

**RECENT TRENDS ON CONTROLLED RELEASE PREPARATION  
OF ANTI-EPILEPTIC DRUGS**

**Lakshmikanta Ghosh<sup>1</sup>, Hirak Kumar Mukhopadhyay<sup>1,2\*</sup>, Chandi Charan Kandar<sup>2</sup>, Sanjoy Kumar Das<sup>2</sup>, Bijan Kumar Gupta<sup>1</sup>**

<sup>1</sup>Department of Pharmaceutical Technology, Jadavpur University, Kolkata – 700 032,  
W.B., India.

<sup>2</sup>Institute of Pharmacy, Jalpaiguri, P.O. + Dist. – Jalpaiguri, 735 101, W.B., India.

**Running Title:** Controlled release preparation and anti-epileptic drugs

**\*Corresponding Author:**

E-mail: [hirakju@yahoo.com](mailto:hirakju@yahoo.com)

Phone: +91 9434491615

Fax: +91 3561-221884

## **ABSTRACT**

In the past few decades considerable interest has been shown in the advancement of drug delivery systems. Research has been carried out to overwhelm the shortcomings of immediate release preparations. As a result, the concept of novel drug delivery system has come out which provides desired concentration of drug in the system for a long period to a target site. The research scientists are usually using different polymers as wall materials and various types of preparation procedures like, spray-drying and spray-congealing, solvent-evaporation, solid-dispersion, supercritical fluid technology, polymerization, gelation technique etc. for designing such extended release formulations. The diseases like epilepsy, diabetes, cancer, arthritis etc. require long term therapy and as a result repeated administration of immediate release preparation for long time leads to various untoward effects. Epilepsy is a chronic CNS disorder resulting from abnormal, excessive or hypersynchronous neuronal activity in the brain and sometimes associated with recurrent and unprovoked seizure. Though several anti-epileptic drugs (AED) are available but complete control of seizures with the existing conventional dosage forms of these drugs are in question because of their side effects and thus poor adherence to anti-epileptic drug therapy for long period. A number of research works have pointed out that the sustained release preparations of AEDs may be beneficial over conventional immediate release preparations with respect to delivery, bioavailability, release profile, toxicity, target specificity etc. The objective of our present study is thus to highlight the recent research work undertaken on controlled release preparation of available anti-epileptic drugs.

**Keywords:** Anti-epileptic drugs, controlled release preparation, epilepsy, method of technique,

## **INTRODUCTION**

In chronic and complicated diseases like epilepsy, hypertension, diabetes, arthritis, cancer, asthma etc. treatment is usually prolonged and large doses of drugs are required to treat these diseases [1]. Thus for patient compliance, proper design of the dosage regimen should be established to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for a prolonged period [2]. Though conventional dosage forms have gained popularity because of their unique properties like simplicity, safety [3] and their convenience over other dosage forms, they do not usually provide any controlled release or target specificity because of their immediate release [4].

Controlled drug delivery systems are considered as reliable means of delivering drug at a controlled and predetermined rate, thus resulting in maintenance of a therapeutically effective concentration of the drug in the systemic circulation over a long period of time and therefore reduce dose frequency, minimize side effects and improve patient compliance [5]. In addition, reduction of total quantity of drug administered leads to the reduction of the cost as well as the severity of its adverse effects [6]. Many drawbacks of conventional dosage forms may be overcome by sustained release formulations. Considering the physicochemical properties of the used chemical, applied techniques, basic principles and modulation of some of the properties of the chemicals, a formulation scientist can achieve a targeted pharmacological effect [7].

To obtain a desirable drug release profile various polymeric materials like ethyl cellulose [8,9], hydroxypropyl methyl cellulose [10], cellulose acetate butyrate [11], chitosan [12], polymethacrylates [13-15], polycaprolactone [16,17], poly(D,L lactide-co

glycolide) [18,19], etc. and their blend in appropriate proportions are used as wall material in the formulation of controlled release system.

The efficiency of the drug delivery system mostly depends on the nature of polymer-drug systems and to some extent environmental factors such as pH, enzymes and inter-patient variance [20]. Therefore the selection of appropriate polymer plays an important role in the formulation of sustained release preparation.

