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Formulation Development and In-vitro Evaluation of Chrono Modulated Compress Coated Tablets of Divalproex Sodium In The Treatment of Partial Epilepsy

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ABSTRACT

Chronotherapeutics also known as pulsatile drug delivery system deals with the study of the temporal changes in absorption, distribution, metabolism and elimination of drugs and thus takes into account the influence of time of administration on these different steps and it focuses on the release of a drug after a lag time at a particular site in order to maintain constant blood levels of a particular drug matching circadian rhythms of various diseases. The role of circadian rhythms in the mechanisms of disease and the pharmacokinetics and pharmacodynamics of medications constitutes a challenge to drug-discovery and drug-delivery scientists. The aim of present work is to develop chrono modulated compress coated floating tablets of Divalproex Sodium in the treatment of partial epilepsy.

Keywords: Chronotherapeutics, Drug delivery, pulsatile drug delivery systems , Divalproex Sodium, compress coated floating tablets.

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INTRODUCTION

The goal in drug delivery research is to meet therapeutic needs relating to particular pathological conditions by developing new formulations. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of oral drug delivery systems. Different technologies are being utilized in the development of triggered, pulsatile, controlled and programmed drug delivery devices has intensified in recent years. Chronotherapeutics is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time because the biochemical, physiological and pathological variations over a 24h period in humans (Figure 1) have been occurred. Chronotherapeutics deals with the medical treatment according to the human daily working cycle that corresponds to a person's daily, monthly, seasonal or yearly biological clock or in order to maximize the health benefits and minimize the adverse effects. The main goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time. If symptoms of a disease are varied the circadian rhythms also varied the drug release. In the treatment of many diseases chronotherapeutics drug delivery offers a new approach in the pharmacologic interventions design for the effective treatment in the different types of diseases.

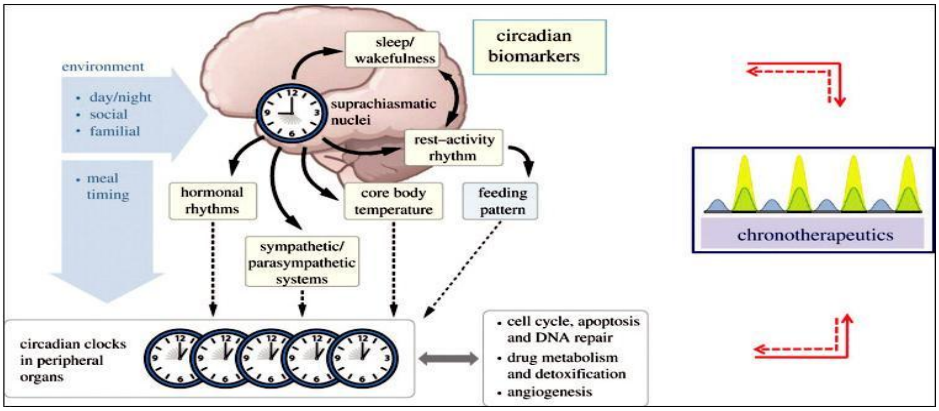

Figure 1: Chronotheraputics – circadian cycle of human body [1]

The "chronotherapeutics" term is mainly new in the field of drug delivery and in the treatment method. It is defined as the widespread term in which disease follow the circadian rhythm which undergoes the metabolic changes. Chronotherapeutics is defined as the method in which drug availability is matched with the rhythms of the disease according to the time structure which results in the maximum therapeutic effects and less adverse effects.

Biological rhythms [2,3]

A biological rhythm is a self-sustaining oscillation of endogenous origin. The spectrum of

biological rhythms is broad as displayed in Table 1. Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuro endocrine system are but a few examples. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (<20 h),light intensities are thought to be the major environmental cue involved in circadian entrainment. Light- signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retino hypothalamic tract. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 h. In fact, in most people, it is somewhat longer, closer to 25 h. Environmental times, termed synchronizers or zeitgebers, the strongest one being the daily light–dark cycle occurring in conjunction with the wake–sleep routine, set the inherited pacemaker circadian timekeeping systems to 24h each day. The human circadian time structure was depicted in Table 1.

