Chapter 1: Introduction
1.0 INTRODUCTION:

1.1 What is Epilepsy

Epilepsy is chronic neurological disease demonstrated by pattern of repeated seizure. The term “Epilepsy” originated from Greek word “epilepsia”, that means "seizure". These seizures are electrical impulses fired by nerve cells of brain at a rate of max. four times higher than normal rate which leads a sort of strong electrical impulse in the brain. Probable causes of seizures include injuries of head, brain tumor, and poor development of the brain cell, genetic and infectious disorder but in most of the cases, no causes are identified. Proper medication helps to control seizures for most of the patients.

About 50,000,000 people in the world having epilepsy & approx. 90% of the population suffering from epilepsy are discovered in developing countries. 70% of time, Epilepsy responds to its treatment and about three fourth of the affected people in developing countries do not receive the proper treatment. Emerging of new affected patients appear most commonly in child & elderly patients. Another cause is a consenescence of brain surgery, epileptic/ convulsant seizures can observed in recovering patients. Epilepsy/convulsion is mainly controlled with medication, it can’t be completely cured. Whereas, more than 30% of population posses epilepsy can’t have seizure control with the best available therapy. Surgical procedure required in complicated cases. Epilepsy is not only a single disease but also instead it is symptomatic with various diversified symptoms involved in episodic abnormal electrical activity in the brain. Antiepileptic drugs are separate group of medicines used in the treatment of epileptic seizures. Main role of anti-epileptic is to reduce the successive firing of the neuron that starts seizures. Anti-epileptic drugs are also known as anticonvulsant or anti-seizure drugs.

The major targets for the marketed anti-epileptic products are voltage gated Na+ (sodium) channel & parts of GABA receptor (GABA\textsubscript{A} receptor, GAT-1- GABA transporter). Other
considerable targets are voltage gated Ca+ (calcium) channels, SV2A & α2δ [http://en.wikipedia.org/wiki/Anticonvulsant (2011)].

Lots of research from longtime was tried to develop a single medication for the treatment of all type of epilepsies but the causes of epilepsy are extremely diverse and for the treatment of Epilepsy, it should be according to the type of epilepsy. [http://en.wikipedia.org/wiki/Automatism (medicine) (2011)].

Drug delivery defined as a very broad range of systems used to deliver therapeutic agents into human body. The aim of any dosage form is to deliver therapeutically effective concentration of active component to the appropriate site of action in the body to get immediately & then maintain the desired drug concentration in the blood. Means, any drug delivery system could deliver therapeutic agent at a rate predicted by the requirement of the body over a pre-define period of time for treatment. Importantly goal of any drug delivery system (DDS) are spatial & temporal release of medicament. Spatial delivery refers to target a medicament to target organ or tissue, whereas, temporal delivery aim to controle the rate of drug release to the target organ. Lots of research had been done towards oral-DDS to satisfy spatial & temporal aspects of various drug delivery system. Additionally, some recent approaches which are under investigation, those may help spatial orientation also [Jantzen, GM et al. (2002)]. 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 existing drug can give new life to drug by maximizing its performance and enhanced market differentiation. With the patient centric approach and growing need for optimization of therapy, controlled release technologies providing tailor-able release profiles become more important especially for drugs for chronic use or with a narrow therapeutic index.

Controlled release (CR) defined as a technique or approach to deliver active entity is made available to a specified target at a rate and extent designed to achieve an intended
results. Oral extended release dosage forms contribute largest share among all other routes as it implies versatility, comfort of administration and most importantly, it improved patient compliance. Oral CR drug delivery system is a dosage form that controls the drug release into the absorption site in the gastrointestinal tract (GIT). It controls the drug absorption rate to achieve the desired plasma profiles defined by the steady-state pharmacology. A typical CR dosage form is designed to deliver a approx. constant drug levels in blood plasma with less fluctuation by slow release of drug over an prolonged time. Controlled release systems are sometimes referred as extended or sustained release systems. Main motives for formulating controlled release products are not only to increase clinical value of drug but also to achieve commercial benefits. Commercial benefits include extended product life by product differentiation, market expansion and patent extension.[Venkatraman S et al. (2000)].

