Since the time of immemorial centuries, oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms [SUDF and MUDF]. Multi particulate dosage forms are receiving a immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical preparations produced (Shettigar et al, 1996; Gu et al 2004).

But soon it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc.) comes along with the single dose formulations. This soon led to the dividing of monolithic dosage forms into multiples. Multiple unit dosage forms (MUDFs), are formulated as granules, pellets, or mini tablets (Sood et al, 2004; Bechgaard et al, 1978). The concept of this multiple unit dosage forms answered many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs. These MUDFs, can either be filled in to hard capsules or compacted to bigger tablets or can be dispensed in a dose pouches or packets.

The most increasingly interesting area in the development of MUDF’S is incorporation into tablets instead of hard gelatin capsules in order to make it more economical to the consumers and gaining more attention currently. The
current review focuses on the pelletized form of multiple units, they are prepared by process called pelletization which is referred to as a size enlargement process and the final product obtained is called pellets.

Thus, being a consumer-friendly alternative, over the single unit dosage forms many of the pharmaceutical companies are switching their product franchise to improve the technology. This technology option can also provide a good platform for patent non-infringing product development. This drug delivery platform shows business potential promise for future in pharmaceuticals and nutraceuticals (Cheboyina et al, 2004; Celik 1994).

**Pellets**

The term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment. These agglomerates includes fertilizers, animal feeds, iron ores, and pharmaceutical dosage units and thus do not only differ in composition but also encompass different things for different industries. Although pellets have been used in the pharmaceutical industry for more than 4 decades, It is only been since the late 1970s, with the advent of controlled release technology, that the advances of pellets over single-unit dosage forms have been realized.

Pellets are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly
for oral administration (Celine et al, 2007; Ghebre 1989). Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and can be blended to deliver incompatible bioactive agents simultaneously and or to provide different releases profiles at the same or different sites in the gastrointestinal (GI) tract. In addition, pellets taken orally disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter-intra patient variability.

**Ideal properties of the pellets**
- Spherical shape and smooth surface.
- The particle size of pellets should be in range of 500-1500 μm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet.

**Advantages**

In many cases the main reason for the use of pellets in the manufacture of products with controlled release properties. However there are reasons to believe that these multiple unit dosage forms in any case can offer a superior therapeutic effect even when modified release is not the primary objective (Paul Wan, 2005; Raymond Rowe et al, 2005).
- Improved appearance of the product which is having fine pharmaceutical elegance.
- Pelletization offers flexibility into the dosage form design and development.
• Pellets improve the flow properties in formulation development.

• They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).

• Pellets are less susceptible to dose dumping.

• It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs (Raymond et al, 2005).

• It improves safety and efficacy of a drug.

• Pelletization is a convenient way to manage the separation of incompatible drugs.

• Pellets offer reduced variation in gastric emptying rate and intestinal transit time.

• Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation. (Pernilla Navsten et al, 2005).

• Pelletization solves the problem of taste masking.

• Coating of pellets can be done with different drugs to enable a pellets release rate.

• The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats (Abbaspour et al, 2005).

• In case of immediate release products larger surface area of pellets enables better distribution.

• Chemically incompatible products can be formed into pellets and delivered in a single dose by encapsulating them.
• In the chemical industries it is used to avoid powder dusting.

• The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral pellets dosage forms. Pellets oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time.

Disadvantages
• Dosing of volume rather than number and splitting in to single dose units as required.
• Involves capsule filling, which can increase the costs or tabletting, which destroy film coatings on the pellets.
• The size of pellets varies from formulation to formulation but usually lies between 0.5 to 1.5 mm.

Theory of Pellet Formation and Growth

Before selection and optimization of any pelletization/granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification of pelletization process, involves three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and
growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer (Harun et al., 2001; Punia et al., 2012).

Nucleation is a stage of pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction of particle size will improve the bonding strength between them. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates. Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering.

Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei. This mechanism requires slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation.

Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction (Fig. 1).
The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.
Formulation Aspects of Pellets

1) Active Pharmaceutical Ingredient

This multiple unit dosage form technology has potential for delivery of variety of drugs. The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets can be formulated with the drugs that can be delivery even subcutaneously and intramuscularly depending on the size variations where the size range is maintained below 600 microns and are called as micro pellets. Pellets technology is widely used to deliver GIT drugs at a specific site to release drug in a controlled manner (Abrahamsson et al, 1996).

2) Binder

They are also called as agglomerating inducers or bridging agents. These are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation and the addition of the binder may be as a solution than the dry form, which is considered to be more efficient than dry mixing followed by liquid addition. When applied as solution form, binders are dissolved or dispersed in organic or aqueous solvent. Choice of binders (gelatin, starch, polyvinyl pyrrolidone, and high concentrations of sugar) may differ from formulation to formulation and depends on the processing and physicochemical properties of the drug. The mechanism of action of the binder involves formation of liquid bridge that holds the particles together, but as the liquid evaporates the precipitating and hardening of binder takes place leading to main bonding force and with a possibility of the soluble constituents to crystallize.
and contribute to the bonding mechanisms (Jan Maschwitzer et al, 2006; Kleinebudde et al, 1993). In drug layering process, the drug is layered onto the surface of the starter material along with the binders. Sequential layering of binder in the desired manner with the drug allows the formation and growth of pellets.

In the spray-drying process, the binder is intimately mixed as suspension or solution form with the drug to provide a fairly cohesive mixture which results in the pellets with appreciable strength after drying. The binders are commonly used in the range of 2-10%w/w or v/v and should be optimized so that the pellets are durable and not friable and yet to maintain the other desirable properties of the pellets, such as releasing the drug at the intended rate. Gelatin, HPC, PVP, sucrose, starch, etc are a few binders used in the pellet preparation.

