particles, thus forming the embryonic microcapsules. As the temperature decreases, one phase becomes polymer-poor (the microencapsulation vehicle phase) and the second phase. (the coating material phase) becomes polymer-rich.
Eg:- microencapsulation of ibuprofen

b. *By incompatible polymer addition*: it involves liquid phase separation of a polymers coating material and microencapsulation can be accomplished by utilizing the incompatibility of dissimilar polymers existing in a common solvent.

c. *By non-solvent addition:* a liquid that is a non-solvent for a given polymer can be added to a solution of the polymer to induce phase separation. The resulting immiscible liquid polymer can be utilized to effect microencapsulation of an immiscible core material.

d. *By salt addition:* there are two types of coacervation: simple and complex. Simple coacervation involves the use of only one colloid, e.g. Gelatin in water, and involves removal of the associated water from around the dispersed colloid by agents with a greater affinity for water, such as various alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form the coacervate. Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are most frequently used, and the coacervation is accomplished mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration.

E. *By polymer-polymer interaction*: the interaction of oppositely charged poly electrolytes can result in the formation of a complex having such reduce solubility that phase separation occurs.

F. *By solvent evaporation:* the processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent, which is dispersed in volatile solvents, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer. In the case in which the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The solvent evaporation technique to product microcapsules is applicable to a wide variety of core materials. The core materials may be either water soluble or water insoluble materials.

Advantages:

- To encapsulate water immiscible liquids
- This technology produce single capsules of 20-80 µm diameter that contains 80 – 90% wt core material

Disadvantages:

- The mechanical and barrier properties of dry capsules are sensitive to moisture.

- **SPRAY DRYING:-**

Spray drying often is used as an coating technique by the food and other industries. A substance to be coated (the load) and a coating material are homogenized as a suspension in water (the slurry). The slurry is then fed into a spray drier, usually a tower heated to temperatures well over the boiling point of water.
As the slurry enters the tower, it is atomized. Partly because of the high surface tension of water and partly because of the hydrophobic/hydrophilic interactions between the coating material , the water, and the load, the atomized slurry forms micelles. The small size of the drops (averaging 100 micrometers in diameter) results in a relatively large surface area which dries quickly. As the water dries, the coating material forms a hardened shell around the load.

- **PRILLING/MELT SPRAYING:-**

Prilling, also known as spray congealing, spray chilling, or melt atomization, is the process of atomizing molten liquids or mixtures and cooling the resultant droplets to form prills or beads that are the final product.

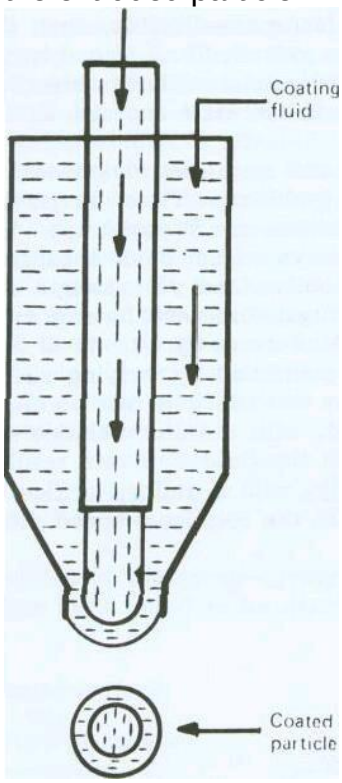
In general, any material that is solid at room temperature and stable in the molten state with a relatively low viscosity can be used in this process.
Examples of materials that have been successfully processed this way include low molecular weight polymers, phytosterols, waxes, fats, hydrogenated vegetable oils, and hydrated salts such as alum. While high melting materials such as metals, glasses and ceramics are routinely processed commercially, this requires special heaters and atomizing sources, so these materials are not typically processed on a toll basis. Materials that are easy to prill generally have melting points below 200 degrees c and melt viscosities lower than 200 cps.

Prilling offers a number of unique benefits in creating free-flowing powders from solids. First, prilling is a relatively inexpensive process for converting molten materials into a solid, easy to handle form. Second, the typical output consists of spherical particles, although the final form can vary from fibers to rods to spheres depending on the melt viscosity. Third, a wide range of final sizes are possible depending on the atomization method and the starting material. A particle size output of 10 to 3,000 microns is readily obtainable. Fourth, throughputs of 2,000 lbs/hour and higher with the above size distribution are easy to obtain. Finally, the process can be used with blended materials very easily.
Eg:-

1) Glimepiride microcapsules were successfully prepared using spray congealing technique.
2) Hot-melt coating technique is used for controlled release of propranolol hydrochloride pellets.

- **CENTRIFUGATION:-**

The liquid material to be coated is extruded through the nozzle of the inner tube into the coating fluid contained in the outer tube. Initially, the fluid extrudes as a rod surrounded by the coating fluid, but the rod ultimately breaks up into droplets, which are then immersed, in the coating fluid. As the extruded droplets pass through the nozzle orifice of the outer tube, the coating fluid forms a surface coat, which encases the extruded particle.



- This is then passed through hardening bath where coated particles are strengthened.
- The centrifugation method is capable of producing microcapsules in the 100-200 *μm* range.

- **INTERFACIAL POLYMERIZATION:-**

- This is usually accomplished by emulsifying the liquid containing the first reactant (dispersed phase) into the continuous phase, which is initially devoid of the second reactant & contains only emulsifying agent.
- Additional continuous phase containing the second reactant is then added.
- This interfacial polymerization reaction produces a continuous film of the formed polymer around the dispersed phase.
- Spray drying, flash evaporation, filtration, or other separation techniques can accomplish the recovery of the microcapsules from the continuous phase.

  Steps :-
  1. Liquid to be encapsulated & 1st reactant = dispersed phase
  2. Dispersed phase + continuous phase(containing emulsifier) = emulsion
  3. Add excess of continuous phase containing 2nd reactant = polymer encapsulated liquid particles.
  4. Separate encapsulated liquid particles & dry.

- The various polymer-coating materials, which have been utilized to prepare microcapsules by the described process, include polyamides (nylon), polyurethanes, polysulfonamides, polyesters, polycarbonates, and poly-sulfonates.
- Particles varying greatly in size, from approximately 3 to 2000 pm in diameter can be prepared.

- **PAN COATING** :-
- The microcapsulation of relatively large particles by pan coating method has become wide spread in the pharmaceutical industry and solid particles greater than 600 µg in size are generally considered essential for effective coating. The coating is applied as a solution or as an atomized spray to the desired solid core passed over the coated materials during coatings are being applied in the coating pans.

- **MELT-DISPERSION TECHNIQUE:-**
- In this technique the coating material is melted by heating upto 80^{o}c. The drug is suspended in it and then emulsified in water containing emulsifying agent at 80^{o}c under stirring. Microcapsules are formed as the temperature of the system reaches to room temperature.

- **VAPOUR COATING OF POWDERS:-**

A liquid or powder material can be dispersed by the application of electrostatic fields. The phenomena, referred to as "electrodispersion" is the dispersion by an intense electric field of part of a static bed of liquid or powder into a stable cloud of rapidly moving particles, and the maintenance of a dynamic equilibrium between the static and dispersed phases. The density of the dispersed cloud of particles varies with a number of factors, including the field strength and the nature of the powder.

The electrodeposition effect is employed to produce a uniform and durable coating of controlled thickness on the individual particles, by the generation of a vapor of the desired coating--typically a metal or semiconductor material--and allowing the vapor to permeate the dispersed particles. The electric field ensures that only the particles are coated, and the dispersed particles, having the same charge, repel each other, avoiding agglomeration. Possibilities include the manufacture of slow dissolving coatings on pharmaceutical powders.

- **Fluidized bed chemical vapour coating:-**
- Fluidized bed chemical vapor deposition (fbcvd) is one of the most efficient techniques to functionalize, to deposit on, or to coat each individual particle of a powder.
- From gaseous species. Fbcvd combines two processes.One is the deposition itself, the other aims in suspending the particles in the deposition zone, most often by flowing gas upwards through the powder.
- fbcvd is generally transport limited.
- Eg :- coatings of titania.

- **DRY PARTICLE COATING EQUIPMENTS:-**

FLUIDIZATION BASED DEVICES:-

MAGNETICALLY ASSISTED IMPACTION COATING(MAIC)
ROTATING FLUIDIZED BED COATING

HIGH INTENSITY MACHINES:-

HYBRIDIZER
MECHANOFUSION
THETA COMPOSER

- **MAGNETICALLY ASSISTED IMPACTION COATING(MAIC):-**

- The oscillating magnetic field generated by the coil is used to accelerate and spin the large magnetic particles mixed with the host and guest particles promoting collision between the particles and with the walls of vessel.
- Since the magnetic particles “fluidize” the host and guest powders, “soft” coating occurs by powder impaction.
- Magnetically Assisted Impact Coating (MAIC, pronounced mace), coats particles onto particles by a peening process.
- By adding a small coating particle and large core particle into an assembly of small oscillating magnets, the small particles are readily coated on to the core particles.
- The process is a continuous method in which the magnets are separated from the product and rates of 100-800 pounds per hour are easily coated.
- Using this process core particles as small as 0.25 microns can also be coated.
- Materials that have been used in this process include glasses , pigments, metals, metal oxide, polymers, organic and inorganic powders.
- One of the unique aspects of this process is the observation that in many cases, the dry coated composite will not dissociate in the dry state or when the composite is put into a dispersion.

