Chapter 2: Literature Review
2.0 REVIEW OF LITERATURE:

2.1 TECHNOLOGY REVIEW

Various drugs are available for the treatment of epilepsy. Specific use of a drug in treatment of epilepsy is not possible it depends upon the type of epilepsy, drug properties and also on the patient compliance. Various dosage form available for different antiepileptic drugs are summarized in table 3.

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Capsule</th>
<th>Injectable</th>
<th>Suspension</th>
<th>Solution</th>
<th>Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Acetazolamide</td>
<td>Acetazolamide</td>
<td>Carbamazepine</td>
<td>Gabapentin</td>
<td>Diazepam</td>
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<tr>
<td>Carbamazepine</td>
<td>Carbamazepine</td>
<td>Diazepam</td>
<td>Felbamate</td>
<td>Oxcarbazepine</td>
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<tr>
<td>Clonazepam</td>
<td>Clorazepate</td>
<td>Lorazepam</td>
<td>Phenytoin</td>
<td>Valproic acid</td>
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<tr>
<td>Clorazepate</td>
<td>Divalproex</td>
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<td>Diazepam</td>
<td>Ethosuximide</td>
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<td>Divalproex</td>
<td>Gabapentin</td>
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<td>Felbamate</td>
<td>Phenytoin</td>
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<td>Ethosuximide</td>
<td>Pregabalin</td>
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<td>Lamotrigine</td>
<td>Topiramate</td>
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<tr>
<td>Gabapentin</td>
<td>Valproic acid</td>
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<td>Oxcarbazepine</td>
<td>Zonisamide</td>
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<td>Tiagabine</td>
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<td>Phenytoin</td>
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<td>Primidone</td>
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<td>Trimethadione</td>
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<tr>
<td>Topiramate</td>
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</table>

In general, Antiepileptic drugs are slightly soluble and exert good absorption i.e. 80-100% of drug reaching to the circulation. All drugs have penetration in to CNS. So they are administered by oral route. Mode of action of most of the antiepileptic drugs is schematically mentioned in the following figure 1.
2.1.1 DIFFERENT RELEASE PATTERN FOR ORAL SOLID DOSAGE FORMS:
Various antiepileptic drugs are available with different release profile. Immediate release dosage forms are either uncoated or coated with immediate release film forming polymers. Modified release (delayed, extended, sustained and/or extended release) dosage forms are either matrix based and/or coating based with dissolution rate controlling hydrophilic or hydrophobic polymers. Based on the pharmacodynamic and pharmacokinetic properties of the Antiepileptic drugs, dosage form design is decided.

Advantages of Modified release Drug Delivery System (MDDS):
1. Maintain therapeutic concentrations and reduce frequent dosing.
2. Avoid high blood concentration of drug.
3. ER dosage forms have the advantage of improving the patient compliance.
4. Drug absorption is slower so it reduces the toxicity.
5. Protect the drug from hydrolysis and other degradation pathways in the GIT (gastrointestinal tract).
6. It minimizes the local & systemic adverse reaction in patients.
7. Improvement of therapeutic efficacy.
8. It minimizes drug accumulation in the body with chronic administration of medication for prolonged time.
9. Improve the bioavailability of some drugs.

Limitations of Modified Release Drug Delivery System (MDDS)
In contrary, oral MDDS suffer from a number of potential disadvantages as follows;
1. Dose dumping
2. Reduced potential for dose change or withdrawal in the event of toxicity
3. Loss of effect due to diarrhea (too fast transit time)
4. Not suitable for drugs having instability in the GI environment
5. Expensive in preparation.
6. Drug release rates can be varied by various physiological factors such as food intake & rate of transit through the gut.
7. Differences in the drug release rate from one dose to another dose.
8. Extended release (ER) formulation consists of a higher drug load, hence any changes or unpredicted damage of the product integrity can impact the drug release characteristics of the finished product.
9. Sometimes target tissue may be exposed to fix amount of drug over prolonged period of time that results in drug tolerance.

2.1.2 WHAT IS PELLETS?
For pharmaceutical application, an agglomeration process that results in agglomerates of a wide size distribution within the range of 0.1 – 2.0 mm, with a high intra-agglomerate
porosity (about 20 – 50%) is named a granulation process, and the agglomerates are called granules.

If the final agglomerates are round spherical, having good flow characteristic, having narrow size distribution with size range between 0.5 – 2.0 mm, with low intra-agglomerate porosity, the manufacturing process is often referred to as pelletization process, the agglomerates are called pellets.

**Advantages:**

- Pellets can be distributed freely throughout the entire area of the gastrointestinal tract after administration, that helps high drug absorption due to large surface area of GIT can be involved in this process.
- Peak plasma concentration of the drug can be optimum as per requirement with the use of spherical particles having different drug release rates; potential adverse effects can be reduced without significantly reducing drug bioavailability.
- The uniform distribution of spherical particles in the gastrointestinal tract, prevents localized accumulation of the drug, which avoid the irritation of the gastric mucosa.
- Modified-release (MR) multi-particulates drug delivery devices are less prone to dose dumping as compared to monolithic unit dosage forms in GIT.

**Disadvantages:**

- Often pellets cannot be pressed into tablets because they are too rigid. In that case, pellets have to be encapsulated into capsules [Punia Supriya et al. (2012)].
- The production of pellets is often an expensive process and / or requires highly specialized equipment.
- The control of the production process is difficult (e.g. the amount of water to be added is critical for the quality of the pellets and over wetting can occur very easily).

**2.1.3 REASONS FOR PELLETIZATION**
Pelletization is very important area of interest in pharmaceutical industry due to various reasons:

- Prevention of segregation of co-agglomerated components, that leads to improvement of uniformity of the content;
- Prevention of dust generation, that leads to improvement of the process safety, reduction of dust explosions and the respiration problem associated with fines particle that leads to cause health upset;
- It improves bulk density of finished product and reduce bulk volume;
- The uniform shape & weight improves appearance of the drug product;
- Improvement of the finished product handling properties, due to the spherical shape of the pellets that also help to free-flowing properties of the product.
- Improvement of hardness and friability of pellets;
- Controlled release application of pellets due to the ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings.

All these aspects can be considered as technological advantages of pelletization.

2.1.4 METHODS OF PELLETIZATION:

Pelletization process involves accumulation of active pharmaceutical ingredients with excipients in spherical beads shape structure, called pellets. Variety of manufacturing processes are available for pellet formation as mentioned below; [Ozarde YS et al. (2012)].

- Powder layering
- Solution/Suspension layering
- Extrusion-Spheronization
- Spherical agglomeration or Balling
- Spray congealing/Drying
- Cryo Pelletization
- Melt spheronization
- Freeze Pelletization
- Hot melt extrusion
2.1.5 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 mechanism of growth and formation of pellets. Most of them are concluded from research while others are postulated from visual observations [Kapur PC et al. (1966), Sastry KVS et al. (1973)].

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

As per various experiments on pelletization technique steps proposed are Nucleation, coalescence, layering & abrasion transfer.

Figure 2: Pelletization process

<table>
<thead>
<tr>
<th>Nucleation</th>
<th>Shattering</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Nucleation Diagram" /></td>
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<table>
<thead>
<tr>
<th>Coalescence</th>
<th>Fragmentation</th>
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<tr>
<td><img src="image3" alt="Coalescence Diagram" /></td>
<td><img src="image4" alt="Fragmentation Diagram" /></td>
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<table>
<thead>
<tr>
<th>Layering</th>
<th>Abrasion</th>
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<tbody>
<tr>
<td><img src="image5" alt="Layering Diagram" /></td>
<td><img src="image6" alt="Abrasion Diagram" /></td>
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</table>

<table>
<thead>
<tr>
<th>Abrasion transfer</th>
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</thead>
</table>
| ![Abrasion Transfer Diagram](image7) | }
2.1.6 FLUIDIZED BED COATING: WURSTER TECHNOLOGY

Conventional coating machine suffer many drawbacks irrespective of coating material is applied by spraying or ladling techniques. Poor mixing leading to non-uniform distribution of coating, poor drying resulting in excessive tackiness, or hazards of dealing with incombustible toxic organic solvents are more difficult to contain. Wide range of coating equipments exists now-a-days and any one type of equipment may be sufficiently suitable for the production of coated ER pellets of particular interest. The multi-processor concept (where main processing unit can be modified by insertion of one the several types of processing chamber has evolved as standard). Three basic processing steps may be used and are represented in figure 3 diagrammatically. These are top spray, tangential spray and bottom spray. The basic principal of these processors and their relative advantages & disadvantages are mentioned in the following table 4.

