MULTIPARTICULATE MODIFIED RELEASE DRUG DELIVERY SYSTEM FOR ANTI-EPILEPTIC DRUG: A REVIEW

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ABSTRACT:
Anti-epileptic drugs are distinct in their physico-chemical properties. Most of the drugs have low solubility and administered by oral route to penetrate into the Central Nervous System (CNS). Many anti-epileptic drugs are available in the pellet dosage form now a day. Modified release multiparticulate dosage forms have gained popularity over other dosage forms due to distinct advantages such as ease of capsule filling because of better flow properties of the perfectly spherical pellets; enhance of drug dissolution; ease of coating; sustained, controlled or site-specific delivery of the drug from coated pellets; even distribution in the gastrointestinal (GI) tract and less GI irritation. Multiparticulate dosage forms can be prepare from number of techniques, including drug layering, spray congealing, roto-granulation, hot-melt extrusion, and spherization of low melting materials. The present review outlines the recent finding on the manufacturing and evaluation of the anti-epileptic drugs. Different techniques have been discussed for the Pelletization. Different characteristics and evaluation of quality of the pellets is discussed with reference to size distribution, pellet shape, surface morphology, specific surface area, hardness and friability, density, surface roughness, porosity. Patents and review on Pelletization for some anti-epileptic drugs like Tiagabine, Topiramate, Sodium valproate and Carbamazepine are compiled.

KEYWORDS: Multiparticulate, Pelletization, Modified release, Sustained release, Delayed release, Controlled release, Anti-epileptic drug, Central nervous system.

INTRODUCTION:
Antiepileptic drugs are different group of pharmaceuticals used in the treatment of epileptic seizures. Main role of anti-epileptic is to reduce the successive firing of the neuron that stat a seizures. Anti-epileptic drugs are also known as anticonvulsant or anti-seizure drugs.

[1] The major marketed anti-epileptic drugs are voltage gated sodium channel and components of GABA system (GABA_A receptor, GAT-1 GABA transporter). Other considerable targets

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are voltage gated calcium channels, SV2A & α2δ.\(^2, 3\)

For a long time it was assumed that a single drug could be developed for the treatment of all type of epilepsy, but the cause of epilepsy are extremely diverse. Etiology specificity for the treatment of Epilepsy should be according to the type of epilepsy.

**Classification:**

**Pharmacokinetic:**

Even Anti-epileptic drugs have different structural and chemical property they shows many common pharmacokinetic properties. These compounds are slightly soluble and exert good absorption (80-100% of drug reaching to the circulation) property. Most of drugs are selected for the oral delivery of drug and all have to penetrate in to CNS.\(^4\)

**Table 1:** Anti-Epileptic Drugs and its Mode of Action\(^5, 6\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Inhibits carbonic anhydrase isozymes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Inhibits voltage gated sodium channels in a use dependent manner</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Benzodiazepine agonist, Enhancement of action of GABA.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Blocks voltage gated sodium channels</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Inhibits carbonic anhydrase isozymes</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Inhibits voltage gated sodium channel</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>T-type calcium channel blocker</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Inhibits NMDA channel currents in use dependent manner</td>
</tr>
<tr>
<td>Primidone</td>
<td>Not well defined, metabolite of primidone modulate the flow of chloride ion through GABA(_\alpha) receptor complex</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Histone deacetylase inhibitor. Enhance GABA activity due to down regulation of GAT-1 &amp; GAT-3 GABA transporter protein</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Inhibits voltage gated sodium channel</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Inhibits voltage gated sodium channel</td>
</tr>
</tbody>
</table>

**Drugs used in Partial Seizures and Generalized Seizures:**
Due to availability of large number of anti-epileptic drugs (AEDs) there is markedly increased treatment option. In the last decade nine new anti-epileptic drugs were introduced in the market. Felbamate, Lamotrigine, Gabapentin, Oxcarbazepine, Tiagabine, Topiramate, Vigabtirin, Zonisamide, Levetiracetam are new anti-epileptic drugs and individual have their own merits and demerits. But our knowledge of toxicity and adverse effect in different population is limited for these new AEDs. So, for the evaluation of efficacy, potency and ADRs randomized clinical trials are performed.

Table shows that most of the drugs are administered by oral route in the different dosage form. Main thing we have to consider during the formulation of oral dosage form is to prevent degradation of active pharmaceutical by metabolism; drug should have adequate absorptivity and permeability. But most of anti-epileptic drugs are having poor solubility and most anti-epileptic drug does not bound to plasma protein results in the poor absorptivity. Pelletization is the very good approach to boost the absorptive of AEDs. Pellets have been used in pharmaceutical industry for more than 4 decades with the advantage of sustained release technology over single unit dosage forms. [7]

Most commonly used and intensely investigated Pelletization techniques are –

- Powder layering
- Solution/Suspension layering
- Extrusion-Spheronization

Other Pelletization techniques that are at the development stage or have limited application –

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**Table 2: List of FDA approved Anti-epileptic Drugs and Dosage form** [5]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Capsule (ER)</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Injectable</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tablet/Chewable Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Capsule (ER)</td>
<td>Oral</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Orally disintegrating Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td>Clorazepate dipotassium</td>
<td>Capsule</td>
<td>Oral</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Injectable</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td>Concentrate</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Gel</td>
<td>Rectal</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Tablet (DR)</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Tablet (ER)</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Capsule (DR pellets)</td>
<td>Oral</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Capsule</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Syrup</td>
<td>Oral</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td>Oral</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Capsule</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Solution</td>
<td>Oral</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Solution</td>
<td>Oral</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Injectable</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Chewable Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td>Oral</td>
</tr>
<tr>
<td>Phenytoin sodium</td>
<td>Capsule</td>
<td>Oral</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Capsule</td>
<td>Oral</td>
</tr>
<tr>
<td>Primidone</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td>Tiagabine HCL</td>
<td>Tablet</td>
<td>Oral</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Capsule</td>
<td>Oral</td>
</tr>
</tbody>
</table>

# ER – Extended Release, DR – Delayed Release
• Spherical agglomeration or Balling
• Spray congealing/Drying
• Cryo Pelletization
• Melt spheronomization
• Freeze Pelletization
• Hot melt extrusion [7]

PELLETS:
Pellets are defined as agglomerate produced systematically and geographically from different process using different starting material. Pellets are small solid particles, free flowing and intended for the oral administration mostly.