Table 1: Spectrum of biological rhythms [2,3]

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	Circamensual (τ~30 days)
[τ>6 days]	Circaseptan (τ~7 days)
	Circannual (τ~1 year)

Circadian time structure [2,3]

The results of numerous biological rhythm studies help define the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock-like diagram like that shown in Figure 2. This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most human beings-sleep in darkness from 10.30 P.M to 6.30 A.M and activity during the light of the day between 6.30 A.M and 10.30 P.M.

The peak gastric acid secretion, white blood cell count (WBC), calcitonin gene-related protein, and atrial natriuretic peptide occurs late at night or early in sleep. Growth and thyroid stimulating hormone (TSH), blood lymphocyte and eosinophil number, and plasma melatonin and prolactin crest during sleep as do the adreno corticotropic (ACTH), follicle stimulating (FSH), and luteinizing (LH) hormones. Plasma cortisol, renin activity, angiotensin, and aldosterone peak in the morning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Hemoglobin and insulin concentrations peak at noon and in the afternoon, as do the spirometric measures of airways caliber FEV_1 (forced expiratory

volume in 1 s) and PEF (peak expiratory flow rate).

The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. The information conveyed in this figure clearly illustrates that the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable and coordinated manner during the 24 h.

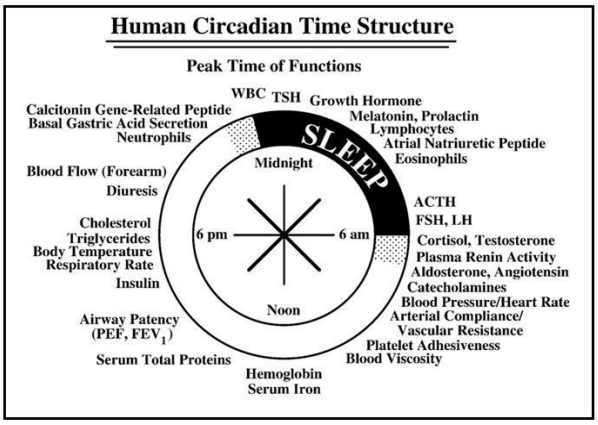

Figure 2: Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to ~10–11 p.m.) alternating with nighttime sleep [2,3].

CHRONOPHARMACOKINETICS [2,3]

Chronokinetics refers to dosing-time, i.e., rhythm-dependent, differences in the absorption, distribution, metabolism, and elimination of medication. Circadian rhythms in gastrointestinal pH can affect drug dissolution, and circadian rhythms in gastric emptying, motility, and blood flow can affect the rate, and in certain cases the amount, of drug absorption

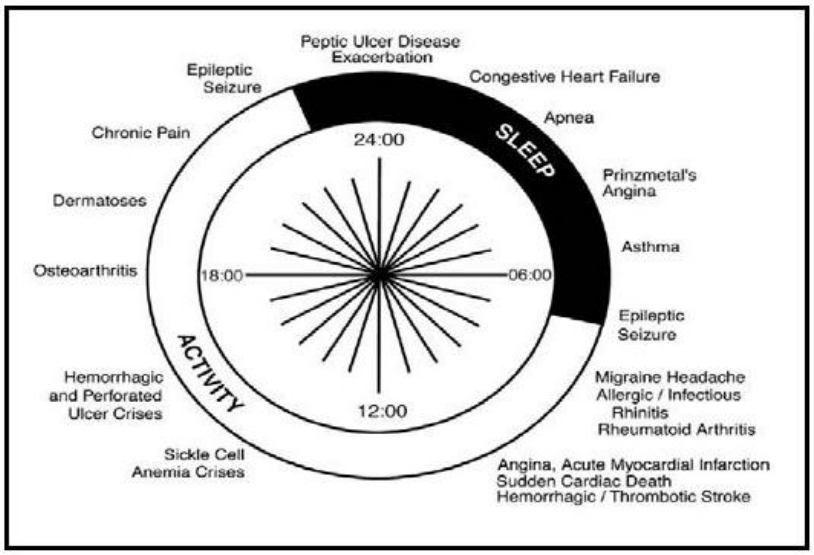

Figure 3: Display in the form of a 24 h clock diagram of the approximate time, in human following the diurnal activity/nocturnal sleep routine, when symptoms or events

of diseases are worst or most frequently [2,3].