Epilepsy is one of the most common chronic neurological disorders characterized by recurrent unprovoked seizures [21, 22] affecting about 50 million people worldwide and 90% of them are from developing country [23]. Children to older persons very oftenly suffer from this deadly disease. The ideal anti-epileptic drugs (AED) should control all seizures with no adverse effects, but currently available anti-seizure drugs fail to control seizure completely in some individuals. Toxicity and poor adherence to AED therapy are the two main reasons creating an obstacle for patients to achieve a completely seizure free state [24, 25]. Conventional dosage forms of anti-epileptic drugs are required to administer repeatedly. Repeated administration of these drugs especially carbamazepine causes significant decrease of elimination half life ( $t_{1/2}$ ) due to enzymatic auto-induction of its own metabolism [26]. It has been reported that extended release preparation of anti-epileptic drugs are free from toxic effects and solves the problems of bioavailability [27] by increasing dissolution rate of poorly water soluble drugs like carbamazepine, phenytoin valproate, ethosuccimide, Phenobarbitone, diazepam, clonazepam, clobazam, vigabatrin, lamotrigine etc. Because of therapeutic relevance, the development of sustained release formulation has therefore gained much attention to the pharmaceutical industry. So our objective of present study is to highlights the recent research works

undertaken for formulation of controlled release preparation of antiepileptic drugs with the objective of preparing a drug delivery device with high potential in term of delivery, bioavailability and targeting.

Machiste *et al.* 1995, [28] prepared carbamazepine-polymer systems using cross-linked polyvinyl pyrrolidone (Polyplasadone XL-10) as dissolution rate enhancer by mixing, milling and solvent evaporation method. The physico-chemical parameters of the systems were characterized by Scanning Electron Microscopy (SEM). X-Ray Powder Diffraction (XRD) and Differential Scanning Calorimetry (DSC). The Dissolution tests showed improved rate of dissolution of the drug from the systems.

Fresta *et al.* 1996, [29] formulated antiepileptic drugs loaded nanocapsules using polyethyl cyanoacrylate (PECA) by insitu polymerization. Carbamazepine ethosuximide and 5, 5-diphenyl hydantoin were used as model drugs. The nanocapsules were prepared by mixing on organic phase containing Miglyol 812 and organic solvent (ethanol, acetone or acetonitrile) with an aqueous phase containing pluronic F68 at different concentrations. The nanocapsules were investigated by freeze-fracture electron microscopy and laser light scattering method. The results showed that high quality nanocapsules were formed when acetone was used. The diameter of PECA nanocapsules were ranged between 100 and 400 nm and loading capacity varied from 1 to 11%. The study concluded that the controlled release delivery of these three antiepileptic drugs was possible which followed diffusion mechanism of release.

Moneghini *et al.* 2000, [30] prepared microspheres of Carbamazepine using vinyl pyrrolidone/vinylacetate copolymer (VP/VAC) by solvent evaporation method, physical characterizations were carried out by differential scanning calorimetry, x-ray deffractometry and by scanning electron microscopy. Solubilization kinetics and dissolution rate studies of microspheres prepared using different drug polymer ratio were performed. The results showed that the microspheres prepared with drug polymer ratio 1: 10 (w/w) was found to show the best dissolution property.

Passerini *et al.* 2002, [31] prepared an enhanced release solvent free microsphere of carbamazepine with different drug polymer ratio by utilizing a spray-congealing technique using a new ultrasonic atomizer. Gelucire 50/13 in different concentration was used as polymer. The *in-vitro* dissolution studies showed a significant increase of carbamazepine release rate from microspheres as compare to pure drug and to drug-Gelucire 50/13 physical mixture. Further more, the results of this study suggested that the spray-congealing technique using the ultrasonic atomizer could be considered as a new and interesting method to enhance the dissolution rate of a poorly water soluble drug as carbamazepine. The microspheres were characterized in terms of thermal analysis by DSC, crystallinity by PXRD and surface morphology and particle size by SEM and Drug polymer interaction by FTIR. The results of these studies showed that spherical microspheres, particle size ranging 150-250  $\mu\text{m}$  containing original polymorph of carbamazepine were obtained with absence of drug polymer interaction.

Filipovic-Grcic *et al.* 2003, [32] prepared carbamazepine microspheres by spray drying technique using chitosan and hydroxyl propyl methyl cellulose (HPMC) as polymer; Low-medium and high molecular weight chitosan and HPMC in different drug polymer ratio were used for the preparation of microspheres. Microspheres were characterized in terms of crystallinity and thermal analysis by X-ray powder diffractometry (PXRD) and differential scanning calorimetry (DSC) respectively and were also studied with respect to particle size distribution, drug content and drug release. The results showed that the entrapment efficiency as well as carbamazepine release profile depended on polymeric composition and drug polymer ratios of the prepared microspheres. It was found that the best entrapment efficiencies were obtained when low molecular weight chitosan or HPMC were used for the preparation of microspheres. The study also indicated that the release profile of carbamazepine from the microspheres was highly correlated with the crystalline changes occurring in the matrix.

Comoglu *et al.* 2005, [33] carried out an investigation on quality control parameters of different conventional carbamazepine tablets commercially available on the Turkish drug market with respect to weight variation, diameter and thickness content uniformity, and friability and dissolution tests.

