



## MULTIPARTICULATES DRUG DELIVERY SYSTEM: A REVIEW

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Article Received on 07/04/2021

Article Revised on 28/04/2021

Article Accepted on 18/05/2021

### **ABSTRACT**

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends indicate that Multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired. 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- 2.00mm.

**KEYWORDS:** Multiparticulate drug delivery system, pellets, palletisation techniques, Melt extrusion, Mini tablet, Natural, Extrusion Spherization.

### **INTRODUCTION**

Orally modified drug delivery systems can be classified in to two extensive group single unit dosage forms & multiple unit dosage forms. Multiple unit dosage forms (MUDF's), such as granules, pellets. The insight of MUDF's was initially presented in 1950s. The production of MUDF's is a common policy to control the release of drug as shown by their reducibility of the release profiles when compared to the ones obtained with single unit dosage form (SUDF's).The progress of mini matrices is a hopeful area in pharmaceutical research concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of drugs and has attracted some attention in the 1990s. Similar too their MUDF's several mini tablets can either be filled in to hard capsules or compacted in to bigger tablets. Then after disintegration, they may release these sub-units as multiple dosage forms. There has been increasing interest in the development of MUDF's incorporated into tablets instead of hard gelatine capsules in order to overcome the higher reduction costs of capsules. In contrast to Monolithic dosage forms a multiple unit dosage forms offer several advantages.<sup>[1,20]</sup>

### **MECHANISM OF DRUG RELEASE FROM MULTI PARTICULATES**

The mechanism of drug release from multiparticulates can be occur in the following ways.

- Diffusion
- Erosion
- Osmosis

#### **Diffusion**

Water diffuses into the particle, when drug comes in contact with GI and dissolution of drug occurs. There are two different methods by which diffusion controlled release can be obtained that includes, reservoir device and monolithic device in monolithic device drug product tend to distribute in a matrix and diffusion may take place through polymer matrix or by crossing between polymer chain and a molecular level. In difference to above said devices, reservoir device is the example in which drug is available as encapsulated or core within polymer film.<sup>[2]</sup>

#### **Erosion**

With the help of osmotic pressure developed within the particle, drug is expelled out into the extrinsic through coating. Osmotic ally controlled DDS (CDDS) based devices are supposed to be the most compatible CDDS especially for drug delivery through oral route. To check

a drug release in a controlled manner by osmotic pressure can be used by special such as driving force. These systems generally consist of osmotic agents such as excipients. Semipermeable membrane, and drug.<sup>[3]</sup>

**Osmosis:** In some of the cases, wherever coatings are particularly designed to wear away gradually with time, and hence these type of drugs which are contained within the particle can be delivered by erosion.<sup>[4, 21]</sup>

### Pellets

Traditionally, the word pellet has been used to describe the variety of systematically produced geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. These products may be fertilizers, Animal feeds, Iron Ores or Pharmaceutical Dosage forms. Pellets are small spherical free flowing units with improved flow properties and flexibility in formulation development and manufacture. Their size and shape allow their administration as injections and also for oral drug delivery. Pellets range in size, typically, between 0.5 – 15 mm, though other sizes could be prepared. Pellets are for pharmaceutical purposes and are produced primarily for the purpose oral controlled-release dosage forms having gastro resistant or sustained release properties or the capability of site-specific drug delivery. For such purposes, coated pellets are administered in the form of hard gelatine capsules or disintegrating tablets that quickly liberate their contents of pellets in the stomach. As drug-delivery systems become more sophisticated, the role of pellets in the design and development of dosage forms is increasing. Formulation of drugs in multiple-unit dosage forms. Such as coated pellets filled in capsules or compressed into tablets, offers flexibility as to target-release properties.<sup>[5,6,7]</sup>

### WHY PELLETS?

- Excellent Stability.
- Dust free Round pellets. Good flow behaviour.
- Easy to dose
- Compact structure.
- Very Low hygroscopic.
- High bulk density.
- Dense, uniform surface.
- Narrow grain size distribution.
- Low abrasion.
- High active ingredient content possible.
- Optimum starting shape for subsequent coating.
- Controlled-release applications.
- Drug absorption.
- The risks of the local damage to the GI tract mucosal.

