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

- **Larry Baum et al., (2011)**[^10] mentioned that Epilepsy is the most common serious chronic neurological disorder and one-third of patients do not respond to all available anti-epileptic drugs due to over-expression of P-glycoprotein (P-gp) in endothelial cells of the blood-brain barrier (BBB) 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 structure-activity-relationship (SAR) models.

- **Willmore James L. et al., (1998)**[^11] reported that occurrence of epilepsy is more in the elderly population. Dose related adverse effects of the old standard AEDs are common in elderly patients because of physiological changes (low renal blood flow, hepatic volume and function and fat to lean ratio of the body composition). Newer generation of AEDs having no enzyme induction effects and renal route of excretion are more favorable to use in elderly patients.

- **Ramadan N. M. et al., (2006)**[^12] 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)**[^13] 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)**[^14] disclosed that differences in the host factors such as 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)**[^15] investigated the scientific rational use of AEDs in the treatment of neuropathic pain and migraine based on the clinical investigation of 5 newer AEDs such as gabapentin, lamotrigine, oxcarbazepine, topiramate and zonisamide and had concluded that newer
AEDs are having better tolerability and fewer drug-drug interactions compared to tricyclic antidepressants.

- **Mike Namaka et al., (2004)** [16] 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 respond to the treatment with at least three different drugs of the same class, then second drug class may be tried. If patients do not respond to monotherapy with either first or second line drug they may respond to combination therapy. Thus treatment protocol can be individualized depends on each patent’s response.

- **Walker M. C. et al., (1995)** [17] 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)** [18] investigated the preventive treatment options for migraine with different medication groups and their mechanism of action to reduce the frequency, duration or severity of migraine attacks. Finally he concluded the preventive medications with the best-documented efficacy were the b-blockers, amitriptyline, divalproex and topiramate. Generally, choice of medication is made based on the proven efficacy of a drug, the physician’s belief about medications not yet evaluated in controlled trials, the adverse effects of a drug, patient preferences on headache profile and the presence or absence of coexisting disorders.

- **Michelle K. Bazil, (1997)** [19] compared pharmacokinetic properties, adverse effects and drug interactions of four new antiepileptic drugs such as felbamate, gabapentin, lamotrigine and topiramate. It appears that they have a broad spectrum of action in seizure control but felbamate having serious adverse effects. Lamotrigine and topiramate have limited interactions compared with older agents. The incidence of adverse effects decreases with sustained-release preparation of carbamazepine which in turn increases patient compliance. These recent advancement improved efficacy and decreased adverse effects for many patients with epilepsy.

- **Elizabeth J. Donner et al., (2006)** [20] compared the indications, mechanism of action, pharmacokinetics, adverse effects, and dosing of the new and old generation of anticonvulsant medications involved in the treatment of epilepsy in children and suggested that the newer drugs
having equal efficacy with better tolerability, pharmacokinetic properties, and side effect profiles as compared with the traditional drugs.

- **Stephen D. Silberstein et al., (2005)**[^21] assessed the clinical efficacy of topiramate as monotherapy for epilepsy and migraine prevention and described management of dosing, titration and adverse events.

- **Emilio Perucca, (1997)**[^22] described pharmacological and clinical review on topiramate as a new Antiepileptic drug including its adverse effects.

- **Michael A. Rogawski et al., (2008)**[^23] described three new molecular targets for several newer antiepileptic drugs such as α2δ, auxiliary subunits of voltage-gated calcium channels through which the gabapentinoids gabapentin and pregabalin exert their antiepileptic and analgesic actions; SV2A, a ubiquitous synaptic vesicle of glycoprotein that may prepare vesicles for fusion and serves as the target for levetiracetam and its analog brivaracetam (currently in late-stage of clinical development); and Kv7/KCNQ/M potassium channels that mediate the M-current, which acts a brake on repetitive firing and burst generation and serves as the target for the investigational AEDs retigabine and ICA-105665. Main mechanisms of all the new targets modulate neurotransmitter output at synapses and suggested presynaptic terminals as critical sites of action for AEDs.

- **Ali R Rajabi Siahboomi, (2003)**[^24] reported the approach to modified release (MR) oral drug delivery systems has changed from a line extension strategy to a clinically superior approach for marketed drugs as well as for new chemical entities. Main advantages offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects, dose dumping and enhanced bioavailability.