Smith *et al.* 2005, [34] formulated sustained release (SR) beads of carbamazepine using SBE7- $\beta$ -cyclodextrin together with hydroxy propyl methyl cellulose (HPMC) or poly vinyl pyrrolidone to investigate the effect of these polymers on the saturated solubility and delivery of carbamazepine (poorly soluble drug) from those SR beads. The reports



showed that the solubility of carbamazepine at room temperature was increased from 0.1 to 5.4 mg/ml due to inclusion complex with 15% w/v SBE7-  $\beta$ -cyclodextrin and with HPMC, the value was 0.26 mg/ml and the value increased to 8.1 mg/ml when HPMC (0.1 % w/v) was combined with SBE7-  $\beta$ -cyclodextrin. Both binary and ternary drug cyclodextrin polymer system improved the release rate and potentially the *in-vivo* bioavailability of poorly soluble drugs that has previously exhibited slow or incomplete release from SR beads, but ternary drug cyclodextrin polymer system was preferable over binary system.

Gavini *et al.* 2006, [35] prepared carbamazepine loaded chitosan microsphere by using spray drying technique for nasal administration. Particle size and morphology was characterized by scanning electron microscopy and thermal behavior by differential scanning calorimetry. *In-vitro-in-vivo* studies of chitosan glutamate microspheres and of pure drug were performed and were compared to those obtained after nasal administration of carbamazepine alone. Carbamazepine loaded chitosan microspheres showed better result than pure drug alone

Zanetti-Ramos *et al.* 2006, [11] formulated carbamazepine loaded cellulose acetate butyrate (CAB) microspheres by solvent evaporation method to investigate the effect of polyethylene glycol and incorporation of cellulose acetate butyrate of different molecular weight (CAB 30,000, CAB 70,000) in the formulation of microspheres on drug content, surface morphology glycol and incorporation of cellulose acetate butyrate of different molecular weight (CAB 30,000, CAB 70,000) in the formulation of microspheres on drug

content, surface morphology and release rate of carbamazepine. The results showed that the addition of PEG 1500 to the formulation led to an increase in surface porosity and the release rate of carbamazepine was significantly increased when CAB 30,000 and PEG 1500 used to prepare micospheres.

Nokhodchi *et al.* 2007, [36] prepared the agglomerates of carbamazepine by quasi emulsion mechanism. Carbamazepine was dissolved in ethanol at 60°C. 5% w/v of the resultant solution was poured into mixture of water (poor solvent) and isopropyl acetate (wetting agent), thermally controlled at different temperature (5,10 and 20°C) under agitation with a propeller agitator. Investigation was carried out to evaluate the effect of stirring rate on carbamazepine agglomerates at different stirring speed (300,400 and 500 rpm). The agglomerates were separated from the solution through vacuum filtration and were dried in an oven at 60°C for three hours. The physical characterization of the agglomerates and the crystallinity of the pure drug were carried out. The results showed that the agglomerates produced at 5°C under 300 rpm stirring speed has superior flow than other agglomerate and agglomerates flowed from the hopper into the die smoothly. The tablets prepared from the agglomerates were found to attain uniformity in weight due to spherical shape of agglomerates. The results also suggested that the carbamazepine agglomerates possessed superior mechanical and better dissolution rate characteristics than untreated crystals.

Dong *et al.* 2007, [37] formulated carbamazepine loaded enteric microparticles using Eudragit L100-55 by coacervation method. The microparticles were characterized in

terms of particle size distribution, morphology, and encapsulation efficiency, and yield, physical stability of the drug, wettability, *in-vitro* release and *in-vivo* bioavailability. The results showed that the resultant microparticles were found to show a yield 90% and high encapsulation efficiency (>85%). When the drug dissolution rate of the microparticles were compared to the physical mixture and to the pure drug. The results suggested that the dissolution rate of drugs from the microparticles was significantly enhanced and hence increased bioavailability than other two.

Patel *et al.* 2007, [38] prepared carbamazepine floating tablets using bees wax and mixture of HPMC K<sub>4</sub>M and /or ethyl cellulose. A simplex lattice design was applied to investigate the combined effect of time formulation variables (amount of hydroxypropyl methyl cellulose, ethyl cellulose and sodium bicarbonate). Results of multiple regression analysis indicated that tablets with low level of hydroxy propyl methyl cellulose and ethyl cellulose and high level of sodium bicarbonate showed better *in-vitro* floating time and dissolution profile.