### Advantages of pellets

- They can be divided in to desired dosage strength without process or formulation changes.
- When pellets containing the active ingredient are in the form of suspension, capsules, or disintegrating,

Tablets. They offer significant therapeutic Advantages over single unit dosage forms.

- They can also be blended to deliver incompatible bioactive agents.
- They can also be used to provide different release profile of the same or different sites in the gastrointestinal tract.
- Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule.
- Pellets disperse freely in GI tract, maximize drug absorption, and minimize local irritation of the mucosa by certain irritant drugs.
- Improved flow characteristics: Spheres have excellent flow properties which can be used in automated processes or in processes where exact dosing is required, e.g. tabletting, moulding operations, capsule filling, and packaging.
- The thickness of coat on the pellets dictates the rate at which the drug or content Released from coated particles.
- The smooth surface and uniform size of pellets permit uniform coating not only each Pellets but also from batch to batch.
- In case of immediate release products larger surface area of pellets produce better Distribution.

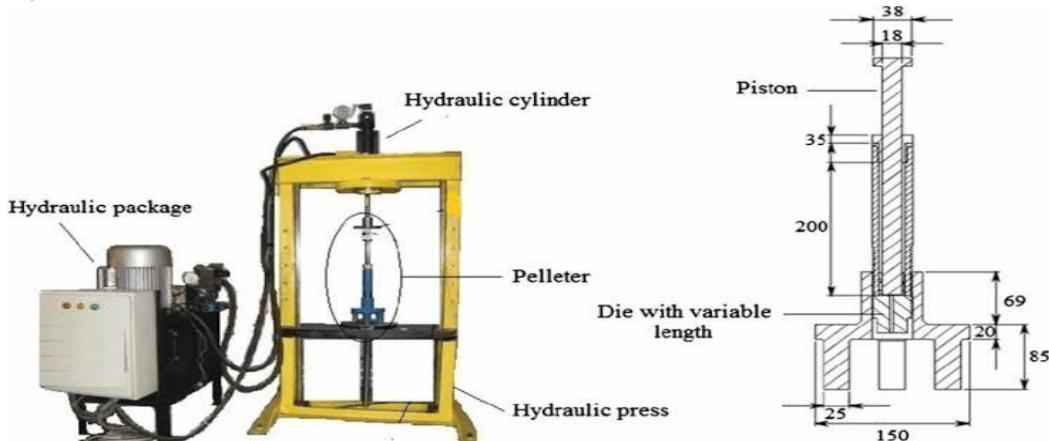
### Disadvantages of Pellets

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tableting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2mm.
- The manufacturing of multiple unit dosage form is more expensive and complicated.
- The filling into gelatine capsule is difficult to accomplish especially in case where Different subunit are involve.

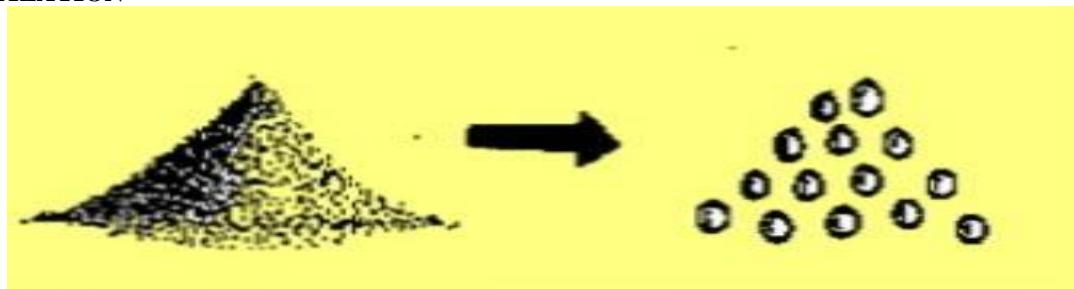
### • Methods for pellets preparation

The most widely used palletisations processes in the pharmaceutical industry are.

## EQUIPMENT



## PELLETIZATION



Pelletization is an agglomeration process that converts fine powder blend of drug(s) and Excipients into small free flowing. Spherical units, referred to as pellets.<sup>[8,9]</sup>

Pelletization is referred to as a size enlargement process and if the final agglomerates are spherical with a size of 0.5-2.0 mm and low intra-agglomerate porosity (about 10%), they are called pellets.