3) Granulating Fluid

Moisture content of the wet mass prepared is the most crucial parameter for pellet growth as it imparts the required plasticity and cohesiveness to the wet mass to extrude it and spheronize it to give a prefect spherical shape. An optimum quantity of moisture content should be there to obtain a good quality pellet. The presence of excess moisture content leads to agglomeration of pellets during the preparation process due to the presence of excess solvent system on the surface of pellets while less quantity leads to generation of fines with large size distribution of pellets. In the case of soluble drug, it gets dissolved by the granulation liquid, thus, resulting in increase of the volume of the liquid phase.
which leads to over wetting of the system and agglomeration of pellets (Isaac Ghebre Sellassie., 1989; Vervaet et al. 1995). Different types of granulating fluid are used for the pelletization process. Besides the use of aqueous forms as a granulation liquid, use of alcoholic or hydro alcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol has also been reported.

4) Spheronizing Enhancer

Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity. Ex: MCC.

5) Fillers

These are the excipients used to form the bulk of the material, in the process of pelletization 70 to 80% of the excipients is formed by fillers. Generally microcrystalline cellulose is used for this purpose. Avicel PH 101 is considered to be the pelletization aiding excipient in this process. Glyceryl mono stearate, Starch RX1500, spray dried lactose are also widely used fillers.

6) Plasticizer

Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. Sometimes drugs and other excipients are employed as plasticizers. It was reported that non-traditional
plasticizers including methyl paraben and drugs such as ibuprofen, were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersion of Eudragit RS30D [Methacrylate polymers]. The plasticizer selection will depend upon its compatibility with the polymer and also solvent employed in the casting of strip. These excipients used in hot melt extrusion can affect the release behavior of the drug. The flow of polymer will be improved with the use of plasticizer that enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients (Wu et al, 1999).

7) Lubricant

In pelletization process, lubricants are rarely used as the high-speed rotary equipments in the preparation of pellets. However, during extrusion-spheronization, lubricants do play a crucial role in the successful manufacture of pellets. Their use reduces the friction between the die wall and material mix during the ejection phase. They also play a significant role in smooth discharge of the pellets from the Spheronizer. Examples of lubricants widely used in pellet processing are calcium stearate, glycerin, PEG, Magnesium stearate.
8) Separating Agents

Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process, binding the pellets together leads to the formation of aggregates due to subsequent addition of binding agents, and agglomeration of pellets due to the wetness of the surface of the pellets coupled with the local concentration of the binding agents. The amount of separating agent used differs with the type of formulation and the manufacturing process and they are used in dry form during spheronization to prevent adhesion of the spheres to the friction plate and the cylindrical wall of the Spheronizer. Ex: Purified Talc (Millili et al, 1990).

9) Surfactants

In most pelletization processes, the initial pellet formation and subsequent growth into fully fledged smooth surfaced spherical pellets depends, to some extent, on the liquid bridges that hold the primary particles together, therefore, liquid (water in most cases) wetting the particles effectively is given more attention. Surfactants are added to the liquid to improve wettability by lowering the interfacial tension between the liquid and drug particles (Rajesh Gandhi et al, 1999). Surfactants help to weaken the liquid bridges and results in more friable pellets. In extreme cases, excess fines might be produced which brings in the
focus to the addition of surfactants for pellet formulations. Care should be taken to avoid using surfactants unless it is absolutely essential for the production of pellets that possess specific properties. Examples of surfactants widely used in pellet processing are Polysorbate, Sodium lauryl Sulphate.

10) pH Adjusters

The pH adjusters are substances that are incorporated in pellet formulations which influence the microenvironment of drug molecules used for many reasons. Generally acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of core in a favorable range. In addition, buffer systems may be included in pellet formulations to enhance the dissolution rate of drugs whose solubility’s are influenced by changes in the pH. This is particularly referred with pellets whose release rates are membrane-controlled as the solubility of the drug plays a major role in determining the rate of release. Therefore, specific buffer systems or dual buffer systems are incorporated in pellet formulations to adjust the solubility of drugs to fit a particular process. Ex: Sodium Carbonate.

11) Release Modifiers

The main requirement of pelletization process is to manufacture spherical drug cores that will be subsequently coated in a separate unit operation. It is also possible to prepare pellet cores that inherently possess specific release profiles
in a single step which can be achieved by the incorporation of release modifiers along with drug during the core formulation. Due to the diversity of chemical composition and physical properties of release modifiers, pellet formulations that provide a multitude of release profiles could be designed (Golam Kibria., et al, 2007). Generally, water soluble low molecular weight excipients, surfactants and disintegrants are incorporated in formulations to enhance the drug release kinetics, while water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics. Examples of release modifiers widely used in pellet processing are ethyl cellulose, carnauba wax, shellac and carbomers.

12) Flavoring Agents

The choice for the flavors changes from individual to individual depending upon the age, ethnicity and liking which plays a significant role in the taste fondness. It was observed that the geriatric population like mint or citrus fruit flavors while younger generation like flavors like fruit punch, raspberry etc. The flavor selection for the particular formulation also depends upon the drug to be incorporated in the formulation. Mint flavor is generally added in products used for gastric related ailments like indigestion. The acceptance of the oral dosage formulation by an individual depends on the initial quality of the flavor which is observed in first few seconds after the administration of the product and shows the after effect which lasts for at least about 10 min. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts
of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the type and strength of the flavor. Preferably up to 10% w/w flavors are added in the formulations. Cooling agents like monomethyl succinate, menthol can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents like Utracoll II can also be used in conjunction with flavors.