Pellets are considered as ideal if they have following properties:
• Smooth surface and spherical shape is desired property for uniform film coating.
• Particle size should be in the range of 600 – 1000 µm.
• In order to maintain the size, quantity of active pharmaceutical should be maximum in the pellets. [8, 9]

THEORY – PELLET FORMATION AND GROWTH:
It is necessary to understand the formation and growth of pellets before selecting the pelletization procedure. Numbers of theories are available for the mechanism of growth and formation of pellets. Some of them are derived from research while others are postulated from visual observations.

Pelletization process mainly involves 3 steps:
• Nucleation
• Transition
• Ball growth

But based on experiments on the Pelletization technique steps proposed are Nucleation, coalescence, layering & abrasion transfer. [10, 11]

In every Pelletization technique Nucleation is the common step, and it occurs when powder is wetted with liquid. Transition is the next phase. Coalescence and layering are the growth mechanism affecting transition region. Coalescence is the formation of large particle by random collision of well-formed nuclei. In the coalescence total mass remains unchanged but count of the nuclei will reduce. Layering involves successive addition of fine on already existing nuclei. Here, total mass increases but number of nuclei remains constant. Decline in the number of collisions, lead to a reduction of pellet growth. This is the indication of starting of Ball Growth phase. [12]

Ball Growth Phase involves mechanism of abrasion transfer. This phase does not involve any change in the total mass or number of particles. However, particles undergo a continuous change in size.

PELLETIZATION TECHNIQUES:
With the advantage of controlled release technology of Pelletization, efforts are made for development of modern approach and procedures to manufacture pellets. Cryo
Pelletization, HME, Melt Spheronization are some of the new emerging Pelletization techniques.

1) Powder Layering:
This is the first equipment used to prepare pellets on the large scale was conventional coating pan however it had significant limitation as Pelletization equipment. Drying process and degree of mixing are not efficient. Parameters like pan shape, rotation speed, tilt angle, baffle arrangement are the parameters must be optimized to eliminate dead spot and to provide uniform drying.

Powder layering is the binding of the finely milled powder and solution to a bed of starter nuclei. Layering starts with the binding of the drug particle to the starting seed and form pellet with the help of liquid bridge produced by the sprayed liquid. This liquid bridge eventually converts in to solid bridge due the addition of binder in the application medium or from the drug substance (any material) which is soluble in the spraying liquid. Successive layering of the drug and binder continue until desired pellet size is obtained. At the end of the process the main problem is the formation of fines due to interparticle and wall to particle friction. Problem can be overcome if application medium sprayed at the end of the process. Care must be taken to control the moisture content if the final product.

Equipment that overcomes the limitation of the conventional coating pan is tangential spray or centrifugal fluid bed granulator. Though they are different in the design, but their basic operational principle is same. During the operation centrifugal force, gravitational force and fluidization air velocity is the critical parameter to get satisfactory yield of final product.

![Fig. 2 - Schematic Representation of Centrifugal Fluid-Bed Equipment and Process](image)

During the layering process those 3 parameters generates spiral, rope like structure of the particles. Rotating disc which rotates at the fix or variable speed produce the centrifugal force inside the pan and this force pushed the particles towards the vertical wall of the stator. Fluidizing air carries particles vertically along with the wall of product chamber in expansion chamber. Here, particles lose their momentum and fall towards the center if rotating disc due to the gravitational force.

Different parameters which affect the degree of mixing are fluidization air volume and velocity, slit width, disc speed, bed size, atomization air pressure, air temperature and moisture saturation determine the final quality and yield of the pellets. [13, 14, 15]

2) Solution/Suspension Layering:
In solution/Suspension layering drug particles are suspended or dissolved in the binding liquid.
Wurster coating process was invented nearly 30 years ago, which had used to manufacture pellets by solution/suspension layering method. Wurster equipment has cylindrical partition in the product chamber and orifice plate. Orifice plate allows the drying air to pass at the high velocity around the nozzle and through the partition. Once, the particles exit the partition they enter in to expansion chamber. Here, velocity of the air decreases than the entrainment velocity. Particles fall on the surrounding area of the partition known as down bed. Particles from the down bed transported to the gap between orifice plate and partition by suction.

Partition height is the gap between orifice plate and partition, controls the rate at which particle enter in to spray zone. It is optimized for the different batch size as it is an important variable. [15]

3) Direct Pelletization:
Solvent or binder system is added in to blended sample material. Mixture is then undergoing the centrifugation. Centrifugation results in the formation of the agglomeration of the particles which produce uniform size pellets.
Size, shape and density of the pellet are the function of speed of rotation. [16]

4) Extrusion and Spheronization:
Pellets are typically prepared by the extrusion Spheronization. Wet mass extrusion- Spheronization also called cold mass extrusion- Spheronization is consider as the method of choice when one want to produce spherical shape and uniform size pellets.

