Review Article

Formulation Technologies for Chrono Therapy of Epilepsy: A Review

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Abstract

Epilepsy is a most common serious disorder of the brain accounting for 1% of the world population. Most of the patients with epilepsy continue to have seizures despite anti-epileptic therapy. Seizure occurrences are diurnal, nocturnal, diffuse or circadian in nature. Epileptic seizures are characterized by sudden, transient, explosive, disorderly firing of neurons. Epileptic seizures with circadian rhythmicity tend to be dependent on origin and type of seizures. The pharmacokinetic and pharmacodynamics parameters aids in the better understanding of the physiology of epileptic seizures such as absorption, distribution, metabolism and excretion of the drugs used in the treatment of epilepsy which helps in enhancing bioavailability of the dosage forms. The review focuses on the chrono pharmacokinetics of AEDs, seizure patterns of epilepsy. The application of chrono therapy helps in optimizing the dose, minimizing toxic effects by altering the time of administration that may provide improved seizure control by maintaining therapeutic plasma concentrations of drug compared to the conventional therapy which lacks specified time of administration of drug, key technologies in chrono pharmaceutical oral drug delivery for epilepsy helps in achieving control of seizures for a better mental and social life.

***Keywords*:** Epilepsy, Circadian rhythm, Chrono Pharmacokinetics, Chrono Therapy, Diurnal, Nocturnal

Introduction

Epilepsy is one of the world's oldest chronic neurological diseases dating back to 4000 B.C with written records. It affects approximately 50 million people worldwide. 80% of the affected people living in low and middle income countries, three fourths of these people with epilepsy do not receive the treatment. An estimated proportion of general population with epilepsy is around 7 to 14 persons per 1000 people. Nearly 2.4 million persons are diagnosed with epilepsy every year as per the WHO report 2015 (WHO, May 2015).

Epilepsy is a chronic disorder of the brain characterized by recurrent seizures with brief episodes of involuntary movement that may involve apart or entire part of the body and are sometimes accompanied by temporary loss of consciousness, disturbances of movement, sensation including vision, hearing and taste or other cognitive functions as well as psychological conditions including anxiety and depression. Seizure episodes are as a result of sudden, transient excessive discharges in a group of brain cells. Seizures may vary in frequency from less than 1 year to several per day (WHO, May 2015). Fear misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries.

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Chrono Pharmacokinetics of Epilepsy

Chrono pharmacokinetics is an upcoming drug delivery system which combines the conventional goal of pharmaceutics with the recent knowledge derived from various disciplines in chrono biology.

The study of biological rhythmicity and their mechanism can be termed as chronobiology (Smolensky and D'Alonzo, 1988). In the year 1959 Franz Halberg coined the term 'CIRCADIAN' derived from the Latin word 'CIRCA' means

about and dies mean a day (Moore-Ede et al., 1982).

Julien Joseph Virey had been credited for his insights and writing in the field of chronobiology (Reinberg et al., 2001). Other researchers who had greatly impacted for the development of chrono pharmaceutics and chrono therapy are Aschoff, Pittendrigh Franz Halberg has been attributed as the founder of modern chronobiology (Pittendrigh et al., 1974, Aschoff, 1965, Halberg et al., 2003).

Hasting et al., (2003) provided some basic aspects of circadian timing in the brain and periphery in relation to health and disease. Repeatable changes in measurement which occurs over a time are called rhythms.

The central mechanisms of epilepsy can be discovered and make it possible with chronobiology

(Poirel and Ennaji, 1991, Poirel and Ennaji, 2000).

Based on the frequency of rhythms (Halberg et al., 1970, Nicolau et al., 1983), classified and listed in Table 1.

Table 1. Classifications of Rhythms

Period (τ)	Major rhythmic components	
Short [τ<0.5 h]	Pulsatiles	(0.1s < τ < 1s)
Intermediate	Circadian	(20 h< τ<28 h)
[0.5 h<τ<6 days]	Ultradian	(0.5 h<τ <20 h)
	Infradian	(28 h <τ<6 days)
Long Period	Circa mensual	(τ~30 days)
[τ>6 days]	Circaseptan	(τ~7 days)
	Circannual	(τ~1 year)

Ultra radian > 1 day includes, EEG, heart rate and hormonal pulses

Diurnal rhythms- daily basis includes, body temperature, sleep/wake cycle, Circa lunar rhythms-once a month.

