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Chronotherapeutic Formulation of Levetiracetam for the Treatment of Nocturnal Epilepsy

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ABSTRACT

In general, as a subclass of epilepsy, nocturnal epilepsy intensify one of the major problems of epilepsy as it is less likely witnessed than daytime epilepsy and therefore it is very difficult to diagnose and characterize and this results in sleep disruption which can cause daytime somnolence and concentration difficulty. So, the present research work was aimed to formulate a programmable pulsatile press coated tablets of levetiracetam inorder to achieve chronotherapy for nocturnal epilepsy. The core tablets containing levetiracetam were prepared by direct compression method and press coated with HPMC K100M and MCC. The prepared pulsatile tablets were evaluated for in-vitro release to get desirable pulsatile release of drug after a lag time of 2.5 h. Drug-excipients compatibility study by IR spectrophotometer showed that all the excipients were compatible with the drug. The stability study was carried out for the desired optimized formulation for a period of 3months and showed insignificant difference.

Keywords: Nocturnal epilepsy, Chronotherapy, Circadian Rhythm, Lag time, Levetiracetam.

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INTRODUCTION

According to WHO, worldwide around 50 million people and 14 people per 1000 population in India have epilepsy. We have obtained a greater understanding for the interactions between sleep, circadian phases and seizures: sleep and circadian phase can affect seizure occurrence, threshold and spread and epilepsy can have a marked effect on sleep- wake cycle, sleep structure and circadian phase. The combination of chronobiology and epilepsy offers novel diagnostic and therapeutic formulations. The understanding of the interactions between epilepsy, circadian rhythms, sleep patterns may provide additional diagnostic options beyond sleep deprivation and novel medication formulations. Chronoepileptology offers opportunities for individualized patient oriented paradigms based on chronobiology, chrono-drug delivery systems. Chronodrug delivery system is an improved method of delivery which may ease dose adjustments according to circadian rhythmicity and periods of increase seizure vulnerability.Nocturnal epilepsy is a form of epilepsy, in which seizures occurs only while sleeping. Several common forms of epilepsy, including frontal lobe epilepsy, can manifest in a nocturnal state. As a subclass of epilepsy, nocturnal epilepsy intensify one of the major problems of epilepsy in general: episodes are less likely to be directly witnessed than daytime seizures and therefore it is very difficult to diagnose and characterize. There are small number of people who only have nocturnal epilepsy and occur either just after falling asleep or before waking hours. There is evidence that sleep activity may influence epilepsy activity. The majority of the patients who have only nocturnal seizures generally have idiopathic epilepsy. If the person maintains this pattern of only having seizures during sleep for several years, there is a chance of daytime epilepsy too. So, in the current work a novel attempt has been made to treat chronotherapeutically by formulating pulsatile release tablets of levetiracetam for invidualized patient oriented treatment of nocturnal epilepsy with a lag time of 2.5 h.

MATERIALS AND METHODS

Levetiracetam was a gifted sample from IPCA laboratories, Mumbai. Microcrystalline cellulose (Avicel PH-102) and Hydroxy propyl methyl cellulose HPMC K100M were obtained from Loba chemicals, Mumbai and Ozone International, Mumbai respectively. Croscarmellose sodium (Ac-Di-Sol)and Talc were procured from Himedia Laboratories, Mumbai. Polyvinylpyrollidone (PVP K 30) was obtained from SD Fine Chemicals, Mumbai. All other chemicals were of analytical reagent grade.

Development of pulsatile release tablets

Formulation of core tablets

The inner core tablets were prepared by direct compression method. As shown in Table 1 powder mixtures of levetiracetam, microcrystalline cellulose, croscarmellose sodium, polyvinylpyrollidone and talc were dry blended for 20 min and compressed by rotator tablet machine (Rimitek-minipress-MT),Karnavati Engineering Ltd, Ahmedabad, India with a 6mm punch and die to obtain the core tablet.