Process involves following steps:
Dry mixing:-
Dry mixing of the ingredients is carry out to get homogenous powder dispersion using planetary mixture, shell blander, high speed mixture and tumbler mixture. [17, 18]
Wet massing:-
Wet massing provides the sufficient plastic mass for extrusion. This process is done by
normal equipment and process as employed in wet granulation. Commonly used granulators are –

- Planetary mixer
- Hobart mixer
- High shear mixer &
- Sigma blade mixer

Evaporation of fluid is the major problem concern with the high shear mixer. Because high shear mixer introduce excess amount of the energy in to wet mass which will transformed into heat and leads to evaporation of granules fluid thus change in the extrusion behavior takes place. Cooling of granulation bowl may eliminate this problem. [19]

**Extrusion:**

Extrusion produce rod shaped particles of uniform dimension. Wet mass forced through the dies to produce small cylindrical uniform size particles. This shaping of wet mass in to uniform size is known as “Extrusion” and long roads are known as “Extrudates”. The extrudates particles break at similar length under their own weight. Thus, the extrudate must have enough plasticity.

Extruders are classified into 3 main categories

- Screw feed extruder (axial or end plate, dome and radial),
- Gravity feed extruder (cylinder roll or gear roll)
- Piston feed extruder (ram) [20, 21]

**Screw extruder** has one or two feeding the wet mass to an axial or radial extrusion screen. They may be of 2 types:

1. Axial type: Screen is placed at the end of screw.
2. Radial type: The transport zone is short. Screen is placed around the screw and discharge the extrudates perpendicular to the axis of screw.

![Fig. 6 - Axial Screw Feed Extruder](image)

**Gravity feed extruders** includes:

![Fig. 7 - Radial Screw Feed Extruder](image)

![Fig. 8 – (A) Rotary cylinder, (B) Rotary gear](image)

They differ mainly in the design of the two counter rotating cylinders.

1. Rotary cylinder Extruder: 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.
2. Rotary gear Extruder: In the rotary gear extruders there are two hollow counter rotating gear cylinders with counter board holes.

In ram extruders which are probably the oldest type of extruders, a piston displaces...
and forces the material through a die at the end. Ram extruders are preferentially used in the development phase, because they can also be used to measure the rheological properties of the formulations. \[22, 23\]

**Fig. 9 - Piston Feed (Ram) Extruder**

**Spheronization:**
This technology first of all introduced by Nakahara. In order to minimize variability in drug release and facilitate the uniform coating of the resultant pellets, it is desirable that pellets are as close to spherical as possible, have smooth surface characteristics and have a narrow particle size distribution. A Spheronizer is also known as Marumerizer. It consists of a static cylinder and a rotating friction plate where extrudates will break in small cylinder with the length equal to their diameter. These cylinders rounded by friction. 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. \[24, 25\]

This includes 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. Friction plates rotate at the speed of 100-2000 rpm. Spheronization involves transition of rod shape to spherical shape. This transfer takes place at the any stage of the process. Usually it takes 5 – 30 minutes. Effect of spheronization on drug release may be evaluated by determining drug release rate. \[26\]

**Fig. 10 - Pelletization Stage in Extrusion and Spheronization**

**Drying:**
This step is important to maintain the desire moisture content. Drying rate should be maintained in order to obtain desire porosity of the pellets. Pellets can be dried at room temperature or at elevated temperature in tray dryer or fluidized bed drier. Bataille *et al.*, 1993 reported the use of microwave oven in final phase of the production process of pellets to evaporate the slurry of the extruded mass during drying process. Huyghebaert *et al.*, 2005 reported the use of freeze dryer in order to maintain viability of living bacterial spores. If solute migration occurs in the wet mass during drying, it may result in increased dissolution rate, strong pellet with modified surface. This may leads to decrease in the adhesion of any film coat. \[27, 28, 29\]

**Screening:**
Screening is necessary to achieve desire size distribution. Sieves are used for the screening. Screening is essentially required after pellets prepared by Extrusion-Spheronization, to avoid pellets having high size polydispersity index. \[30, 31\]
OTHER PELLETIZATION TECHNIQUES:

Spray drying:
In this technique drug incorporated in solution or suspension without excipients. And in the next step this solution or suspension sprayed in to a hot stream. Dry and spherical particles will produce. This process mainly used to increase the solubility of poorly soluble drugs, there for increase the bioavailability. [32]

Spray congealing:
The transition of a melt from a soft or fluid state to a rigid or solid state by cooling is called congealing. In this process first of all drug is allow to melt and dissolve in wax, gum or fatty acid. This solution used for the formation of droplet and spherical shaped pellets. The various droplet formation techniques and the efficient droplet / air contact make the spray drying concept ideal for making spherical particle powder by congealing of melts. Depending upon physic-chemical property of the drug and other excipients, one can prepare both immediate and sustained release pellets. [32, 33]

Cryo Pelletization:
In this technique aqueous – organic suspension or emulsion are dropped in to liquid nitrogen to form spherical particles. These particles are then lyophilized to organic solvent or water. [34]

Hot Melt Extrusion:
Hot-melt extrusion (HME) is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. HME offers many advantages over other pharmaceutical processing techniques. Molten polymer during extrusion process can function as thermal binder and can act as drug depots upon cooling and solidification. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion.

It has been estimated that as many as 40% of all new molecular entities have poor bioavailability because of low aqueous solubility. HME has been used to improve the bioavailability of drug substances especially those having low water solubility by formation of molecular dispersions. HME requires a pharmaceutical grade polymer that can be used at relatively low temperature. All components using in the HME process should be thermally stable during the short duration of heating process. [35]

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME is a potential “continuous process”</td>
<td>May not be applicable for heat labile Drugs (proteins, peptides, etc.)</td>
</tr>
<tr>
<td>No organic solvents or water are needed</td>
<td>Must be relatively moisture free</td>
</tr>
<tr>
<td>Less labor and equipment demands</td>
<td>Non-traditional equipment &amp; requires education and training</td>
</tr>
<tr>
<td>Shorter and more efficient processing times</td>
<td></td>
</tr>
<tr>
<td>Favorable product cost</td>
<td></td>
</tr>
<tr>
<td>Can produce “solid solutions or dispersions” which may lead to improved solubility and bioavailability</td>
<td></td>
</tr>
</tbody>
</table>
HME Equipment:
Pharmaceutical class extruders have evolved and use for the production of wet granulations. Typically, metallurgy of the contact parts must not be reactive, additive or absorptive with the product.