**Table 4: Comparative advantages & limitations of different fluidized bed processes**

[Hogan J (2013)]

<table>
<thead>
<tr>
<th>Process &amp; Description</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Top spray: Adaption of fluidized bed granulation, with spray nozzle that positioned inside product container | • Spray nozzle is easily accessible  
• Suitable for manufacturing of large batches  
• Good uniform mixing characteristics  
• Less susceptible to impact of inter-particle size and density differences on coating uniformity. | • Lower coating efficiency  
• Produce highly porous films particularly with organic solutions  
• Not suitable for high weight gains |
| Bottom spray: Wurster process | • Uniform coating  
• Minimum spray drying  
• Adaptable to wide range of coating applications | • Nozzles not readily accessible, leading to interruption of process when nozzle blockage occurs |
| Tangential spray:  
Adaption of roto-processor granulation or spheronization process | - More susceptible to impact of interparticle size and density differences on coating uniformity  
- Requires tallest expansion chamber  
- High application rates possible  
- Easily accessible nozzles  
- Less susceptible to impact of interparticle size and density differences on coating uniformity.  
- Flexible in terms of batch size & changes of batch size during processing. | - Relatively expensive  
- Product is subjected to high mechanical stress  
- Generally accommodates small batch sizes |

Figure 3: Bottom spray, Top spray & tangential spray  

Principle of wurster technology  
[www.imco.es/pdf/421111.pdf]

The wurster or bottom spray technique is a fluid bed method of choice for particle coating processes. The basis of this technology is a circulating fluid bed. Zones of stronger and weaker airflow are created. The wurster inner partition divides the fluid bed
into zones of differing airflow. The movement sequence in the wurster process can be divided into 4 zones as represented in following figure 4.

**Figure 4: Four-stage movement and movement sequence of the fluidized particles in the fluid bed wurster process**  [www.imco.es/pdf/421111.pdf]

Zone A: Up-bed zone
The air speed in this zone is much faster than the final speed of the particles. The particles are transported upwards pneumatically. The upbed zone is where the particles attain their highest speed, are wetted with a fine mist of spray liquid droplets and have already begun to dry before reaching zone B.

Zone B: Zone of slowed upward movement
The particles leave the upbed zone and enter the transition zone, where they decelerate. Their parabolic flight paths carry them further upwards for a while before they lose their lift and begin to fall in the downbed zone. The particles continue to dry in this phase.

Zone C: Downbed zone
In the downbed zone, the particles continue to fall downwards with the fluidized product bed before reaching the gap between the downbed and upbed zone. The particles must already be as dry as possible to prevent them from sticking together.
Zone D: Compact product bed

The particles slowly move out of this zone, which can be described as a compact product bed, in the direction of the upbed zone.

This means that, in total, the particles only spend a short time in zones A, B and C. This time must be adequate for the drying of the last layer of coating on the particle. If this is not the case, the particles in zone D can stick to each other and form agglomerates, as a large accumulation of particles arises in this zone. The particles therefore spend a comparatively long time in zone D. It is very important that the temperatures in this zone are not too high, particularly when processing active and coating substances that are very sensitive to temperature. The length of time spent in this zone depends heavily on the loading of the machine and the fluidization conditions. Following table 5 and figure 5 dictates process parameters and its influence on coating process and in turn, on product characteristics.

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**Figure 5: General process parameters of wurster processes** [Porter SC et al. (1994), Chan LW et al. (2006)]
Table 5: Influence of parameters on the coating process and product in the wurster coater

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Influence on Process</th>
<th>Influence on Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner partition height</td>
<td>Fluidization behaviour</td>
<td>Uniform coating, reproducibility</td>
</tr>
<tr>
<td>Bottom plate</td>
<td>Fluidization behaviour</td>
<td>Uniform coating, reproducibility</td>
</tr>
<tr>
<td></td>
<td>Distribution of inlet air to the upbed and downbed zone</td>
<td></td>
</tr>
<tr>
<td>Inlet air flow</td>
<td>Fluidization behaviour Energy intake</td>
<td>Uniform coating, reproducibility</td>
</tr>
<tr>
<td>Inlet air temperature</td>
<td>Energy intake</td>
<td>Agglomeration, spray desiccation, uniform coating, reproducibility</td>
</tr>
<tr>
<td>Inlet air humidity</td>
<td>Process humidity/product Temperature</td>
<td>Agglomeration, spray desiccation, uniform coating, reproducibility</td>
</tr>
<tr>
<td>Spray pressure</td>
<td>Droplet size</td>
<td>Agglomeration, spray desiccation, uniform coating, reproducibility</td>
</tr>
<tr>
<td>Spray rate</td>
<td>Process humidity / product Temperature</td>
<td>Agglomeration, spray desiccation, uniform coating, reproducibility</td>
</tr>
</tbody>
</table>

2.1.7 ADVANCEMENTS IN MULTIPARTICULATE DRUG DELIVERY

This section briefly introduces innovative pelletization techniques from GLATT and coating technology from Huttlin. Introduction of the the FDA’s QbD initiative led to apply PAT (Process Analytical Technology), among various PAT tools modern process analyzers to monitor and control process are described briefly. Also, this section highlights platform technologies in the field of multiparticulates.

2.1.7.1 GLATT Innovative Technologies

With existing & established pelletization techniques, it is not possible obtain all the desired benefits & hence application of multiparticulates is generally limited to the capsule dosage forms. In order to extend applicability of multiparticulates to other potential dosage forms such as MUPS tablet, oral suspensions without sandy feel in mouth there is pressing a need of technology which can consistently produce micropellets in the size range of 100-500 micrometer, nearly uniform particle size distribution, smooth surface, high density & high drug loading (refer figure 6). This can be achieved by
Innovative GLATT pelletization technologies, namely CPS, MicroPx & ProCell technology as represented in figure 7. Elaborative discussion on these techniques is available online on GLATT website.

![Figure 6: Drug products](http://www.glatt.com/times/times25site/tms25_innovative_1.htm)


### 2.1.7.2 Huttlin (Bosch Huetttlin GmbH, Schopfheim, Germany) [Ahmed SU et al. (2013)]

offers a FBP technology with 3 in 1 function includes granulation, coating & drying on the same equipment, named Huttlin Dryer-Granulator-Coater (HDGC). It performs its operations in minimum time as compared to conventional fluid bed processor. This technology enables the formulator to coat pellets & powders as small as 5 micrometer, also allows preparing denser & more uniform granules. In contrast to fluidized bed processor it does not use any moving part such as rotor or bottom mesh. Following
unique features of the Huttlin overcomes the shortcomings of conventional drying machine & top or bottom spray (wurster) granulator or coating technologies:
Stationary bottom disc plate having 3% openings creates a pressure difference necessary that get max. velocity of air passing through the air distribution slots cutted at 45º angle. Flow of the processing air through the plate is at 45º angle with high velocity capable of generating a constant & uniform circular movement of the product fluidized at minimum possible min. height. Spiral movement of product under fluidization, ensure that none of the product drops through the air distribution openings & helps to complete both processes, coating & drying. During loading and unloading of product process air flow is kept on.
Spray nozzle for both coating & granulation process is mounted at 45º angle across the air distribution plate. This design ensures a concurrent direction for process air and minimizes the distance between spray nozzle & fluidized bed while spraying operation. Spary nozzle does not contain any inside needle or moving part like conventional spray gun & spray the spray liquid.
Filters are in build within the expansion chamber that allows for additional 40% surface area for spray granulation & drying processes. The no. of filter socks available are 5 to 6 depending on the FBP equipment size, each filter socks are blown back into the product.