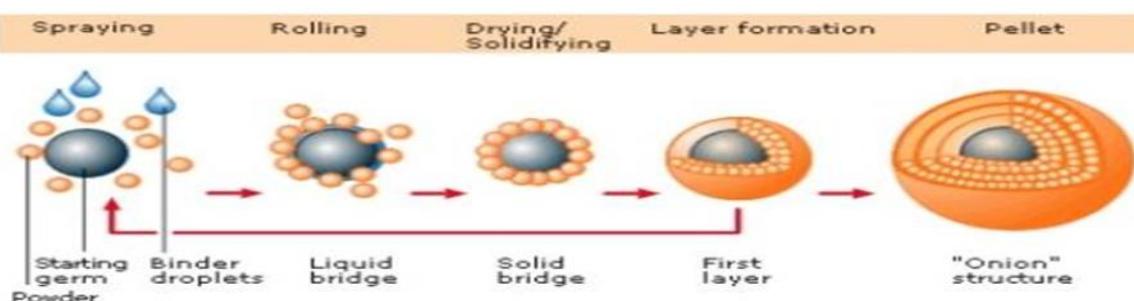
### PELLETIZATION TECHNIQUES

- Powder layering Solution/Suspension layering.
- Extrusion-Spheronization.
- Spherical agglomeration or balling Spray congealing/ drying.
- Cryopelletization and.
- Melt Spheronization.

### Powder layering

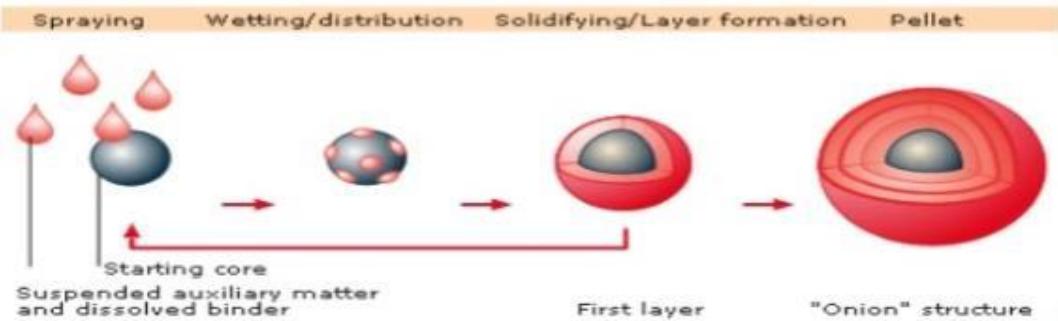
Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on

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. 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.



**Fig: Principle of powder layering process.**

### 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. A starting grain or a pellet can be presented as the starting material. The pellet is built up to the required grain size by adding the layering substance one layer at a time. Powder and binders, suspensions or solutions make suitable layering substances. Thick layers can be applied to the starting grains, which in the case of layers containing active ingredients, allow large amounts of active ingredient to be incorporated. 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.

#### Advantages

- Reduce dust.
- Reduce waste.
- Require less Storage area.
- Reduce the Appearance of Hay belly.
- Prevent Horses from Sorting feed.

#### Disadvantages

- Decrease eating time, creating more boredom.
- Increase the cost of the feed due to the pelleting process.
- Decrease the amount of fibre a horse receives.
- Poor-quality feed ingredients can be hidden In a pellet.
- Excessive heat during the pelleting process may decrease the availability of amino acids such as lysine and may destroy some vitamins.
- Greedy eaters may be more prone to choke, colic, or other digestive disorders.