Most pharmaceutical extrusion utilizes ‘screw extrusion’ rather than ram extrusion because it gives better control of temperature profiles and product homogeneity. Screw extruder consists of 3 different parts:
- Conveying system for material transport and mixing,
- Dye system for extrudates formation and
- Downstream auxiliary equipment for cooling, cutting and collecting the extrudates product. [36]

Basically, there are 2 types of screw extruder:
- Single screw
- Twin screw

The single extruder is the most widely used extrusion system in the world. (Especially for plastics). Twin-screw extruder is used in Pharma application. This utilizes 2 screw usually arranged side by side. In Twin-Screws extruder, screws can rotate in the same or opposite direction. Generally counter rotating extruder has disadvantage of air entrapment, generation of high pressure and low maximum screw speed and output. While co-rotating extruder provides the high screw speed and thus output while maintain the good mixing characteristics. So, they are the industrially the most important extruder. [37]

In typical extrusion process screw dimensions are in 20 to 40:1 (L/D) range or longer. Residence time of screw is 5 second to 10 minute depending upon the L/D ratio, type of extruder, screw design & how it operates.

Screw is typically divided in to 3 sections along the length of barrel:
- Feeding
- Melting or Compression
- Metering

Die is attached at the end of barrel and shape of the dye dictates the physical form or shape of extrudates.

Film & laminating system are used to combine melt extrusion with substrate for transdermal and transmucosal application. Film thickening can be adjust by die opening, screw speed, rotation speed of chill roll, mass flow rate introduced into the extruder or the torque winder.

Polymer with low melt viscosities and high thermal conductivities exhibit a more efficient melting process. Changes in the screw design are sometimes useful to improve the melting process and improve mass flow through the extruder. Solidified polymer component can block the channel if melting is incomplete. Differential scanning calorimetry, gel permeation chromatography and thermo gravimetric analysis. [38]

Application:
HME is an innovative and viable approach to produce various pharmaceutical drug delivery systems. Different formulations like pellets, granules, immediate and modified release tablets, transmucosal and transdermal delivery system, oral fast dissolving system can be produce with the help of HME.

HME and Advanced Technology:
Now day drug particle engineering, nanotechnology, has been widely used to increase the solubility and bioavailability of the poorly soluble drug. However there are some limitations like particle aggregation, poor Wettability and morphological instability. By overcoming these problems HME can be widely used in nanoparticle engineering. [39]

Freeze Pelletization:
It is a new and simple technique for producing spherical pellets. Here, molten-solid matrix is added as droplet into inert column of liquid in which molten droplet is immiscible. Droplets move upward or downward in the column depending upon its density with respect to the liquid in the column. [32]

INNOVATIVE TECHNOLOGIES:
Other than existing and established Pelletization technology, some other new technologies are developed. By these technologies we have opportunities to achieve small pellet size range of 100 – 500 µm, smooth particle surface, uniformity in particle size distribution and also high density and high loading can be achieved.

1. CPS™ Technology:
(Reviewed Release Pelletizing Technology)

It is a direct Pelletization process and advanced fluid bed rotor technology allowing the preparation of matrix pellet. Extremely low dosed and high potent drug can be formulated. Drug concentration can be very from <1% up to 90%. CSP technology works with conical shaped rotating disc and additional devices ensuring a directed particle movement. (Fig. 11)

For the CSP technology inert beads are not required. MCC is used as basic excipient; moreover, other functional excipients polymers, disintegrates, solubilizer can be part of CSP formulation in combination with active compound. Starting powder can be wetted with pelletizing liquid until required stage of moisture has been achieved. Pelletizing liquid can be organic solvent or water which may also contain different functional compounds. Dry powder may be fed into the process as an option. [40, 41, 42, 43]

By measuring the torque at the CSP rotor, the endpoint of the Pelletization can be defined. A defined densification of the pellets can be achieved by characteristic rolling particle movement and there by application of different forces. Finally pellets are dried in CSP or classical fluid bed dryer. [41]
Fig. (A) Shows characteristic of CSP pellets containing 75% of API in comparison with the same pellet formulation manufactured by extrusion (Fig. B). Due to particular Spheronization process CSP pellets are prepared of higher density. Their surface is smoother than the pellets prepared by extrusion and provides ideal properties for coating.

Product characteristics of CSP pellets are:
- High density / low porosity of pellets with low attrition and friability
- Broad potency range for APIs
- Dust free surfaces of the pellets having mean particle size range in between 100-1500 µm with narrow particle size distribution.
- Controlled drug release from the CPS matrix. [41]

2. MicroPx Technology:
The MicroPx™ technology is a fluid bed agglomeration process resulting in matrix type pellets. Particle size could be rather small, E.g. <400 µm together with a high drug loading of typically 95%.

The MicroPx™ technology is a continuous fluid bed process: again for the Pelletization, no starting cores are required. Typically all formulation components like the API, binders and other functional ingredients are contained in a liquid which is fed into the MicroPx™ process via spray guns; the spraying liquid can be a solution, emulsion or suspension. [43-46]

Fig. 12 - MicroPx Technology Pilot and Commercial scale

The direct Pelletization process starts with spraying the API containing liquid into the empty MicroPx™ fluid bed unit. Initially, powder is generated by spray drying; the powder is stepwise agglomerated to seeds. The online provided seeds are continuously layered with droplets from the bottom spray nozzles ending up in onion-like structured micro pellets.