- **ROTATING FLUIDIZED BED COATER:-**

- This newly developed coating device operates on the principle of a rotating fluidized bed.
- The host and guest powder mixture are placed the rotating bed and is fluidized by the radial flow of gas through the porous wall of the cylindrical distributor, as seen in figure.
- Due to the high rotating speed, very high centrifugal and shear forces are developed within the fluidized gas-powder system leading to the break-up of the agglomerates of the guest particles.
- Moreover, the very large flow of gas needed to fluidize the particles at high rotating speed and the motion of bubbles when operating the bed above minimum fluidization condition creates strong mixing and hence good coating is achieved.
- The RFBC has the capability of being operated in a continuous mode, by feeding guest particles in with the fluidizing gas and operating the RFBC in a vertical position so that host particles can be continuously fed into and removed from the device by gravity.

- **HYBRIDIZER:-**

- The hybridizer consists of a very high-speed rotating rotor with six blades, a stator and a powder re-circulation circuit made with ceramic or stainless steel.
- The powder (host and guest particles) placed in the processing part of the vessel is subjected to high impaction and dispersion due to the high rotating speed of the rotor.
- The particles undergo many collision, and this allows for break-up of fine agglomerates and powder coating due to the embedding or filming of the guest particles onto the surface of the host particles.

ADVANTAGES:-

- Very short processing times are required to achieve coating.
- The rotor of the hybridizer can rotate anywhere from 5000 rpm to 16000 rpm. Due to the strong forces applied to the materials at this high rpm, very short processing times are required to achieve coating.
- The device consist of a re-circulating unit that continuously moves the particles in and out of the processing vessels and against the blades of the rotor.
- There is a temperature build-up due to the high impaction forces caused by the high rotation speed , which aids in coating the guest particles onto the surface of the host particles.

- **A New and Versatile Coating Method of Particles at Room Temperature:-**

- New coating method, which is based on the vibrational motion of microparticles in the electrostatic field between parallel electrodes.
- The metallic elements of Mn, Mo, W, Os, Ir, Cr and Pb and the nonmetallic elements of B, C, Si and Ge were successfully coated on to Fe, Cu, Al and brass substrates.
- Threshold voltages of 3 and 5 kV for metallic and nonmetallic materials, respectively, exist.
- The particle sizes examined were larger than 0.1 μm^{φ}. This method requires a minimum one hour to complete.
- The uniformity in thickness is fairly good, compared to that obtained using a vacuum-evaporation method. It is a dry method used at room temperature, and is very simple to use. Furthermore, the coated materials show strong adhesion and the used remnants are recyclable.

TASTE - MASKING CONTENTS:-

Introduction
Definition of taste
Factors affecting taste perception
Properties of ideal taste-masking process & formulation

TECHNIQUES USED FOR TASTE-MASKING:-

SENSORY APPROACH:-

1. Using flavoring and sweetening agents
2. Inhibiting bitterness
3. Numbing of taste buds
4. Using Co_2 generating substance

BARRIER APPROACH:-

1. Applying polymer coatings
2. Microencapsulation
3. Taste-masking by viscosity modifications
4. Liposomes
5. Emulsions

COMPLEXATION & ADSORPTION:-

1. Complexation with ion exchange resins:
2. Use of amino acids in taste masking
3. Inclusion complex formation with cyclodextrins
4. Wax-embedding of drugs
5. Molecular complexes of drugs with other chemicals

CHEMICAL APPROACH:-

1. Formation of salt derivatives
2. Prodrugs

OTHER TECHNIQUES:-

SOLID DISPERSIONS:-

a) Melting method
b) Solvent method
c) Melting-solvent method

FREEZE-DRYING PROCES

TASTE MASKING AS A CONSEQUENCE OF THE ORGANISATION OF POWDER MIXER

ORALANCE TECHNOLOGY

TASTE MASKING BY MELT EXTRUSION TECHNIQUE:-

a) Taste masking by ionic interaction
b) Salt formation
c) Pellatisation

EVALUATION OF TASTE MASKING EFFECT:-

A. Involving BIOMIMETIC TASTE SENSING SYSTEM (BMTSS) & other equipments:-
   1. E-Tongue
   2. E-nose
   3. Olfactory Gas Chromatography
   4. In vitro cell Cultures

B. SENSORY ANALYSIS

INTRODUCTION:-

- In earlier times, the taste of medicine played in important role in curing of disease, more bitter drugs, the better the cure.
- Today most of the drugs are unpalatable and unattractive in their natural state but modern pharmaceutical preparation present them to patient as colorful, flavorful formulation attractive to sight, smell and taste.
- Taste is an important parameter governing patient compliance for drugs administering orally.
- Undesirable taste is one of the important formulation problems encountered with many drugs and so the administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers.
- Skillful taste masking is needed to hide this bitterness. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Taste masking technologies offer a great scope for invention and patents.
- Medicines have always been unique as the only product that consumers took on blind faith; however, consumers now have a greater power of choice than ever before, and as with any orally consumed product, taste is the deciding factor.
- Taste, smell, texture and after taste are important factors in the development of dosage forms. These are important factor in product preference. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. Good flavor and texture are found to significantly affect sell of the product. Undesirable taste is one of the important formulation problems encountered with most of the drugs.S

TASTE:-

- The biological definition of taste (gustation) is a chemical reaction derived from sensory responses from the four main taste perceptions: salt, sour, bitter, and sweet. These perceptions are elicited by the tongue and interpreted by the brain.
- Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste.[2]
- Two other perceptions (umami and trigeminal) should also be considered.
- Umami is derived from the presence of glutamate, such as monosodium glutamate, resulting in the fullness sensation from certain foods.
- Trigeminal is the burning sensation derived from such foods as spices and peppers.

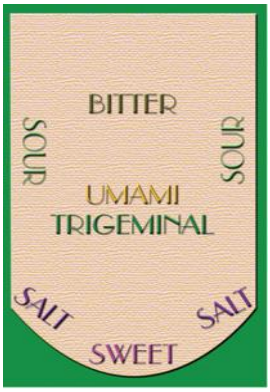


Figure 1. Taste sensors locations around the tongue.

FACTORS AFFECTING THE PERCEPTION OF BITTERNESS

- Taste Interactions.
- Medium of Presentation.
- Viscosity & Temperature.
- Taste Modifiers.
- Salivary Status and
- Age.

An ideal taste masking process and formulation should have the following properties:-

1) Involve least number of equipments and processing steps.
2) Require minimum number of excipients for an optimum formulation.
3) No adverse effect on drug bioavailability.
4) Require excipients that are economical and easily available.
5) Least manufacturing cost.
6) Can be carried out at room temperature.
7) Require excipients that have high margin of safety.
8) Rapid and easy to prepare.

TECHNIQUES USED FOR TASTE MASKING:-

- In order to ensure patient compliance bitterness masking becomes essential. The methods most commonly involved for achieving taste masking include various chemical and physical methods that prevent the drug substance from interaction with taste buds. The simplest method involves use of flavor enhancers. Where these methods fail more complex methodologies are adopted. Various techniques have been identified for taste masking which include polymer coating, inclusion complex formation with cyclodextrin, use of ion exchange resins, solubility limiting methods, liposome, multiple emulsions, use of anesthetic agents, etc

SENSORY APPROACH:-

- This approach is however not very successful for highly bitter and highly water soluble drugs.
- Besides taste masking this approach is also used to improve the aesthetic appeal of the product specially to make it more attractive for the pediatric patients as well as used for liquid formulation and solid formulation like chewable tablets, mouth-dissolving tablets.
- Approaches
    1. Using flavoring and sweetening agents
    2. Inhibiting bitterness
    3. Numbing of taste buds
    4. Using Co_2 generating substance

1.) USE OF FLAVOURS & SWEETENERS

USE OF FLAVOURS

- Natural Flavours
    - Juices - Raspberry
    - Extracts - Liquorice
    - Spirits - Lemon & Orange
    - Syrups - Blackcurrant
    - Tinctures - Ginger
    - Aromatic waters - Anise & Cinnamon
    - Aromatic Oils – Peppermint & Lemon.

- Synthetic Flavours
    - Alcoholic solutions
    - Aqueous solutions
    - Powders
- Natural Vs Synthetic
    - Cheaper
    - More readily available
    - Less variable in chemical composition
    - More stable
- Basis of Choosing a Flavor

- Complementary to existing flavor of the drug
- Known popularity of particular flavors
- Age of patients
- Allergy

- Use of flavor enhancers are limited only to unpleasant tasting substances, and is not applicable to oral administration of extremely bitter tasting drugs like various antibiotics.
- Apart from these conventional materials many compositions have been found to show effective taste masking abilities with improved flavor such as alkaline earth oxide, alkaline earth hydroxide or an alkaline hydroxide.
- Another composition includes phosphorylated amino acid such as phosphotyrosine, phosphoserine, and phosphothreonine and mixtures thereof.
- Anethole effectively masked bitter taste as well as the after taste of zinc, which is used in treating the common cold.
- Clove oil and calcium carbonate have been found to be particularly useful to mask the unpalatable active in formulations which are intended to be chewed or dissolve in mouth prior to ingestion in solution.