### Extrusion Spheronization

Compared to single-unit dosage forms, oral multiparticulate drug-delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation in the gastro-intestinal tract. There are different pelletizations and granulation techniques available to prepare drug loaded spherical particles or granules. Extrusion Spheronization is one of them and utilized in formulation of beads and pellets. Limitations related to bioavailability and site specific drug delivery can be overcome by this technique. Today this technology has gained attention because of its simple and fast processing. Extrusion spheronization is widely utilized in formulation of sustained release, controlled release delivery system. The main objective of the extrusion spheronization is to produce pellets/spheroids of uniform size with high drug loading capacity. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids. It is especially useful for making dense granules for controlled-release solid dosage oral forms with a minimum amount of excipients. Extrusion/spheronization begins with extrusion process in which the wet metered mass is placed into the extruder where it is continuously formed into cylindrical rods of uniform size and shape. Amount of granulating fluid and uniform dispersion of fluid plays an important role in preparation of wet mass as optimum plasticity and cohesiveness directly affect the final production of pellets. Once the extrudates are prepared, they are then taken to spheroniser where it is spheronized or rotated at higher speed by friction plate that breaks the rod shaped particles into smaller particles and round them to form spheres. The size of the spheroids mainly depends on the diameter of circular die that modifies the diameter of cylindrical rods produced in extrusion stage.<sup>[11]</sup>



Fig: Extrusion Spheronization.

**The extrusion-preconisation process can be broken down into the following steps**

- Dry mixing of the active ingredients and Excipients to achieve a homogeneous powder.
- Wet massing, with binder added to the dry mixture
- Extrusion into a spaghetti-like extrudate

- Spheronization to from the extrudate in to spheroids of uniform size.
- Drying
- Dry sizing, for sifting (optional) to achieve the desired size distribution
- TheCoating (optional)<sup>[17]</sup>

## EQUIP



**Fig: The extrusion-spheronization process can be broken down.**

### Product features

- Dust free.
- High spheroid.
- Free flowing.
- Compact structure.
- Low hygroscopic.
- High bulk density.
- Low abrasion.
- Narrow particle size distribution.
- Smooth surface.



**Fig: Product features.**

### MELT EXTRUSION

Melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry Today this technology has found its place in the

array of pharmaceutical manufacturing operations. Melt extrusion process are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts.<sup>[12]</sup>

### OVERVIEW

Process of converting a raw material into a product of inform shape and density by forcing it through a die under controlled conditions. Continuous process, capable of consistent product flow at relatively High throughput rates. An extruder consists of two distinct parts.

The conveying system which transports the material and impart a Degree of distributive and dispersive mixing The conveying system which transports the material and impart a degree of distributive and dispersive mixing The die system which forms the material into the required shape.

### Type

Two types of system

- 1) Molten system under temperature control Here heat is applied to the material to control its viscosity and enable its flow through the die.
- 2) A semisolid viscous system Semisolid systems are multiphase concentrated dispersions containing a high proportion of solid mixed with liquid phase.

### 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-swell able and water insoluble nature.
- Are used in this process.
- Fewer processing steps.
- equipment and low production costs.

#### **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.

#### **Applications in the pharmaceutical industry**

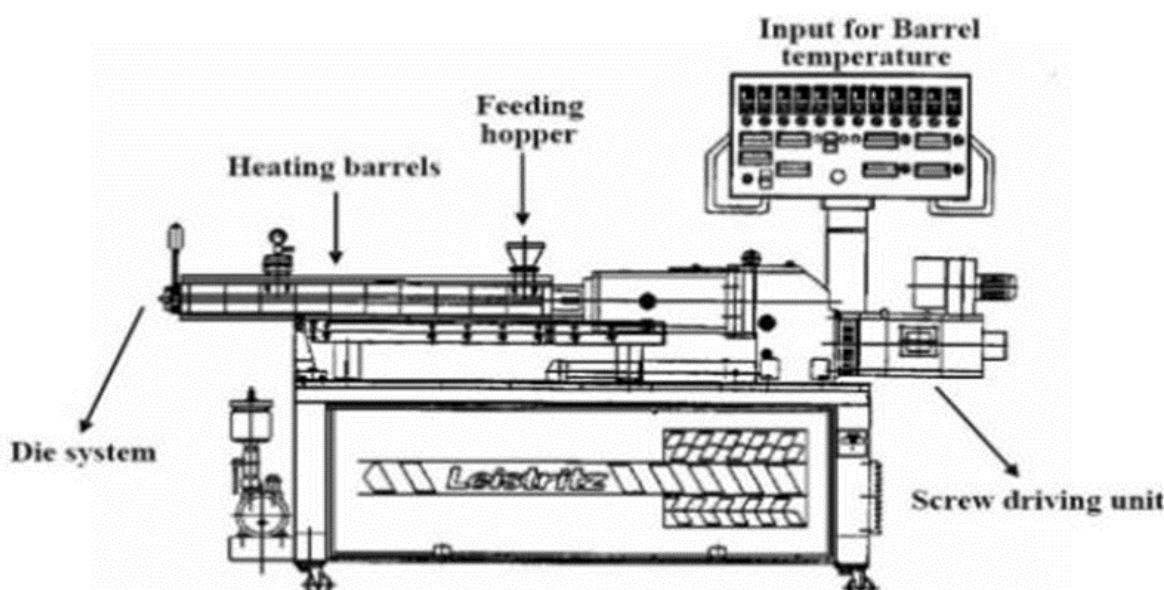
In pharmaceutical industry the melt extrusion has been used for various purposes such as.