Improved drug delivery systems may potentiate pharmaceutical dosage form’s therapeutic and market value, it can distinguished one product from its competitors. Oral route of finished product (FP) delivery is the most preferred mode of delivering FP for systemic action of solid oral dosage forms. Pharmacologically, oral dosage form improves the pharmaco-economics of drugs by lowering side effects, improving therapeutic effect, efficacy, safety, easy to administer & compliance to patient. New drug delivery systems make pharmaceutical product much easy to patients by easing the dosing regimen & improve the oral administration with reducing dosing frequency. These improvements booster patient compliance and quality of life with reduce costs. Commercially, drug delivery technologies provide better life to existing medicine with new & improved therapeutic benefit with commercial advantage. The drug's market value can be sustained by prolonged the API’s life cycle by making new and effective drug delivery systems; a) To give a product a competitive advantage. b) To enable or accelerate market entry. c) NDDS (Novel drug delivery systems) can prolong a product's patent validity. d) Develop an improved product. [Baichwal Anand R et al. (2001)].

1.2 Oral Anti-epileptic Modified Drug Delivery System (MDDS ®) Technology:
Modified Release system also known as SR (Sustained-release), ER (extended-release) or CR (controlled-release) technology designed to control the drug delivery for prolonged period of time. Modified release (MR) drug delivery system is defined by USP as “dosage form whose drug release rate with time and/or location are chosen to achieve clinical or patient compliance that are not offered by any conventional dosage forms, whereas one of the class of modified release (MR) dosage form is an extended-release (ER) dosage form defined as a system which allows two-fold lowering in the dosing frequency and increase in the patient comfort or therapeutic benefit. The U.S. Pharmacopoeia refers that the terms controlled release; prolonged release & sustained release are inter-changeable with extended release or modified release term. The rational for the MDDS technology is as follows;

1) The main objective of this technology is to get steady state blood conc. or tissue distribution which is pharmacologically required & non toxic for prolonged period of time.

2) This goal can be achieved by increasing the drug’s bioavailability.

3) This is achieved by increasing the GIT absorption of target drug.

4) Patient compliance for ease to administer as once a day dosage frequency.

5) Protecting the stomach from the exposure of the active compound.

Over solid oral dosage forms, multi-particulate drug delivery system (DDS) have achieved major pharmaceutical market occupancy, because of their superior therapeutic performance, possibility of various formulation options, advances made in the multi-particulate DDS. Multi-particulates distributes more homogeneously in the GIT (gastrointestinal tract), thus resulting uniform drug distribution & absorption, hence it minimizes patient to patient variability. Multi-particulates reduces the risk of local irritation and possible lodging in intestinal of non-digested polymeric material upon chronic dosing leading to superior clinical performance. Multi-particulate pellet units can be formulated with different drug candidate for various application forms such as conventional capsules, pellets compressed to tablets (Multi Unit Particulate System-MUPS) or pellets for oral suspension. Advancements in multiparticulate drug delivery system such as innovative pelletization techniques from GLATT, coating
technology from Huttlin and coating systems enable possibilities to achieve tailored drug release patterns\textsuperscript{[Srivastav S et al. (2010)]}.

1.3 Problems with conventional drug therapy:
- When dosing interval is not adjusted as per the biological elimination half life of the drug, large peaks & troughs in drug concentration may be observed.
- The drug concentration in blood may not be between therapeutic window at initial time.
- Patient non compliance with multiple dosing regimens.

Immediate Release Vs. Controlled release formulations:
As compared to IR (immediate release) formulations, CR (controlled release) formulations can reduce the frequency of dosage administration which may require to maintain clinically effective plasma drug conc. Additionally, by producing constant blood concentration of drug, such formulations can reduce the major changes in plasma drug conc. between subsequent doses. With controlled release dosage forms, the time to reach peak plasma concentration is extended because the amount of drug released at once is not as high enough as it with immediate release formulation.

1.4 Regulation for Oral Modified release Drug Delivery System (MDDS)
FDA of USA introduced regulations which governs bioequivalence & in-vitro vs. In-vivo correlations for CR (controlled-release) drug products. Pharmacokinetic property evaluations of drug product involves: relative bioavailability after a single dose; relative bioavailability after multiple doses; food effect; dose proportional which includes unit dosage strength proportional; unit dose bioequivalence study (various strengths); in-vivo vs. in-vitro drug release comparison; pharmacokinetic & pharmacodynamic (PK/PD) behaviors.