❖ Flavoring agents for taste masking

Basic Taste	Masking agents
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry.
Sour	Citrus flavor, licorice, root beer, raspberry.

USE OF SWEETENERS

- Complement flavors associated with sweetness
- Soothing effect on the membranes of the throat

Natural Sweetener

- Sucrose, glucose, fructose
- Sorbitol, mannitol, glycerol
- Honey, liquorice

Artificial sweetener

- Saccharin, Saccharin sodium
- Aspartame

Artificial Sweetener

- Intense sweetener
- Sugar free preparation
- Enhance degree of sweetness
- Disadvantage – bitter or metallic after taste

- Nutritive: Sucrose, Fructose and Glucose

- Polyols: Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol.

- Non-Nutritive: Aspartame, Sucralose, Neotame, and Saccharine
- Novel sweeteners: Trehalose, Tagatose

List of FDA approved Non-Nutritive Sweeteners

(Sweetness factor, Sucrose = 1)

Asparatame	180-200
Sucralose	600
Acesulfame K	200
Neotame	7,000-13,000
Saccharin	300

2.) INHIBITING BITTERNESS:-

- Lipoproteins composed of phosphatidic acid and beta-lactoglobulin were effective in suppressing bitter taste of drugs such as caffeine, propranolol, promethazine and quinine.
- The addition of phosphorylated amino acids such as phosphotyrosine and phosphoserine, to mixture consisting of ibuprufen, acetaminophen, dextromethorphan hydrochloride, chlorpheniramine maleate and pseudoephedrine inhibited the unpleasant taste of the drugs with out substantially affecting the overall taste of the formulations.

3.)NUMBING TASTE-BUDS:-

- Temporary numbing of taste buds by certain anesthetizing agents such as phenol and sodium phenolate has also been used to mask the unpleasant taste of drugs such as aspirin.
- This anesthetic agent numbs the taste buds sufficiently within 4 to 5 seconds and helps to mask bitter taste.

4.)USING CARBON-DI-OXIDE GENERATING SUBSTANCE:-

- Co_2 producing substance like citric acid or tartaric acid with sodium bicarbonate can also reduce bitter taste of formulation. The carbonated water partly disguises unpleasant taste of saline medicaments that are administered as effervescent granules or tablet.
- Dispersible formulation of cetrizine gave the dispersion having pleasant taste.

BARRIER APPROACH:-

1.) APPLYING POLYMER COATINGS:-

- Coating of drugs using a suitable polymer offer an excellent method of concealing the drug from the taste buds. The coated composition may be incorporated into

much number of pharmaceutical formulations, including chewable tablet, effervescent tablets, powder, and liquid dispersion.

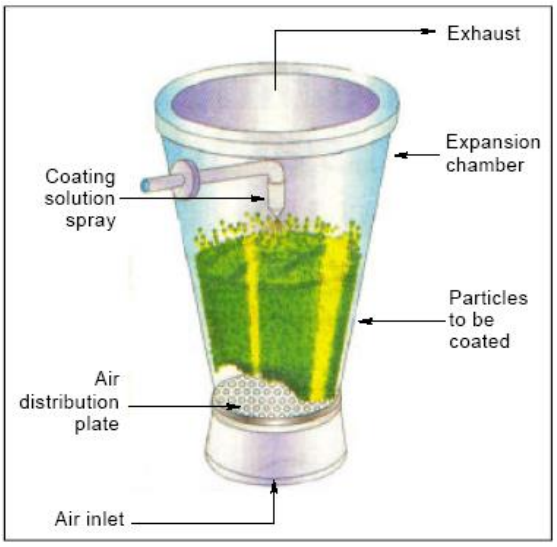
- Kato *et al.* studied the low melting point substances for masking bitter taste of the drug. Beef tallow (a low melting point substance) was mixed with micropulverized active ingredients (e.g. antiulcer methyl benactyzuim bromide) and the mixture was nozzle sprayed to form coated spheres having homogenous particle size.
- Maccari *et al.* conducted a special study to assess the bioavailability of a Flucoxacillin preparation microencapsulated for taste abatement with 17 % ethyl cellulose made up as a granular product for extemporaneous resuspension when compared to commercially available Flucoxacillin preparations. Both dosage forms were bioequivalent proving that Flucoxacillin microencapsulated for taste abatement is as available from the dosage form as the raw unprocessed antibiotics.
- Yajima *et al.* developed a method of taste masking using a spray congealing technique. The spray congealing technique, which uses a spray dryer, is an effective method of taste masking because this method is cost effective and requires no solvent and it can produce a more dense film than other methods without moving materials for drying. They reported spherical matrices containing Clarithromycin (a macrolide antibiotic), amino alkyl-methacrylate, polymer-E (AMCE) and glyceryl monosterate as the ingredients, the objective being prevention of drug release in the mouth while ensuring rapid release in GIT.
- T-Mask® works to produce a basic coated formulation of the active ingredient that is better tasting and easier for patients to swallow. This positive effect is achieved by applying a coating, which does not change the composition or characteristics of the underlying compound.
- The taste masking coating compositions generally include a copolymer of acrylate and methacrylate with a quaternary ammonium group in combination with sodium carboxymethylcellulose and a polyvinyl alcohol-polyethylene glycol copolymer.

COATING MATERIALS

- **Meltable Coatings**
- Meltable materials such as hydrogenated vegetable oils, vegetable waxes or saturated fatty acids such as stearic acid can be utilized as either distinct coatings over drug particles or as matrix materials containing dispersed drug particles.
- Polymers
- Eudragit E100 is finding fairly broad utility in taste-masking drugs when a rapid release is needed. It is a copolymer with one of the units containing tertiary amine functionality.
- Neutral polymers such as methacrylate copolymers, ethyl cellulose or cellulose acetate butyrate. Eudragit RS, which contains a small amount of quaternary amine functionality, can also provide sufficient time delay for use in taste-masking.
- Water-soluble polymers such as HPMC may be added to the core particles of coated formulations to increase release rates after the time-delayed water absorption. The same additive may be used to decrease barrier properties of taste-masking coatings.

COATING OF DRUG PARTICLES:-

- Various inert coating agents can be used to coat bitter drugs. They include starches, polyvinyl pyrrolidones (povidone) of various molecular weights, gelatin, methylcellulose, hydroxyl methylcellulose, microcrystalline cellulose and ethyl cellulose.
- These coating agents simply provide a physical barrier over the drug particles. One of the most efficient methods of drug particle coating is the fluidized bed coating.
- In this approach, powders as fine as 50 µm are fluidized in an expansion chamber by means of heated, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spray through a nozzle.
- Increasing the length of the coating cycle can increase coating thickness. Taste-masking of Ibuprofen has been successfully achieved by this technique to form microcapsules.

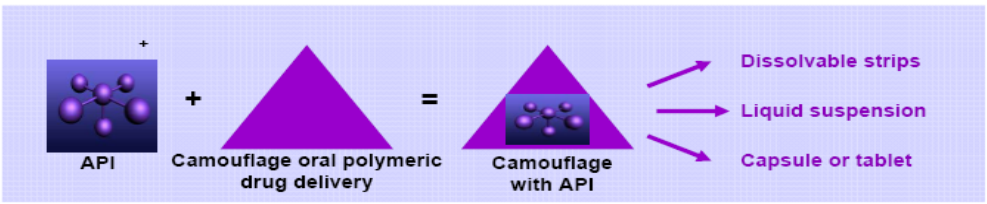


Fluidized bed coating technique

CAMOUFLAGE TECHNOLOGY

Polymeric taste masking process

- Simple to use
- Cost effective
- Colorless
- Tasteless, taste masking
- Sugar free
- High drug loading
- Dissolves rapidly
- Non-systemic absorption of polymer
- Enhances stability
- Used in approved products



2.)MICROENCAPSULATION:-

- Microencapsulation is a process of applying relatively thin coating to small particles of solids, droplets of liquids and dispersions, using various coating agents, such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnauba wax and shellac.

- Bitter-tasting drugs can be first encapsulated to produce free flowing microcapsules, which are then blended with other excipients and compressed into tablets.
- Microencapsulation also increases the stability of the drug. It can be accomplished by a variety of methods, including air suspension, coacervation-phase separation, spray drying and congealing, pan coating, solvent evaporation and multi-orifice centrifugation techniques.
- Among these, coacervation-phase separation technique appears to be more relevant and suitable for taste-masking applications.
- It has been reported that the bitter taste of paracetamol was completely masked on microencapsulation using cellulose-wax combination.