13) Sweetening Agent

Sweeteners have become the significant part of the food products as well as pharmaceutical dosage forms intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more preferred especially in case of pediatric population. Natural sweeteners as well as synthetic sweeteners are used to improve the palatability of the formulations. The traditional source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is dissolved rapidly in the saliva compared to sucrose and dextrose and also sweeter than sorbitol and mannitol for which it’s used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are considered less carcinogenic and do not have
bitter after taste which is a vital aspect in formulating oral preparations. The sweetness property of the polyols is less than half of that of sucrose except xylitol and maltitol which have similar sweetness as that of sucrose (scale of 0.8-1.0). However the use of such natural sugars is restricted in the case of diabetic patients and diet conscious patients. Due to this reason, the synthetic sweeteners have gained more popularity both in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the synthetic sweeteners followed by acesulfame-K, sucralose, alitame and neotame that fall under the second generation artificial sweeteners (Leon et al, 1987).

Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200–300 time sweetness but these synthetic sweeteners carry a disadvantage of after taste effect which can be reduced by mixing or blending the natural and synthetic sweeteners. The flavor quality of these synthetic sweeteners is different than the natural sweeteners and is generally disliked by patients accustomed by the natural sweeteners. The amalgamation of sweeteners may lead to synergism and improvement in the taste of the formulations. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.
14) Coloring agents

Coloring agents are generally used in order to improve the appearance and make it more patient compliance. Pigments such as Titanium dioxide or FD&C approved coloring agents are used either in the dry form or mixed with the granulating fluid during the formulation.

Methods of Preparing Pellets

Compaction and Drug layering are the most widely used Pelletization techniques in the pharmaceutical industry, of the compaction techniques used, extrusion and spheronization is the most popular method. There are other few Pelletization methods, such as fluid bed coating, pan Coating, melt pelletization, globulation, balling and compression are also used in the development of pharmaceutical pellets.

Various Approaches of Pellet Preparation

1. Drug Layering

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid (Fig. 2, Fig. 3) (Gamlen 1985). In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the
addition of powder. Conventional pan coaters have been used from the very beginning of the history of drug layering pelletization.

**Fig. 2: Drug Layering by Using Solution**

**Fig. 3: Drug Layering by Using Suspension**

2. **Direct Pelletizing**

Sample material is blended and solvent or binder system is added to it. The material bed is then subjected to a centrifugal motion. The centrifugal forces
act on the material in this process resulting in the formation agglomerates, which get rounded up into uniform sized dense pellets and model of machine used (Fig 4). The size, density and shape of the pellets formed are influenced by the speed of rotation. The moist pellets formed are then dried up in the fluid bed. Organic solvents can also be used if required.

![Diagram of Direct Pelletization Process](image)

**Fig. 4: Direct Pelletization Process for Preparation of Pellets**
3. Pelletization by Extrusion and Spheronization

Pharmaceutical pellets are typically manufactured via extrusion spheronization, a three-step process introduced in the late 1960s, that results in spherical granulates roughly 1 mm in diameter. Wet mass extrusion spheronization also called cold-mass extrusion spheronization has become the method of choice. When one is desirous of having dense spherical pellets of uniform size and shape. It involves the following steps;

(a) Dry Mixing

Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer (Harrison et al, 1985; Fielden et al, 1992, Nakahara et al, 1964; Conine. 1970).

b) Wet Massing

Wet massing is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most commonly used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer. Evaporation of the fluid phase is a major problem with high shear mixers as they introduce a high amount of energy into the wet mass which is partly transformed into heat and induces evaporation of the granulation liquid thus changing the extrusion behavior of the wet mass. Cooling of the granulation bowl may avoid this problem.
c) Extrusion

This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. Such shaping of the wet mass into long rods, commonly termed ‘extrudate.’ The extrudate particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity to deform but not so much that the extrudate particles adhere to other particles when rolled during spheronization process. Extruders are classified into three categories namely, Screw feed extruder (axial or end plate, dome and radial), the screw extruder consists of one or two (twin -screw) feeding the wet mass to an axial or radial extrusion screen. In the axial type, (Fig. 5 &6) the screen is placed at the end of the screw, while in radial type the screen is placed around the screw (Fig. 7), discharging the extrudate perpendicularly to the axis of the screw. Gravity feed extruder (cylinder roll or gear roll) and Gravity feed extruders include rotary cylinder and rotary gear extruders, which differ mainly in the design of the two counter rotating cylinders. In the rotary cylinder extruder, one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller (Fig. 8; Fig. 9; Fig. 10).
Fig. 8: Gear Roll Type

Fig. 9: Radial Type

Fig. 10: Axial Piston Extruder
(d) Spheronization

The spheronization technology was first introduced by Nakahara in 1964. A spheronizer also known as merumerizer consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. During spheronization process different stages can be distinguished depending upon the shape. The friction plate, a rotating disk with a characteristically grooved surface to increase the frictional forces, is the most important component of the equipment. Two geometric patterns are generally used (Rowe et al, 1985; Wes et al, 1988; Hasznos et al, 1992; Hellen et al, 1992).

It includes a cross-hatched pattern with grooves running at right angle to one another, a radial pattern with grooves running radially from the center of the disc. The rotational speed of the friction plate varies from 100-2000 rpm. Spheronization process involves transition from rods to spheres that might occur in various stages which usually take 5 to 30 minutes provided mass should not be too dry wherein no more spheres are formed and the rods will transform as far as dumbbells only.

(e) Drying

A drying stage is required in order to achieve the desired moisture content. Drying rate also important an increase drying rate gave more porous pellets due to decrease pellet densification during that drying process. The pellets can be dried at room temperature (Wan et al, 1993; Souto et al, 2005), or at elevated
temperature in a tray drier/ oven. (Lian-Dong 2006; Thommes et al, 2006; Bataille et al, 1993) or in a fluidized bed drier (Huyghebaert et al, 2005; Joshi et al, 1993; Baert et al, 1993; Pinto et al, 1992). Bataille et al, reported the use of microwave oven in the final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process. Huyghebaert et al., reported the use of freeze dryer in order to maintain viability of living bacterial spores. If solute migration occurs during drying of the wet mass, this may result in an increased initial rate of dissolution, stronger pellets with modified surfaces, which might reduce adhesion of any added film coats.