Over this ground, pharmaceutical manufacturers are identifying that DDS are a powerful marketing tool to distinguish products from other competitor and increase product life cycles, that leads to subdue many marketing challenges. Delivery of a drug with a novel &

Following list of drugs were converted from immediate release (IR) formulation to ER (Extended Release) formulation as a part of product life extension. This in turn extends the life of the product. Hence with this background it is hypothesized to develop controlled drug delivery of some anti-epileptic drugs. Following list of drug provides an overview on life cycle management of some of the existing drugs. It can be inferred that most of the drugs are being converted from multiple dosing to single CR dosing.

**Table 1: Drugs used in Partial Seizures and Generalized Seizures**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Tablets, Capsules (ER)</td>
<td>Oral, Oral</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tablets, Chewable Tablets, Suspension, Capsules (ER)</td>
<td>Oral</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Tablets, Orally disintegrating Tablets</td>
<td>Oral</td>
</tr>
<tr>
<td>Clorazepate dipotassium</td>
<td>Tablets, Capsules</td>
<td>Oral</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Tablets, Injectable, Concentrate</td>
<td>Oral, Parenteral</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Tablets (DR), Tablets (ER), Capsules (DR pellets)</td>
<td>Oral</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Capsules, Syrup</td>
<td>Oral</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Tablets, Suspension</td>
<td>Oral</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tablets, Capsules, Solution</td>
<td>Oral</td>
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Most of the companies, already present in the antiepileptic market include Abbott Lab., GlaxoSmithKline, Cephalon, Johnson & Johnson (J&J), Sanofi-Aventis SA, Shire, Novartis AG, Pfizer and UCB Pharma. Pfizer having the largest market share in the antiepileptic market with 26% for its two products, Neurontin and Lyrica ($2.96 billion combined sales in 2008). Antiepileptic drug market of all Innovators are threatened by generic competition which has elevated dramatically after patent expirations of several major branded antiepileptics drug products. Generic drug products are generally 40-60% cheaper than branded drug products, this could slow down prices and decrease sales achievable by branded antiepileptics drug products. [http://www.wikinvest.com/wiki/Antiepileptic_Drug_Market (2011)].

Recent anti-epilepsy drugs (AEDs) are better acceptable than the older AEDs. They often cause less sedation & require less monitoring. Specific choices of AED depends on individual patient’s condition & particular adverse effects of the AED. None of the AEDs has emerged as superior to either old standard or newer AED drugs. [http://www.umm.edu/patiented/articles/what_specific_medications_used_epilepsy_00044_7.htm (2011)].
Almost every antiepileptic drugs can increase the risks of suicidal thinking & behaviour. Some of the newer AEDs are as follows; [http://www.unm.edu/patiented/articles/what_specific_medications_used_epilepsy_000044_7.htm (2011)].

Table 2: Newer anti-epileptic drug

<table>
<thead>
<tr>
<th>Valproate and Divalproex Sodium</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Barbiturates (Phenobarbital and Primidone)</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>Ethosuximide and Similar Drugs</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Clonazepam and Similar Drugs</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Tiagabine</td>
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</table>

Present work was an attempt to develop extended release reservoir based pellets to be filled in capsules of an antiepileptic drug using fluidized bed processor bottom spray assembly (wurster technology) and compare it with a reference product.

1.6 Problem on hand (Background of the Present Research):

Present research shall be continue with Topiramate API as one of the newer antiepileptic drugs. Topiramate is a sulfamate substituted mono-saccharide class of drug which is available as immediate release drug product with brand name, TOPAMAX® from Ortho-McNeil Pharmaceutical Inc., U.S.A. as immediate release tablet and sprinkle capsules, had been approved for use in the indication of epilepsy, as secondary therapy with partial onset seizures or primary generalized tonic-clonic seizures, & prescribed for prevention of epilepsy &/or migraine. [http://www.rxlist.com/script/main/art.asp?articlekey=3285, http://www.topamax.com/tools-resources--prescribing-information.html].