MICROCAPS TECHNOLOGY

- Microencapsulation is a versatile and very precise coating technique used to encapsulate individual drug particles.
- Microcaps technology efficiently and uniformly coats drug particles (droplets if the drug is in liquid form) with polymeric membranes of varying degrees of porosity using Coacervation/phase separation processes.
- The membranes create an inert barrier between the drug and the taste buds. These processes result in individual particles of a drug substance being enveloped into a membrane.
- The type and level of membrane applied is determined by release rate requirements, organoleptic features and the dosage form application.
- Microcaps technology enables:
    - Taste and odor masking
    - Taste masking with modified release

3.)TASTE-MASKING BY VISCOSITY MODIFICATIONS:-

- Increasing the viscosity with thickening agents such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds.
- This provides a taste masked liquid preparation for administration of a relatively large amount of unpleasant tasting medicines.
- The composition of such a formulation comprises a taste-masking liquid base with a high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxy methylcellulose.
- Surprisingly, it has been observed that the high viscosity liquid excipient base provides taste-masking benefits to such an extent that extra strength compositions can be prepared with high concentrations of bitter tasting ingredients.
  For example, guaifenesin, which is normally administered in doses of not more than 100 mg in 5 ml of liquid, may be administered in doses of 200 mg/5 ml, without the feel of bitter taste.

4.)LIPOSOMES:-

- Incorporation of drugs into vesicles or liposomes is although an ideal technique, yet a challenge to formulate without altering the regulatory status of the product (in vitro dissolution kinetics, physical or chemical stability or bioavailability).

5.)EMULSIONS:-

- Another novel technique employing multiple emulsions has also been reported.
- By dissolving drug in the inner aqueous phase of w/o/w emulsion under condition of good shelf stability, the formulation is designed to release drug through oil phase in the presence of gastric fluid.
  In one of the method drugs with bitter taste are combined with nonionic surfactants to form composites by hydrophobic interactions resulting in taste masking.

COMPLEXATION & ADSORPTION:-

1.)COMPLEXATION WITH ION EXCHANGE RESINS:

- The adsorption of bitter drugs onto synthetic ion exchange resins to achieve taste coverage has been well documented.
- Borodkin *et al.* prepared high potency adsorbates of methapyrilene, dextromethorphan, ephedrine, pseudoephedrine by column procedures using a polymethacrylic acid ion exchange resin. Taste evaluation of the adsorbates showed a significant reduction in the bitterness of the drugs. Coating the adsorbate particles with 4:1 ethyl cellulose - HPMC mixture reduced the bitterness further. Taste coverage was maintained after incorporation of the coated adsorbate into chewable tablets.
- Strong acid cation resins (sulfonated styrene divinylbenzene copolymer product) can be used for masking the taste of basic drugs.
- Extreme bitterness of quinolones has been achieved by ion exchange resin such as methacrylic acid polymer cross linked with divinylbenzene.
- For drugs with cationic functionality (e.g. -COOH or Na / K salts): DUOLITE™ AP143.
- For drugs with anionic functionality (-NH_2, HCl salts):
- AMBERLITE™ IRP64, AMBERLITE™ IRP69, AMBERLITE™ IRP88.
- In the another study, an attempt has been made to mask the bitter taste of roxithromycin by complexation technique. Weak cation exchange resins Indion 214 and Amberlite IRP64, polymer carbopol 934P were used in formulation of complexes with the drug. Amberlite IRP64 was found to be better complexing agent for masking the bitter taste of roxithromycin.

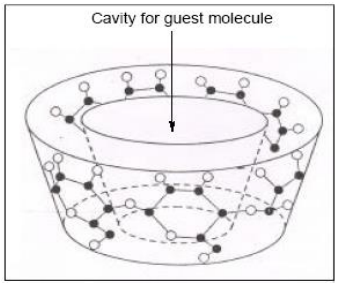
2.)USE OF AMINO ACIDS IN TASTE MASKING

The present invention relates to taste-masked pharmaceutical oral dosage formulations comprising complexes of a drug and polylysine or polyarginine for taste-masking, and to methods of masking the taste of a drug, and preventing sublimation of the drug while providing good bioavailability.

- By combining amino acids or their salts with bitter drugs, it is possible to substantially reduce the bitterness.
- Some of the preferred amino acids include sarcosine, alanine, taurine, glutamic acid, and glycine.
- The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

3.)INCLUSION COMPLEX FORMATION WITH CYCLODEXTRINS

- Cyclodextrin is the most widely used complexing agent for inclusion complex formation which is capable of masking the bitter taste of the drug either by decreasing its solubility on digestion or decreasing the amount of drug particles exposed to taste buds there by reducing its perception of bitter taste.
- Bitter taste of ibuprofen and Gymnema sylvestre has been effectively masked by cyclodextrin.



4.)WAX-EMBEDDING OF DRUGS

Taste masked wax embedded granules of ephedrine hydrochloride, chlorpheniramine maleate, diphenhydramine hydrochloride were prepared in stearic acid and other waxes.

5.)MOLECULAR COMPLEXES OF DRUGS WITH OTHER CHEMICALS

- Lowering drug solubility through molecular complexation can decrease the intensity of bitterness.
- The bitterness of caffeine was completely masked by the formation of a molecular complex of caffeine and gentisic acid in 1:1 and 1:2 molar ratios. The complex was prepared by rapid cooling of the hot aqueous solution of the mixture. The resulting microcrystalline powder precipitate was washed with water and dried under vacuum.

CHEMICAL APPROACH:-

- Chemical modification such as derivatization or lipophillic counter ion selection may be an effective method for reducing aqueous solubility and taste.

1.)FORMATION OF SALT DERIVATIVES:-

- In this approach, an attempt is made to modify the chemical composition of the drug substance itself, so as to render it less soluble in saliva and thus make it less sensitive to the taste buds.
- Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin.
- D-chlorpheniramine maleate is a taste-masked salt of chlorpheniramine.
    - Erythromycin monohydrate, a bitter tasting drug with a solubility of 2 mg/ml is chemically converted into erythromycin ethyl succinate; the aqueous solubility is reduced to the < 50 mcg/ml. This form is tasteless and can be administered as a chewable tablet.

2.)PRODRUGS:-

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. Examples of drug with improved taste are given below.

Table 2: Prodrugs with improved taste

Sr. no.	Parent drug	Prodrug with improved taste
1	Chloramphenicol	Palmitate ester
2	Clindamycin	Palmitate ester
3	Triamcinolone	Diacetate ester

- Palmitate ester of chloramphenicol has been used in pediatric formulation with inhibited bitter taste of chloramphenicol.
- clinadmycin–2-acylestres of varying chain lengths, namely palmitate, laurate, hexanoate and acetate were synthesized. The taste of the palmitate ester is much better than the other esters, and clindamycin-2-palmitate hydrochloride is essentially tasteless.

OTHER TECHNIQUES:-

SOLID DISPERSIONS

- They are dispersions of one or more active ingredient in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter drugs.
- Carriers used in solid dispersion systems include povidone, polyethylene glycols of various molecular weights, hydroxypropyl methylcellulose, mannitol and ethylcellulose. Various approaches for preparation of solid dispersion are described below.

Melting method: In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

Solvent method: In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

Melting-solvent method: In this method the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 70^{o}C.

FREEZE-DRYING PROCES

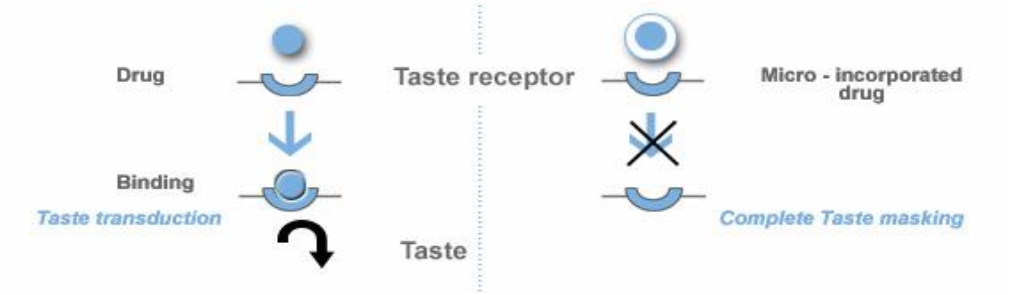
- Various drugs have been taste masked by Zydis technology. This includes the drugs like lorazepam, piroxicam, loperamide, Ondansetron, rizatriptan, loratadine, olanzapine, selegiline etc.