(f) Screening

Screening may be necessary to achieve the desired size distribution, and for this purpose sieves are used. In case of pellets prepared by extrusion-spheronization, screening is essentially required after manufacture, in order to avoid pellets having high size polydispersity index (Husson et al, 1992).

4. Pan Coating Process

The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Following are the some of the Coating equipments used for this purpose Most of the coating processes use one of three general types of equipments.

1. The standard Coating pan.
2. The Perforated Coating pan.
3. The Fluidized bed coater.
a) The standard coating pan

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

b) The perforated Coating Pan

Neocota is an automatic coating system for tablets and pellets. This model efficiently carries out the following operations, a) Aqueous film coating of tablets/pellets, b) Non-aqueous organic solvent based film coating of tablets/pellets and c) enteric film coating of tablets/pellets. The basic units of the system are: Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet accommodating the gearbox, AC variable drive, power panel, hot air unit, exhaust unit and an air fitter. Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun, and inter-connecting flexible hoses (Gupta et al, 2001).
c) Pelletization by Fluid Bed System

Fluidized bed processor with wuster is equipment that can perform multiple functions like coating, drying, granulation and pelletizing. It has highly efficient drying system and uniform, continuous product coating achieved. Ideal for a wide range of process applications includes coating, heating, drying, agglomeration and granulation. Protects product against moisture, light, air. Ideal for control release film coating, pellet granulation and hot melt coating. Applied to specific manipulation of the particle surface characteristics. With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. (Wesdyk et al, 1990; Claudio et al, 2000; Laichera 1994) Different types of fluidized bed processors include top spray coating, bottoms spray coating (Wurster coating) and tangential spray coating (Rotor pellet coating). Depicts the types fluid bed processors.

Top Spray Coating

This process is used to spray binder solution for powder granulation. Particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate (Fig.11). The binder solution is sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Air volume is adjusted to have the center of the particle stream very close to the nozzle. Drying takes place as the particles to move upwards in the air flow. It is preferred when a taste masking coating is applied, additionally suitable for the
application of hot melt coating. Continuous spray coater is particularly suitable for protective coatings/ color coatings (Wesdyk et al, 1990; Claudio et al, 2000; Laichera M1994).

**Bottom spray coating**

The process is suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients. In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle(Fig.12). Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. Preferred for the application of modified release coatings to a wide variety of multi particulates and also suitable for drug layering when the drug dose is in the low to medium range (Wesdyk et al, 1990; Claudio et al, 2000).

**Tangential spray coating (Rotor pellet coating)**

This process is particularly suitable for pellet powder coating, suspension coating or film/sugar coating. In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the
granulation area (Fig.13). The passage of air causes the cores to roll on the turntables. At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size. It is suitable for the application of modified release film coatings to a wide range of multi particulate products, ideal for drug layering when the dose is medium to high and also useful as a spheronizing process for producing spheres from powders (Wesdyk et al, 1990; Claudio et al, 2000).
Fig 11: Fluid bed coating Top Spray

Fig 12: Fluid bed coating Bottom Spray

Fig 13: Fluid bed Coating Tangential Spray
Other pelletization methods

Other Pelletization methods such as globulation, cryopelletization, balling, and compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

a) Spray drying

It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs (Ghebre et al, 1985).

b) Spray congealing

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and sustained released pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

c) Cryo-pelletization

This technology was first developed to lyophilize bacterial suspension in the nutrition industry and now a days it is used in the pharmaceutical industry to produce drug loaded pellets for immediate as well as controlled release formulations. Immediate release formulation typically consists of drugs, fillers
(lactose and mannitol) and binders (gelatin and PVP) while cross-linked polymers of collagen derivatives are used in the sustained release formulation. In this technique, droplets of liquid formulation such as aqueous-organic solutions, suspensions or emulsions are converted into solid spherical pellets by using liquid nitrogen as the solidifying medium. These pellets are then freeze dried or lyophilized to remove water or organic solvents. Solid content and temperature of the liquid formulation determine the amount of liquid nitrogen used in the whole process (Sreekhar Cheboyina et al., 2004).

d) Compression

It is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure (Ann Debunne et al., 2004). The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing. Influence of formulation and compression parameters on the properties of tablets containing enteric coated pellets and on the integrity of the enteric polymer of the individual pellets often compression.

e) Balling

It is the Pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process
consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid.

f) Melt-Extrusion Technology

Wet mass extrusion is the most frequently used method current a part from extrusion spheronization technique for producing spherical pellets, many drugs exhibit stability problems since granulating fluid employed in this process is generally water. In addition to this, pellets exhibit a rapid drug release and require a film coating to provide if controlled release properties are to be maintained (Christopher Ryan young et al., 2004; Gavin Walker et al, 2005).