Table 1: Formulation of Levetiracetam core tablets

Drug& excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levetiracetam	100	100	100	100	100	100	100	100	100
MCC	95	50	75	100	100	100	100	100	100
Croscarmellose sodium	5	2.5	2.5	-	7	9	15	25	12
Talc	1	1	1	1	1	1	1	1	1

Formulation of barrier layer granules for press coated tablet

A wet granulation process was used to prepare barrier layer granules. HPMC K100M and MCC were accurately weighed as per Table 2. 7.5 % PVP solution (hydro alcoholic mixture of iso-propyl alcohol and water in the ratio of 70:30) was used to wet mass the HPMC K100M and MCC. Then the wet mass was passed through a sieve of 710μm aperture size. It was dried for 2 h at 45^0C in a hot air oven. Then the dried mass was screened through a sieve number of 500 μm aperture size.

Table 2: Formulation of Levetiracetam press coated tablets

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC	240	260	280	20	40	60	300	_	150
MCC	60	40	20	280	260	240	_	300	150
Hydro alcoholic 7.5% solution of PVP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of press-coated tablets

The core tablets were press coated with 300mg of barrier layer granules.150mg of barrier layer granules were weighed and transferred into a 8mm die then the core tablet was placed manually at the center. The remaining 150mg of the barrier layer granules were added into the die and directly compressed to prepare press coated pulsatile tablets (F1-F9).These formulations varied in their HPMC and MCC ratio.

Drug- excipient Interactions

The IR spectrum of the coated tablets was recorded and compared with that of pravastatin sodium to confirm the chemical integrity of the drug in the coated tablets. The powdered mixture

was taken in a diffuse reflectance sampler and the spectra recorded by scanning in the wavelength of 400 to 4000cm-1in a FTIR spectrophotometer- 430 (Jasco, Japan).

***In-vitro* drug release studies**

The *in-vitro* drug release from press-coated tablets was carried out using USP paddle apparatus at 50 rpm and 37± 0.5ºC. Initially tablets were subjected to dissolution in 0.1NHCl (pH1.4) for 2h and after that media was changed to phosphate buffer 7.4 till 7h. The samples were analyzed by UV spectrophotometer(shimadzuUV/V170) at 221nm for the presence of drug. Dissolution tests were performed in triplicate.

Rupture test

The time at which the outer coating layer starts to rupture is defined as the lag time and was determined visually by using the USP dissolution apparatus II (900ml of 0.1N HCl for initial 2h and then media was changed to to phosphate buffer 7.4, 37± 0.5ºC and 50 rpm, (n=3).

Stability studies

The stability study of the optimized batches in which the tablets were monitored upto 3 months as per ICH guidelines at room temperature and relative humidity (25◦C±2◦C, RH75 ±5%). The tablets were analyzed for appearance, weight, thickness, hardness, drug content, drug release.

RESULTS AND DISCUSSION

Design of Pulsatile press coated tablets:

The pulsatile drug delivery system consisted of inner core tablet containing drug reservoir and outer coating layer with combination of water insoluble microcrystalline cellulose(MCC, Avicel PH-102) and water soluble polymer hydroxy propyl methyl cellulose (HPMC K100M). MCC was chosen for its rupturable and for its wicking effect. HPMC K100M was selected for its swelling behaviour.

Drug- excipient Interactions

The IR spectra of press coated tablet of levetiracetam was compared with the standard spectrum of levetiracetam. As there was no appearance and disappearance of chararacteristic peak, it confirmed that there was no interaction and hence the excipients were compatible with the drug (Figure 1 and Figure 2)