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.

- Controlling or modifying the release of the drug.
- Masking the bitter taste of an active drug
- 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 Srockel and co workers. In 1994 Follonier and co-workers investigated hot-melt extrusion technology to produce sustained release pellets.

#### **Process and Equipment**

To convert a homogeneous mixture of APIS. Polymeric excipients, and other additives such as plastic series Gyas, and sutactantinto product under high temperature and high shear inverter. 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.



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

The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels a conveyor 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. The

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

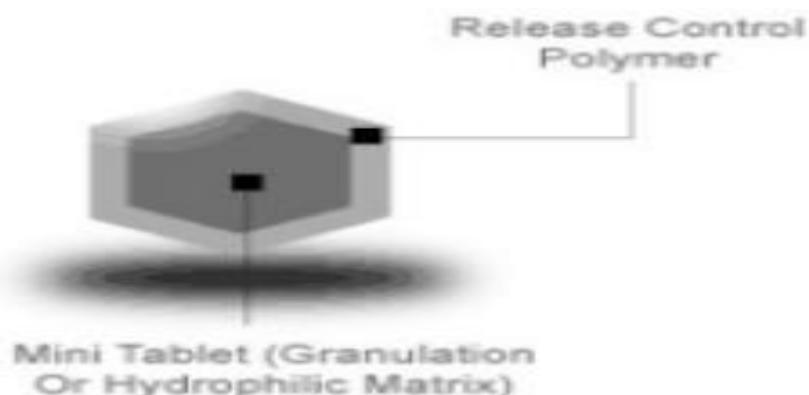
## LIMITATIONS

- The drug substance should meet specific requirement
- Potential air entrapment
- Not suitable for all thermo labile material
- Frequent addition of plasticizer
- Various process parameters are involved Requires polymerizing TABLET.

## MINI TABLETS

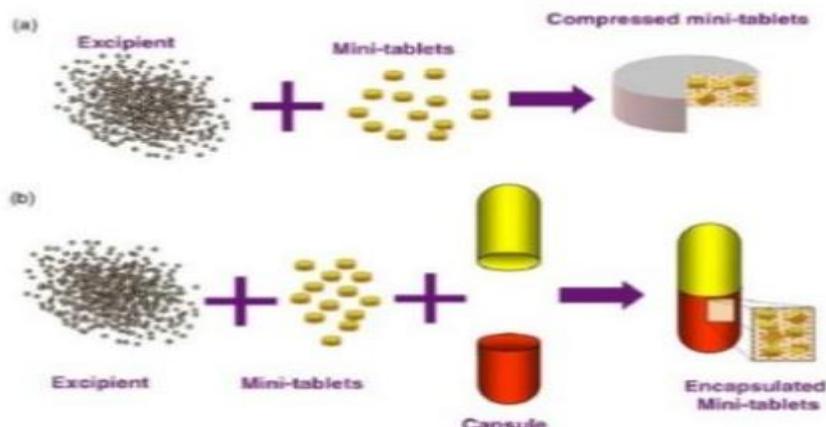
It is well known that solid oral dosage form, particularly tablets, are the most acceptable form of delivering

medication. However, some new variations are beginning to emerge such as mini-tabs, which offer formulation flexibility. Mini-tabs are small tablets with a diameter typically equal to or less than 3 mm that are typically filled into a capsule, or occasionally further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule.<sup>[13, 22]</sup>



**Fig: Mini Tablet**

## MINI TABLETS



**Fig. Mini-tablets delivered as a tablet (a) or a capsule (b).**

These combinations may include immediate release, delayed release, and/or controlled release mini-tabs. It is also possible to incorporate mini-tabs of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements. Mini-tabs could also offer a solution to the

current issue in the pharmaceutical industry representing a lack of dosage forms which are suitable for paediatrics.