A novel hot-melt extrusion and spheronization process has been recently reported to produce spherical pellets without the use of water or other solvents. This method eliminates instability problems during processing due to water and also proven advantageous as the pellets produced by melt extrusion do not require additional film coating since the drug release is diffusion controlled. Hot melt-extrusion is initially used in the plastic industry, slowly gaining popularity in the pharmaceutical industry for the production of pellets; immediate and sustained release tablets and transdermal drug delivery systems (Follonier et al, 1994; Repka et al 1999; Zhang et al, 2000) and also the technique is being approved in the USA, and it is a fast, simple, continuous, solvent-free process with fewer processing steps. Melt extrusion process consists of three basic steps: melting or plasticizing a solid material, shaping the molten material and solidification of the material into the desired shape. A hot melt extrusion line
consists of a material feed hopper, extruder inside a heated barrel, having three different sections, and spheronizer. The feed hopper holds the material and continuously feeds it into the extruder, which has a heated barrel containing the rotating screw. The extrudate is then cut into uniform cylindrical segments, which are spheronized to generate uniform sized pellets. The temperature maintained in the spheronizer should be high enough to soften the extrudate partially and facilitate its deformation and eventual spheroid formation.

g) Freeze Pelletization

Freeze pelletization technique is a simple and novel technique for producing spherical matrix pellets containing active ingredients. In this technique, a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. These droplets can move either in upward or downward directions, depending on their density with respect to the liquid in the column and solidify into spherical pellets. The technique involves less process variables and also offers several advantages over other pelletization methods, in terms of quality of pellets and process cost. The pellets produced by this technique are spherical in shape with narrow size distribution. Since the pellets are solid at room temperature, they do not require drying (Cheboyina et al, 2004; Cheboyina et al, 2008).
Applications

Pellets have varies applications in a number of industries and an innovative use of it’s could achieve maximum profitability.

1. Taste masking

Pellets are ideal for products where perfect abatement of taste is required. Although various technique have been utilized to mask the bitter taste of a drug such as the addition of sweeteners and flavors, filling in capsules, coating with water insoluble polymers or pH dependent soluble polymers, complexing with ion-exchange resins, micro- encapsulation with various polymers, complexing with cyclodextrins and chemical modifications such as the use of insoluble prodrugs, few reports have described the masking of unpleasant taste without lowering of bioavailability especially for oral products. The pelletization technique solves difficult taste masking problem while maintaining a high degree of bioavailability due to their high surface area, especially for oral products.

Furthermore, because of the special design of the manufacturing process, dust fractions that representing an uncoated fragments which could cause taste problems are absent in pellets. Many products, such as antibiotics (clarithromycin, roxithromycin and cephelexin) and anti-inflammatory drugs with a bitter taste, can now be formulated in products with high patient compliance, thus increasing the sales potentially in the pharmaceutical markets for the product (Costa et al, 2003; Dashevsky et al, 2004).
2. **Immediate release**

Administering drugs in pellet form leads to an increased surface area as compared to traditional compressed tablets and capsules which would considerably reduce the disintegration time and have the potential for use in rapidly dispersible tablets.

3. **Sustained release**

The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate. Pellets are being increasingly used in the manufacture of sustained release dosage form of drugs. The advantage of the dosage form is well known. (Bodea *et al*, 1998)

4. **Chemically Incompatible Products**

At times such ingredients are required to be delivered in a single dose. In the compressed tablet dosage form separate tablets would have to be administered, but the pellets can be administered in a single capsule.

5. **Varying dosage without reformulation**

Pellets have excellent flow properties, due to this, they can be conveniently used for filling capsules and the manufacturer can vary the dosage by varying the capsule size without reformulating the product. (Thommes *et al*, 2006)
<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bontril SR</td>
<td>Carnick laboratories, Inc</td>
</tr>
<tr>
<td>Brexin LA</td>
<td>Savage laboratories, Bangalore</td>
</tr>
<tr>
<td>Catayzme S</td>
<td>Organon Pharmaceuticals, USA</td>
</tr>
<tr>
<td>Compaziline</td>
<td>Smith &amp; French, Mumbai</td>
</tr>
<tr>
<td>Dilgard XL 180</td>
<td>Smith Kline &amp; French, Mumbai</td>
</tr>
<tr>
<td>Elixophyline</td>
<td>Cipla Ltd, Ahmedabad</td>
</tr>
<tr>
<td>Fastin</td>
<td>Berlex laboratories, USA</td>
</tr>
<tr>
<td>Hispril</td>
<td>Berlex laboratories, USA</td>
</tr>
<tr>
<td>Ibugsic SR 300</td>
<td>Cipla laboratories, Ahmedabad</td>
</tr>
<tr>
<td>Indocrin SR 300</td>
<td>Merk Sharp, Mumbai</td>
</tr>
<tr>
<td>Nicobid T.S</td>
<td>U.S Vitamin, USA</td>
</tr>
<tr>
<td>Ornade</td>
<td>Smith Kline.</td>
</tr>
<tr>
<td>Effexor XR</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Flomax</td>
<td>Borhenger</td>
</tr>
</tbody>
</table>
AIMS AND OBJECTIVES OF THE INVESTIGATION

Multiparticulate dosage forms (MPDF) are receiving immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical preparations produced.

The most increasingly interesting area in the development of MPDF’S is incorporation into tablets instead of hard gelatin capsules in order to make it more economical to the consumers and gaining more attention currently. The current review focuses on the pelletized form of multiple units, they are prepared by process called Pelletization which is referred to as a size enlargement process and the final product obtained is called pellets.

Pellets provide a reduction in the dosage regimen and gastrointestinal irritation moreover controlling the drug release and increasing the absorption of the active ingredient. Also one of the advantageous properties of the pellet formulations is being good candidates for the delivery of the drug substances due to minimizing the dose dumping effect. The reproducibility of the release characteristics from pellet formulations is also much better with respect to the single-unit dosage forms. They are suitable systems for film coating with respect to the low surface area-volume ratios. Also, resistance to external factors such as moisture, air and light are the most advantageous properties of these dosage forms. (Palsson et al, 1990; Wu et al, 1998; Zhon et al, 2003; Iyer et al, 1993).
In the present investigation pan coating is employed for the preparation of diltiazem HCl and verapamil HCl pellets. In pan coating method, a core material is coated with the drug substance following a secondary coating process in which the release controlling polymer material is introduced (Mustafa et al, 2007).