Apu *et al.* 2009, [39] prepared carbamazepine matrix tablets using Eudragit RSPO and combination of Eudragit RSPO and RLPO to evaluate the effect of polymers on the physical property and release characteristics of carbamazepine matrix tablets. The results showed that the hardness and release rate were higher in case of tablets prepared with mixture of Eudragit RSPO and RLPO as compared to the tablets formulated with Eudragit RSPO alone.

Kuminek *et al.* 2009, [40] performed the pharmacokinetic study of carbamazepine nano emulsion in beagle dogs. The concentration profiles were determined after i.v. bolus administration of a 5mg/kg carbamazepine nanoemulsion and compared to the corresponding carbamazepine/hydroxyl propyl- $\beta$ -cyclodextrin complex solution. They reported that both formulations showed similar pharmacokinetic profiles and could represent valuable formulations in case of emergencies and could be used when rapid action in the central nervous system is desirable.

Rajkumar *et al.* 2010, [41] prepared porous microspheres of carbamazepine using Eudragit as release retardant, compritol as core forming agent and hydroxyl propyl methyl cellulose (HPMC) as recrystallization inhibitor for short term sustained delivery of carbamazepine. Microspheres were prepared by emulsion solvent diffusion method and were characterized with respect to surface morphology, particle size distribution (SEM) thermal analysis (DSC) crystallinity (PXRD) and *in-vitro* drug release. DSC and PXRD reports indicated that there was no drug polymer interaction and the drug was presented in partially crystalline form in the microsphere. They reported that encapsulation efficiency was insufficient to deliver the high dose drug like carbamazepine. They also suggested that further investigation could be carried out to reduce the amount of polymer in microsphere that could provide maximum drug loading and acceptable dosage form.

Raymond *et al.* 1990, [42] formulated phenytoin sodium loaded microspheres using biodegradable acid treated gelatin to determine amount of drug retained in the

microspheres as well as its release from the microspheres. *In-vitro* and *in-vivo* testing was performed. *In-vitro* studies showed the amount of glutaraldehyde added to the formulations. *In-vivo* data and subsequent statistical testing enabled comparison of the effect of microsphere formation and the effect of microsphere dose on selected pharmacokinetic parameters.

Brazeau *et al.* 1996, [43] prepared PLGA microspheres of phenytoin to evaluate the effect of microsphere size and /or reconstitution solvent on myotoxicity using isolated rodent skeletal muscle model. The results showed that microspheres of larger size and reconstituted with saline or normal saline with 0.5 % (w/v) carboxy methyl cellulose were low myotoxic than the microspheres of smaller size and reconstituted with distilled water.

Giannola *et al.* 1997, [44] prepared phenytoin microspheres with oleaginous materials such as stearylalcohol and glyceryl esters of various fatty acids. Microspheres prepared with glyceryl monostearate dilaurate and stearyl alcohol at a ratio of 3:17 were found to be reproducible, free flowing and were formulated by melting and dispersion of drug containing oleaginous material in aqueous medium. The oily droplets were converted into solid under rapid stirring. The particle size range of the lipospheres was reported to be 100-800  $\mu\text{m}$ . The drug content and *in-vitro* release profile of the lipospheres were determined. The results showed that drug content was 23.8% w/w and encapsulation efficiency was found to be 93.6%. The drug release from the lipospheres were reported to be followed diffusion controlled mechanism.

Al-Helw *et al.* 1997, [45] prepared chitosan microspheres containing phenobarbitone by glutaraldehyde cross-linking of an aqueous acetic acid dispersion of chitosan in light liquid paraffin containing sorbitan mono oleate as a stabilizing agent. They reported that the molecular weight and concentration of chitosan as well as the concentration of stabilizing agent affected the preparation and performance of the prepared microspheres. The dissolution studies indicated that the release rate of the drug from the microspheres prepared from high molecular weight chitosan was slow in comparison with that prepared from medium and low molecular weight chitosan.

Al-Helw *et al.* 1998, [46] prepared phenobarbitone loaded sustained release microspheres using natural (casein-chitosan) and synthetic polymers (Eudragit RL). The results showed that the percent yield, actual drug content and encapsulation efficiencies of the prepared microspheres increased with increasing the drug polymer ratio and mean diameter of microspheres increased with increasing amount of polymer from 1:1 to 1:4 ratios. The dissolution studies indicated that the phenobarbitone release was extended and delayed when the drug polymer ratio was decreased. When these two type microspheres were compared, the result showed that a prolonged and slower drug release was obtained with Eudragit microspheres than the microspheres those prepared with casein-chitosan polymer.

Benelli *et al.* 1998, [47] worked on preparation and characterization of poly (D, L-lactide-co-glycolide) (PLGA) microspheres containing clonazepam. The microspheres were prepared by emulsion solvent evaporation and spray drying method. The microspheres

prepared by these two methods and using PLGA of different molecular weight were characterized in terms of morphology, physico-chemical properties and *in-vitro* dissolution behaviour. The results showed that only spray drying was suitable for preparing clonazepam loaded PLGA microspheres and more sustained release of drug is achieved with polymer of high molecular weight.