The process is characterized by a permanently balanced ratio of spray drying and layering of already existing seeds. Well-sized pellets are continuously discharged out of the process through a rotary valve after classification by the zig-zag sifter. In order to allow spray drying besides the layering of existing pellets the product bed in the process must not be too high; this requirement is also true when the directed product flow towards the sifter should be put into effect. [41, 47]

Fig. 13 - Zig-Zag Sifter

As a certain degree of spray drying is an important requirement for the performance of the continuous Pelletization process it is easily understandable that the product temperature is typically higher than in a Wurster layering or coating process where losses of product by spray drying must be absolutely avoided.
Product characteristics of MicroPx Pellets:
- Spherical and smooth pellet surfaces those are ideal for coating applications like taste masking controlled release coating etc.
- High density / low porosity of pellets with high drug loading: typically 95%
- Low attrition and friability with dust free surfaces.
- Mean particle size range: 100-500 µm with narrow particle size distribution.
- Inclusion of bioavailability enhancers, controlled release polymers etc.

MicroPx technology can ideally be applied when taste-masked pellets are manufactured. E.g.: an extremely bitter tasting antibiotic can be taste-masked by MicroPx technology to be given to children. [41, 47]

3. ProCell Technology:
This is a spouted-bed type pelletizing process for the preparation of very high concentrated pellet shaped particles. Ideally for the formation of particles no additional excipients are required. Here, particles consisting of pure API are reached.

Particles are fluidized in the ProCell™ spouted bed by vertical process airflow: the process air enters the processing chamber through slots at the side and not through the usual bottom screen or inlet air distribution plate as in conventional fluid bed processing. (Fig-14)

![ProCell Technology](image)

Fig. 14 – ProCell Technology

The cross section of the processing chamber becomes significantly broader towards the top, resulting in a sharp decrease of the fluidizing velocity of the process air. This effect provides a controlled flow pattern and circulation of the particles in the processing chamber. Spray nozzles are usually arranged in the bottom spray position; right in between the two inlet air slots; in this position they spray at the point of the highest energy input inside the unit. [41, 44, 45]

ProCell technology performs in the most effective way when a melt of a material is processed, as here neither organic solvent nor water has to be evaporated. Pellets formation takes place by spray solidification and agglomeration. So, high through-puts and cost effective processes are possible. Product can be fractionated online by zig-zag sifter or offline by sieving unit.

Product characteristics of ProCell pellets:
- High density / low porosity of particles with very high drug load up to 100%
- Mean particle size range from 50-1500 µm with optimum narrow particle size distribution
- Low attrition and friability justifying its suitability for processing of particular products with inherent stickiness. [41, 48-50]

PELLET COATING PROCESS:
Coating process carry out to modify the release of the drug from the pelletized drug delivery system.

Coating equipment:
Most of the coating process use one of the following equipment –
1. The standard coating pan
2. The perforated coating pan
3. The fluidized bed coater

a) The standard coating pan:
It consists of the circular coating pan mounted angularly on a stand. Hot air is directed into the pan and on to the bed surface. Coating
solution is applied by spraying the solution on to bed surface. [31, 51]

b) Perforated coating pan:
Perforated coating pan have efficient drying system with high coating capacity. It can be automated for both sugar and film coating. Coating solution is applied on to the surface of coating pan of pellet through spraying nozzles that are positioned inside the drum. [51]

c) Fluidized bed coater: (FBC)
FBC has very effective coating technique. Major advantage of FBC is with coating, granulation and pellet formation is also take place in same equipment. FBC is currently a widely used technique because it allow with other application crystals and granules to be coated with variety of coated material to provide gastro resistance or control release system. [50, 52]

This technology mainly used in the film coating of pellets. Coating suspension is sprayed as atomizer droplet. Film coat will form around the pellet with successive dispersion of coating material accompanied by solvent evaporation due to the heat supplied by fluidizing air. [53, 54]

Evaluation of Multiparticulates:

Size distribution:
Drug release kinetic is depends on the size distribution. So, size distribution of the pellets should be done properly. In most case size distribution is carried out by simple sieve shaker. Size distribution is also determined by the use of Vernier calipers. [31]

Pellet shape:
Pellets shape can be determine by various methods. Pellets are mounted in the microscope fitted with camera Lucida and image of the pellet were drawn manually. Shape factor calculate the amount by which the image of particle deviate from the circle. For the approval of quality of pellet, roundness index should be within 1-1.2. Visual determination by the microscope and stereomicroscope are the other method to determine particle shape. For the perfect circular image, shape factor should be 1. Value of 0.6 describes a particle of good sphericity. [55, 56, 57]

Surface morphology:
Scanning electron microscopy (SEM) is used to examine the cross section of pellets and surface morphology. Pellets are mounted onto the aluminum stub, coated with thin layer of Platinum under Argon atmosphere. These pellets are checked under scanning electron microscopy. SME used to observe the effect of different fillers. It was observed that MCC and corn-starch gives best quality pellets with smooth surface. [58, 59]

Specific Surface Area:
Surface area is directly related with size and shape of pellet. Knowledge of surface area is important in both film coated and uncoated pellets. Specific surface area of pellet is determined by gas adsorption technique. [60]
1. Mathematical calculation:
Spherical pellet has minimum surface area per unit volume and can be characterized by its diameter. Surface area of pellet is equal to $\pi r^2$.

2. Gas adsorption technique:
Here, volume of nitrogen that is absorbed by the substrate contained in an evacuated glass bulb is determined at various pressures. Result is interpreted using liner plot of BET equation for the adsorption of nitrogen on a substrate. [31]

Hardness and Friability:
Mechanical property of the pellets is very important for processing. Dust formation take
place during shipping, handling, storage, coating process and other unit operations. Variation in the process or raw material significantly result in the variation in the Hardness or Friability of the pellets. Hardness of pellets can be determined using Kahl pellet-hardness tester, but it will not give accurate result. Friability of pellets are determined by using Erkewa type tablet friabilator or turbula mixer for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index. Friability can also be determined using fluidized bed with Wurster insert by using stream of air. [61, 62]

Density:
Density is affected by change in the formulation or process. This may affect the other factors such as filling and packaging characteristic during tablet compression and capsule filling. It can be determined by USP density apparatus.