Moreover, circadian rhythms in hepatic blood flow and enzyme activity can significantly affect drug biotransformation and metabolism, and rhythms in hepatic bile function and flow as well as renal blood flow, glomerular filtration, and tubular function can affect drug elimination. The pharmacokinetics, for example, the parameters of the time to peak concentration, peak height, elimination rate, volume of distribution and area under the time-concentration curve, of a number of medications have been found to be influenced by circadian rhythms.

Drug Absorption:

In humans, for orally administered drugs, absorption was shown to be affected by CIRCADIAN rhythm as gastric acid secretion and gastric pH, gastric motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of day. These changes may have an impact on the time-dependent difference of drug absorption. For instance, circadian changes in pH may affect drug ionization according to its physicochemical properties. On the other hand, gastric emptying time is another important factor in the absorption of drugs. Gastric emptying rates were compared between morning (8am) and evening (8pm) in male subjects and it was found that gastric emptying t½ for the evening meal was significantly longer for solids but not for liquids compared with those of the morning meal. The increase in evening meal gastric emptying time may also cause a delay in reaching peak plasma concentrations for several drugs. Such variations may be related to the physicochemical properties of a drug, since most lipophilic drugs seem to be absorbed faster in the morning as compared to evening. The mechanisms underlying the chronokinetics of lipophilic drugs involve a faster gastric emptying time and a higher gastrointestinal perfusion in the morning. However, such changes have not been shown for hydrophilic drugs. Feeding conditions also contributes to dosing time-dependent difference in drug absorption. Drug absorption by other than oral route of administration is also influenced by biological rhythms.

Molecular mechanism of circadian gene regulation[5]:

Maintenance of the circadian clock involves coordinated feedback regulation of transcription and translation of CLOCK genes to achieve the oscillatory levels of activators and repressors Figure 4 ;. In a primary loop, CLOCK and BMAL1 (also known as ARNTL) form a large complex in the cytoplasm and translocate to the nucleus after being phosphorylated by protein kinases (e.g., CK1ε/δ) to activate the transcription of PERIOD (PER1, PER2, and PER3) and CRYPTOCHROME (CRY1 and CRY2) genes. The PER-CRY complex then subsequently binds to CLOCK-BMAL1 complex to repress their transcriptions. PER and

CRY are degraded through the ubiquitin-proteosomal pathway (e.g., FBXL3-dependent) and this whole process takes about a 24 h cycle. An additional feedback loop is at work with nuclear hormone receptors such as ROR (RORa, RORb, and RORc) and REV-ERBα/β to modulate the expression of clock-controlled genes (CCGs) and clock-modulated genes. Several circadian modulators such as DEC1/2 (also called BHLHE40/41), DBP, and E4BP4 (also called NFIL3) provide the additional level of circadian regulation. In the promoter region of core CLOCK genes and CCGs, E-box elements are recognized by BMAL1-CLOCK, D-box elements by DBP-E4BP4, and REV-ERBα/ROR-regulatory elements (RORE) by ROR. CLOCK, BMAL1, and PER1 are acetylated in response to the environmental stimuli to adjust the activity of core clock proteins. Changes or disruption in this multi-step regulation influences the 24-h period by shortening or lengthening it.

Circadian regulation of ion channels and membrane excitability: Neurotransmitter receptors and ion channels have been shown to have rhythmic expression and activity under circadian regulation. Radioactive ligand binding assay of several neurotransmitter receptors in rat brains showed that the cortex has the highest variation and that the cerebellum has the lowest. Hippocampus has circadian patterns of ligand binding activities of α1 adrenergic and benzodiazepine receptors. Although the studies have been limited mostly to the visual system (photoreceptors, retinal neurons, and suprachiasmatic nucleus), cGMP-gated ion channel, T- and L-type Ca channels, and voltage-gated K channels have been shown to be under circadian control. Clock gene products are involved in rhythmicity of membrane excitability and electrical activities mostly due to changes in potassium conductance. The expression of pyridoxal kinase, an enzyme involved in metabolism of pyridoxal phosphate and neurotransmitters (e.g., serotonin and dopamine), has shown to be regulated by circadian PAR bZIP transcription factors. Thus, circadian rhythm modulates neuronal excitability at the multiple levels, may trigger the hyperexcitability out of delicate control.