Ferranti *et al.* 1999, [48] prepared primidone loaded poly- $\epsilon$ -caprolactone nanocapsules by interfacial deposition technique. Mean diameter of nanocapsules were found to be in the range of 308-352 nm and the encapsulation efficiency was 74%. The studies showed that primidone release was independent of pH of the release medium and slower as compared to the oily controlled solution.

Hazendar *et al.* 2004, [48] prepared acetazolamide loaded microspheres using Eudragit (RS and RL) microspheres by solvent evaporation method using acetone/liquid paraffin solvent system. The influence of formulation factors (stirring speed, polymer drug ratio, type of polymer, ratio of the combination of polymers) on particle size, encapsulation efficiency and *in-vitro* release characteristics of the microspheres were investigated. Results showed that the mean particle size of the micorspheres was influenced greatly by varying drug polymer ratio and stirring speed of the system. The results also further indicated that the release of acetazolamide from Eudragit RS micorspheres were very slow and incomplete but were fast from Eudragit RL microspheres, the release rate slowed down and achieved the release prsperties suitable for per oral administration.

Serajuddin *et al.* 2006, [50] studies the effect of physico-chemical factors like solubility, intrinsic dissolution rate as function of pH, type of dosage form, pH of dissolution medium and conversion of sodium salt to phenytoin on the release of phenytoin sodium form slow release dosage forms. They reported that though the different formulations showed the similar dissolution rate patterns in water but the extent of drug release under pH range of 1 to 8 could differ greatly indicating lower steady state level of phenytoin in human plasma due to incomplete release of drug from a slow release dosage form following oral administration.

Shaji *et al.* 2009, [51] prepared gelatin chitosan mucoadhesive microspheres of clonazepam using emulsion cross linking method to evaluate *in-vitro* and *ex vivo* drug release patterns. *In-vivo* studies were carried out in rats by administering the clonazepam microspheres intranasally and clonazepam solution intravenously. Results obtained indicated that intranasally gelatin-chitosan cross linked mucoadhesive microspheres have the potential to be developed as a brain-targeted drug delivery system for clonazepam.

In Roni *et al.* 2011, [27] work, solid dispersion (SD) of an anti-epileptic drug was prepared to improve the solubility and release profile of poorly soluble clonazepam by incorporating hydroxyl propyl methyl cellulose (HPMC) as crystallization inhibitor and poloxamer 407 as wetting agent using melt granulation technique. After that the SD of clonazepam was compressed into tablet by adding microcrystalline cellulose, sodium starch glyconate and talc. The physicochemical properties of SD were characterized by Scanning Electron Microscopy, Differential Scanning Calorimetry, particle size analyzer and drug content by HPLC with UV connector. The result showed that both HPMC and



Poloxamer can improve solubility and release profile of clonazepam from solid dispersion and tablets. The concentration of the polymers, the particle size and crystalline state of the drug were influenced by the quantity of the polymers used. They also pointed out that *in-vivo* may be carried out to evaluate the potential of these solid dispersion tablet preparation.

Florence *et al.* 2011, [52] worked on preparation and characterization of clobazam mucoadhesive microemulsion to assess brain drug uptake and protection against pentylenetetrazole (PTZ) induced convulsions in mice. For investigation, clobazam microemulsion and clobazam mucoadhesive microemulsion were prepared by titration method. The results of investigation suggested an improved brain uptake following intranasal administration of mucoadhesive microemulsion of clobazam. They also pointed out that extensive animal studies and clinical trials to be performed for developing a product suitable for emergencies of acute seizures in status epilepticus and the problems associated with the patients using long term treatment for epilepsy, schizophrenia and anxiety.

Fidalgo *et al.* [53] prepared wet sol-gel silica matrices under different hydrolysis conditions of phenytoin sodium for using as drug delivery devices. The kinetics of *in-vitro* release of phenytoin sodium was studied at 37°C using water and artificial cerebrospinal fluid as dissolution medium. The results indicated that the matrices with less total porosity and smaller average pore size were proven better for long term release.

## **CONCLUSION**

The study represents the recent works on controlled release preparation of anti-epileptic drugs introduced in order to meet the shortfalls of immediate release preparation of these drugs by modifying the physicochemical properties of the used drugs and improving their bioavailability, reducing side effects and releasing drug in a controlled manner to the appropriate site of action and thus improving patient compliance.