Bulk density of the pellet can be measure with automated tapper. True density of the pellet can be measure using air-comparison pycnometer. Solvent displacement method can also be used. Bulk density indicates packing property and true density indicates the extent of compactness. [63, 64]

Surface roughness:
Samples were mounted on a non-reflective black plate, which was placed on an air-bearing table and the surface roughness measured with a laser profilometer. Sensor aperture angle was 53° and light spot diameter of the sensor was 1 mm. Measurements were performed in 3D at a frequency of 100 points and a measuring depth of ±50 m. The area scan was performed across the 2.00mm X-transverse, with a resolution of 1000 points/mm and the 0.20mm Y-transverse, with a resolution of 200 points/mm. [65]

Porosity:
Porosity affects capillary action of dissolved drug, hence influence the release of the drug from the pellets. Porosity can be measured by mercury porosimetry. The porosity of the pellets can also be determined qualitatively by SEM with image analysis and rarely by using optical microscopy. Determination of the porosity of pellets by mercury porosimetry is a very well-established method and gives reproducible results. [66]

Disintegration and Dissolution are the important characteristics of the immediate release and sustained release pellets.

Dissolution study recognized as important element both in drug development and quality assessment. This test is performed to understand release behavior of the different formulation in different dissolution medium. Release of the drug from pellet mainly depends on the composition, hardness and size of pellets and it is determined by using USP Apparatus I or by USP Apparatus II. Drug release profiles from pellets also depends on the Polymer and binder used, aqueous solubility of the drug, physical state of the drug in the pellet, drug loaded into the pellet and the presence of additives such as surfactants. [67]

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 various 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 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. [68, 69]

RECENT APPLICATIONS:

1) Preparation of Tiagabine HCl / 2-HPβCD Complex Pellets by extrusion-spheronization:

Tiagabine Hydrochloride (TGB) is an antiepileptic drug used as an adjuvant for the treatment of partial epilepsy in adults and children above 12. Tiagabine marked in tablet dosage form. Chemical stability of this dosage form is maintained by ascorbic acid or α-tocopherol. Other methods can also be used to improve chemical stability while performing the synergic effect of 4 antioxidants. Chemical stability of TGB can also be improved by complexation with 2-HPβCD. This will enhance the dissolution profile of TGB. Cyclodextrin cages drug in their hydrophobic cavity and enhance solubility, improves bioavailability and lowers the toxic effect of drug. Inclusion also protects the drug from chemical degradation. Pellet development using TGB/2-HPβCD inclusion complex might also be important as TGB has weak chemical stability, particularly when the water content of the pellets is reduced or even excluded. MCC used as pellet forming agent in the pharmaceutical industry. MCC provides good cohesiveness to the wetted mass; however some incompatibility with drug were observed due to direct interaction with MCC. Glycerol Monostearate (GMS) was used to replace MCC as pellet forming agent. Chatchawalsaisin et al. evaluated the influences of incorporating GMS into formulations and drug release properties of pellets produced by extrusion/Spheronization. Objective of this study was to formulate drug loaded pellets 800-1000 µm, which were easy to coat and offers good flow property. [70-74]

Method:
Preparation of TGB/2-HPβCD Inclusion Complex: This complex was prepared by freeze drying method. TGB disperse in 2-HPβCD aqueous solution and mixed with magnetic stirrer for 24 hr at room temperature. The suspension was filtered through a 0.45 μm mesh. The filtrate was frozen at -45°C for 8 hrs and then lyophilized using a freeze dryer. Lyophilizes were stored in the refrigerator at 4°C in airtight amber color containers.

Preparation of the Pellets: First step of the pellet preparation is granulation. Granulation was done using the planetary mixer. Suitable quantity of TGB and MCC were mixed. Add binding solution simultaneously while mixing. Quantity of binder liquid was determined with trial and error method. The GMS was pre-treated by various methods and added to mixture of pellet formulation as follows:
1) Direct mixing of GMS and MCC mixture with TGB
2) Incorporation of TGB into melted GMS
3) Mixing of GMS with binder liquid

All parameters for blending, extrusion/spheronization and particle size separation were fixed to ensure the reproducibility of results. Extrusion/Spheronization process was carried out on roll extruder. 1.0mm mesh screen was operated at 20rpm. Extrudates were spheronized for 4 mnt at 700 rpm in Spheronizer. [75]

Different characteristics were checked for pelletization process, like particle size determination, Hardness and Friability of the pellets, Dissolution rate study, Scanning Electron Microscopy for determines surface morphology.

Result:
Incorporation of GMS as binder liquid led to significant decrease of water quantity in mixture. An acceptable level of sphericity was also obtained using 30% GMS in the formulation with a minimum quantity of water (2%).

Controlled release Pellets of Tiagabine produced by using dispersion rate controlling polymer, which provides therapeutic effective plasma levels of Tiagabine for the period of at least 12 hr, preferably 24 hr or more. ‘Rate controlling polymer’ includes hydrophilic or hydrophobic polymer or mixture of both polymers that are capable of retarding the release of Tiagabine in vivo when Tiagabine is dispersed in a polymeric matrix formed from the rate controlling polymer. E.g.: Hydroxy propylcellulose, HPMC, alkyl-cellulose such as ethyl cellulose, poly(ethylene)oxide etc...

The controlled release preparation according to invention includes auxiliary agents, such as diluents, lubricants, binders. Preferably excipients are selected to minimize water content of preparation. To improve the stability of the preparation anti-oxidant is also included. [75]


Topiramate pellet proposed delayed/extended release dosage form. Upon administration it provides steady state blood level of Topiramate. Bioavailability of the Topiramate can be increased by many ways. In certain embodiments, the pharmaceutical composition contains extended release pellets disposed in an enteric-coated gelatin capsule.