2.1.8 REGULATORY NEED

According to the FDA's new initiative of QbD approach, quality can’t be determined into the finished products; instead the quality should be in built in the product by design. One of the approaches to accomplish this goal is by PAT with the objective of final product quality. Therefore aim of the PAT suggests understanding & controlling of the manufacturing process steps. Various PAT tools are described in the guidance document by the US-FDA & objective is to provide efficient & effective means for getting required information to facilitate understanding on the process, further improvement & risk-mitigation plans. Only modern process analyzers used in literature to control & monitor at the end point of coating process are reviewed in the following section. PAT tools can be divided as following 4 tools design:
i. Multivariate application for design, data acquisition & analysis
ii. In-Process &/or overall process analysis instruments
iii. In-process & complete process control instruments
iv. More improved & knowledge management tools

This regulatory need leads to the development of various analytical methods to observe & control of coating in-process parameters by mainly three methods: 1). at-line (samples are removed, isolated & analyzed in close vicinity to process stream), on-line (samples are diverted from main process stream & may be returned to main process stream), in-line (samples are not separated from main process stream) analysis can be carried out by using following modern process analysis techniques as reported in various literature.

- Raman spectroscopy
- Near infrared spectroscopy
- Image analysis
- TPI (Terahertz pulsed imaging & other terahertz pulsed analysis).

2.1.9 PLATFORM TECHNOLOGY IN MODIFIED RELEASE MULTIPARTICULATE DRUG DELIVERY

Similar concept for multiple drugs to improve therapeutic effectiveness is the basic approach of the platform technologies. The development cost of a new chemical entity (NCE) is high with associated risk of failure in clinical trials. However, developing a new drug delivery for an existing drug can give new life to drug by maximizing its performance and enhanced market differentiation. Product development by platform technologies is mainly focused on patient-centric drug delivery systems. Patient centric approach not only positively impacts the quality of life of patients by improving therapeutic efficiency & encouraging adherence to dosing regimens but also can be utilized to target different patient populations & can improve market value of products by life cycle management (extended patent protection & avoiding generic entry).
Table 6: List of Drug delivery companies & their platform technologies

<table>
<thead>
<tr>
<th>Company</th>
<th>Platform technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptalis pharmaceutical technology [<a href="http://www.BendResearch.com">www.BendResearch.com</a>]</td>
<td>Diffucaps technology</td>
</tr>
<tr>
<td>Bend research [<a href="http://www.flamel.com">www.flamel.com</a>]</td>
<td>Melt-Spray-Congeal (MSC) microspheres technology</td>
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<tr>
<td></td>
<td>Spray layered multiparticulates (SLM) technology</td>
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<tr>
<td></td>
<td>Micropump technology</td>
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<tr>
<td></td>
<td>CODAS (Chrono-therapeutics Oral-Drug-Absorp.-System)</td>
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<tr>
<td></td>
<td>PODAS (Programmable Oral-Drug-Absorp.-System)</td>
</tr>
</tbody>
</table>

2.1.10 COATING OF MULTIPARTICULATES:

Mainly the coating of pellets can be done by polymeric solutions as well as polymeric dispersion. In such type of coating the mechanism in film formation is the critical step. Film coating done by spraying, drying of coating polymer during the coating process,
coating dispersion which is mainly consists of 3 phases: polymeric particles, gas phase & aqueous phase. Water evaporates & solidify the polymeric solid. These residual solid composed of discrete particle, become a homogenous film.

Muroi [Muroi S (1970)] reviewed many proposed theory for film formation and its application in pharmaceuticals was reported by Lehmann et al. [Lehmann KOR (1989)] and Steuernagel et al [Steuernagel CR (1989)]. Film formation & Fusion of polymeric particles may be explained by following theories:

i. By Wet sintering theory [Vanderhoff JW et al. (1966)]

ii. By Capillary pressure theory [Brown GL (1956)]

iii. By Dry sintering theory [Dillon RE et al. (1951), Henson WA et al. (1953)]

2.1.10.1 FILM COATING FORMULATION & PROCESSING FACTORS

[A] Film coating polymer’s particle size:
The film formation is stronger with the reduce in size of dispersion of polymer & difficult in film formation from large size dispersion polymer. Latexes and pseudo latexes are easier for film formation due to its submicron size. Nakagami et al [Nakagawa H et al. (1991)] reported effect of coating polymer particle size on film formation.

[B] Film-forming temperature:-
Polymers are deformable above $T_s$ which is necessary for film formation. The softening polymer films, associated with G.T. (glass transition) temperature of polymer to the sharp increase in polymer chain mobility [Okhamafe AO et al. (1988)]. Amer et al [Amer GI et al. (1988)] explained relation within $T_g$ & product bed temperature. Author concluded that when film coating is done at 10ºC or less above the $T_g$ the film formation was complete but such operation may lead to the agglomeration of pellets which is minimized by powder dusting directly into the coating chamber.

[C] Plasticizer:-
Plasticizer is used to decrease $T_s$ & $T_g$ values. The degree of decrease in $T_s$ depends on the plasticizer concentration and physiochemical properties of plasticizer. In order to improve
polymer mobility and flexibility, plasticizer must be compatible with the polymer. Toyoshima et al. [Toyoshima K et al. (1973)] explained the capacity of plasticizer to break the bond between molecules.

[D] Blend polymer:-
Blending of polymer is done to adjust the softening temperature of the polymer. For example: Eudragit NE30D has low $T_s$ at 18°C & when it is blended with Eudragit RS30D. Up to 40% of Eudragit NE30D, there is slight decrease in temperature but with more than 40% of NE30D, there is a significant change in the glass transition temperature for coating film formation. The blend of Eudragit RS30D / Eudragit NE30D are in the ratio of 2:3 with $T_s$ of 53°C. Release profile of this blend was very fast indicating poor film formation.

[E] Hydration of polymer:-
For excellent film formation hydration of polymer is important apart from polymer particle size. For example: Eudragit L30 D55 shows the excellent film forming ability due to its small size and also it contains hydrophilic methacrylate 50% w/w as a molar fraction of unit molecule [Lehmann KOR (1989)]. The hydrogen bond between the polymer and pendent ester can be separated by water molecules and hydration causes lowering of mechanical strength of particle and polymer particle to deform. Hydrogen bond between water and carboxyl groups act as driving force for coating film.

[F] Core surface:-
Core used must be porous granules. Protiman and Brown et al [Protzman TF et al. (1960)] described that application of an aq. Coating dispersion of copolymer of ethyl acrylate-methyl methacrylate (EA-MMA) to the porous surface resulted in higher minimum film forming temperature (MFT) values which indicates lesser period for capillary pressure to act due to moisture penetration resulted in incomplete film formation.

Since most of the drugs are surface active, they move from core to film layer which decreases the capillary pressure (driving force for film formation). Yang and
Ghebre-Sellassie reported this problem \cite{YangSTetal(1990)} resulted in poor film former. Migration of the drug can be avoided by slow down the coating process at initial stage of seal coating of the core surface.

**[G] Excipients:-**

Solid excipients that are not soluble in water can be used as pigments (TiO$_2$, food dyes) in coloring the coating, membrane diluents to thicken the membrane, example: talc or magnesium stearate \cite{GoodhartFWetal(1984)} and also act as anti-adherent, anticoagulant used to separate interactive polymeric particle & avoid agglomeration. The colloidal silicon dioxide in surelease containing coating preparation & oily acetylated monoglyceride in aqueous based formulation act as an anti-adherent and anti-coagulant respectively. Very few amount of excipient suppresses coating film permeability but excessive excipients resulted in non-continuous coating film formation \cite{WaldieJM(1981),HarrisMRetal(1989)}.