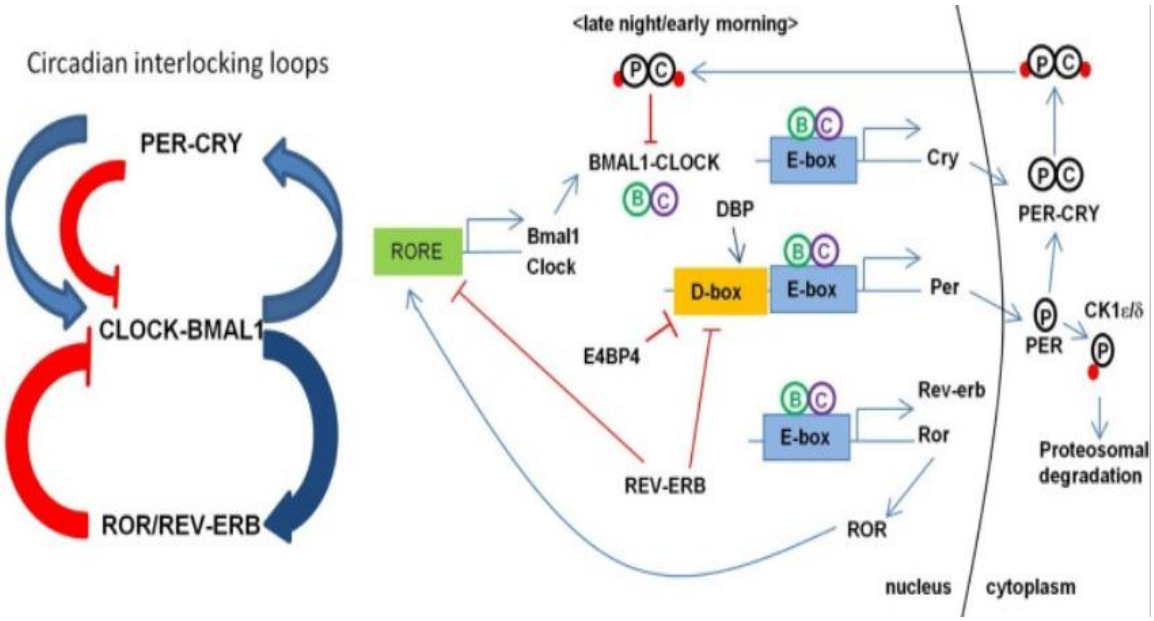

Figure 4: **Transcriptional regulation circuit of clock genes in mammals[5].**

(A) Circadian interlocking loops show that a primary loop of CLOCK-BMAL1 and PER-CRY complexes and an additional feedback loop of ROR/REV-ERB, conferring a tight transcriptional regulation. The blue arrows indicate the transcriptional activation and the red lines indicate the inhibiting activity of the targets. ROR as an activator and REV-ERB as a repressor regulate the expression of BMAL1. **(B)** Transcription of BMAL1 and CLOCK is regulated by ROR and REV-ERB through binding RORE elements at their promoters. CLOCK and BMAL1 activates the expression of CRY, PER, REV-ERB, ROR, and other CCGs (clock controlled genes) through binding to E-box element at their promoters. CRY-PER complex is phosphorylated and transported back to the nucleus inhibiting the CLOCK-BMAL1 activity. PER is phosphorylated to degrade through proteosomal pathway via CK1ε/δ.

Epilepsy[5]:

Neuronal excitability is homeostatically controlled between excitatory and inhibitory drives in the nervous system. Hyperexcitability, caused by the disruption of this delicate balance at the microcircuit level, may trigger the excessively synchronized electrical discharges of neurons in the brain which can manifest as epileptic seizures. As a global health issue, epilepsy affects ~1% of the general population. Temporal lobe epilepsy (TLE), especially, is often pharmacologically refractory and is the most common type of acquired epilepsy that involves the hippocampus, entorhinal cortex, and amygdale .