Topiramate extended release (XR) composition can be prepared by many ways. XR comprise one or more release rate controlling polymer. Ratio of the polymer can be adjusted to control the release profile. Topiramate XR pellets can be prepared by coating drug layered inert pellets with release controlling polymer.

Inert pellet is coated with a drug layer or a drug loaded granule is prepared. This drug loaded pellet is coated with release controlling polymer. Polymer can be applied immediately outside the core by conventional coating techniques such as pan coating or fluid bed coating. Solution of polymer can be prepared in water or suitable organic solvent. Release controlling polymer can also separate another drug layer on the core. For E.g. after coating the active pellet with polymer, another drug layer can be applied and followed by another release controlling polymer layer. EUDRAGIT, HPMC, polyvinylpyrrolidone can be used as release controlling polymer.

E.g.: Hydroxy propylcellulose, HPMC, alkyl-cellulose such as ethyl cellulose, poly(ethylene)oxide etc...
Sometimes, the core that consist of release controlling polymer further coated with the enteric coating layer to prevent from the degradation of drug in unfamiliar environment in the stomach. Pellets are disposed in the gelatin capsule and if needed sealed with the sealing composition. This enteric coating delays the release of Topiramate by 0.1-16 hours after administration based on the fed state of the patient. Topiramate pellet can be prepared by performing different steps like blending of the drug and excipients; Granulation is done with HPLC grade water; Extrusion with 0.8mm screen and speed was adjusted to 10 rpm. Finally Spheronization is done with crosshatched patterned Spheronization plate. Speed of plate was adjusted at 1250 rpm and nitrogen gas supplied at 120 psi. Spheronization was continued until pellets visually appeared of round shape. Drying was carried out at 50°C. The dried pellets were immediately refrigerated after drying.

This invention for pharmaceutical composition gives once-daily or alternate day dosage forms of Topiramate. This sustained release single dosage form is equivalent to the immediate release multiple dose daily regimen. Upon administration of this dosage form gives steady state blood level of Topiramate. This sustained release dosage form is more advantageous over the multiple dose regimen in term of reduce adverse effects and better patient compliance. [76]

3) Properties of enteric coated sodium valproate pellets
Aqueous polymeric dispersion is applied to the solid oral dosage forms to facilitate targeted drug release to upper GI tract. Enteric polymer coating plays important role in protecting the drug which are susceptible to acidic or enzymatic degradation in the stomach. Enteric coating also protects the gastric mucosa from some irritating drugs (NSAIDS).
Eudragit® L30D-55 is an anionic copolymer based on methacrylic acid and ethyl acrylate, with free carboxyl group in a ratio of 1:1 with the ester groups. Carboxylic acid tends to solubilize at pH 5.5 and above, rendering the polymer unaffected in the stomach but it solubilize in the intestinal fluid. Gastric resistance varies from polymer to polymer. [77]
There are 4 mechanisms which controls the drug release are:
- Transport of drug through flaws or uncoated system
- Transport of drug through media field pores in the coating
- Transport through swollen film
- Transport of drug through nonporous film due to permeability of the drug in film. [78]

Subcoat of polymeric film is done prior to the enteric coating to prevent escape of water soluble drug into enteric polymer film. This prevents the degradation of acid liable compounds such as Omeprazole.
Here, main objective is to investigate the influence of polymeric subcoat and organic acids on the dissolution properties of enteric coated sodium valproate pellets. The pellets were produced by either solution-layering or wet-mass extrusion processing and coated with
Eudragit® L 30D-55. Organic acids were incorporated into the pellet matrices or into a subcoat prior to coating with the enteric polymer. [79]

a) Preparation of sodium valproate pellets using the layering technique:
Non-pareil 800–1000 μm were layered with a 2% (w/w) solution of HPMC containing sodium valproate until 20% drug loading was achieved. The solution was applied to the non-pareil by a top spray technique in a fluidized bed coater using an inlet temperature of 60°C and an outlet temperature of 50°C. Solution was sprayed at a rate of 1 g/min with a 1 mm size nozzle diameter at 2 bar atomization pressure. [80]

b) Preparation of sodium valproate pellets by wet-mass extrusion:
Sodium Valproate and Avicel® PH101 were mixed properly in twin-shell blander for 15 min. Solution of Kollidon® K90 was added to prepare a wet mass. Citric acid 1, 5, 10, 15 and 20% (w/w) amount were added in pellet core to lower micro environment pH. Wet mass was then extruded using a LCI Banchtop Granulator with 1.2 mm screen. Spheronization was done by using Caleva model 120 Spheronizer. [80]

c) Preparation of film coating:
A 30% (w/w) dispersion of Eudragit® L 30 D-55 was diluted to final solid content of 15% (w/w) based on dry polymer weight. TEC, 15% (w/w) was added to the dispersion and equilibrate for at least 30 min with Eudragit® L 30 D-55 before the coating. Talc, 50% (w/w) was dispersed in water using polytron® mixer and combined with Eudragit® L 30 D-55. [80]

d) Preparation of subcoat:
The subcoat applied to the solution-layered pellets consisted of a 10% (w/w) solution of HPMC. The wet-mass extruded pellets were subcoated with Opadry® AMB. Coating solution was prepared by adding polymer to water and agitating with Lightnin™ variable speed mixer for 45 min before coating. [80]

Drug Release Studies:
Drug release study was determined according to USP 24, delayed release article, method A, apparatus 2 at 100 rpm and 37°C. Samples were removed from the dissolution medium at various intervals for 2 hr. After 2 hr pH was increased to 6.8 with the addition of 250 ml of 0.20 M sodium phosphate triphosphate to dissolve the enteric coating. After 3 hr pellets were homogenized using mixer. The final drug content of the pellet was determined. Percent drug released was calculated from the actual drug content of each dosage form. [81]