Taste masking as a consequence of the organisation of powder mixes:-

Usually, chemical or technological operations are used to mask the taste of unpleasant-tasting drugs. To reduce the development cost of such drugs,a new approach is proposed which does not require the modification of the existing formulation nor the use of additional costly technological operations. Different particle size fractions of two unpleasant-tasting drugs (niflumic acid and ibuprofen) were blended in binary mixes with different particle size fractions of two non-tasting excipients (ethyl cellulose and hydroxypropyl methylcellulose). By selecting the appropriate mixes of identical composition but different organisations, as predicted from surface energy data, it was possible to use the different organisations to modify the taste of the mixes for a panel of 10 healthy volunteers

ORALANCE TECHNOLOGY:-

- The Oralance® technology efficiently hides the taste of the most difficult molecules even formulated in aqueous media

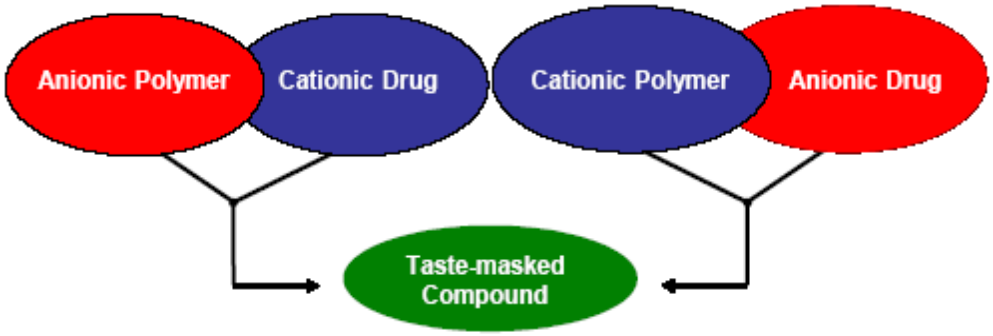


TASTE MASKING BY MELT EXTRUSION TECHNIQUE:-

- Melt extrusion is a familiar technology in the plastics and food industry. It is a high-throughput, high efficiency and a high-quality continuous process.
- Pharma polymers provide both functionalities with its range of EUDRAGIT® polymers. EUDRAGIT® polymers are thermoplastics that can be processed in extruders.
- A very wide range of active substances can also be processed in extruders.

TASTE MASKING BY IONIC INTERACTION

- For this technology, two combinations are possible: using an anionic drug and a cationic polymer, or a cationic drug together with an anionic polymer.

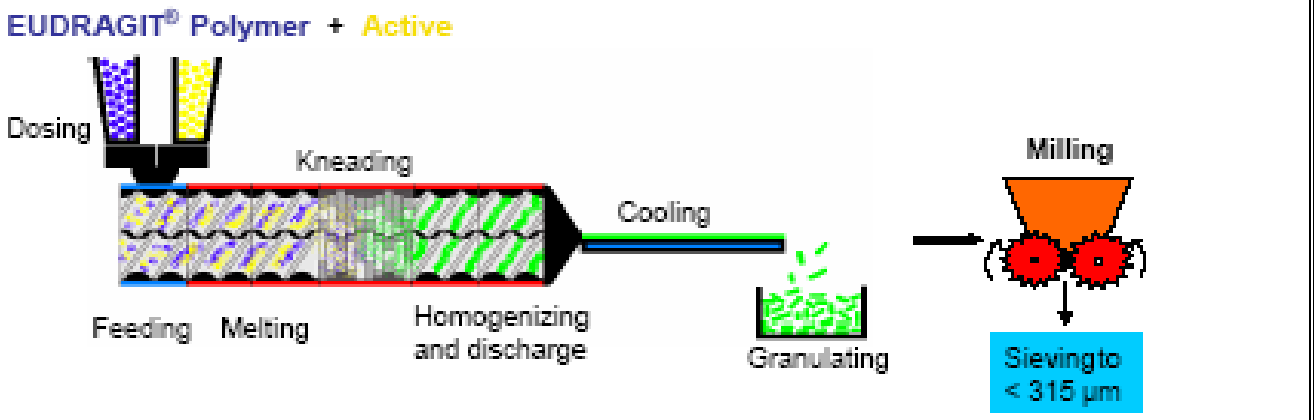


SALT FORMATION

- During extrusion both the active and the polymer are melted.
- The complementary ionic functional groups of active and polymer can then form a salt.
- Salt (carboxylate) formation between the active substance and the polymer takes place without the need for any solvent, such as water or other ingredients.
- This process is reversible when the formulation is dissolved.

PELLATISATION

- Both the EUDRAGIT® and the active are fed into the twin-screw extruder, conveyed forward,
- Melted, kneaded and homogenized. The melt comes out of the extruder die as a strand, which is
- Cooled and pelletized. The pellets can then be milled for later use in tablets or capsules.



Taste masking is achieved when the bitter value is decreased three times by the power of ten.

BV = bitterness value

BV is determined as the reciprocal drug concentration that tastes slightly unpleasant (according to German Pharmacopeias DAB 10).

EVALUATION OF TASTE MASKING EFFECT:-

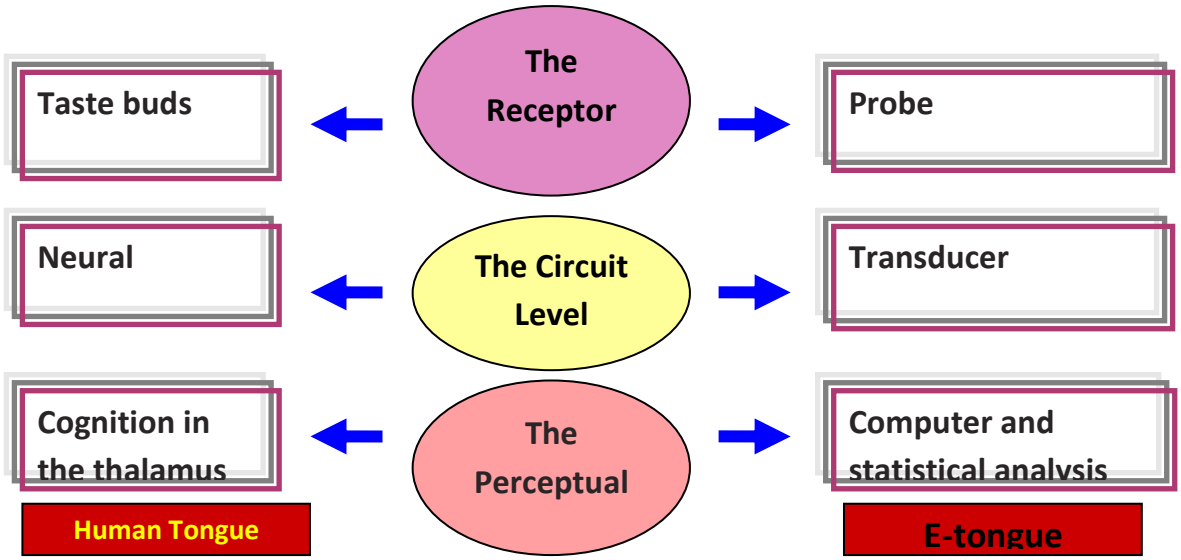
PHARMACEUTICAL TASTE-ASSESSMENT TYPICALLY REQUIRES

1) Trained taste panel, and sophisticated interpretation.
2) ASTREE E-Tongue & VOLTAMMETRIC E-Tongue ALSO KNOWN AS **BIOMIMETIC TASTE SENSING SYSTEM**
3) E-Nose
4) Olfactory Gas Chromatography
5) In vitro cell Cultures

- Soutakagi, *et al.* invented a multichannel taste sensor whose transducer is composed of several kinds of lipid/polymer membrane with different characteristics, which can detect taste in manner similar to human gustatory sensation.
- Taste information is transformed into a pattern composed of electrical signals of membrane potential of the receptor part.
- It was reported that suppression of bitterness of Quinine and a drug substance by sucrose could be quantified by using multi channel taste sensor.
- The present method can be expected to provide new automated method to measure the strength of drug substance in place of sensory evaluation.
- Evaluation of the taste masking effect from coated microspheres can de done by determining the rate of release of the drug from the microspheres.
- Similarly for evaluating the taste masking effect by ion exchange resin, the drug release rate can serve as an index of the degree of masking achieved.
- Other methods include evaluation by a trained flavor profile panel and time intensity method in which a sample equivalent to a normal dose was held in mouth for 10 seconds. Bitterness level are recorded immediately and assigned values between 0-3.

E- TONGUE:-

The e- tongue mirrors the three levels of biological taste recognition:



- ❑ The Receptor level
  - The e-tongue uses a seven-sensor probe assembly to detect dissolved organic and inorganic compounds.
  - The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe's sensitivity and selectivity.
  - Measurement is potentiometric, with readings taken against an Ag/AgCl reference electrode.
  - Each probe is cross-selective to allow coverage of full taste profile.

- ❑ The Circuit level
  - The system samples, quantifies, digitizes, and records potentiometer readings.
- ❑ Perceptual level
  - Taste cognition happens not in the probe, but in the computer, where the e-tongue's statistical software interprets the sensor data into taste patterns.

  Eg:- Quinine sulphate pellets for flexible pediatric drug dosing evaluation of taste-masking efficiency using the electronic tongue.

- ❑ **Key benefits of e- tongue evaluation**
  - ➢ Help to quantify bitterness of drug actives when limited basic taste information is available, especially if the drug supply is limited.
  - ➢ Developing suitable matching bitter placebos for blinded clinical testing
  - ➢ Conduct comparator studies (Benchmark analysis)
  - ➢ Developing optimized taste- masked formulations.
  - ➢ Serving a quality control function for flavored product and excipient.