Circadian pattern of epileptic seizures in human and animal models[5]

The circadian pattern of seizures tends to be well preserved over the years in individuals and some PWE experience the episodes at the certain time of the day. However, the majority of one type over the other (nocturnal vs. diurnal) in the epileptic population is not always

consistent in the literature. This may be the result of heterogeneity between the cohorts recruited for each study. For instance, Gowers and Patry described independently that seizures are more frequent during the daytime than the night among the PWE they have observed. On the contrary, Janz and Hopkins independently found that nocturnal seizures are more prevalent than the diurnal ones. It is not straightforward to compare their findings because PWE were not classified based on seizure type, age, or other possibly important factors (e.g., comorbidity) of PWE in individual study. Additional studies, possibly collaborations at multiple epilepsy clinics, with a standardized protocol to recruit PWE, a clear classification of epilepsy/seizure types, and continuous monitoring and data analysis, are needed in order to provide a better picture of the phenomena.

In studies with a small cohort, epileptic seizures with circadian rhythmicity seem to be dependent on the origin and type of seizures. For example, de Weerd and colleagues used the video-EEG monitoring to describe that complex partial and temporal seizures in adults have the peak activity during 11:00–17:00 h period, and parietal seizures occurs more frequently during 17:00–23:00 period. In addition, frontal seizures showed the age-specific peak activities during 23:00–5:00 period in adults and 17:00–23:00 in children. Children with generalized seizures showed that tonic and tonic-clonic seizures were more frequently observed during sleep, whereas clonic, absence, atonic, and myoclonic types of seizures have various peak times in wakefulness.

Animal models of epilepsy also display circadian patterns of seizures. Chronically epileptic KCNA1 null mice have peak seizure occurrence early in the morning (at Zeitgeber 2.3), and seizure occurrence and rest-activity rhythm are inversely correlated. KCNA1 null mice have a longer circadian period than wild-type mice, and they are either phase-delayed or -advanced. A kainate rat model of TLE showed the higher seizure prevalence during the day and those placed in constant darkness (light-deprived) displayed spontaneous seizures that still followed a circadian pattern, suggesting that there is an endogenously mediated circadian pattern. This diurnal tendency has been also found in several different epilepsy models. Human and rodent models of TLE showed higher seizure prevalence during the day regardless of the species difference in the sleep-wake cycle. No direct association has been established between abnormalities (e.g., mutation) of major CLOCK gene products and epilepsy.

The mTOR pathway in epilepsy and circadian regulation[5]

The mTOR signaling pathway play major roles in regulating gene transcription and protein translation and it has been deeply involved in several physiological and pathological conditions. This pathway has also been recognized as a major signaling pathway in acquired

epilepsies as well as a few mutation-based epilepsies. Rapamycin, an mTORC1 kinase inhibitor, blocks epileptogenesis and reduces the seizure frequency in the pilocarpine/kainate-injected rats when repeatedly administrated. Rapamycin also suppresses axonal sprouting of somatostatin-positive interneurons in the dentate/hilus. A study shows that the sclerotic hippocampi of human specimen with refractory TLE, as well as kainate mouse model, have over-activated mTOR markers in reactive astrocytes. Relatively high levels of basal mTOR activity have been reported in SCN. Its maximal activity occurs during the subjective day and minimal activity during the late subjective. Phosphorylated (activated) S6, a ribosomal protein important in protein synthesis and a downstream target of mTORC1, oscillates synchronously with PER1 expression, and photic stimulation elicits a coordinate upregulation of PER1 and mTOR activation in SCN. Interestingly, some of the key molecules in the mTOR pathway have been shown to be regulated in circadian manner. By genome-wide RNAi screening in a model cell line, 17 gene products have been identified as strong circadian clock modifiers in period length and amplitude. These proteins showed a "network effect"—leading to dynamic changes in protein-protein interaction, phosphorylation, trans-activation, or trans-repression when affected. An insulin signaling pathway (mTOR-dependent) has been shown to regulate the circadian clock.

In addition, by genetically manipulating signaling molecules in *Drosophila in vivo*, PTEN-AKT-Rheb-TOR-S6K pathway has been shown to affect the circadian. SGG (*Drosophila* homolog of GSK3β) is phosphorylated by AKT and S6K1 and it phosphorylates TIMELESS (*Drosophila* homolog of CRYPTOCHROME), modulating its nuclear translocation with PERIOD (Figure 5 GSK3β may also modulate CLOCK, *BMAL1*, and REV-ERBα. Conditional knockout PTEN mice driven by the NSE-Cre promoter have a lengthened period. PI3K and mTOR are periodic and cyclic, and IRS and 4EBP1 are cyclic. High-fat diet lengthened the locomotor activity rhythm and modulated CLOCK genes at the molecular level in mice.