**[H] Film coating of fine powders:-**

Manufacturing of multi-particulate formulation by spray film coating techniques, resulting of agglomeration problem especially with fine powder. In fine powder case, the inter-particulate bridge of membrane material is formed leading agglomeration \cite{FukumoriYetal(1992)}. This inter-particulate bridge needs to be separated in order to avoid agglomeration but conventional top sprayed fluidized bed, usually can’t generate sufficient strength to separate this bridge. Hence, wurster process, which is best suited for fine powder coating, is used where particles lesser than 100µm can be film coated discretely, and smallest size particle can be coated by wurster process, depending on the adhesive strength of the film coating material. The condition that is maintained in wurster bottom process for fine powder dispersion is: the mass median diameter is kept at 12µm at spray atm. of 2.3 kg/cm$^2$ pressure & spray rate of 4ml/ minute. This is the dispersion spray condition that can be used. In aqueous suspension, it produces intense segregation of particles because of the collision between particles. Brittle particles are easily shattered & lactose crystal becomes roundish \cite{FukumoriYetal(1987)}. 
2.1.10.2 APPROACHES TO FORMULATING COATING SOLUTION
Advantage of film coating is to modify the release characteristic of the drug from a dosage form. Approaches to formulate modified release coating are:

i. Film – forming material dissolved in organic solvent.
ii. Aqueous polymer dispersion.
iii. Hot melts.

2.1.10.3 DRUG RELEASE MECHANISM FROM COATED PELLETS:
Pellets are film coated with the various polymers which are insoluble in GI track as well as soluble in the GI track. Here we will focus on the mechanism of release to justify the in-vivo characteristic of the pellet formulation. The drug release mechanism depends on the coating material & method of coating. Drug release kinetics depends on the solubility nature of coating material in GI condition and core formation. Drug release mechanism is divided according to following 3 general types:

(1) Insoluble coat material in physiologically relevant conditions.
(2) Solubility of coating material variation along GI tract.
(3) Coating slowly erodes under GI condition.

1. Insoluble coat material in physiologically relevant conditions:
   [A] Drug diffusion
Film coating polymers form continuous phase with plasticizer & additives, these materials are uniformly dispersed through out the film coating. Drug diffusion from amorphous polymer phase involves inter-dependent movement of drug & polymer chain segment around the film coat [O’Neill WP (1980)]. Temperature fluctuations between adjacent chains permits drug release by diffusion. The frequency of diffusion of drug depends on (i) size and shape of drug, (ii) force of attraction within nearby polymer chain, & (iii) rigidity of polymer chains. Generally, if coating film is continuous i.e. Absence of pores,
then film coat is become flexible which improves drug affinity for polymer as compared to water, these process describe the drug diffusion mechanism for drug release.

[B] Drug diffusion through plasticizer channels
It assumed that if plasticizer is uniformly distributed in high concentration then it forms the patches in the channels. Diffusibility into plasticizer is lower than into water as plasticizer is more viscous than water. Ozturk et al [Ozturk AG et al. (1990)] determined K value from solubility ratio to distribution coefficient for phenyl-propanol-amine HCl between water and 4 plasticizers. K value ranges which suggested this mechanism is nor enough to explain the drug release rate which has observed.

[C] Drug diffusion from aqueous pores
Coating isn’t uniform & continuous, it is having lots of pores. These pores are generally filled with aqueous solution as soon as it comes in aqueous medium, that facilitates diffusion of drug solution. This mechanism is seen in coating done with aqueous dispersion as pseudo-latexes as compared to organic dispersion as pseudo-latexes, because coating polymer particles do not fuse efficiently, this resulted into pore formation in the film coating formed.

[D] Osmotic drug release
Drug release may be due to the osmotic pressure within core materials & drug release environment. Osmotic pressure in core is created by excipients such as sugar which constitutes core pellets of nutral pareil seeds & the drug. Drug which is released by osmotic pressure, must be of low molecular wt. Osmotically driven drug release started when pellets put into water, it imbibes water to the core, then drug & excipients get dissolved in water that generates osmotic pressure.

2. Solubility of coating material variation along GI tract:
Film coating which are pH sensitive have increased solubility in the GI tract which is used to inhibit drug-dissolution in stomach but complete drug dissolve occurred in intestine. The pH difference is about 5 pH units [Dressman JB et al. (1990)] between stomach & small intestine at fasted state but it is reduced when food is ingested as gastric fluid
become buffered with food. Thus a narrow range is provided, above that the coating solubility must change. Achieving release in colon is difficult than small intestine, due to the pH difference within ileum & proximal colon is much lesser than within stomach & small intestine.

3. Coating slowly erodes under GI condition:
To achieve prolong release using enteric-coating one can impart heterogenous coating such as shellac \cite{SaffranM}. The acidic property of hydro-lysate explains delayed release properties. Uniformity of composition demonstrate prolong release of drug. Triglycerides & either wax or fat are also used for coating to provide prolong drug release, digestion & dissolution are modulated by lipase release in pancreatic juice & bile salts. To predict in-vivo release, include biological amount of pancreatin enz. & bile-salts as emulsifier in drug release media. The high degree of colony by bacteria in colon, flavour designing of site-specific release to colon \cite{SimonGL}. This is used for treating inflammatory bowel disease as the high concentration of the drug is achieved in local tissue. The Azoreductases is used in colon-specific delivery and studies are going on the use of glycosidic linkage. In bio-erodible coating, the polymer includes catalyst like polyorthoesters to speeden the release as bioerodible polymer alone erode too slowly in GI tract. By including anhydride phthalic in poly-orthoester matrix, a surface erosion is achieved, resulting in a zero-order drug release due to water penetration rate into the polymer is rate limiting step of it’s erosion. The advantage of this design are of three folds:

1. Drug release are relatively independent of the GI condition.
2. Manipulating the drug dissolution rate by adjusting the conc. of the catalyst, &
3. Absolute drug release is possible if polymer degrade fully within GI transit time.

Example: Cyclobenzaprine HCl formulation, produce drug release for 10 to 15 hours. Short term drug release formulation design was described by Heller et al \cite{HellerJ}.
2.1.11 MARKETED EXAMPLES ON SUSTAINED RELEASE ANTIEPILEPTIC DRUGS:

1. **Formulation of Topiramate pellets (Patent No. – US 8298580 B2):**
   
   Sugar spheres are used in the formulation of Topiramate pellets. It is one of the extended release type dosage form. In this the spheres were firstly seal coated then the drug layering is done by using fluidized bed processor. Then pellets were subjected for rate controlling layer coating using polymers like ethylcellulose, methylcellulose at level of 2-4% coating. This formulation reduces the adverse effects related to the CNS which are shown by immediate release dosage form of Topiramate [Likan Liang et al. (2012)].


   Extended release formulation containing carbamazepine is formulated by blending carbamazepine with rate controlling polymer and pharmaceutically acceptable excipients by granulation followed by sifting, extrusion and spheronization, pelletization, micropelletization etc. Then these pellets coated with enteric polymer using fluid bed processor. The rate controlling polymers include cellulose derivatives, starch, PVP, alginates, acrylic acids. Suitable enteric polymer such as CAT (cellulose acetate trimellitate) and CAP (cellulose acetate phthalate), HPMC phthalate acetate, HPMC acetate succinate, Methacrylic acid copolymer such as Eudragit L100-55, L30-D55 etc. These pellets were filled in the capsule. The resultant capsule shows its release in the intestine, it will not show its release in the stomach [Kesarwani AK et al. (2007)].