## REFERENCES

1. M.H. Shoaib, J. Tazeen, H.A. Merchant, R.I. Yousuf, Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC, *Pak. J. Pharm. Sci.* 19(2) (2006) 119-124.
2. P. Rout, B.S. Nayak, U.K. Nayak, Statistical evaluation of losartan microspheres prepared by W/O emulsion method using factorial design and response surface methodology, *Asi. J. Pharm. Clin. Res.* 2(4) (2009) 1-9.
3. K.D. Tripathi, *Essentials of Medical pharmacology*, fifth ed., Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, 2003, .pp. 3-10.
4. L.V. Allen, N.G. Popovich, H.C. Ansel, Modified-release solid dosage forms and drug delivery systems, in: *Pharmaceutical dosage forms and drug delivery systems*, Lippin Cott Williams & Wilkins, New Delhi, eighth ed., 2005, pp. 260-275.
5. H.K. Raslan, H. Maswadeh, In vitro dissolution kinetic study of theophylline from mixed controlled release matrix tablets containing HPMC and glycerylbehenate, *Ind. J. Pharm. Sci.* 68(3) (2006) 308-312.
6. S.K. Sahoo, A.A Mallick, B.B. Barik, P.C. Senapati, Formulation and in vitro evaluation of eudragit microspheres of stavudine, *Trop. J. Pharm. Res.* 4(1) (2005) 369-375.
7. M. Palanisamy, J. Khanan, Cellulose-based matrix microspheres of prednisolone inclusion complex: preparation and characterization, *AAPS PharmSciTech.* 12(1) (2011) 388-400.
8. A.L. Behera, S.V. Patil, S.K. Sahoo, Formulation and characteristics of 5-fluorouracil microsphere by solvent evaporation method, *Internat. J. Pharm. Pharma. Sci.* 3(1) (2011) 32-35.
9. N. Yadav, D.D. Mohite, K.R. Powar, U.R. Powar, S.B. Bhise, T.A. Sande, Synthesis and characterization of sustained release atenolol microspheres by solvent evaporation technique, *J. Pharma. Sci. Tech.* 3(2) (2011) 559-562.

10. H.A. Merchant, H.M. Shoaib, J. Tazeen, R.I. Yousuf, Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using HPMC: a technical note, *AAPS Pharm. SciTech.* 7(3) (2006) E1-E6.
11. B. Zanetti-Ramos, M. Soldi, V. Soldi, E. Lemos-Senna, The effect of polyethylene glycol on drug content, particle morphology, and carbamazepine release profiles of sustained release microspheres prepared from cellulose acetate butyrate, *Acta. Farma. Bonaer.* 25(2) (2006) 177-183.
12. S.K. Bajpai, R. Tankhiwale, A novel approach for testing the Hixon-Crowel model for in vitro release of vitamin B<sub>2</sub> from chitosan coated calcium alginate beads, *J. Macromol. Sci.* 43 (2006) 621-626.
13. B.K.Kim, S.J. Hwang, J.B. Park, H.J. Park, Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method, *J. Microencap.* 19(6) (2002) 811-822.
14. B.C. Behera, S.K. Sahoo, S. Dhal, B.B. Barik, B.K. Gupta, Characterization of glipizide-loaded polymethacrylate microspheres prepared by an emulsion solvent evaporation method, *Trop. J. Pharma. Res.* 7(1) (2008) 879-885.
15. S.K. Basu, R. Adhiyaman, Preparation and characterization of nitrendipine-loaded Eudragit RL 100 microspheres prepared by an emulsion-solvent evaporation method, *Trop. J. Pharma. Res.* 7(3) (2008) 1033-1041.
16. X. Wang, Y. Wang, K. Wei, N. Zhao, S. Zhang, J. Chen, Drug distribution with in poly ( $\epsilon$ -caprolactone) microspheres and in-vitro release, *J. Mater. Proces. Tech.* 209(1) (2009) 348-354.
17. K. Aysegul, S. Ozlem, K. Muge, B. Tamer, Poly ( $\epsilon$ -caprolactone) microparticles containing levobunolol HCl prepared by a multiple emulsion (w/o/w) solvent evaporation techniques: effects of some formulation parameters on microparticle characteristics, *J. Microencap.* 26(1) (2009) 63-74
18. S.M. Sivakumar, N. Sukumaran, R. Murugesan, T.S. Shanmugarajan, J. Anbu, L. Sivakumar, B. Anilbabu, G. Srinivasrao, V. Ravichandran, Immune augmentation of

single contact hepatitis B vaccine by using PLGA microspheres as an adjuvant, *Ind. J. Pharma. Sci.* 70(4) (2008) 487-490.