The catalytic subunits (α1 and α2) of AMP protein kinase (AMPK), which is an upstream regulator of mTOR kinase, regulate circadian rhythms. AMPK phosphorylates and modulates the activity of CRYPTOCHROME. Ketogenic diet (KD), a strict dietary plan to reduce the frequency and severity of seizure episodes in some population of epileptic patients, has been shown to be mTOR-dependent. In epileptic KCNA1 null mice, KD reduces frequency and periodicity of seizures, and it also improves diurnal rhythmicity. Since KD works through mTOR pathway, it will be interesting to see if mTOR inhibitors will have a beneficial effect on this mouse model. Therefore, it is a plausible that the circadian rhythmicity of seizure episode is mediated by the fluctuation in activity of the mTOR signaling molecules.

However, there is no direct evidence so far to support this hypothesis. Examining the circadian pattern of activity and expression of mTOR signaling molecules in epilepsy models, and studying the behavioral rhythm of null mice of those molecules will be valuable.

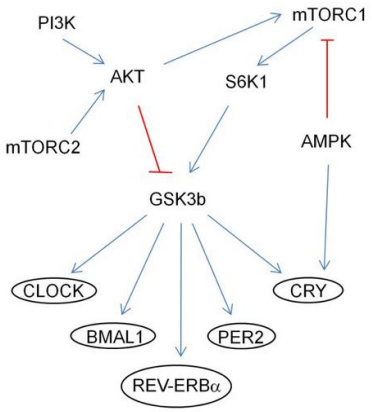

Figure 5: Regulation of CLOCK proteins by the mTOR pathway through GSK3β[5]: The arrows (in blue) indicate activation of the targets and the ones (in red) indicate inhibition by phosphorylation.

MATERIALS AND METHOD

Divalproex Sodium, Crosscarmellose, PVPK30, magnesium Stearate, Talc, Poly ethylene Oxide, NaHCO3, are received from Himedia laboratories.

Methods[6]:

Formulation Development:

For preparing tablets of Divalproex Sodium, initially the immediate release core tablets containing drug were prepared and the tablets were compression-coated using mixture of hydrophilic swellable polymer. To obtain buoyancy, sodium bicarbonate was included in the coating layer.

Preparation of Immediate Release Core Tablets of Divalproex Sodium:

The immediate release core tablets were prepared by weighing the drug, along with superdisintegrants and PVP K30 (dry binder), and passing them through sieve #44 to break the lumps and also for proper blending of powder; to this powder blend magnesium stearate and talc were added and mixed. The powder mixtures were punched using flat-faced punches using a 10 station automatic rotary compression machine (Rimek Mini Tablet Press-1, Mumbai, India). The composition of the tablets is given in Table 2.

Preparation of chrono modulated compress coated tablets:

Chrono modulated compress coated tablets were prepared by compression/press-coating method as per the composition given in Table 2. The ingredients were passed through sieve #44 to break the lumps. PEO and sodium bicarbonate were mixed and then magnesium stearate and talc were added and mixed. The mixture was directly compressed in which the

half weight of coating mixtures was filled into the die, core tablet was placed in the center of die, and then the rest of the coating mixtures were filled and compressed using flat-faced plain punches on a 10-station rotary compression machine (Rimek Mini Tablet Press-1, Mumbai, India).

Table 2: Formulation of Chrono modulated compress coated tablets

Ingredients	F1	F2	F3
Formulation Of Core Tablet			
Divalproex Sodium	125 mg	125 mg	125 mg
Crosscarmellose	20	25	30
PVPK30	10mg	15mg	20mg
magnesium Stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg
Total Weight	**165mg**	**175mg**	**185mg**
Formulation of coat for chrono release			
Polyethylene Oxide	100mg	150mg	200mg
Sodium Bicarbonate	100mg	100mg	100mg
magnesium Stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg
Total Weight	**210mg**	**260mg**	**310mg**

In Vitro Evaluation of FPRTs

Physicochemical Characteristics of Tablets

Physicochemical characteristics of core tablets as well as compressed coated tablets were studied. The diameter, thickness, and hardness of the tablets were determined using monsatos tablet Hardness tester. The % friability of the tablets and disintegration time of core tablets were determined. Weight variation test of the tablets and drug content in 0.1 N HCl + 2% SLS was also determined.