In the present investigation fluid bed coating process is employed for the preparation of diltiazem HCl and verapamil HCl pellets. Fluidized bed processor is an equipment that can perform multiple functions like coating, drying, granulation and pelletizing. FBC has high efficient drying system and also uniform, continuous pellet coating can be achieved. It is ideal for a wide range of process applications includes coating, heating, drying, agglomeration and granulation. This process protects the product against moisture, light and air. It is ideal for control release film coating, pellet granulation and hot melt coating. It is applied to specific manipulation of the particle surface characteristics. With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. (Wesdyk et al, 1990; Claudio et al, 2000; Laichera 1994)

Diltiazem HCl is a calcium channel blocker which is widely used in the treatment of variant angina, hypertension and supraventricular tachyarrhythmias. It is freely soluble in distilled water, chloroform and methanol. Diltiazem HCl is rapidly absorbed (90%) after oral administration but availability in only 30-40% in systemic circulation and bioavailability varies between individual. The low bioavailability after oral administration is due to its high first pass hepatic
metabolism. It has elimination half-life of 3 – 5 hrs and slightly prolonged after multiple dosing.

Verapamil hydrochloride is a calcium channel blocker and a class IV antiarrhythmic drug. It is a white crystalline powder, soluble in water; sparingly soluble in alcohol, freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Verapamil is approximately 90% absorbed from the GI tract but the bioavailability is only about 20% due to first-pass metabolism in the liver. It has terminal elimination half-life of 2 to 8 hours and prolonged after repeated oral doses. Its plasma protein binding is up to 90%. Based on the above physical, chemical, biopharmaceutical, properties and clinical relevance, diltiazem HCl and verapamil HCl were selected as drug candidates for developing controlled release pellet formulations.

The present investigation was mainly focused on the development of controlled release pellets of diltiazem HCl and verapamil HCl with ethyl cellulose and hydroxypropyl methyl cellulose phthalate by employing pan coating and fluid bed coating techniques. Ethyl cellulose 7cps a high viscosity grade controlled release polymer was mainly used as coating agent for regulating the drug release from pellets. HPMCP, an enteric coating polymer was used in the present study to regulate the drug release at varied G.I pH conditions. An attempt was made to optimize the composition of these two polymers to achieve the controlled release of drugs from the pellets. HPMC E5 was used a film former in the present investigation. Croscarmellose sodium was used as disintegrant to create channels in the coating for drug release. Povidone was used as binder to
achieve uniform drug layering in the present investigation. The dissolution studies of diltiazem HCl were carried out and compared with the USP dissolution test 6. The dissolution studies of verapamil HCl were carried out in accordance with the USP 2004 <711> to meet the criteria of once a day formulation.

Pelletization was one of the popular methods employed to formulate controlled release dosage forms. Several methods of pelletization were discussed in the introduction part. The present study was mainly focused on the comparative evaluation of processing variabilities in the formulation of controlled release pellets by pan coating technique with that of fluid bed coating technique based on in vitro dissolution studies and by characterization of prepared pellets by SEM and DSC studies.

The main objectives of the investigation

1. To develop controlled release pellets of diltiazem HCl and verapamil HCl by using sugar pellets with ethyl cellulose and HPMCP as controlled release polymers by pan coating method.

2. To develop controlled release pellets of diltiazem HCl and verapamil HCl by using sugar pellets with ethyl cellulose and HPMCP as controlled release polymers by fluid bed coating process.

3. To study the flow properties of controlled release pellets such as angle of repose and carr’s index and also pellet size by sieve analysis method.
4. To evaluate the percent yield and drug content and friability for the produced controlled release pellets.

5. To perform the in vitro dissolution studies on various controlled release diltiazem HCl and verapamil HCl pellets and to compare the release profiles of all the prepared pellets with marketed pellet formulations by using similarity and dissimilarity factors assessment.

6. To evaluate the dissolution parameters like, first order constant, higuchi constant, peppas constant from the in vitro dissolution studies performed for various controlled release pellets.

7. To evaluate the surface characteristics by SEM analysis for some selected controlled release pellets.

8. To check the stability and crystal morphology of optimized pellets by DSC and FTIR spectral studies.

9. To evaluate the variability’s araised in processing of controlled release pellets by pan coating and fluid bed coating techniques based on the dissolution studies and characterization of prepared pellets by SEM, DSC and XRD studies.

10. To perform the in vivo studies for optimized controlled release pellets on suitable animal models.

11. To conduct the accelerated stability studies for some selected controlled release pellets.
DRUG USED IN PRESENT INVESTIGATION

DILTIAZEM HYDROCHLORIDE

Diltiazem HCl is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist).

Chemical name

(2S-cis)-3-(acetyloxy-5-[2-(dimethylamino) ethyl]-2, 3-dihydor-2-(4-methoxy -phenyl)-1.5-benzothiazepin-4 (5H) - one monohydrochloride

Structure

![Structure of Diltiazem HCl](image)

Therapeutic category: Calcium channel blocker

Physical properties: It is a white to off white crystalline powder. It is odorless and has a bitter taste. Melting point is about 210 °C. It is freely soluble in distilled water, chloroform and methanol.
Pharmacokinetics

Diltiazem HCl is rapidly absorbed (90%) after oral dose. After administration of single oral dose, bioavailability is about 30 to 40% and is dose related, but variable between individuals. Oral administration of a solution of diltiazem results in peak plasma levels 38 minutes after dosing. Peak plasma concentration ($C_{\text{max}}$) of diltiazem are achieved within 1.5 hrs of ingestion of the fast release formulations and 3 to 4 hrs after intake of slow release formulations. (Deshpande et al, 1993 ; Beck et al, 2002 ; Bledsoe et al, 2001 ; Consoulin et al, 2002).