Use of Electronic Nose to Optimize Flavor Profile

- Companies that commercially produce e-nose:
  Alpha M.O.S. (DeMotte, IN),
  AromaScan (Hollis, NH), and
  Neotronics (Gainesville, GA).
- Human nose: 10,000 odor sensors (nonspecific) but can be very sensitive to certain odors.
- Signals from human olfactory sensors are transmitted to the brain for processing.
- The brain then interprets what the sum of all these signals is describing in terms of odor.
- Electronic Nose instruments attempt to do the same with many fewer sensors and a simulated brain consisting of a computer and sophisticated software.
  The purpose of this study was to apply an electronic nose system for evaluation of unpleasant odor in tablets containing L-cysteine, an unpleasant odor drug, and demonstrate the odor masking ability of thin-layer sugarless coated tablets, which we have newly developed, by both electronic nose system and sensory evaluations. We demonstrated the qualitative evaluation of the unpleasant odor using air as a reference indicator and the quantitative evaluation of the unpleasant odor using the distances between air and samples in the electronic nose system evaluation. The electronic nose system evaluation was positively and well-correlated with the sensory evaluation by volunteers. It was suggested that the electronic nose system evaluation is appropriate as an alternative or a support method for sensory evaluation by volunteers.

Use of Cell Cultures & Receptors to Optimize Flavor Profile

- Advances in molecular biology may hold the key to future developments.
- Cloning of receptor proteins, individual receptors or the whole sensory organ may produce detection systems with similar function to the human sensory organs.
- However, it will be necessary to deconvolute the signals obtained from these systems to convert them into terms typically used to describe our perception of stimuli.

Olfactory Gas Chromatographic Technique

- Olfactory GC techniques permitted the division of identified volatiles into odor-active and non-odor-active.
- New analytical methods deal with measurements of volatile release in the mouth by a novel nose sampler and oral vapor GC. These useful tools clarify the effects of breathing, chewing, and saliva flow on flavor release.

SENSORY ANALYSIS:-

Sensory analysis has been used in developed countries for years to characterize flavors, odors, and fragrances. In recent times much progress has been made in development of instrumentation methods for characterizing odors and flavors.

METHOD		DESCRIPTION
Discrimination test	Difference	Differentiate between samples Qualitatively & Quantitatively
	Ranking test	Ranks a series of samples in order of a specific characteristics, such as sweetness or softness of feel
Scaling Test	Scoring	Uses a score sheet to collect information on specific product attribute
Expert tester		One or more experts in a category evaluate Qualitatively & Quantitatively measures
Affective tastes	Paired preferences	Measures the responses to 2 products (A & B)
	Acceptance	Measures the degree of like or dislike of a product or special attribute. Eg. On a 7 or 9 point scale ranging from “like extremely” to “dislike extremely”

PELLETS AND INNOVATIONS

Pellets are defined as *small, spherical* particulates produced by the *agglomeration* of fine powders or granules of drug substances and excipients using appropriate equipments.

They are usually *free flowing*.

The size of pellets vary from formulation to formulation but usually lies between *1 and 2 mm*.

CHARACTERISTICS:

Uncoated pellets:

- Uniform Spherical Shape
- Uniform Size
- Good Flow Property
- Ease Of Packing (E.G. Into A Hard Gelatin Capsule)
- High Mechanical Strength
- Low Friability
- Ease Of Coating

Coated pellets:

- All above and desired drug release characteristics according to the type of coat material.

ADVANTAGES:

They can be dispensed as such, *filled into a capsule* as well as can be compressed into a tablet.

They can be also used *to dispense incompatible bioactive agents* together into a single formulation.

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

Different release profiles in a single formulation can be met.

Release of drugs at different sites in the GIT.

Upon oral administration, they *maximize absorption* as they freely disperse in GIT.

DISADVANTAGES:

If the pellets are volume filled, for example in capsules, it may lead to the problems of *content uniformity* and *differences in dosing.*

If the pellets are coated, then upon compression into a tablet, there are chances that the *coat of pellets may rupture*.

Pronounced *surface roughness* of pellets may *hinder the filling process.*

If the pellets are coated with *an ethyl cellulose film*, the batches could not be filled to an acceptable standard because *electro-static charges* develop that lead to blocking during the filling process.

PELLETIZATION PROCESS:

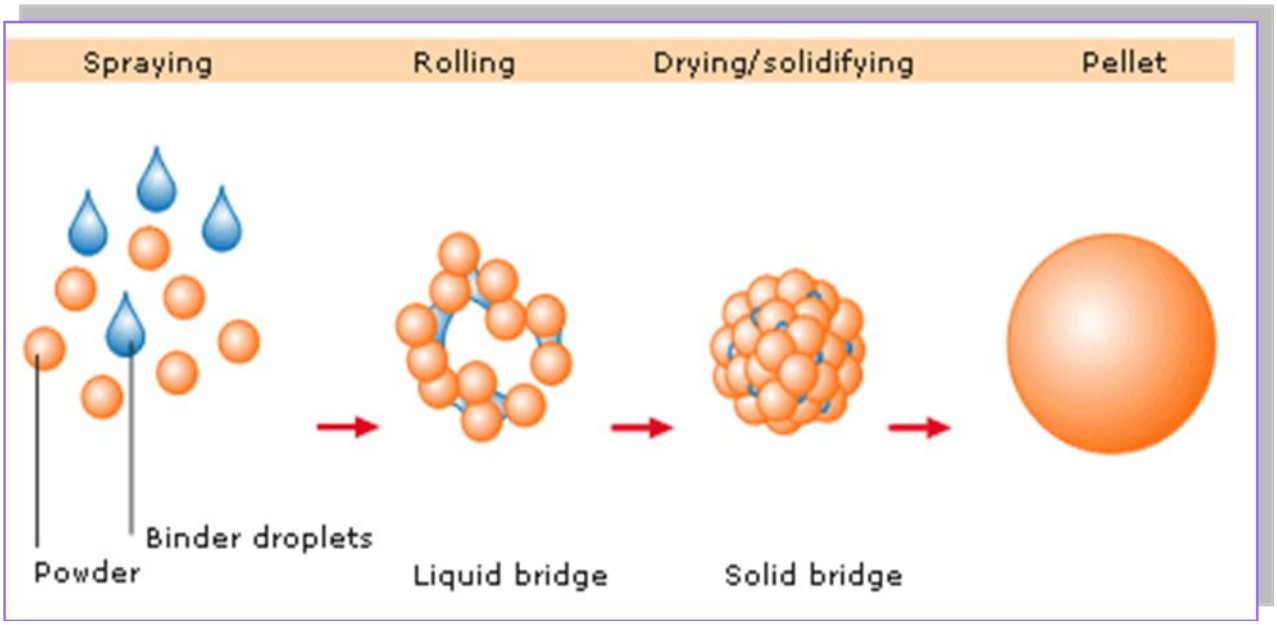
-Direct palletizing

-Pelletization by layering

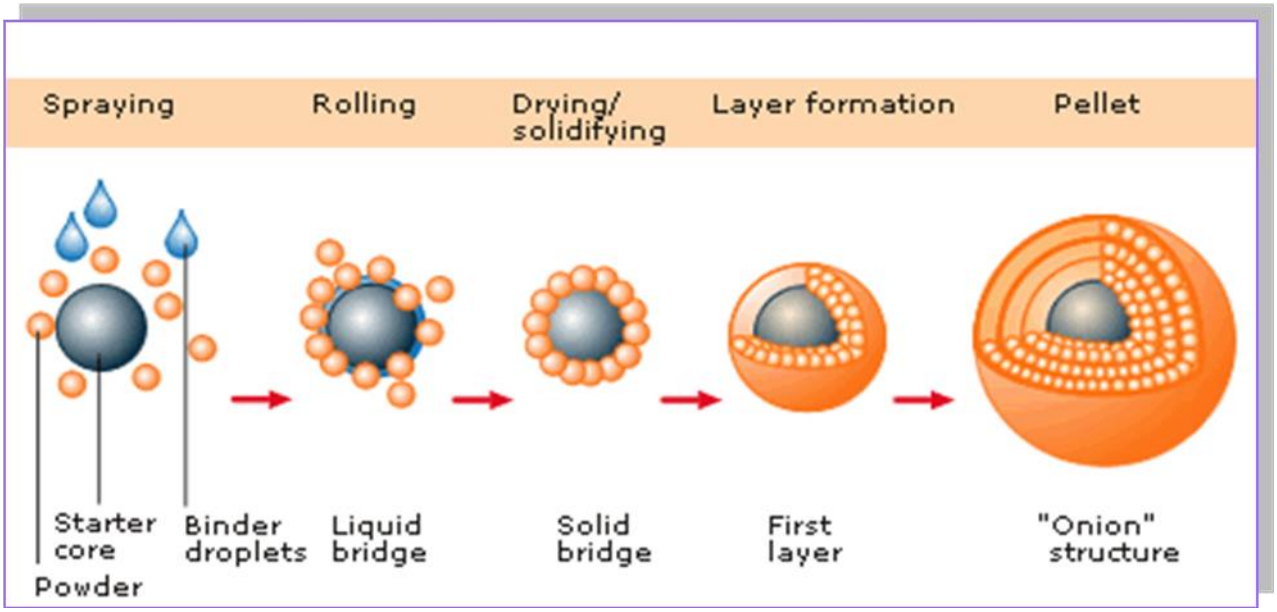
-Extrusion-spheronization

-Sugar spheres

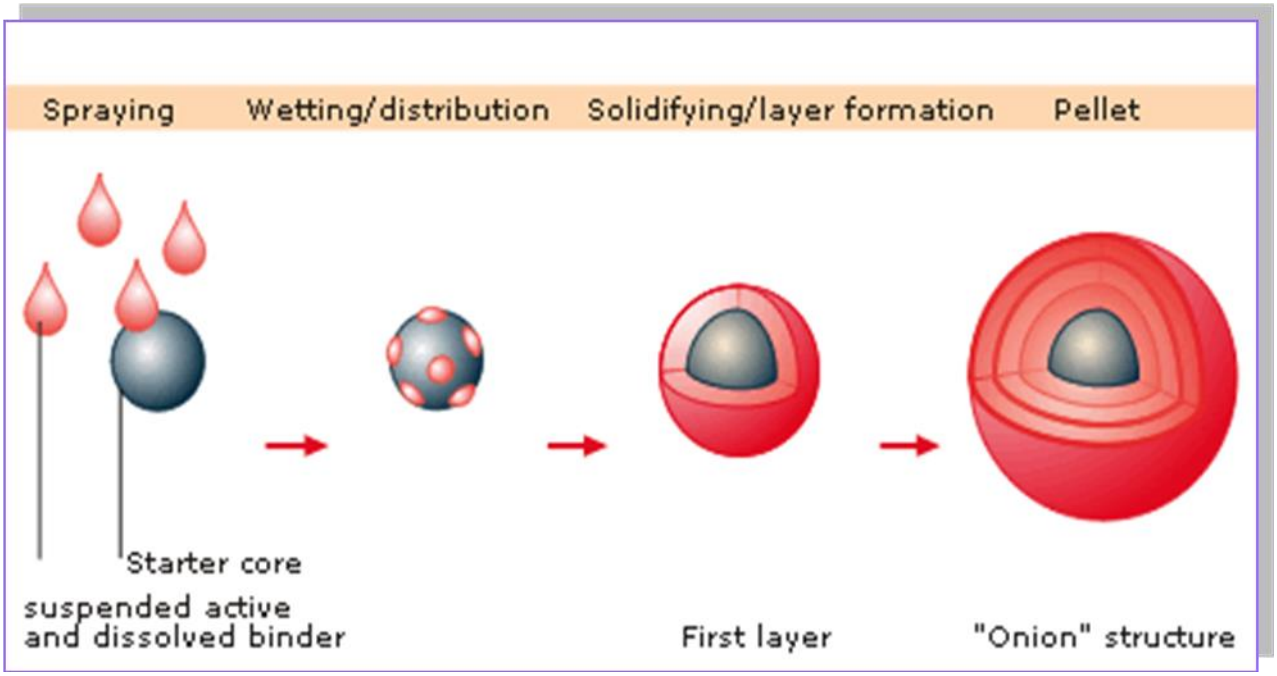
DIRECT PELLETIZING:



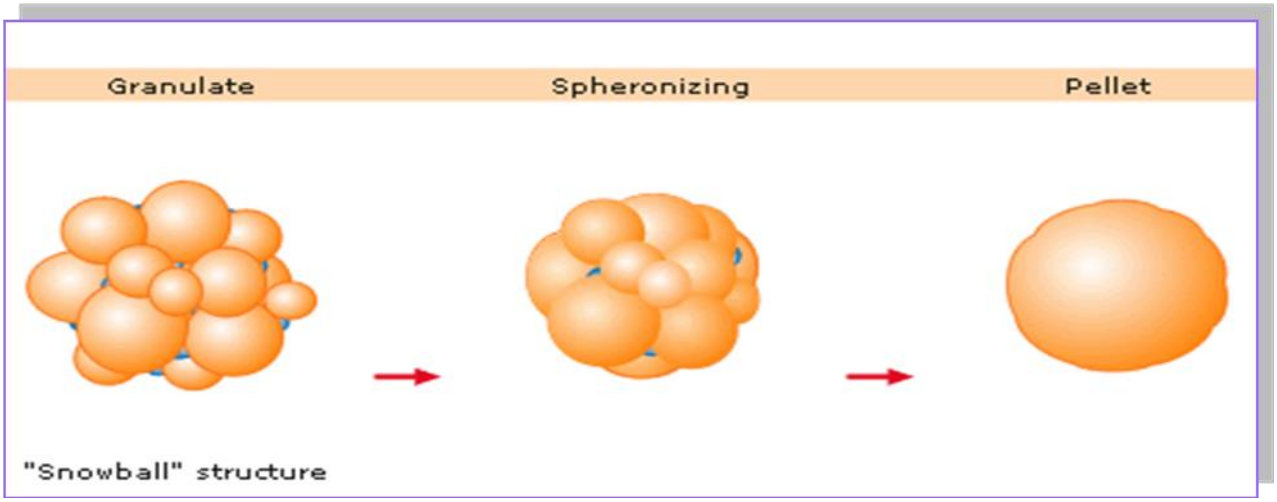
PELLETIZING BY LAYERING:



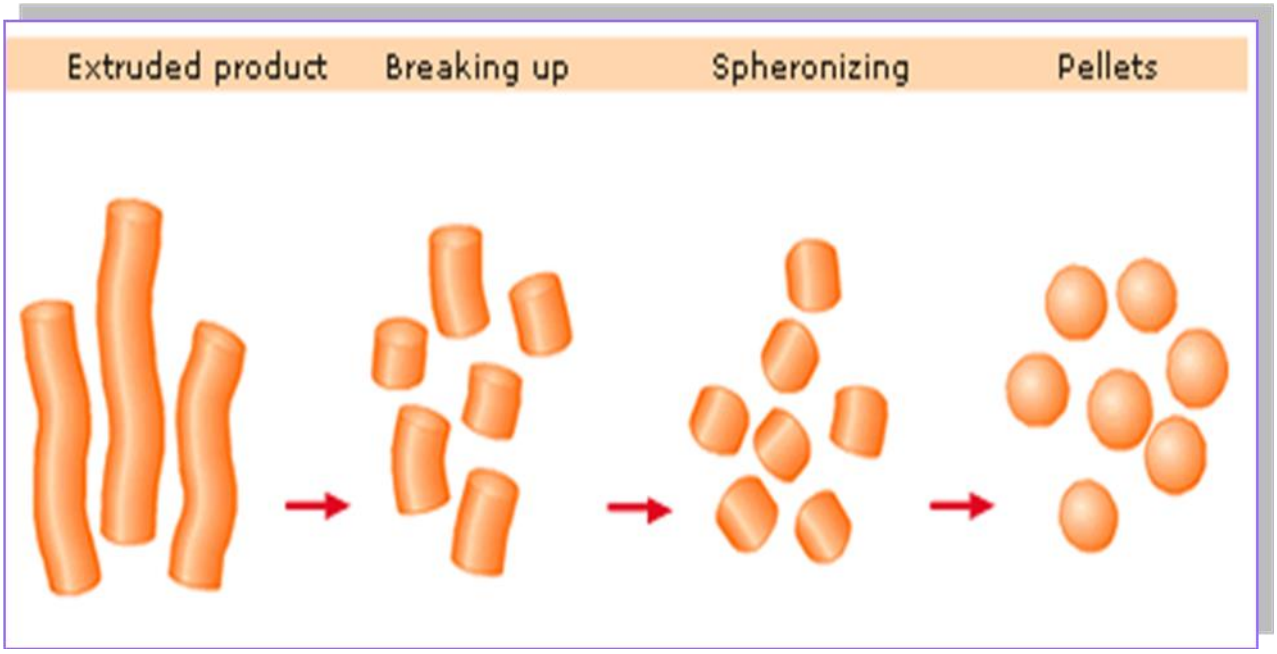
PELLETIZING BY SOLUTION/SUSPENSIONLAYERING PROCESS;



PELLETIZING BY SPHERONISATION;



EXTRUDED PRODUCT SPHERONIZING PROCESS;



SUGAR SPHERES:

Sugar spheres are produced, preferably using *layered sugar-coating structure*.

The ideally *rounded spheres* are then *coated* with the active substance and sustained release additives.

Sugar spheres characteristically consist of *sucrose* and *corn starch*, which are pharmacologically indifferent, digestible excipients frequently occurring in normal diet.

Sugar spheres mush have *adequate mechanical stability* to withstand the loads during subsequent coating, including contact with solvent.