In Vitro Buoyancy Studies:

The buoyancy of the tablets was determined in triplicate. A tablet was located in a glass beaker containing 200 ml of 0.1 N HCl, kept for stirring at 200 rpm and maintained at 37 ± 0.5°C. The time required for its buoyancy from tablet introduction (floating lag time) and the time during which tablet remains buoyant (total floating duration) were noted.

Drug Release Studies:

The in vitro release studies of the tablets were carried out using USP Dissolution Testing Apparatus, type-II, at 75 rpm. The study was performed in 900 mL of 0.1 N HCl solution (pH 1.2) containing 2% SLS solution at 37 ± 0.5°C. 1 ml samples were taken from the dissolution apparatus at every one hour till 12 h and filtered through a 0.22 µ syringe filter and the samples were estimated by UV. 1 ml of fresh medium was added to the medium for every sample withdrawal to maintain sink condition.

Drug excipient Compatibility studies:

The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quick as possible, real and possible interactions between potential formulation excipients and the active pharmaceutical excipient . Homogeneous mixtures of drug and excipients were prepared and filled in glass vials and self-seal LDPE (Low density Poly Ethylene) bags. The glass vials were maintained at 60^0 C 2^0 C for 2 weeks. Those packed LDPE bags were maintained at 40^0 C 2^0 C/75 5% RH for 1 month. Controlled conditions (2-8^0 C) maintained for comparison purpose. The results of Drug exicipients Compatibility study are given in table no 7.

RESULTS AND DISCUSSION:

Standard graph of Diclofenac sodium:

X axis – concentration

Y axis – absorbance

Medium – 0.1N HCl

Wavelength - 211nm

Table 3: Standard graph of Diclofenac sodium

Sl. no	Concentration(µg/ml)	Absorbance
1	2	0.010
2	4	0.019
3	6	0.029
4	8	0.037
5	10	0.046

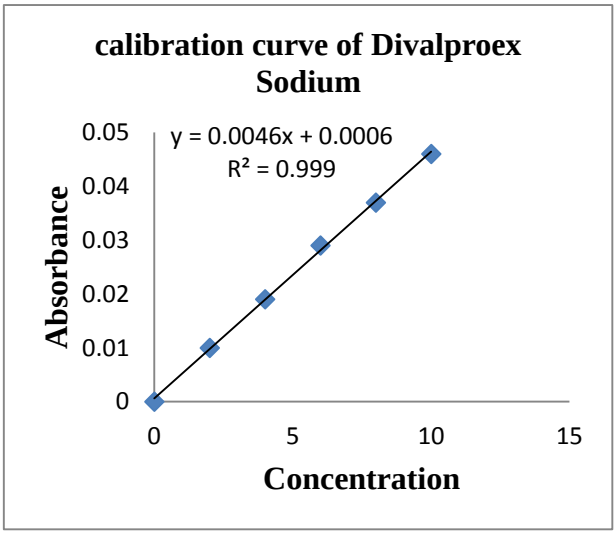

Figure 6: Standard graph of Diclofenac sodium

Evaluation of Divalproex Sodium Immediate Release Core Tablets:

Table 4: Physicochemical Characteristics of Core Tablets

F	Thickness (mm) n=3	Diameter (mm) n=3	Hardness (kg/cm^2) n=3	Friability (%) n=10	In-vitro dispersion time (sec) 0.1NHCl	Wt. Variation (% deviation) n=10	Disintegration time (Sec)
F1	4.46 ± 0.03	5.36	2.1	0.05	48	1.11	50
F2	4.48 ± 0.02	5.33	2.0	0.06	45	1.13	48
F3	4.50 ± 0.03	5.35	2.1	0.08	46	1.20	49

In-vitro drug release profile of core tablet:

Table 5: In-vitro drug release profile of core tablet

S.No	Time	Formulation		
		F1	F2	F3
1.	5	10.88	13.26	18.22
2.	10	55.92	62.54	68.15
3.	15	88.62	95.69	99.81

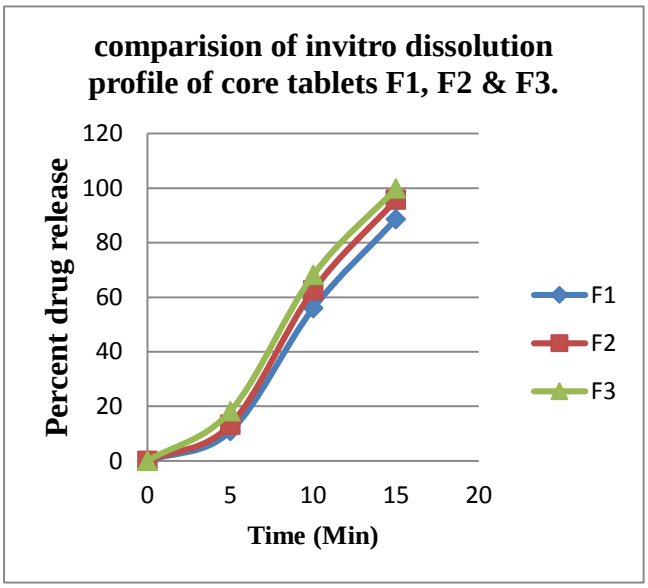

Figure 7: Comparison of in-vitro dissolution profile of core tablets F1, F2 & F3.

Evaluation of Divalproex Sodium compress coated Tablets:

Table 6: Physicochemical Characteristics of Divalproex Sodium compress coated Tablets

F	Thickness (mm) n=3	Diameter (mm) n=3	Hardness (kg/cm^2) n=3	Friability (%) n=10	Wt. Variation (%deviation) n=10	Floating lag time (Sec) n=6
F1	4.46 ± 0.03	5.36	7.8	0.099	0.98	31
F2	4.48 ± 0.02	5.33	7.5	0.098	0.95	25
F3	4.50 ± 0.03	5.35	7.4	0.099	0.96	20

In-vitro drug release profile of Divalproex Sodium compress coated Tablets:

F_1: F_1 has shown initial drug release after a lag time of 5 hours

F_2:F_2 has shown initial drug release after a lag time of 6 hours

F_3:F_3 has shown initial drug release after a lag time of 8 hours

Table 7: Drug/ exicipients Compatibility study

S. No	Composition Details	D:E Ratio	Observation at various storage conditions and durations						
			Initial	40/75% RH		60± 2^0 C		2-8^0 C	
				2W	4W	1W	2W	2W	3W
1	Dival proex Sodium (D)	-	Off White	NC	NC	NC	NC	NC	NC
2	D +PVPK30	1:10	Off White	NC	NC	NC	NC	NC	NC
3	D + Cross carmellose	1:3	Off White	NC	NC	NC	NC	NC	NC
4	D + polyethylene oxide	1:10	Off White	NC	NC	NC	NC	NC	NC
5	D + Talc	1:0.5	Off White	NC	NC	NC	NC	NC	NC
6	D + Mg.Stearate	1:5	Off White	NC	NC	NC	NC	NC	NC
7	D + Sodium bi carbonate	1:10	Off White	NC	NC	NC	NC	NC	NC

NC: No change

CONCLUSION:

Chronotheraputics has importance in drug therapy depending according to biological rhythms and this has led to a new approach to the development of drug delivery systems. If symptoms of a disease display circadian variation, drug release should also vary over time. In the recent years different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices to get optimal clinical outcome with constant plasma concentrations.in the present studies total 3 formulation were prepared using different ratios of cross carmellose as superdisintegrating agent and polyethyeleneoxide as release retardant. all the three formulation has shown good result in all aspects such as friability, hardness, dissolution, disintegration, etc. where as F1has shown initial drug release after a log time of five hours with low concentrations of cross carmellose and polyethylene oxide and other two formulations that is $F_{2\&}F_3$ has not shown better difference in all aspects when compared to F_1 in concentrations of cross carmellose and poly ethylene oxide point of view. Hence F_1 can be declared has optimized formulation.

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