In the therapy of epilepsy / convulsant, recommended dose of Topamax® is 400 mg per day as single or divided doses. In case of adult patients having epilepsy, starting dose of the treatment is 25-50 mg/day, then the dose need to evaluate in an increments of 25-50 mg per weekly intervals to achieve recommended dose. Side effects of administration of immediate release Topamax® include ataxia, dizziness, abnormal vision, difficulty with memory, speech disorders, psychomotor slowing, paresthesia, renal tubular acidosis, acute myopia, diplopia, renal calculi (kidney stones), hepatic failure, pancreatitis and
secondary angle closure glaucoma

However, topiramate has a long elimination T_{1/2} (half-life) of 21 hours in body, it has not been prescribed as a once daily-dose because of severe side-effects due to peak plasma conc. of the drug when administer in high doses. Whereas Topamax® is prescribed in multiple doses, usually as BD (twice-a-day). Taking medicine in this manner by patient is tedious & patients may forget to take their medicine in prescribe frequency. Each administration of a dose is associated with a peak & valley in plasma concentrations of API vs. Time profile. The instability in blood concentration is associated with the peaks and valleys of blood plasma concentration of the drug which are not acceptable. Hence, there is a strong requirement for a novel pharmaceutical product of topiramate, which minimizes or eliminates the adverse effects, related to peak fluctuation in plasma conc. of the drug with time, preferably novel formulation can be administered in once-daily regimen to improve patient comfort and efficacy.

It is an intention of this research proposal to satisfy the unmet need of the anti-epileptic disease area to provide better patient compliance by selecting molecules which has significant effect. Topiramate is selected here as one of the Anti-epileptic drug (AED) to focus of this research proposal. Topiramate is similar in therapeutic properties as that of phenytoin & carbamazepine. It is effective & safe for the treatment of wide variety of epileptic seizures in adults & children.

Topiramate is one of the drugs belonging to the class of antiepileptic drugs used in treatment of epilepsy and migraine. For an effective therapy for these chronic indications, drugs have to be delivered at a controlled or modified rate with minimal fluctuations in the plasma concentration for longer duration. Various technologies can be developed to achieve this; the objective of this research project is to design and develop a generic formulation of single unit oral modified release drug delivery technology comprising of
loading and maintenance dose of drug for delivering of therapeutic conc. of drug throughout the GI track.

A NDA application for formulation of topiramate extended release oral capsule was under review and approved by USFDA on 16th August 2013. The branded product of the same named “Trokendi XR” is available in the USA market from September 2013 onward with exorbitant price tag, the innovator of this product is Supernus Pharmaceuticals Inc. Innovator uses multiple bead technology such as immediate release bead population, first extended release bead population and second extended release bead population in their extended release dosage form which offers sustained and continuous delivery of drug for 24 hrs. In order to reduce the cost of the product and to provide a cost effective alternative medicine, a generic product is highly desirable and since the technology is patented, there is a need to develop for a different technology which behaves similarly as that of the innovator product at in-vitro and in-vivo conditions. Strategies were chosen as the innovator profile had an initial slow release followed by a faster profile maintained over 24 hours.

1.7 Importance of the Present Research:
1. Generic drugs are generally cost effective than reference product, hence patients in need can afford to buy the medicine when there are no medical insurance coverage for the patient.
2. If Government is paying the prices for medicine of insured patients, the generic drugs will be very cost effective for the Government also.
3. Innovatory company can not keep the monopoly in the market if any alternate generic bio-equivalent and stable pharmaceutical product is available in the market, hence cost of the reference product also will be available at comparatively lesser price.
4. Research based pharmaceutical companies are encouraged to focus on finding newer & better medicines that have patent protection to make generic of the same for helping patients, governments and its own company growth.
5. Generic have a safe and inexpensive alternative to the brand name drugs.
6. Generic products are cost effective, as generic drug manufacturers do not have to
spend as much as branded drug manufacturers spent for extensive research and development, sales and marketing.

1.8 Scope of the project:
In the present research, an attempt has been made to formulate a Modified release drug delivery system (MDDS) of the Topiramate in order to release the drug at sustained rate for a specific time duration for the treatment of Epilepsy which is pharmaceutically equivalent to the reference product (Trokendi XR) with the help of following step by step approach:
1. To formulate generic version of reference product of Trokendi XR 25mg, 50mg, 100mg & 200mg
2. To do Reference product’s patent evaluation
3. To Choice of excipients for Stable and Bio-equivalent Pharmaceutical formulation of generic version.
4. To perform API characterization and pre-formulation studies
5. To develop analytical method mainly for assay, related substances and dissolution test
6. To perform Reference product evaluation
7. To develop Prototype formula composition and evaluate various manufacturing feasibility
8. To finalize Formulation design and Manufacturing process
9. To optimize Formulation composition
10. To evaluate Reproducibility of batch
11. To optimize and set Scale-up process parameter for manufacturing feasibility
12. To perform In-vivo pharmacokinetic study for evaluation of bio-equivalence with respect to reference product.