In single and multiple-dose studies in normal subjects and patients with coronary artery disease, Diltiazem was 78 to 87% bound to plasma proteins and 14 to 23% was present as the unbound drug in the serum. Single dose studies in healthy subjects have shown the mean volume of distribution of diltiazem to be approximately 5.3 % 1/kg (ranging 3-8 1/kg) (Claas et al 2005) while the volume of distribution in the patients with unstable angina was 4.12 and 7.05 1/kg (Connor et al., 1999).

Diltiazem undergoes extensive first-pass metabolism after oral administration predominantly due to hepatic metabolism. The three metabolic pathways are O-deacetylation, N-demethylation and O-demethylation which produce six metabolites. Some metabolites are conjugated with glucuronides or sulphates prior to excretion.
Trace amount (0.1-4%) of diltiazem is eliminated in the urine. N-monodemethyl diltiazem is excreted in unconjugated form. The other metabolites are excreted in urine as the glucuronides or sulphate conjugate. The elimination half-life of orally administered diltiazem averages about 4.5 hrs (range 2 to 11 hrs) and may be slightly prolonged after multiple dosing. After intravenous administration the half-life of diltiazem was ranged from 2 to 5 hrs. The metabolites such as deacetyl diltiazem and N-monodemethyl.

**Plasma concentration and clinical effects**

It was reported that the plasma concentration of diltiazem after 4 hrs of oral administration was between 100-200 ng/ml who responded for the treatment. When plasma concentration was below 100 ng/ml the treatment was ineffective. It was reported that patients with angina, whose plasma diltiazem concentrations of over 100 ng/ml were required to produce vasodilatory response. There was no consistent correlation between plasma diltiazem concentration and the magnitude of hemodynamic changes elicited. However, a minimum plasma concentration of 0.10 mg/l is associated with hemodynamic change and symptomatic improvement in patients with angina pectoris and patients with malignant hypertension.

**Side effects**

The incidence of adverse effects arising during diltiazem treatment is generally very low. The principle adverse effects of diltiazem include headache,
flushing and peripheral oedema. Hypotension may also occur secondary to vasodilatation. Diltiazem may cause prolongation of atrioventricular conduction in some patients, especially those on concomitant treatment with β-adrenergic blocking agents.

Preparations available:

Diltiazem hydrochloride is available in the form of tablets and controlled release tablets.

Therapeutic uses:

Diltiazem, a calcium channel blocker which is used widely to treat high blood pressure (hypertension) and certain types of chest pain (angina).

VERAPAMIL HYDROCHLORIDE

Chemical Name

Benzene acetonitrile, \[3 - \{(2 - (3, 4 - \text{dimethoxyphenyl}). \text{Ethyl]} \text{methyl amino] propyl} \]-3, 4 - \text{dimethoxy - \(\alpha\) - (1-methyl ethyl) monochloride.}

Structure
**Therapeutic Category**

Calcium ion influx inhibitor (slow – channel blocker (or) calcium antagonist)

**Physical Properties**

It is a white or practically white crystalline powder. It is practically odorless and has a bitter taste. It is soluble in water, methanol and chloroform.

**Pharmacokinetics**

More than 90% of the orally administered dose of verapamil hydrochloride is absorbed. Because of rapid biotransformation of verapamil due its first pass through portal circulation bioavailability ranges from 20% to 35%. Peak plasma concentrations are reached between 1 and 2 hrs after oral administration. The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. In some studies, after repetitive dosing, the half-life increased to a range from 4.5 to 12.0 hours. Half-life of verapamil may increase during titration. Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly. In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces with in 5 days. About 3 to 4% is excreted in urine as unchanged drug. Approximately 90% is bound to plasma proteins. (Anavekar et al, 1981; Bauer et al, 1992)
**Adverse Reactions**

Serious adverse reactions are uncommon when verapamil hydrochloride therapy is initiated with upward dose titration with in recommended single and total daily dose. The principle adverse effects of verapamil include constipation, hypotension, headache, dizziness.

**Preparations Available**

Verapamil Hydrochloride is available in the form of tablets, controlled release tablets and in the form of injection.

**Therapeutic Uses**

Verapamil Hydrochloride is used widely in the treatment of angina, arrhythmias and essential hypertension.
POLYMERS USED IN PRESENT INVESTIGATION:

ETHYL CELLULOSE

Nonproprietary Names:

1. Ethylcellulose (BP)
2. Ethylcellulose (PhEur)
3. Ethylcellulose (USP-NF)

Synonyms:

Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

Chemical Name: Cellulose ethyl ether.

Empirical Formula and Molecular Weight:

Ethyl cellulose is partially ethoxylated. Ethyl cellulose with complete ethoxyl substitution (DS = 3) is C_{12}H_{23}O_{6} (C_{12}H_{22}O_{5}) nC_{12}H_{23}O_{5} where n can vary to provide a wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages. (Narisawa et al, 1994; Dressman et al, 1995)
Functional Category: Coating agent; flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Glass transition temperature: 129–133°C.

Density: 0.4 g/cm³.

Moisture content: Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Applications in Pharmaceutical Formulation or Technology

- Ethylcellulose is widely used in oral and topical pharmaceutical formulations.
- The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.
- Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation.
• Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films.

• Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.

• An aqueous polymer dispersion of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

• Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized.

• In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets.

• Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation.
Pharmaceutical Grades of Ethyl Cellulose:

Viscosity

<table>
<thead>
<tr>
<th>Designation</th>
<th>Viscosity, mPa.s (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5.3</td>
</tr>
<tr>
<td>7</td>
<td>6.6</td>
</tr>
<tr>
<td>10</td>
<td>10.3</td>
</tr>
<tr>
<td>20</td>
<td>20.0</td>
</tr>
<tr>
<td>45</td>
<td>43.5</td>
</tr>
</tbody>
</table>

Regulatory Status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (Oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Safety: Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys. Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material.
HPMC PTHALATE

**Synonyms:** cellafecate; cap; cellulose acetate hydrogen phthalate

**Chemical Structure:** Cellulose acetate hydrogen 1,2 benzene dicarboxylate; cellulose acetate monophthalate; Cellulose acetate phthalate; Cellulose acetayl phthalate; monopthalic acid ester of hydroxyl propyl methyl cellulose.

![](image)

**Physical state:** white to off white powder or flakes.

**Solubility in water:** swells to form viscosity colloidal solution.

**Solvent solubility:** soluble in most organic solvents and insoluble in hot water, alcohol.

**Stability:** stable under ordinary conditions.
Applications

- HPMC phthalate is an enteric film coating material or a matrix binder in solid dosage forms.
- It is used as a controlled release agent, film former, stabilizer, dispersant, lubricant, binder, emulsifying agent and suspending agent.
- Other applications include adhesives and glues agriculture, building materials personal care products, detergents and surfactants, paints and printer links and coating pharmaceuticals, food products.

Regulatory Status: Included in the FDA Inactive Ingredients Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Safety: Hypromellose phthalate is widely used, primarily as an enteric coating agent, in oral pharmaceutical formulations. Chronic and acute animal feeding studies on several different species have shown no evidence of teratogenicity or toxicity associated with hypromellose phthalate. Hypromellose phthalate is generally regarded as a nonirritant and nontoxic material.
HYDROXYPROPYL METHYLCELLULOSE

Non-proprietary name

1. BP : Hypromellose
2. USP–NF : Hydroxypropyl methylcellulose

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether

where R is H, CH₃ or [CH₃CH(OH)CH₂]

Synonym: Methylhydroxy propylcellulose; hydroxypropyl methylether, Benecel MHPC; Metolose; Pharmacoat, Methocel, Tylopur.

Molecular Weight: 10000-1500000.

Description: Hydroxypropyl methylcellulose is an odorless and tasteless, white or creamy—white colored fibrous powder (Humberstone et al, 1997; New 1997).

Acidity/Alkalinity: pH 5.5-8.0 for a 1% w/w aqueous solution.
**Melting Point:** Browns at 190-200°C, chars at 225-230°C, glass transition temperature is 170-180°C.

**Moisture Content:** Hydroxypropyl methyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Solubility:** Soluble in cold water, forming a viscous colloidal solution. Practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and dichloromethane. Certain grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propane-2-ol and other organic solvents.

**Viscosity:** Typical viscosity value of 2% solution in water is 4 - 6 cps

**Table.2: Pharmaceutical Specifications of HPMC**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Test</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH</td>
<td>5.0-8.0</td>
</tr>
<tr>
<td>2</td>
<td>Loss on drying</td>
<td>≤5.0%</td>
</tr>
<tr>
<td>3</td>
<td>Sulphated ash</td>
<td>≤1.5%</td>
</tr>
<tr>
<td>4</td>
<td>Heavy metals</td>
<td>≤20ppm</td>
</tr>
</tbody>
</table>
**Application in Pharmaceutical Formulation or Technology:** (Rowe et al 1980; Banker et al, 1981; Hogan et al, 1989; Wilson et al, 1989.)

- In oral products, hypromellose is primarily used as a tablet binder, in film coating and as an extended release tablet matrix.

- Depending upon the viscosity grade, concentration of 2-20% w/w are used for film-forming solutions to film coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

- Hypromellose at concentration between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solution.

- Used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

- Used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**Storage condition:** It should be stored in a well-closed container, in a cool, dry place.

**Regulatory Status:** GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal...
preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian list of acceptable non-medicinal Ingredients.

**Safety:** HPMC is widely used as an excipient in oral, ophthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. HPMC is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake for HPMC since the levels consumed were not considered to represent a hazard to health.

**CROSCARMELLOSE SODIUM**

**Nonproprietary Names**

1. Croscarmellose Sodium (BP)
2. Croscarmellose Sodium (JP)
3. Croscarmellose Sodium (PhEur)
4. Croscarmellose Sodium (USP-NF)

**Synonyms:** Carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

**Chemical Name and CAS Registry Number**

Cellulose, carboxymethyl ether, sodium salt, cross linked [74811-65-7]
**Empirical Formula:** Croscarmellose sodium is a cross linked polymer of carboxy methyl cellulose sodium.

**Structural Formula:** Carboxymethylcellulose sodium.

**Functional Category:** Tablet and capsule disintegrant.

**Description:** Croscarmellose sodium occurs as an odorless, white or grayish white powder. (Botzolakis *et. al*, 1988; Dahl *et al*, 1991)

**Applications in Pharmaceutical Formulation or Technology** (Botzolakis *et al*. 1988; Gissinger *et al*. 1980; Gordon *et al*. 1987)

- Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.
- In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes.
- When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.
- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.
**Regulatory Status:** Included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

**Safety:** Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems. In UK, croscarmellose sodium is accepted for use in dietary supplements.

**POVIDONE**

**Nonproprietary Names**
BP: Povidone
JP: Povidone
PhEur: Povidone
USP: Povidone

**Chemical Name:** 1-Ethenyl-2-pyrrolidinone homopolymer

**Empirical Formula and Molecular Weight:** \((\text{C}_6\text{H}_9\text{NO})_n\) 2500–3 000 000

**Functional Category:** Disintegrant; dissolution enhancer; suspending agent; tablet binder.
Description: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.

Applications in Pharmaceutical Formulation or Technology

- Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.
- Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions.
- Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.
- Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.
- Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorlysoluble active drugs may be increased by mixing with povidone.