Circadian rhythm is a biological rhythmic process generated and maintained by biological clock formed by the cells of supra chaismatic nucleus, endogenously mediated by 24 hours cycles of physiological process in which changes can be observed in the melatonin levels, hormone production and core body temperature (Hastings and Maywood, 2007).

Chrono kinetics is concerned with dosing interval rhythm dependent differences in Absorption, Distribution, Metabolism and Elimination of drugs. Changes in gastrointestinal P^H can affect drug solubility, changes in gastric emptying, motility and blood flow can affect the rate and extent of drug absorption.

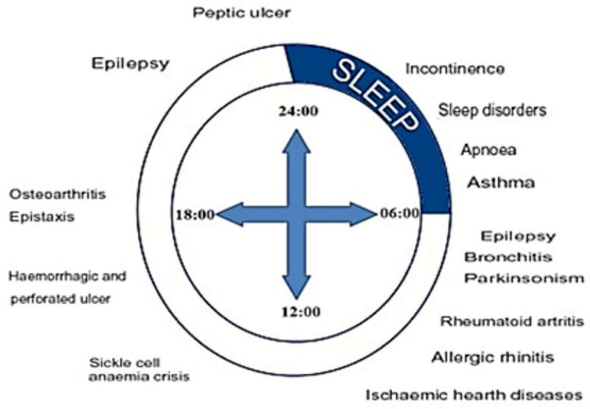

Figure 1. Diseases shown to display circadian Rhythms

Drug biotransformation, metabolism are affected due to circadian rhythmicity in hepatic blood flow and enzyme activity. Drug elimination can be effected by circadian rhythms in hepatic bile function flow as well as renal blood flow and tubular function. Chrono toxicology refers to the toxic adverse effects of the medications due to dosing time, rhythm dependent differences of different classes of medications which have narrow therapeutic range are likely to show significant dosing time differences in safety. Pharmacological aspects of chronobiology is termed as chrono pharmacology which can be classified as chronotherapy, Chronopharmacokinetics, chronotoxicology.

Chrono therapy refers to the treatment of a disease with specific time interval which matches the rhythmicity of the disease to optimize therapeutic outcomes and minimize side effects. Chrono therapy is gaining importance as an emerging therapy due to its specificity of time that matches the time of taking the medication taken by the patients.

Ideal characteristics of chrono drug delivery system

- Should be non-toxic in nature
- Adaptability to circadian rhythm of the disease
- Should be bio-degradable and bio compatible
- Dosage convenience enhanced patient compliance
- Economic in cost
- Ability to maintain constant therapeutic concentration levels in the blood.

Advantages of Chrono drug delivery

- Reduced dosing frequency
- Enhanced patient convenience and compliance
- Instantaneous drug level matching exact biological and physiological needs to treat the

disease at each time point.

- Decreased total therapeutic or preventive dose.
- Chrono drug delivery develops a new schedule in patient's life like getting up and sleeping early.

Disadvantages

- Delayed attainment of Pharmacodynamic effect
- Reduced bioavailability
- Enhanced hepatic first pass metabolism
- Possibility of dose dumping in case of technological failure
- Dosing in flexibility

Pharmacokinetic Parameters of Anti-Epileptic Drugs

The pharmacokinetics and pharmacodynamics aspects of epileptic medications are affected by endogenous cycles. Pharmacokinetics parameters such as peak drug plasma concentration (Cmax), time to reach maximum concentrations (Tmax), Area under the concentration-time curve (AUC), volume of distribution (vd), protein binding , metabolism and elimination of drugs in the body.

Absorption

Absorption may be varied based on dietary cues and circadian gene expression. Physicochemical properties of the drug such as nature (lipophilicity or hydrophilicity), area, structure of the bio membrane, gastric emptying, motility, gastrointestinal blood flow can influence the absorption process following oral drug administration.