- **Shajahan Abdul et al., (2010)**[^25] suggested MR multiple unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. Final dosage form of multiparticulates could be single-unit dosage forms such as filling them into hard gelatine capsules or compressing them into tablets. They mainly discussed the issues of compaction of pellets into tablets and mechanisms involved during compaction of multiparticulates to produce multiple-unit pellet system (MUPS) or pellet containing tablets that could disintegrate rapidly into individual pellets in-vivo.

- **Emilio Perucca, (2009)**[^26] suggested rational design of extended release formulation of AEDs for clinical benefit apart from longer dosing intervals with minimizing fluctuations in serum drug levels.
Careful monitoring of clinical response and attention for dose adjustment is the prime need for all new extended release anti-epileptic formulations.

- **Praveen Khullar et al., (2010)**[27] 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)**[28] described the various process of pelletization and its coating; they suggested their advantages as multiple unit dosage form over single unit dosage form for controlled release preparations.

- **Niklas Sandler et al., (2005)**[29] 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)**[30] 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)**[31] 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)**[32] summarized the USP and non-pharmacopeial dissolution testing methods for conventional and novel pharmaceutical dosage forms and suggested possible alternatives in drug dissolution study design to choose appropriate dissolution condition for each type of dosage form to predict good in-vitro in-vivo correlation during initial research and development.

- **Siepmann J. et al., (1999)**[33] investigated the effect of the composition of diffusion based controlled release devices on the drug diffusivity and the resulting release kinetics in a quantitative way. The benefit of the presented method was to calculate the required composition of diffusion controlled drug delivery systems to achieve desired release profiles.

- **Goran Frenning et al., (2003)**[34] described a mathematical model of drug release from coated pellets with a granular core, that includes a dynamic description of all three main processes contributing to drug release from such a system, i.e. liquid inflow, drug dissolution, and liquid efflux caused by diffusion across the coating.

- **Mehta Atul M., (1986)**[35] 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)\(^{36}\) developed a more practical and systematic method in order to achieve a similar granule size in the scaling up of the fluidized granulation process from small (5 kg scale) to medium (30 kg scale) and to production fluid bed scale (120 kg scale).

Claudia S. Leopold et al., (2011)\(^{37}\) found in the development of the shellac coated sustained release formulation that the application of modifying sub-coat with calcium chloride, citric acid or Eudragit E respectively was an easy and effective means to achieve tailor made sustained release profiles from shellac-coated dosage forms.

Rajesh N. et al., (2011)\(^{38}\) 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)\(^{39}\) described the preparation and evaluation of high-dose nicotinic acid loaded sustained-release pellets coated with double polymer and combined with immediate release coating of simvastatin. The drug release behavior of nicotinic acid was very similar to the reference product by Abbott in different media and simvastatin release was more rapid than that of the reference product.

Lian-Dong Hu et al., (2006)\(^{40}\) developed sustained-release metformin hydrochloride pellets preparation and performed in vitro/in vivo evaluation of the same.

Yam Noymi V; Shivanand Padmaja; Kimbel Rhea et al., (2005) US2005/0136108\(^{41}\) disclosed a controlled release dosage form as bilayer or trilayer capsule shaped tablet comprising a compartment having semi permeable wall, an exit orifice, an expandable layer located within the compartment remote 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 prolonged period of time at a stepwise, increasing rate.

Jenkins Scott A. et al., (2006) US2006/0121112\(^{42}\) disclosed controlled-release pharmaceutical composition consists of: (A) an immediate-release component comprising from about 5 mg to about 250 mg of topiramate which was released in the body within about 1 hour after administration; and (B) a delayed-release component comprising from 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 hours to 24
hours 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** disclosed a controlled release matrix tablet comprising: (a) Topiramate or a pharmaceutically acceptable salt as active ingredient; (b) a first intelligent polymer component; and (c) a second intelligent polymer component having opposite wettability characteristics to said first 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** 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.; Wang, Hua.; Bhatt, Padmanabh P. et al., (2008) US2008/0118557** filed by Supernus Pharmaceutical disclosed method of preparing a sustained release formulation of topiramate, comprising an extended release (XR) component and an optional immediate release (IR) component, wherein at least said XR component was contained in at least one population of beads characterized by its own rate of release, said method comprising: forming at least one population of topiramate-containing beads; coating each population of beads with its own release controlling coating; curing said coating in a curing apparatus for a period of time to produce the release controlling coating specific for each bead population; and incorporating the beads of every population into the formulation in the amounts determined according to a pre-determined release profile.