NEWER TECHNOLOGIES:

Melt spheronization

Spray drying and Spray congealing

Cryopelletization

Freeze pelletization

CRYOPELLETIZING:

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

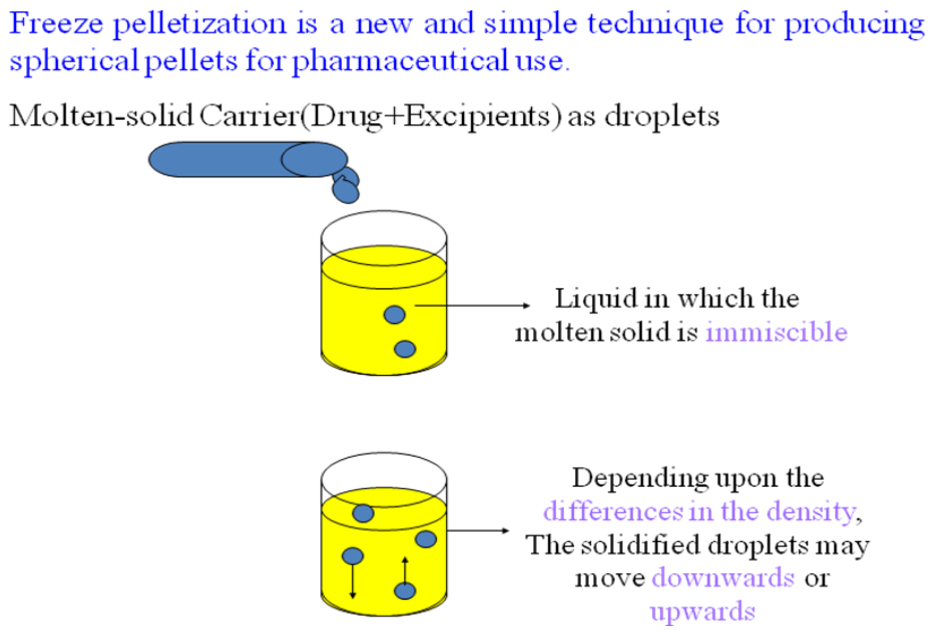
The procedure permits *instantaneous* and *uniform freezing* of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The pellets are *dried in conventional freeze dryers*.

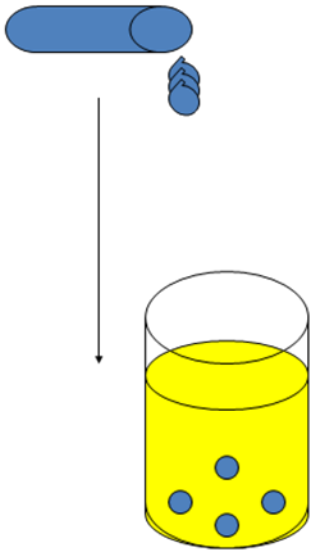
The equipment consists of a container equipped with *perforated plates at the bottom*. Immediately below the plates at a predetermined distance is a *reservoir of liquid nitrogen*. In which a *conveyor belt* with transport baffles is immersed.

The conveyor belt has a *variable speed* and can be adjusted to provide the residence time required for *freezing the pellets*. The perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen below.

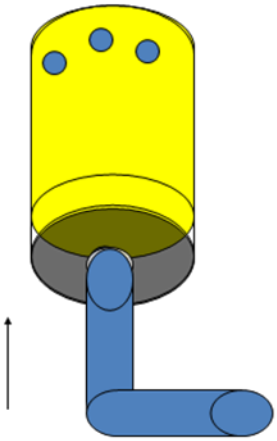
The frozen pellets are transported out of the nitrogen bath into a storage container at *-60°C before drying*.

FREEZE PELLETIZATION:





If the density of molten droplets is *higher* than that of liquid, then the droplets are passed from *upwards*, and thus they solidify when they *reach the bottom* of the liquid filled vessel.



If the density of molten droplets is *lower* than that of liquid, then the droplets are passed from *downwards*, and thus they solidify when they reach the *top* of the liquid filled vessel.

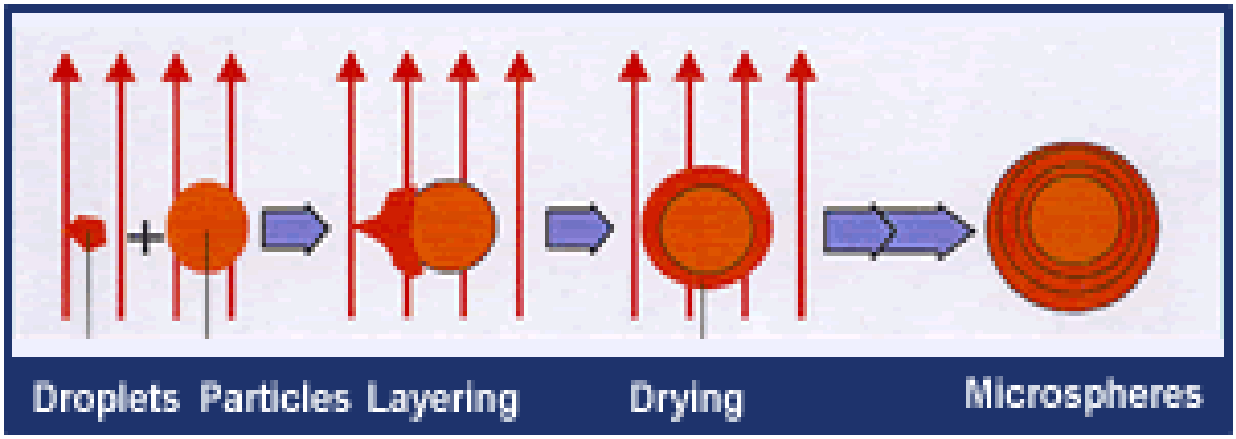
RECENT INNOVATIONS:

MICROPX™ TECHNOLOGY:

The Micro Px™ Technology consists of a *continuous fluid bed process.*

After liquid spraying and coating of APIs, generated micropellets are classified by applying a *vertical online air sifting system.*

The Micro Px™ Technology process results in manufacturing of high drug loaded matrix-type micropellets. *Drug loadings of produced pellets can be up to 95%.*



ADVANTAGES:

- small particle size
- spherical pellet shape
- manufactured Micro Px™ pellets reach very homogeneous and narrow particle size distribution
- drug loads achievable of up to 95%

PROCELL™ TECHNOLOGY:

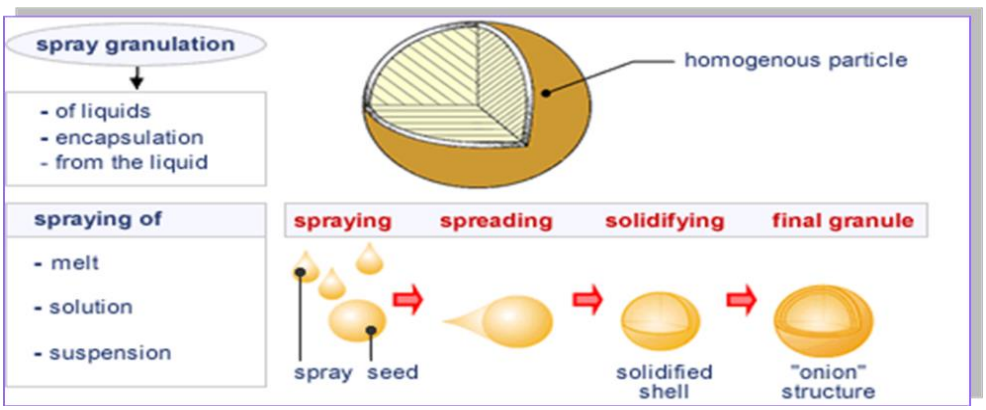
Process Technology for the manufacture of *very high concentrated spherical particles*

Modified fluid bed granulation process
– in particular performed as melt granulation
– no inert starting beads required
– controlled particle movement

Controlled material circulation through *special air flow design*

Special processing chamber design, no bottom sieve

ProCellTM: Spray granulation-Mechanism



Product Characteristics:

Very high material concentration (up to 100%)

Particle size range from 50 – 1500 µm

High density, low porosity

Particularly suitable for processing of products with inherent stickiness

Processing of excipients and drug substances

FAST DISSOLVING PELLETS:

Fast Dissolving Pellets are manufactured using proprietary pelletisation techniques.

Fast Dissolving Pellets consist entirely of very water soluble and/or swellable excipients and can be compressed into orally dispersible tablets (ODTs).

CHARACTERISTICS:

- Narrow particle size distribution, e.g. 100 - 400 µm
- Smooth mouth feel
- Highly water soluble & swellable pharmacopoeial constituents with low hygroscopic behaviour
- Addition of flavoring agents possible
- Spherical pellets with porous structure; porosity facilitates disintegration and dissolution
- Mechanically very stable; easy product handling
- Packaging into conventional stick packs feasible

CELLETS:

Homogenous distribution of the active agent and the controlled release are two fundamental advantages of this dosage form.

Due to the uniform concentration of highly active agents more reliable formulations can be achieved.

As an inert, odorless and tasteless excipient, microcrystalline cellulose is extremely versatile. Therefore our Cellets® are made from certified MCC and water only. Allowing combining the benefits of neutral pellets with the unique properties of cellulose.