Most of the lipophilic drugs absorbs faster when the drug is taken in the morning compared to evening but is not the case with hydrophilic drugs (Bruguerolle, 1998). Administration of carbamazepine prior to the consumption of breakfast delays the absorption of delayed release forms disproportionately compared to conventional dosage forms (Theisohn Massion and Werner, 1989). Valproic acid is absorbed faster with empty stomach compared to taken after the meals (Ohdo et al., 1992).

Distribution

Variations in biological fluids, tissues in relation to distribution of drug are recorded to vary according to time of day due to circadian rhythms. Changes in blood flow are known to be circadian time dependent which possibly explains diurnal increase or decrease of blood flow may explain a possible difference in drug distribution depending on dosing time.

The distribution of anti-epileptic drugs are likely to vary in relation to the circadian and diurnal rhythms .In an another study conducted the plasma levels of carbamazepine were noted and the related metabolites were higher during the 24 hours post dose in the night time in comparison to the day time (Olano et al., 1998).

Plasma protein binding of drugs plays an important role in the distribution of sodium valproate, maximal free concentration of the drug occur between 2-8 am, valproate is most likely to be protein bound during 4-8 pm (Patel et al., 1982).

Metabolism

Enzyme activities shows circadian time dependent difference in brain, kidney and liver metabolism of drugs in the liver are imparted by selected enzyme expression (Stokkan et al., 2001). The cyp3A4 gene may be expressed diurnally required for digestion of carbamazepine which was demonstrated in an IN-VITRO study (Takiguchi et al., 2007).

Excretion

Circadian time dependent changes can be observed in renal physiological functions such as renal blood flow, urinary P^H. glomerular filtration and tubular resorption. These physiological functions may impart the manner in which the kidney excretes the metabolites from medications. The plasma concentrations of 3-oxo vpa, 4OH vpa and creatinine were determined following collection of samples during 24h with 6 diurnally active male volunteers.

The urinary excretion of 3-oxo VPA, 4OH –vpa and glucoronides were found to decrease between 2000H-0800H when compared to between 0800H-2000H which indicates diurnal variations renal Clearance (Reith et al., 2001). Trials in chrono pharmacotherapy in epilepsy up to date only fewer studies were made an attempt to utilize the principles of pharmacology in differential dosing trials.

Studies were conducted to evaluate the effect of differential chrono therapeutic dosing trails of carbamazepine and phenytoin in epileptic patients (Yegnanarayan et al., 2006). Yegnanarayan and others changed administration times in patients with diurnal seizures which were not controlled by phenytoin/carbamazepine. Their findings revealed that by adjusting the time of administration from 0800 H to 2000 H therapeutic drug levels were achieved more easily and toxic manifestations were reduced.

Nocturnal medication

A more targeted approach towards differential dosing was attempted in a pilot trial (Guilhoto et al., 2011). In this study 18 patients with nocturnal /early morning conventional to refractory AED therapy were studied.

The study was designed in such a way that patients were treated with the evening dose was twice the morning dose

keeping the total dose of the medication constant of 18 patients, 11 patients became seizure free following a mean follow up time of 5.3 months and 4 patients had a 75%-90%reduction of seizures. The study suggested chrono therapeutics can provide improved seizure control compared to conventional therapy.

Seizure Patterns in Epilepsy

Early observations on diurnal patterns in epilepsy linking to sleep wake cycle can be dated back to the year 1800's.

Early Observations

In the late 1800's Gower's made observations on diurnal patterns in epilepsy linking to sleep wake cycle (Gower's, and Wood, 1885). Over the last few decades additional patterns in epilepsy were revealed, some of the seizure patterns in epilepsy were identical in relation to the sleep wake cycle, biological clock and circadian rhythms. Other factors such as seasonal variations in climate (Cortez et al., 1997) may be accounted for seizure patterns such as variations in occurrences of seizures throughout the year.

Human seizure occurrences tend to exhibit 24 hours rhythmicity depending up on where seizure originates in the brain lobe (Hofstra et al., 2009, Pavlova et al., 2004, Quigg et al., 1998, Quigg et al., 2000). The above findings are supported from the experimental models of Limbic epilepsy on rats .Rats showed continuous limbic seizures occurrences with identical patterns were found when rats were made to free run in constant darkness (Quigg and Straume, 2000).