Additional benefits of mini-tabs include excellent size uniformity, regular shape and a smooth surface, thereby offering an excellent substrate for coating with modified release polymeric systems. They can be produced via direct compression and can be manufactured using

conventional Tableting machines with only minor equipment modifications. For example, in order to increase production speeds, multiple tip tooling has been employed routinely. Furthermore, mini tabs can be coated using either a perforated coating pan or a fluid bed adversary.<sup>[14]</sup>

### Eudragit Polymer

**History:** Eudragit is trademark of GmbH & Co. KG. Darmstadt in Germany, first marketed in 1950s. Eudra prepared by the polymerization of acrylic and methacrylic acids or their esters. E.g. butyl ester or dimethyl- amino- ethyl ester.<sup>[15,16]</sup>

### Applications of Eudragit Polymers

**Gastrointestinal Drug Delivery:** The need for gastroretentive dosage forms has led to extensive effort in both academia and industry towards the development of such drug delivery systems. These efforts emitted in gastroretentive dosage forms that were designed, in large part, based on the following approaches, Low density form of the dosage form that causes buoyancy in gastric fluid High density dosage from that is retained in the bottom of the stomach Bio adhesion to stomach mucosa Slowed motility of the gastrointestinal tract by concomitant administration of drug or pharmaceutical excipients Expansion by welling or unfolding to a larger size which limits emptying of the dosage form the pyloric sphincter. All the techniques we can achieved with different takes of eudragit.

**Intestinal Drug Delivery:** Sustained intestine delivery of drugs was developed that could bypass is the stomach and release the loaded drug for long periods into the intestine by coating of eudragit polymer. Eudragit L& Eudragit S are two form of commercially available enteric acrylic resins. Best of them produce film resistant in gastric fluid. Eudragit L&S are soluble in intestinal fluid at pH 6 & 7 respectively. Eudragit L is available as an organic solution (isopropanol), said or aqueous dispersion.

**Colon Drug Delivery:** Colonic drug delivery in a relatively recent approach for the treatment of disease like ulcerative colitis, Crohn's disease, and irritable bowel syndrome, pH sensitive polymers' that dissolve, or above pH 7 used for colonic drug delivery 37. Tegaserod maleate was used as for irritable bowel syndrome, where Eudragit L. 10 and S100 mixture (1:1, 12. und 1:3) were med.

**Ophthalmic Drug Delivery:** A major problem being faced in ocular therapeutics in the attainment of an optimal concentration at the site of action. Per availability of drops tot ocular dosage forms is mainly due to the tear production, min-productive abruption, transient residence time, and permeability of corneal epithelium. Eudragit cohabites faceable behaviour, much as so toxicity, positive choice and controlled release

poolike this mule them suitable for ophthalmic application.<sup>[18]</sup>

**Buccal and Sublingual Drug Delivery:** The oral means in general are somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the pemeability of the buccal mucosa is 44000 times greater than that of the skin. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. At physiological pH the mucus network carries a negative charge due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Major limitation of the buccal route of administration is the lack of dasage farm retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery system. Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Diverse classes of polymers have been investigated for their potential e as mucoadhesives. These include synthetic polymers such as monomeric a cyanoacrylate, polyacrylic acid, and poly methacrylate derivatives. An ideal buccal film should be flexible elastic and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength that it is retained in the mouth for the desired duration. To prevent discomfort, swelling of the film should not be too extensive. The mechanical, bioadhesive, and swelling properties of buccal films are critical and must be evaluated.<sup>[19]</sup>

### CONCLUSION

The modern market for MDDS has enormous rate of growth. Recent technologies for drug delivery can be developed by assimilating drug into various drug delivery system, which is a booming area in the pharmaceutical industry. It includes pelletisation process that gain more popularity because of their easy portability improved patience compliance and ease of administration and flexibility in the fabrication as tablets or capsules or packed simply as a single dose packlets. They can be applied by both oral and buccal routes. This technology show its parturient in a unique way most of the pharmaceuticals companies to develop pelletized dosage forms for wide range of active pharmaceuticals ingredients.

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