   In this patent the Acetazolamide Pellets were prepared by the Extrusion Spheronization method. Acetazolamide itself act as a binder so binder free pellets were prepared and then these pellets were coated with a rate controlling membrane.
Rate controlling membrane consists of polymers like ethyl cellulose, waxes etc & MCC as a moisture controlling agent. Acetazolamide containing pellets can be filled into soft or hard gelatin capsules otherwise presented in a unit dosage form [Payne Nicholas Ian et al. (1996)].

| Table 7: Composition of Pellet Core |
|-------------------------------------|-----------------|
| Ingredient                         | % Composition, dry basis |
| Acetazolamide                      | 80.0             |
| MCC                                | 19.94            |
| SLS                                | 0.06             |

| Table 8: Composition of Coated Pellets |
|----------------------------------------|-----------------|
| Ingredients                            | % Composition, Dry basis |
| Acetazolamide Pellets                  | 94.52           |
| Ethylcellulose(100 cps)                | 0.72            |
| HPC (6 cps)                           | 2.86            |
| Mineral oil                           | 0.41            |
| Colorant                              | 1.46            |

2.1.12 LITERATURE SURVEY ON RELATED RESEARCH

A comprehensive literature search was carried out to capture information about disease condition, pathophysiology of epilepsy, treatment options, dosage form, research done on a similar type of systems by referring scientific journals, research papers, books, patent data base, etc, as enumerated below;

- **Larry Baum et al., (2012)** [Chunbo Zhang et al. (2012)] mentioned that convulsion or epilepsy is regarded as most common serious chronic neurological disorder and one-third of patients did not responded to all available anti-epileptic drugs due to over-expression of P-gp (P-glycoprotein) in endothelial cells of the BBB (blood-brain barrier) in epilepsy patients. They disclosed that P-gp expression was increased in epileptic brain tissues and AEDs were become substrate of P-gp in several *in vitro* and *in vivo* clinical and laboratory testing. Finally they discussed the criteria to identify the substrate status of AEDs by using SAR (structure-activity-relationship) models.
Willmore James L. *et al.*, (1998) reported that occurrence of epilepsy or convulsion is more in the aged population. Dose dependent side-effects of old standard AEDs are common in elderly patients because of physiological changes (hepatic volume and function, low renal blood flow, fat to fasting ratio of the body ingredients). Newer generation of AEDs having no enzyme induced effects & renal route of elimination are more favorable to recommended in aged patients.

Ramadan N. M. *et al.*, (2006) described the various mechanisms involved in the acute and prophylactic treatment of migraine by using different class of new and existing antiepileptic drugs, but novel therapeutic targets for migraine prevention are yet to discover.

Owen T. Jones, (2002) disclosed the important role of the voltage-dependent calcium channels in the epilepsy based on the insights gained from molecular genetics and pharmacology.

Johannessen Landmark C. *et al.*, (2011) disclosed that differences in host factors such as a individual’s genetic character, gender, age, ethnicity, specific pharmacological and pathological conditions can alter the pharmacokinetic properties of AEDs that affects the delivery of the AEDs to the site of action which leads to variability in the pharmacological responses between and within patients.

Marco Pappagallo, (2003) investigated the scientific rational utilization of AEDs in the treatment of neuropathic pain & migraine based on clinical investigation of 5 recent AEDs such as gabapentin, zonisamide, lamotrigine, oxcarbazepine & topiramate had concluded that newer AEDs are having better tolerability & fewer drug-drug interactions compared to tricyclic antidepressants.

Mike Namaka *et al.*, (2004) proposed a treatment strategy for neuropathic pain management that can be adopted by health care professionals. They divided the treatment options in four-line of drug classes. First-line of drug classes should be the starting point in the neuropathic pain treatment. If patient does not show response to the treatment with at least three different drugs of the same class, then 2nd drug class may be tried. If patients don’t respond to monotherapy with either
1\textsuperscript{st} or 2\textsuperscript{nd} line drug, they may show response to combination therapy. Thus treatment protocol can be individualized depends on each patient’s response.

- **Walker M. C. et al., (1995)** [Walker MC et al. (1995)] devised a scoring system to evaluate the pharmacokinetics of available and new AEDs including few prodrugs and found that vigabatrin, levetiracetam, gabapentin, and topiramate appear to have the most favourable, while ralitoline and stiripentol have the least favourable pharmacokinetic profiles.

- **Stephen D. Silberstein, (2006)** [Stephen D. Silberstein (2006)] investigated the preventive treatment options for migraine with different medication groups and their mechanism of action to lower the duration, frequency or severity of migraine attacks. Finally he concluded that preventive therapy with best-documented evidence of efficacy were amitriptyline, divalproex, b-blockers & topiramate. Generally, choice of medicine is depending on the established therapeutic efficacy of a drug, physician’s assurance about medications was not evaluated yet in the controlled clinical trials, adverse effects of a drug, presence or absence of any co-existing disease & patient preferences on headache profile.

- **Michelle K. Bazil, (1997)** [Michelle K. Bazil et al. (1997)] compared pharmacokinetic properties, adverse effects and drug interactions of 4 new anti-epileptic drugs such as gabapentin, lamotrigine, felbamate and topiramate. Even though, it seems that they had a broad spectrum of action in seizure control, but felbamate has serious adverse effects. Topiramate & lamotrigine have low interactions as compared with older AED agents. Incidence of adverse effects decreases with sustained-release preparation of carbamazepine which in turn increases patient compliance. These recent advancement improved efficacy & reduced adverse effects for many patients with epilepsy.

- **Elizabeth J. Donner et al., (2006)** [Elizabeth J. Donner et al. (2006)] compared indications, pharmacokinetics, mode of action, side effects & dosing of the recent & old generation of anti-epileptic medicines involved in the therapy of epilepsy/convulsion in children & suggested that newer drugs having equal therapeutic efficacy along
with better tolerability, adverse effect profiles & pharmacokinetic properties as compared to traditional medicines.

- **Stephen D. Silberstein et al., (2005)** [Stephen D. Silberstein et al. (2005)] assessed the clinical success of topiramate as mono-therapy for epilepsy / convulsion along with reduction in migraine are escribed for the management of dosing, titration & side effects.

- **Emilio Perucca, (1997)** [Emilio Perucca (1997)] described pharmacological & clinical review on topiramate as a new anti-epileptic drug including its adverse effects.

- **Michael A. Rogawski et al., (2008)** [Michael A. Rogawski et al. (2008)] described three new molecular targets for several newer anti-epileptic drugs. Main mechanisms of all new molecular targets regulates neurotransmitter secretion at synapses, this mechanism suggested that presynaptic terminals are critical sites of action for AED medicine.

- **Ali R Rajabi Siahboomi, (2003)** [Ali R Rajabi Siahboomi (2003)] reported an approach of modified release oral drug delivery systems (MDDS) had replaced a line extension strategy to a clinically superior approach for branded/ generic drugs and for NCEs (new chemical entities). Main advantages offered by MDDS includes reduced dosing frequency that improves patient compliance and acceptance for the MDDS, superior therapeutic effects with lesser side effects, dose dumping & improved bioavailability.

- **Shajahan Abdul et al., (2010)** [Shajahan Abdul et al. (2010)] suggested MDDS multiparticulate system more efficient clinical substitute to conventional IR dosage forms. Final dosage form of multi-particulates could be monolithic dosage forms by filling into capsules or tablets. They mainly discussed the issues of compression of pellets to get tablets & mechanisms involved during compression of multi-particulates to get MUPS that could rapidly disintegrate to unit pellets in-vivo.

- **Emilio Perucca, (2009)** [Emilio Perucca (2009)] suggested rational design of extended release formulation of AEDs for clinical benefit apart from longer dosing intervals with lowering fluctuations in plasma drug levels. Careful monitoring of clinical response & attention for dose adjustment is the prime need for all new extended release anti-epileptic formulations.
Praveen Khullar et al., (2010) described the rational for pelletization due to its flexibility in dosage form design in the pharmaceutical developments and utilized to improve the safety and efficacy of bioactive agents.

Kumar Vikash et al., (2011) described the various process of pelletization and its coating; they suggested their advantages as multiparticulate dosage form over monolithic unit dosage form for controlled release preparations.

Niklas Sandler et al., (2005) investigated the extrusion-spheronization process of pelletization by using in-line modern analytical technology at each stage to find out the phase transitions in nitrofurantoin and theophylline formulations during pelletization.

Ali Javed et al., (2009) explained the various method of pelletization techniques and the evaluation parameters for identification quality pellets as better oral drug delivery system.