Diurnal patterns of epilepsy have been observed in various epilepsy models in animal studies. In studies conducted on rodents with limbic epilepsy more spontaneous seizures have been observed during the exposure to light than during darkness (Bertram et al., 1994; Gorter et al., 2001, Hellier et al., 1998, Quigg et al., 1998, Quigg et al., 2000).

Due to suspected association of seizure occurrences with some of the biological rhythms epilepsy can be an excellent candidate for chrono pharmacological treatment approaches.

The influence of circadian rhythms and spike wave discharges, motor activity with experimental animal model of generalized absence epilepsy were conducted under entrained and constant dim light conditions with EEG recordings. The study showed a clear circadian patterns for seizures and motor activity (G van Luijtelaar, et al., 2001).

Diurnal patterns of seizures

The frequency of occurrence of seizures were observed more during 11:00H to 17:00H and that of the period from 2300H to 0500H the frequency of occurrence of seizure was less. Seizures are extemporal (children) and Temporal (adults) in origin. Day time peak seizure tendencies were more for all types of seizures with more distinguishing for complex partial seizures. The tendency of complex partial seizures and tonic seizures were low during 2300H to 0500H.Un even seizure distribution have been observed all through the day depending up on the seizure origin in the lobe.

Frontal lobe seizures occur mostly early in the morning during 1100H to 1700H,while temporal lobe seizures occur most probably in the afternoon time during 2300H to 0500H which may also have an additional morning peak.

Parietal lobe seizures occur frequently during 1700H to 2300H (Hofstra et al., 2009). The authors discovered that frontal lobe seizures occur frequently during 6-12 hours after melatonin onset while temporal lobe seizures occur frequently 6 hours before melatonin onset. Advances in research are essential to associate the occurrence of epileptic seizures to circadian rhythm.

Lunar patterns in seizures

The timing of epileptic seizures were believed to be long associated with the changes in lunar phases. The frequency of seizures may decrease during full moon by the presence of nocturnal light as suggested by the study (Baxendale and Fisher, 2008). In a research study conducted using patient data from an epilepsy monitoring unit the timing of epileptic seizures with respect to the moon phase due to the correction clarity of the night these findings disappeared.

Sleep deprivation and epilepsy

Strong relationships are there between sleep deprivation and epilepsy. A wide variety of sleep abnormalities can be seen in patients with epilepsy including more awakenings and more fragmented sleep. Temporal patterns in epilepsy are seen in patients whose seizures cluster at late night or early in the morning.

In a study concerned evaluating the presence of epileptic form discharges among patients undergoing sleep deprivation 52% of patients presented with spike activation on EEG following sleep deprivation .Sleep deprivation plays a major role in patients whose seizures disrupt sleep (Fountain et al., 1998).

Melatonin and epilepsy

Melatonin was first isolated by Lerner and colleagues as N-acetyl 5-methoxy tryptamine as the active principle from beef pineal gland (Lerner et al., 1958). Wurtman, Axelrod and colleagues had shown that melatonin is synthesized from tryptophan by formation of serotonin in the mammalian pineal gland.

Melatonin levels are found to be high in the night time and low in the day time. The levels of melatonin are regulated by supra chaismatic nucleus through inhibition and production

of melatonin (Kalsbeek et al., 2000) which provides an association between melatonin and sleep cycle.

The relationship between epileptic seizures and melatonin had been studied intensively, several animal studies had shown the relationship between anti convulsant effects against electrically induced seizures (Lapin et al., 1998; Mevissen and Ebert, 1998). Following seizures melatonin levels were noted to rise this changes contributed to reports that indicate an anticonvulsant effect of melatonin .melatonin suppress seizure activity at certain doses. Recent review of the literature revealed that published trails of melatonin therapy were limited and resulted in conflicting results.

Low base line levels of melatonin were reported in people with epilepsy (Bazil et al., 2000; Fauteck et al., 1999; Laakso et al., 1993: Yalyn et al., 2006). Some of the authors found elevated melatonin levels (Schapel et al., 1995; Molina- Carballo et al., 1994). Similarly elevated levels of melatonin were found during and after Generalized tonic clonic seizures and complex partial seizures were described by (Bazil et al., 2000; Molina-Carballo et al., 2007) some of the author had observed no changes after generalized tonic clonic seizures and complex partial seizure (Rao et al., 1989).