19. J. Emami, H. Hamishehkar, A.R. Najafabadi, K. Gilani, M. Minaiyan, H. Mahdavi, A. Mirzadeh, A. Fakhari, A. Nokhodchi, Particle size design of PLGA microspheres for potential pulmonary drug delivery using response surface methodology, *J. Microencap.* 26(1) (2009)1-8.

20. M.V.K. Varma, P. Amareshwar, K. Hemamalini, K. Sreenivas, K. Anwesh Babu, K. Kranthi, Preparation and in vitro evaluation of Diclofenac Sodium loaded Ethyl cellulose composite magnetic microspheres, *Internat. J. Pharma. Anal.* 1(2) (2009) 40-45.

21. Commission on Epidemiology and prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy, Commission on Epidemiology and Prognosis, International League Against Epilepsy (1993), *Epilepsia.* 34(4) (1993) 592-596.

22. W. Blume, H. Luders, E. Mizrahi, C. Tassinary, W.V.E. Boas, J. Enjel, Glossary of descriptive terminology for ictal semiology; report of the ILAE taskforce on classification and terminology, *Epilepsia.* 42(9) (2001) 1212-1218.

23. Epilepsy: aetiology (Sic), epidemiology and prognosis, World Health organization. 2001. Archived form the original on 2007-05-18.[http://web.archive.org/web/20070518073641/http://www.who.int/mediacentre/facsheets/fs165/en/Retrieved 2007-06-14](http://web.archive.org/web/20070518073641/http://www.who.int/mediacentre/facsheets/fs165/en/Retrieved%202007-06-14).

24. T.A. Pedley, M.L. Scheuer, T.S. Walczak, Epilepsy, in: L.P. Rowland (ed.), *Merritt's text book of neurology*, Williams & Wilkins., Baltimore, ninth ed., 1995, pp. 845-868.

25. I.E. Leppik, Contemporary diagnosis and management of the patient with epilepsy, in: *Handbooks in Healthcare*, Newtown, PA sixth ed., 2002, pp. 119-127.

26. S.M.A. Sadat, Md. S. Islam, S.T. Jahan, J.A. Chowdhury, R. Jalil, Effect of cellulosic and polymethacrylic polymers on drug content, particle morphology and carbamazepine release profiles from sustained release ethyl cellulose microspheres, *Dhaka. Univ. J. Pharm. Sci.* 9(2) (2010) 75-82.

27. M.A. Roni, Md. S. Islam, G. Kibria, S.M.A. Sadat, Md. R. Rony, Md. H. Rahaman, R. Jalil, Effects of poloxamer and HPHC on the dissolution of clonazepam-polyethylene Glycol Solid dispersions and tablets, *Ind. J. Pharm. Edu. Res.* 45(2) 2011 139-144.
28. E.O. Machiste, P. Giunchedi, M. Setti, U. Conte, Characterization of carbamazepine in systems containing a dissolution rate enhancer, *Internat. J. Pharmaceut.* 126 (1-2) (1995) 65-72.
29. M. Fresta, G. Cavallaro, G. Giammona, E. Wehrli, G. Puglisi, Preparation and characterization of poly ethyl-2-cyanoacrylate nanocapsules containing antiepileptic drugs, *Biomater.* 17(8) (1996) 751-758.
30. M. Moneghini, D. Voinovich, F. Princivalle, L. Magarotto, Formulation and evaluation of vinyl pyrrolidone/ vinyl acetate copolymer microspheres with carbamazepine, *Pharma. Dev. Tech.* 5(3) (2000) 347-353.
31. N. Passerini, B. Perissutti, M. Moneghini, D. Voinovich, B. Albertini, C. Cavallari, L. Rodriguez, Characterization of carbamazepine-gelucire 50/13 microparticles prepared by a spray-congealing process using ultrasounds, *J. Pharm. Sci.* 2002; 91(3): 699-707.
32. J. Filipovic-Grcic, B. Perissutti, M. Moneghini, D. Voinovich, A. Martinac, I. Jalsenjak, Spray-dried carbamazepine-loaded chitosan and HPMC microspheres: preparation and characterization, *J. Pharm. Pharmacol.* 55(7) (2003) 921-931.
33. T. Comoglu, N. Gonul, Quality control studies on conventional carbamazepine tablets available on the Turkish drug market, *Turkish J. Medi. Sci.* 35 (2005) 217-221.
34. J.S. Smith, R.J. MacRae, M.J. Snowden. Effect of SBE7- $\beta$ -cyclodextrin complexation on carbamazepine release from sustained release beads. *Eur. J. Pharma. Biopharma.* 60(1) (2005) 73-80.
35. E. Gavini, B. Hegge, G. Rassa, V. Sanna, C. Testa, G. Pirisino, J. Karisen, P. Giunchedi. Nasal administration of carbamazepine using chitosan microspheres: In-vitro/in-vivo studies, *Internat. J. Pharma.* 307(1) (2006) 9-15.
36. A. Nokhodchi, M. Maghsoodi, D. Hassanzadeh, An improvement of physico-mechanical properties of carbamazepine crystals. *Ind. J. Pharma. Res.* 6(2) (2007) 83-93.