Saurabh Srivastava et al., (2010) described fluid bed technology or air suspension process in details including its various type of application and selection of suitable process parameter to develop novel multiple unit dosage systems for better therapeutic and economic benefit.

Raimar Lobenberg et al., (2007) summarized the U.S. Pharmacopoeia & non-pharmacopoeial dissolution profile methods for conventional & novel pharmaceutical dosage forms. Also suggested possible alternatives drug dissolution profile study design to choose an appropriate dissolution test condition for every type of formulation product to predict good in-vitro & in-vivo correlation during initial research and development.

Siepmann J. et al., (1999) investigated the effect of formula composition of diffusion based CR devices on the drug diffusivity & the resulting drug release kinetics model in a quantitative direction. The advantage of the published method was to calculate the required formula composition of diffusion based CR drug delivery systems to get desired release profiles.
Goran Frenning et al., (2003) described a mathematical model for any drug release system from coated multarticulate (pellets) with a granular core, that involved a dynamic characteristic of all three main processes that contributing to drug release from such system such as liquid penetration, drug solvation & drug solution moving out of the system, these entire process of diffusion occurred across the CR/ER/XR/MR coating film.

Mehta Atul M., (1986) enumerated all the process variables involved in the scale-up operation of coated controlled release products by three types of fluid bed processes and their optimization as the process variable could affect the performance of the end product.

B. Rambali et al., (2003) developed a more logical & systematic method to achieve uniform granule size while scaling up of fluidized granulation process from small scale (5 kg) to medium scale (30 kg) to production scale (120 kg).

Claudia S. Leopold et al., (2011) found in the development of the shellac coated SR (sustained release) formulation that the application of modifying sub-coat with CaCl$_2$ (calcium chloride), Eudragit E or citric acid respectively was an easy & effective means to achieve tailor made SR profiles from shellac-coated dosage forms.

Rajesh N. et al., (2011) disclosed the formulation and evaluation of controlled release diltiazem hydrochloride pellets made up of chitosan and microcrystalline cellulose blends to reduce the unwanted side effect of diltiazem hydrochloride, whose drug release profile was equivalent to commercially available oral formulation Adalat CR 20mg capsule.

Xing Tang et al., (2010) described the preparation & analysis of a high-dose nicotinic-acid loaded SR pellets coated with two polymers & combined with immediate release coating of simvastatin. The drug release behavior of nicotinic acid was very close to reference product, manufactured by Abbott, in different dissolution media & simvastatin release was very rapid than that of reference product.

Yam Noymi V; Shivanand Padmaja; Kimbel Rhea et al., (2005) US2005/0136108 [Yam Noymi V et al. (2005)] disclosed a controlled release dosage form as bilayer or trilayer capsule shaped tablet comprising a compartment having semi permeable wall, an exit orifice, an swell-able layer located within the compartment away from exit orifice, a drug layer adjacent to exit orifice, the drug was characterized by high dosage, low solubility, poor dissolution rate. The composition was having a disintegrants and no surfactant to release as an erodible solid over a extended period of time at stepwise, increasing rate.

Jenkins Scott A. et al., (2006) US2006/0121112 [Jenkins Scott A et al. (2006)] disclosed CR (controlled-release) pharmaceutical composition consists of: (A) an IR (immediate-release) component consists of about 5 mg to about 250 mg of topiramate which was released in the body within approx. 1 hour after administration; and (B) a DR (delayed-release) component consists of about 5 mg to about 250 mg of topiramate which was released in the body (the colonic region of GIT) over a period of time of about 6 hrs. to 24 hrs after administration. This formulation was osmotic delayed release matrix based pharmaceutical composition to release the drug in the colonic region.

Nghiem Tien et al., (2008) US2008/0292700 [Nghiem Tien et al. (2008)] disclosed a controlled release matrix tablet comprising: (a) Topiramate or its pharmaceutically acceptable salt as active ingredient; (b) a first intelligent polymer component; & (c) a second intelligent polymer component having reverse wettability characteristics to said 1st intelligent polymer component; where the first intelligent polymer component was more hydrophobic than the second intelligent polymer component; and the first and second intelligent polymer components constitute a substantially homogeneous matrix, wherein the topiramate or pharmaceutically acceptable salt was substantially homogeneously dispersed in the substantially homogeneous matrix.
- **Park Jin Woo; Shin Young Hee; Shin Kwang Hyun et al., (2007)**
  US2007/0224281 [Park Jin Woo et al. (2007)] disclosed a sustained-release topiramate preparation produced using double granules obtained by a process comprising the steps of granulating topiramate or a pharmaceutically acceptable salt using a solid dispersant by a solid dispersion method (first granulation); and further granulating the resultant granules using a release-sustaining material by a dry or a wet granulation process (second granulation).

  [Liang Likan et al. (2008)] filed by Supernus Pharmaceutical disclosed method of preparing a SR formulation of topiramate, comprising an ER component and an optional IR component, wherein at least said XR component was contained in at least one population of beads characterized by its own rate of drug release, said method comprising: forming at least 1 population of topiramate containing beads; coating each population of beads with its own release controlling coating; curing said coating in a curing apparatus for specific period of time to produce the release controlling coating specific for each bead population & incorporating the beads of every population into formulation in specific amounts determined according to a pre-determined release profile.

- **Mandal Jayanta Kumar; Pandya Nitesh Nalinchandra et al., (2009)**
  US2009/0196923 [Mandal Jayanta Kumar et al. (2009)] disclosed once-a-day CR oral formulation of anti-epileptic/ anti-convulsant drugs in capsule dosage form filled with IR & CR tablets, consists of: A) IR tablets provide quick therapeutic effect & consists of: i) Tablet core containing API & pharmaceutical excipients. Optionally coated with, ii) Film coating consists of polymers & pharmaceutical excipients. B) CR tablets having drug release at pH 5 to 6 of GIT comprising: i) Tablet core of API & pharmaceutically acceptable excipients. ii) Film coating consists of film forming polymer & pharmaceutical excipients; & iii) CR coating comprising CR polymer able to drug release at pH 5 to 6 in GIT & pharmaceutical excipients. C) CR tablets able to drug release at pH 6 to 8 in GIT comprising: i) Tablet core of API and pharmaceutical excipients. ii) Film coating comprising of polymer & pharmaceutical
excipients; & iii) Control release coating comprising CR polymers suitable to release the drug at pH 6 to 8 of GIT & pharmaceutical excipients.

- **Almarsson Orn; Remenar Julius et al., (2003) US6699840** [Almarsson Orn et al. (2003)]
  invented a pharmaceutical composition comprising a pharmaceutically acceptable topiramate salt, a pharmaceutical polymorph, dehydrate, co-crystal, anhydrous, solvate, hydrate or amorphous form & a pharmaceutical excipient or diluent.

- **Chen Andrew Xian; Kigin Patricia D., (2008) US2008/0220079** [Chen Andrew Xian et al. (2008)]
  disclosed a composition consists of: (a) an API; (b) a hydrophobic agent; & (c) a spheroidizing agent; wherein (i) the composition was in pellets form, (ii) the composition has an in-vitro dissolution profile of the API measured by US. Pharmacopoeial basket dissolution method of at most about 90% of the API released after 2 hours & (iii) the in-vitro dissolution profile did not require the SR barrier coating on multi-particulate beads/pellets.

  disclosed a process for preparation of a modified release dosage form consisting metformin hydrochloride prepared by using dual retard technique to control the release of metformin, wherein the said dual retard technique was a combination of a matrix formulation and a reservoir formulation, said process comprising: a) preparing micro matrix particles consisting of metformin hydrochloride and one or more hydrophobic release controlling agents & b) coating said micro matrix articles with one or more hydrophobic release controlling agents of waxes selected from carnauba wax, beeswax, microcrystalline wax & ozokerite; fatty alcohols selected from stearyl alcohol, cetostearyl alcohol, & myristyl alcohol, fatty acid esters selected from glyceryl mono-stearate, glycerol monooleate, glycercyl palmito-stearate, glycercyl behenate, acetylated mono-glycerides, tristearin, tripalmitin, cetyl esters & hydrogenated castor oil.