Melatonin can be used to prevent seizures had been studied (Fauteck et al., 1999; Peled et al., 2001). With the above findings epilepsy can be treated with melatonin alone or in combination with conventional anticonvulsant drugs and has the ability to control circadian rhythm.

Melatonin has anti-oxidant property which has the ability to reduce stress in epileptic patients. The basis for the effect of melatonin on seizures includes anti-oxidant activity or GABA potentiating effects. However melatonin can be used as chrono therapeutic medication to adjust circadian rhythm and therefore has a role in the alignment of the circadian rhythm. Conventional dosage forms need to be administered two to four times a day but an ideal chrono pharmaceutical drug delivery allows administering once a day.

Advantages of chrono drug delivery includes attainment of steady state plasma drug oncentration on reducing dosing ,frequency enhanced compliance and convenience matching exact biological and physiological needs to treat the disease thus reducing total therapeutic dose.

Key Technologies in Chrono pharmaceutical Oral Drug Delivery

Key technologies in chrono pharmaceutical oral drug delivery are listed in Table no 3 which includes cap technology is a unit dosage form such as capsule for delivering drugs into the body capsule comprising of one or more drug containing particles (beads, pellets, granules). Each pellet exhibits predetermined sustained release profile with a predetermined time of 3-5 hours. The active mode of the drug comprises inert particle coated with an API containing film forming formulation. Diffucap technology is designed to provide plasma concentration time profile in a circadian manner which varies according to physiological need during the day (Percel et al., 2003).

Chrono topic Technology

Chrono topic technology is comprised of drug containing core with an outer release containing coating. Single and multiple dosages such as tablets, capsules or Minitab lets and pellets have been designed as inner drug formulation. Cores present in the formulation are meant either for prolonged release or immediate release of active ingredients.

The main focus has so far been on the attainment of rapid and transient delayed release. The outer barrier consists of swellable polymers of different viscosity grades mainly HPMC polymers are exploited for this purpose (Youan,

Table 2. Key technologies in chrono drug delivery systems

Key technologies	References
Diffucaps Technology	Percel et al., 2003
Chrono topic Technology	Youan, 2004
Egalet Technology	Verma and Sanjay, 2001
Oroset Technology	Youan, 2004; Verma et al., 2001; Ohdo et al., 2001
Geoclock Technology	Panoz and geoghegan, 1989
Port Systems	Crimson and Vieira, 2003
Ceform Technology	Fuisz, 1996
Codas Technology	Prisant et al., 2000; Youan, 2009
Contin Technology	Leslie, 1986
Three dimensional Technology	Katstra et al., 2000; Rowe et al., 2000; Monkhouse et al., 2003
Timerx Dimensional Printing	Baichwal and Staniforth, 2000; Staniforth and Baichwal, 2005

2004). The mechanism chronotropic technology is erosion, diffusion and dissolution when outer layer comes in contact with aqueous fluids undergoes glassy rubbery transition. The technology has shown to provide pulsatile release behaviour *in-vitro* as well as *in-vivo* release.

Egalet Technology

This technology is designed for delayed release comprising of an impermeable shell with two lag plugs enclosed with active drug in the middle of the unit .The shells are made of slow biodegradable polymers such as ethyl cellulose while the complex can be utilized as a matrix in control release formulation because it is a semipermeable membrane .the technology used in the development of sustained release tablets (Verma and Sanjay, 2001).

Oroset Technology

Chrono set is a dominion of OROS delivery system that reproducibly delivers a bolus drug dose in a time or site specific manner to the gastro intestinal tract using Oroset technology the drug formulation is completely protected from chemical and enzymatic degradation in the gastro intestinal tract before release and the timing of release is unaffected by gastrointestinal contents by specifically balancing the osmotic engine the semipermeable membrane and the other attributes of the system configuration drug release onset time varying from 1-20 hours can be achieved .the formulation consists of two layers one is core tablet which consists of active pharmaceutical ingredient embedded in the polymer and the next layer is surrounded by semipermeable membrane .The formulation is drilled with delivery orifice through which the gastric fluid comes in contact with active pharmaceutical ingredient (Youan, 2004; Verma et al., 2001; Ohdo et al., 2001).