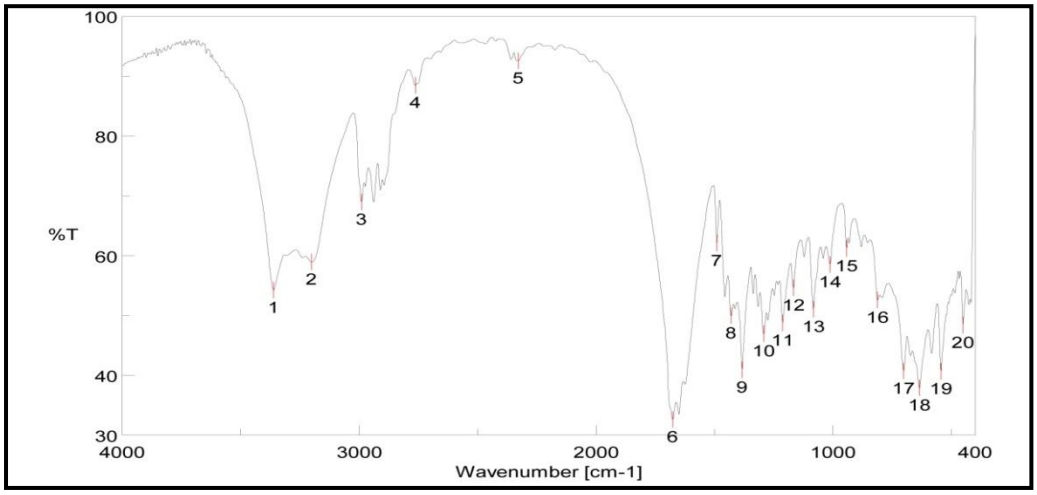

Figure 1: FT-IR spectrum of pure drug of Levetiracetam

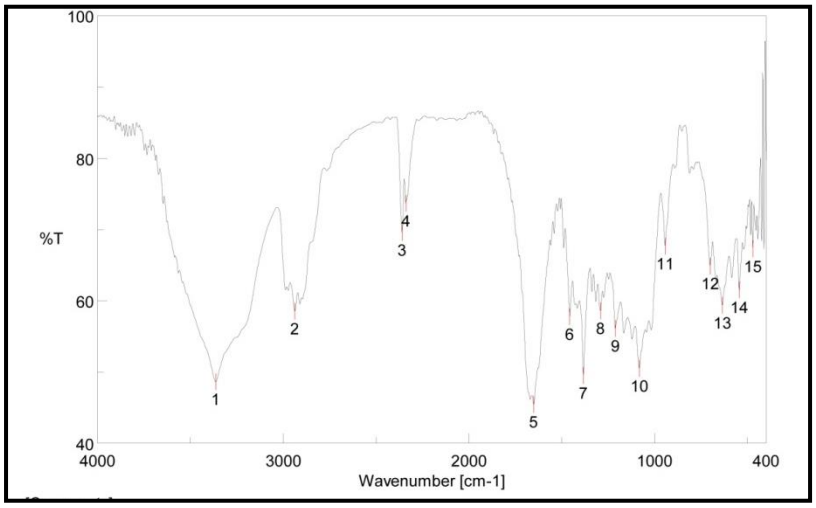

Figure 2: FT-IR spectrum of Levetiracetam pulsatile release tablets

***In vitro* dissolution studies**

The core tablet showed 80% of drug release within 2 h upon contact with dissolution medium, core tablet got eroded and released the drug as given in Figure 3. All press coated tablets (F1-F9) made with different concentration and combination of HPMC K100M and MCC in simulated gastric fluid (pH 1.4 acid buffer for initial 2h) followed by simulated intestinal fluid (pH 7.4 phosphate buffer) showed pulsatile release behaviour with distinct lag time and formulation F3(280:20) showed optimized pulsatile release with a lag time of 2.5 h and 90% drug release in 7h. (Figure 4). The addition of MCC in the inner core could improve the flow and bond prosperities of excipients during direct compression. HPMC was mixed in outer coating to alter the lag time of tablet and the dissolution profile of pulsatile tablets of levetiracetam. In higher proportion release was less as compared to lower proportion. The release profile clearly indicated

that the levetiracetam released from the press coated pulsatile tablets exhibited a unique release profile depending on the amount of HPMC and MCC used.