- **Barker Nicholas; Wolfe Janet L., (2006) US2006/0198815** [Barker Nicholas et al. (2006)]
  invented sustained delivery pharmaceutical compositions consisting a solid ionic complex of a pharmaceutically API & an ionic macromolecule were described by the present invention. The pharmaceutical compositions of present invention allow for
loading of high concentrations of API & for delivery of a API for prolonged periods of time, e.g., one month, after administration. Methods for preparing these pharmaceutical compositions, as well as methods of using them to treat a subject were also provided.

- **Nangia Avinash; Verma Daya D.; Jacob Jules., (2008) US2008/0085306** disclosed a pharmaceutical composition of topiramate, where the topiramate was micronized to get a median particle size range of 0.5-50 microns or a pharmaceutical formulation of topiramate, comprising 3 regions: a) 1st & 2nd regions, each consists of a CR or XR (CR/XR) topiramate & an IR topiramate component; & b) a 3rd region completely free of topiramate & consisting a pharmaceutical excipient; wherein the 3rd region separated the 1st region from the 2nd region.

- **Najarian Thomas; Tam Peter Y.; Wilson Leland F., (2009) US2009/0304789** disclosed a CR composition for treating obesity, diabetes or related condition in a subject containing an therapeutic effective concentration of topiramate; microcrystalline cellulose and methylcellulose.

- **Cardinal John R; James Jack Lawrence. et al., (2010) US2010/0159001** disclosed a matrix-forming, sustained-release pharmaceutical formulation comprising: i) an effective amount of at least one drug substance; ii) at least one water-swellable, pH independent polymer; iii) at least one anionic, pH-dependent, gel-forming copolymer; and iv) at least one polymer chosen from the group of a cationic polymer and a hydrocolloid, the formulation of which was substantially free of non-aqueous solvent.

- **Remon Jean Paul; Debuinne Ann. (2002) WO2002/17877** invented a controlled release pharmaceutical pellet composition based on at least one drug having low solubility under acidic conditions, wherein the drug constitutes at least 0.5% by weight and less than 40% w/w of the composition, the said composition being able to provide a release of at least 75% of the said drug within 45 minutes in phosphate buffer pH 6.8, and the said composition further comprising a blend of microcrystalline cellulose & one swell-able polymer in respective amounts.
such that the ratio of the polymer to microcrystalline cellulose in the mixture was more than 5:100 and up to 30:100.

### 2.1.13 PATENTED LITERATURE

Recently filled patents on extended release multiparticulate drug delivery systems suggest the growing interest of formulation scientist in developing such multiparticulate dosage forms. Following table 9 briefly discusses few such patents.

**Table 9: Recently filled patents on extended release multiparticulate drug delivery.**

<table>
<thead>
<tr>
<th>Patent No.</th>
<th>Inventors</th>
<th>Abstract</th>
<th>Ref No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 7,820,203 B2</td>
<td>Gopi Venkatesh, James Clevenger</td>
<td>A dosage form, such as capsule, for delivering a skeletal muscle relaxant active, such as cyclobenzaprine hydrochloride, into body in an ER or SR fashion comprising one or more populations of drug containing multi-particulate.</td>
<td>Gopi V et al. (2010)</td>
</tr>
<tr>
<td>US 7,410,978 B2</td>
<td>Padmanabh Bhatt, Argaw Kidane, Henry Flanner, Arash Raoufinia</td>
<td>A pharmaceutical formulation of trospium, which upon oral consumption to patient, provide a steady state blood conc. of trospium with a min. ( C_{\text{min}} ) &amp; max. ( C_{\text{max}} ) blood conc. of about 0.5 to 2.5 ng/ml &amp; 2.0 to 6.0 ng/ml respectively.</td>
<td>Kindane A et al. (2008)</td>
</tr>
<tr>
<td>US 8,168,209</td>
<td>Gregory Went, Timothy Fultz,</td>
<td>The invention provides methods and compositions for administrating an NMDA</td>
<td>Went GT et</td>
</tr>
<tr>
<td>B2</td>
<td>Seth Porter, Laurence Meyerson, Timothy Burkoth</td>
<td>receptor antagonists (e.g., memantine) to a subject.</td>
<td>al. (2012)</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>US</td>
<td>Arthur Deboeck, Francis Vanderbist, Antonio Sereno</td>
<td>An oral Tramadol containing pharmaceutical composition designed for once daily administration, which contains Tramadol or its salt, providing in vivo, a time of Tramadol peak plasma concentration ($T_{\text{max}}$) of greater than 10 hours, and peak Tramadol plasma concentration obtained ($C_{\text{max}}$) which are less than three times the plasma concentration obtained 24 hours after administration ($C_{24h}$) of such formulation.</td>
<td>Deboeck A et al. (2010)</td>
</tr>
<tr>
<td>US</td>
<td>Robert Noack, John Heimlich, Ernest Lee</td>
<td>The present invention is directed to an extended release multiparticulate formulation of a therapeutic agent, wherein coated core multiparticulate particles of the therapeutic agent are overcoated with a binder-dispersing agent, such as povidone or cross-povidone. The invention is also directed to compressed tablets of the extended release multiparticulate formulation of the invention, and to a method of oral administration of compressed tablets of clindamycin to a subject to treat or prevent a gram-positive bacterial infection therein. The binder-dispersing agent in the formulations of the present invention ensure that compressed tablets formed therefrom will remain intact through oral administration, and dissolve</td>
<td>Noack R et al. (2004)</td>
</tr>
<tr>
<td>US</td>
<td>Nobert Otterbeck</td>
<td>An orally administrable pharmaceutical multi-particulate preparation for the treatment of intestinal tract is disclosed, which consists a core and an enteric coating polymer, the core including, as a pharmaceutical active compound, amino-salicylic acid or a pharmaceutically tolerable salt or a derivative.</td>
<td>Otterbeck N (2013)</td>
</tr>
</tbody>
</table>
shortly thereafter, enabling the multiparticulates to release the therapeutic agent contained therein over an extended period of time.

| US 7,931,915 B2 | Manesh Dixit, Xiu Xiu-Cheng, Chih Ming, Avinash Nangia | A CR dosage form of venlafaxine that consists of an immediate release pellet and an extended release pellet. | Dixit M et al. (2011) |

### 2.2 DISORDER REVIEW [McNamara JO (2006)]

Epilepsy is a chronic non-communicable disease of brain that affects population of all ages. The epilepsies are very common & frequently degenerative disorders, affecting around 50,000,000 population worldwide. Nearly 80% of population having epilepsy are available in developing countries. Epileptic seizures often causes a silent degenerative consciousness, leads to individual at risk of own injury & often inter-fare with education & employment. People having epilepsy & their families can suffer from stigma & discrimination in many parts of the world. Currently, available drugs reduces seizures only but neither effective prophylaxis nor cure is possible. Drug candidate “Topiramate” of interest can be used to treat patients having partial seizures or generalized tonic-clonic seizures. Following table explains various type of epilepsy along with its feature & recently developed antiepileptic drugs.

### 2.3 DRUG REVIEW

#### 2.3.1 MICRODETAILS OF THE TOPIRAMATE [McNamara JO (2006)]

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Formula</td>
<td><img src="https://example.com/struct.png" alt="Structural Formula" /></td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Hetero Drugs Ltd</td>
</tr>
</tbody>
</table>
Ph.D Thesis (Pharmaceutical Sciences)

Manufacturing site | Hyderabad  
Batch No./Lot No. | TA0560413  
Chemical (IUPAC) Name | 2,3:4,5-bis-O-(1-Methyl-ethylidene)-β-d-fructo-pyranose sulfamate.  
Molecular Weight | MW: 339.36  
Appearance, color, odor and taste | White to off-white crystalline powder with bitter taste  
Polymorphism | Not available  
Solubility | It is freely soluble in acetone  
pH (1% solution) | 5.51  
pKa | 11.09  
Melting point | 125.84 °C  
Storage Conditions | Tightly  
BCS Class | Class II  
LogP/Hydrophobicity | 1.29  
Activity | Experimental Observations  
% LOD (at 105 for 5 minutes) | 0.59 %  
BD | 0.217 gm/ml  
TD | 0.307 gm/ml  
Angle of repose | 47.73°  
Compressibility index (C.I)% | 29.316  
Hausner ratio (H.R) | 1.415  

2.3.2 PHARMACOKINETIC PROPERTIES [http://www.drugbank.ca/drugs/DB00273, http://www.drugs.com/pdr/]

Topiramate has a long plasma half-life.