37. W.Y. Dong, P. Maincent, R. Bodmeier, In-vitro and in-vivo evaluation of carbamazepine-loaded enteric microparticles. *Internat. J. Pharma.* 331 (2007) 84-92.
38. D.M. Patel, N.M. Patel, N.N. Pandya, P.D. Jogani, Gastroretentive drug delivery system of carbamazepine: Formulation optimizing using simplex lattice design: a technical note, *Amer. Assoc. Pharma. Sci. Tech.* 8(1) (2007) 11.
39. S.A. Apurba, H.P. Atiqul, S. Dilasha, K. Golam, J. Reza-ul, Investigation of *in-vitro* release kinetics of carbamazepine from Eudragit RSPO and RLPO matrix tablets, *Trop. J. Pharma. Res.* 8(2) (2009) 145-152.
40. G. Kuminek, J.M. Kratz, R. Ribeiro, R.G. Kelmann, B.V. de Araujo, H.F. Teixeira, C.M. Simoes, L.S. Koester, Pharmacokinetic study of a carbamazepine nanoemulsion in beagle dogs, *Internat. J. Pharma.* 378 (1-2) (2009) 146-148.
41. M. Rajkumar, S. Bhise, Carbamazepine-loaded porous microspheres for short-term sustained drug delivery, *J. Youn. Pharmaci.* 2 (2010) 7-14.
42. G. Raymond, M. Degennaro, R. Mikeal, Preparation of gelatin: phenytoin sodium microspheres: an in-vitro and in-vivo evaluation, *Drug. Dev. Indus. Pharm.* 16(6) (1990) 1025-1051.
43. G.A. Brazeau, M. Sciame, S.A. al-Suwayeh, E. Fattal, Evaluation of PLGA microsphere size effect on myotoxicity using the isolated rodent skeletal muscle model, *Pharma. Dev. Tech.* 1(3) (1996) 279-283.
44. L.I. Giannola, V.D. Caro. Entrapment of phenytoin into microspheres of oleaginous materials: process development and in-vitro evaluation of drug release, *Drug. Dev. Indus. Pharm.* 23(12) (1997) 1145-1152.
45. A.A. Al-Helw, A.A. Al-Angary, G.M. Mahrous, M.M. al-Dardari, Preparation and evaluation of sustained release cross-linked chitosan microspheres containing phenobarbitone, *Adv. Drug Deliv. Rev.* 28(1) (1997) 25-42.
46. A.M. Ei-Helw, A.M. Al-Hazimi, A.M. Hazimi, R.M. Youssef, Preparation of sustained release phenobarbitone microspheres using natural and synthetic polymers, *J. Microencap.* 15(3) (1998) 373-382.

47. P. Benelli, B. Conti, I. Genta, M. Costartini, L. Montanari, Clonazepam microencapsulation in poly-D, L-lactide-co-glycolide microspheres, *J. Microencap.* 15(4) (1998) 431-443.
48. V. Ferranti, H. Marchais, C. Chabenat, A.M. Orecchioni, O. Lafont, Primidone loaded poly- $\epsilon$ -caprolactone nanocapsules: incorporation efficiency and in-vitro release profiles, *Internat. J. Pharma.* 193 (1) (1999) 107-111.
49. S. Hazendar, B. Dortune, Preparation and *in-vitro* evaluation of Eudragit microspheres containing acetazolamide, *Internat. J. Pharma.* 269(1) (2004) 131-140.
50. A.T.M. Serajuddin, C.I. Jarowski, Influence of pH on release of phenytoin sodium from slow-release dosage forms, *J. Pharma. Sci.* 82(3) (2006) 306-310.
51. J. Shaji, A. Poddar, S. Iyer, Brain-targeted nasal clonazepam microspheres. *Ind. J. Pharma. Sci.* 71(6) (2009) 715-718.
52. K. Florence, L. Manisha, A.K. Babar, K. Ankur, A.K. Mishra, A. Misra, Intranasal clobazam delivery in the treatment of status epilepticus, *J. Pharma. Sci.* 100(2) (2011) 692-703.
53. A. Fidalgo, T.M. Lopez, L.M. Ilharco, Wet sol-gel silica matrices as delivery devices for phenytoin, *J. Sol-Gel Sci. Tech.* 49(3) (2009) 320-328. DOI: 10.1007/S 10971-008-1880-3.