Sodium valproate pellet prepared by either method required high weight gain of Eudragit® L 30D-55 in order to pass the USP enteric test. Drug release from the coated pellet was reduced when citric acid was added to the subcoat polymer applied to solution-layered pellets or to the core of wet mass extruded pellets. Addition of 5% (w/w) amount of citric acid to wet mass extruded pellet cores coated with 15% weight gain of Eudragit® L 30D-55, decreased release of sodium valproate release in acid from 68-0% after 2 hr. citric acid was also functioned to plasticize the Eudragit® L 30D-55 film coating. Thus, increased gastric resistance was obtained. Drug content of the pellet was maintained by limiting the amount of citric acid and controlling drying time and temperature. Sodium valproate pellet containing 5% (w/w) citric acid and enteric coating of 15% Eudragit® L 30D-55 passed the USP enteric test. [80]


Carbamazepine is first line drug in the treatment of patient suffering from partial
seizures. The half-life of carbamazepine is relatively long, ranging between 25 to 85 hours after a single dose. Its effect is substantially reduced after repeated dosing due to auto induction. Currently the dosage regimen for conventional carbamazepine formulation typically required 3-4 doses per day to maintain effective blood concentration. This leads to poor patient compliance. Sustained release dosage form provides improved therapy, decrease incidence of adverse drug reaction and increase patient compliance.

Composition include at least one extended release unit comprising carbamazepine, one or more rate controlling polymer or other excipients and at least one enteric release unit comprising of one or more enteric polymer over an extended release core of carbamazepine.

Process for preparation of modified release carbamazepine pellets:
- Prepare an extended release unit containing carbamazepine
- Prepare an enteric release unit by enteric coating polymer over a core containing carbamazepine.
- Mixing the extended release and enteric release units in the proportion of 20:80 to about 80:20 by weight and fill in the capsule.

Methods:

A) Preparation of extended release unit:
Carbamazepine, HPMC, MCC were granulated with an aqueous solution of copolymer of polyvinylpyrrolidone and vinyl acetate in water. The wet mass was extruded, spheroned, dried and sieved to get spherical unit.

B) Preparation of enteric coated unit:
Carbamazepine, MCC, lactose, citric acid and sodium lauryl sulphate were granulated with aqueous solution of polyvinylpyrrolidone and vinyl acetate in water. The wet mass was extruded, spheroned, dried and sieved to get spherical unit.

| Table 4 – Ingredients and its Quantity |
|-----------------|----------------|
| Ingredients     | Percent w/w   |
| Carbamazepine   | 76.5          |
| MCC             | 16.5          |
| HPMC            | 4.7           |
| Polyvinylpyrrolidone and Vinyl acetate | 2.3 |
| Water           | q.s.          |

| Table 5 - Ingredients and its Quantity |
|-----------------|----------------|
| Ingredients     | Percentage w/w |
| Carbamazepine   | 71.0           |
| MCC             | 19.0           |
| Lactose         | 4.7            |
| Citric acid     | 2.4            |
| Sodium lauryl sulphate | 2.4 |
| Copovidone      | 0.5            |
| Water           | q.s.           |

These spherical units were coated with the coating solution up to a weight build up to about 15%.
C) Preparation of Modified release carbamazepine composition:
The extended release units and enteric release units were blended in desired ratio and filled in to capsule. [82]

**Table 6 – Enteric coating composition**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percent w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit L 30 D 55</td>
<td>54</td>
</tr>
<tr>
<td>Talc</td>
<td>39</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>5.5</td>
</tr>
<tr>
<td>Colloidal SiO₂</td>
<td>1.5</td>
</tr>
<tr>
<td>Water</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

**BENEFITS OF PELLET DOSAGE FORM:**
- Pellets can be used to formulate tablets, capsules and caplets that deliver single as well as multiple active compounds, within single dosage form.
- Improved appearance of the product which is having fine pharmaceutical elegance.
- Offers flexibility into the dosage form design and development.
- Improves the flow properties in formulation development.
- Pellet based NDDS increases dissolution area, thus decrease the gastrointestinal side effects.
- Pelletization is a convenient way to manage the separation of incompatible drug.
- Pellet solves the problem of taste masking.
- It improves safety and efficacy of a drug.
- Reduces peak effect in blood level to lessen the potential of toxicity.
- Pellets can be used as site specific drug delivery.
- Sustained release pellets can be formulated by the use of different polymers for the release of drug over an extended period of time.
- Decrease variability of Gastric emptying.
- Decrease dependency on the nutrition state.
- Reduce risk of dose dumping.
- Lower Intra and Inter patient variability.
- Onset time of drug release can be controlled.
- Product life can be improved against accidental breakdown.
- Minimize experimental variables.
- Chemical incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- In case of immediate release products larger surface area of pellets enables better distribution.
- More meaningful and reproducible data can be generated.
- Reduce number of in process & productivity by increasing flexibility in bath size. [41, 83, 84]

**CONCLUSION:**
This brief review on the Pelletization technology for the Anti-epileptic drugs hereby concludes with a note that they are considered as most promising drug delivery system today which is catching up with the pace of speed to have a high existence in pharma world. This system gain more popularity because of their easy portability improved patient compliance and ease of administration and flexibility in the fabrication as compared to dosage form like tablets or capsules or packed simply as a single dose packets. Pelletization is the best method to administer drug with an oral route. It provides the sustained release of drug by coating with different polymer. Epileptic drugs like Tiagabine, Carbamazepine, Topiramate and Sodium Valproate are available in the pellet dosage form. In the past two years three new anti-epileptic drugs Gabapentin,
Lamotrigine & Falbamate have been approved for use in USA. Pelletization technology is growing in fast pace challenging most of the pharmaceutical companies to develop palletized dosage forms for other anti-epileptic drugs and other wide range of active pharmaceutical ingredients.

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