Absorption

Topiramate is fastly absorbed. After oral intake of 100 mg of topiramate to healthy volunteer, a peak plasma conc. (Cmax) was achieved within 2 to 3 hours. It is having relative bioavailability of 80% as compared to oral solution. There is no food effect on the bioavailability of topiramate.

Distribution

It was found that 13-17% w/w of drug is bound to plasma proteins.

Metabolism

Topiramate drug is not metabolized & elimination was unchanged via urine.

Elimination
In humans, the main route of elimination of unchanged drug & metabolites is through the kidney.


**Therapeutic indications:** Topiramate is an anti-epileptic medicament indicated for mono-therapy of epilepsy/convulsion; primary mono-therapy in patient’s more than 2 years of age with seizures.

**General pharmacology:** Topiramate retard voltage modulated Na\(^+\) currents in cerebellar granule cells. Topiramate activates a hyperpolarizing K\(^+\) current, enhances postsynaptic GABA\(_A\)-receptor currents.

**Route of administration:** Oral route

**Dosage and administration:** 25 to 50 mg per day, the dosage should be increased to weekly interval to an effective dose by increments of 25-50 mg. The max. daily dose is 200-400 mg per day in two divided doses.

**Drug-drug interaction:** Topiramate is reactive with various antiepileptic drugs such as phenobarbital, lamotrigine, primidone, phenytoin, carbamazepine, valproic acid. It also interacts with CNS depressants, oral contraceptives, metformin, lithium & other carbonic anhydrase inhibitors.

**Adverse drug effects:** It includes psychomotor slowing, weight loss, fatigue, dizziness, nervousness, confusion & difficulty with memory etc.

**Contraindications:** None

2.4 EXCIPIENTS REVIEW

The properties of final dosage forms in terms of bioavailability and stability depends on the excipients, its conc. & interaction with API & other inactive ingredients, hence the choice of excipients is much more important aspect in dosage form development. The profile of excipients which are used in formulation development is as follows.

2.4.1 SUGAR SPHERES [Handbook of Pharmaceutical Excipients (2009)]
Pharmaceutical Sciences

Pharmacopoeial references:
BP, PhEur, USP-NF

Functional category
Tablet and capsule diluents and/or carrier

Description
US. Pharmacopoeia mentioned sugar spheres as approx. spherical granules of a labeled-size range with a uniform diameter & containing NLT 62.5% and NMT 91.5% of sucrose, as calculated on anhydrous basis.

Typical properties

<table>
<thead>
<tr>
<th>Particle size distribution</th>
<th>The following mentioned sizes are available from various suppliers:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#45–60 ASTM mesh (250–355 µm), #40–50 ASTM mesh (300–425 µm),</td>
</tr>
<tr>
<td></td>
<td>#35–45 ASTM mesh (355–500 µm), #35–40 ASTM mesh (420–500 µm),</td>
</tr>
<tr>
<td></td>
<td>#30–35 ASTM mesh (500–600 µm), #25–30 ASTM mesh (610–710 µm),</td>
</tr>
<tr>
<td></td>
<td>#20–25 ASTM mesh (710–850 µm), #18–20 ASTM mesh (850–1000 µm),</td>
</tr>
<tr>
<td></td>
<td>#16–20 ASTM mesh (850–1180 µm), #14–18 ASTM mesh (1000–1400 µm).</td>
</tr>
</tbody>
</table>

Applications:
Sugar spheres are mainly utilized as inert cores particularly in multi-particulate of SR/ER/XR formulations.

Note: Physico-chemical Properties of all other excipients such as hypromellose, Povidone, talc, triethyl citrate, simethicone, ethyl cellulose, Eudragit RS30D, Eudragit L30D55, Eudragit S100, Cellulose acetate, Polyethylene glycol, sodium benzoate etc are mentioned in “Hand book of excipients”.

2.5 WORK PLAN AND METHODOLOGY:

A flow of work would be in following direction:

1. Literature review
   Literature search for related information will be a continuous process from starting till the finalization of the research activity. The sources would be Books,
Standards references like IP, USP, Ph.Eur, BP, WHO guidelines etc., Journals including National and International, Patent applications and published patent and Internet.

2. **Design of strategy & Intellectual Property Clearance**
   Based on the literature search, all the available related formulation designs will be critically studied and will be designed out of scope generic economic modified release formulation having defined therapeutic benefit to the targeted patients.

3. **Procurement of actives, raw material, Packaging Material**
   Reliable sources for all the raw materials, active pharmaceutical ingredients (API) and packaging materials will be identified to get Pharmacopoeial standard materials and will be store in the proper temperature and humidity condition maintained storage area.

4. **Preformulation studies**
   Preformulation studies will be planned with an intention to get the critical information about the API, Raw materials characteristics and their interaction at stress condition. This experiment is planned to predict the stability of the product on long-term storage condition in real time situation.

5. **Development of analytical methods**
   Quality of the finished product is always depends on the accurate, precise and stability indicating analytical test method for that product. So, at the initial stages of formulation development, all the required critical analytical test methods such as Assay, Related substances and Bio-relevant multimedia dissolution and quality control (QC) dissolution test methods will be developed.

6. **Formulation development trials (Bench scale development)**
   Based on the Intellectual Property Clearance, various out of scope formulation design strategy will be planned. Then formulation development trials will be taken as per the design plan and fine adjustment of the composition will be done based on the dissolution test results.

7. **In-vitro dissolution studies**
Developed formulations will be screened in Bio-relevant multimedia dissolution condition and final formulation will be tested in QC dissolution condition initially and during complete stability analysis.

8. **Optimization trials (Lab-scale development)**

Based on the initial formulation development trials and their evaluation, qualitative formulation composition will be selected. Final qualitative and quantitative formula composition and manufacturing process will be decided based on the optimization trial results.

9. **Reproducibility trials**

Reproducible batch will be taken with final qualitative and quantitative composition and will evaluate them to check the consistency of the result with previous batches having same qualitative and quantitative composition.

10. **Stability studies & Packaging evaluation**

Initially bench scale development batches with two different packaging systems will be kept in accelerated stability condition (40°C/75%RH) for 3 months to find out stable composition and suitable packaging systems.

11. **Scale up & Process evaluation**

Best stable composition will be scale-up to 10 times than the lab-scale batches with an intention to set-up the tentative process parameter at bigger scale to get the product of desired quality. Process evaluation batches will be taken to check the effect of various process parameters at each stage of product development. So, that the operating range of the process will be finalize to get final product with desired quality.

12. **In-vivo Pharmacokinetic studies**

Finally, after getting satisfactory in-vitro analytical results of final scale-up batch with 1 month accelerated stability data, an in-vivo bioavailability study of single unit modified release drug delivery system of topiramate with two immediate release dosage form of topiramate (Topamax capsule) will be planned with an intention to check the therapeutic benefit of the modified release dosage form of the topiramate.
Proposed Technologies for formulation development:

1. **Modified Release Pellets by extended release coated bead:**

   ![Diagram of modified release pellets process](image)
2. Modified Release Pellets by Immediate release and Extended release coated bead:

Sugar pellets → Drug layering → ER Coating → Drug Layering

MR pellets in Capsule

Moisture protective coating
MCC pellets
Drug layering
ER Coating
Drug layering
Moisture Barrier coating