- **Mandal Jayanta Kumar; Pandya Nitesh Nalinchandra et al., (2009) US2009/0196923** disclosed once a day controlled release solid oral formulation of anti-epileptic drugs in the form of capsule filled with immediate release and controlled release tablets; of which: A) Immediate release tablets provide quick drug action and comprises of: i) Tablet core of active pharmaceutical ingredient and pharmaceutical acceptable excipients. Optionally coated with, ii) Film coating comprising of film
forming polymers and pharmaceutically acceptable excipients. B) Controlled release tablets which release drug at pH 5 to 6 of gastrointestinal tract comprising: i) Tablet core of active pharmaceutical ingredient and pharmaceutically acceptable excipients. ii) Film coating comprising film forming polymer and pharmaceutically acceptable excipients; and iii) Control release coating comprising control release polymer suitable to release the drug at pH 5 to 6 of gastrointestinal tract and pharmaceutically acceptable excipients. C) Controlled release tablets which release drug at pH 6 to 8 of gastrointestinal tract comprising: i) Tablet core of active pharmaceutical ingredient and pharmaceutically acceptable excipients. ii) Film coating comprising film forming polymer, and pharmaceutically acceptable excipients; and iii) Control release coating comprising control release polymers suitable to release the drug at pH 6 to 8 of gastro-intestinal tract and pharmaceutically acceptable excipients.

- **Almarsson Orn; Remenar Julius et al., (2003) US6699840** [47] invented a pharmaceutical composition comprising a pharmaceutically acceptable salt of topiramate, or a pharmaceutically acceptable polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof, and a pharmaceutically acceptable excipient or diluent.

- **Chen Andrew Xian; Kigin Patricia D., (2008) US2008/0220079** [48] disclosed a composition comprising: (a) an active ingredient; (b) a wax-like agent; and (c) a spheronizing agent; wherein (i) the composition was in the form of pellets, (ii) the composition has an in vitro dissolution rate of the active ingredient measured by standard USP basket method of at most about 90% of the active ingredient released after 2 hours, and (iii) the in vitro dissolution rate of the active ingredient did not require the presence of a sustained release barrier coating on the pellets.

- **Vaya Navin; Karan Rajesh S.; Nadkarni Sunil S. et al., (2006) US7976871** [49] disclosed a process for the preparation of a modified release dosage form comprising 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 consisting of poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1; poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2; and poly(ethyl acrylate, methyl methacrylate) 2:1; and b) coating said micro matrix articles with one or more hydrophobic release controlling agents selected from the group consisting of waxes selected from the group consisting of beeswax,
carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols selected from the group consisting of cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters selected from the group consisting of glycerol monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glycercyl palmitostearate, glycercyl behenate and hydrogenated castor oil.

- **Barker Nicholas; Wolfe Janet L., (2006) US2006/0198815**[^50] invented sustained delivery pharmaceutical compositions comprising a solid ionic complex of a pharmaceutically active compound and an ionic macromolecule were provided by the present invention. The pharmaceutical compositions of the invention allow for loading of high concentrations of pharmaceutically active compounds and for delivery of a pharmaceutically active compound 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**[^51] disclosed a topiramate pharmaceutical composition, wherein the topiramate was micronized to have a median particle size range of 0.5-50 microns or a topiramate pharmaceutical composition, comprising three regions: a) first and second regions, each comprising a controlled or extended release (CR/XR) topiramate component and an immediate release (IR) topiramate component; and b) a third region substantially free of topiramate and comprising a pharmaceutical excipient; wherein the third region separated the first region from the second region.

- **Najarian Thomas; Tam Peter Y.; Wilson Leland F., (2009) US2009/0304789**[^52] disclosed a controlled release composition for treating obesity, diabetes or a related condition in a subject comprising: an effective amount of topiramate; microcrystalline cellulose; and methylcellulose.

- **Cardinal John R; James Jack Lawrence. et al., (2010) US2010/0159001**[^53] 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 selected from the group consisting of a cationic polymer and a hydrocolloid, the formulation of which was substantially free of non-aqueous solvent.

- **Remon Jean Paul; Deburne Ann. (2002) WO2002/17877**[^54] 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% by weight 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 a microcrystalline cellulose and a swellable polymer in respective amounts such that the weight ratio of the said polymer to the microcrystalline cellulose in the blend was above 5:100 and up to 30:100.