Geoclock Technology

Geoclock technology is an approved oral drug delivery with a predetermined lag time for the release of drug from the tablet not depending on food or p^H.Geoclock technology can be used for single as well as multiple dosage units with predetermined time intervals between the drugs. Geoclock technology consists of two layers inner active drug core and an outer tablet layer comprising a mixture of lipophilic wax and breakable material. The composition develops lag time not dependent on p^H before to the release of the active drug .The active drug from the tablet is released by either by eruption or controlled release pattern and the release characteristics of inner core can be modified to achieve the desired profile (Panoz and geoghegan, 1989).

Port Systems

Programmable oral release technologies are meant for delivery of drug candidates to either specific intestinal sites or releases drug at predetermined time points. Drugs with low solubility are coated with solubilizing agents ensuring control release from the dosage form. The tablet core comprises polymer coated with semipermeable controlling polymer. Matrix of the plugs consists of a mixture of pharmaceutical excipients including polymers like ethylene oxide (Crimson and Vieira, 2003).

Ceform Technology

Ceform technology consists of microspheres uniform in size and shape prepared by melt spinning method .the microspheres thus obtained are spherical with a diameter of approximately 150-180µm allows for incorporation of high drug content . Microspheres can be used in wide variety of dosage forms such as tablets, capsules, effervescent tablets and sachets for controlled release action microspheres can be coated with enteric coating /can be combined with sustained release mechanism (Fuisz, 1996).

Codas Technology

Chrono therapeutic oral drug absorption system is a multi-particulate drug delivery system specifically designed for night time dosing consisting of water insoluble polymer and water soluble polymer .the release of the drug is delayed due to the presence of non-enteric coating to drug loaded beads. The release mechanism follows diffusion followed by dissolution and swelling of polymer matrix the release mechanism is independent of presence of food and p^H (Prisant et al., 2000; Youan, 2009).

Contin Technology

This technology comprises of molecular co-ordination complexes formed between cellulose polymer and a non-solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the group directly with an aliphatic alcohol by melt method. In capsule form hard gelatin capsule is coated with a semipermeable membrane rate controlling polymer. Active medicaments are mixed with osmotic agents kept inside the cell. Water insoluble plug is used to seal the capsule shell.an immediate release dosage can be added above the plug to complete the closing (Leslie, 1986).

Three Dimensional Printing

Three dimensional printing is a novel solid free form fabrication technology of complex pharmaceutical drug devices .using 3-DP process immediate extended release tablets, double order release. Printing parameters can be modified to achieve release properties such as lag time and release rate, HPMC, lactose and Eudragit 100 were used for dual release with the use of surface degradation /erosion system (Katstra et al., 2000; Rowe et al., 2000; Monkhouse et al., 2003).

Timerx Technology

Timerx technology is a hydrogel based controlled release system (Baichwal and Staniforth, 2000), combining a hetero dispersed mixture composed primarily of two polysaccharides xanthan gums and locust beans in the presence of dextrose .The release of the drug is controlled by the rate of water penetration from the gastro intestinal tract into the gum matrix which swells to form gel and after while release active drug substance. The release of drug from gum matrix can be controlled by varying the changing the proportion of gums along with tablet coating and process of manufacturing (Staniforth and Baichwal, 2005).

Conclusion

Application of chrono pharmaceutical drug delivery systems are beneficial for better understanding of epilepsy which is circadian in origin .Epilepsy is an electrical hyperactivity of brain cells causing seizures in turn causing motor and sensory disturbances .The pharmacokinetics and pharmacodynamics of medications vary depending up on biological rhythms .The study of absorption, distribution, metabolism and excretion of drugs helps us to understand and optimize the dosage strength of medication. Currently available conventional dosage forms of epilepsy does not meet the therapeutic concentrations of the medication during the occurrences of seizures following circadian rhythm. The use of chrono therapy with the use of pharmacokinetics helps us to synchronize the drug concentrations to circadian rhythms in epilepsy. One of the approaches to increase the efficiency of chrono therapy for epilepsy is administering the drugs when they are best tolerated .The use of available chrono drug delivery technologies minimizes adverse effects improves the therapeutic strategies by optimizing the current therapy, while further more research is needed for better control of epileptic seizures.

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