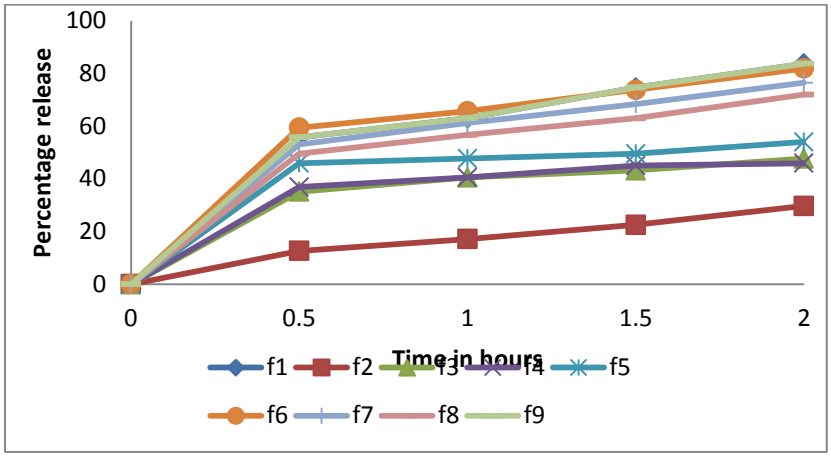

Figure 3: Dissolution profile of core tablet at pH 1.4

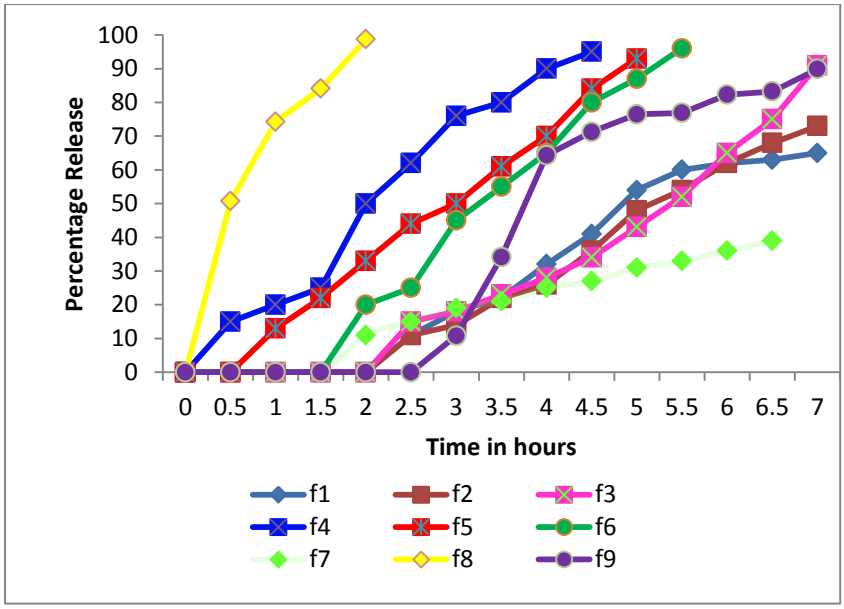

Figure 4: Dissolution profile of formulation F1- F9 at pH 7.4

Rupture test

This was done to determine the lag time of the formulations and the results revealed that the rupture/ lag time increased with higher concentrations of HPMC (Figure 5a,b,c)

a: 0h

b:2h

c: 2.5h

Figure 5: Rupture test

Stability studies

There was no significant difference either before or after 3 months storage both in physical properties as well as in its release profile (Table 3 and 4).

Table 3: Stability studies (Physical Characteristics)

Tests Performed	Initial/Zero month	1st Month	2nd Month	3rd Month
Hardness (kg/cm^2)	3.1	3.1	3.1	3.1
Friability (%)	0.7	0.7	0.71	0.71
Thickness (mm)	3.9	3.9	3.9	3.8
Content uniformity (%)	100.8	100.8	100.7	100.7

Table 4: Stability studies (Dissolution profile)

S.No	Time	Media pH1.4	pH7.4
1.	0	0	0
2.	0.5	0	0
3.	1	0	0
4.	1.5	0	0
5.	2	0	0
6.	2.5	-	12.9
7.	3	-	22.2
8.	3.5	-	79.3
9.	4	-	82.8
10.	4.5	-	89.4
11.	5	-	94.4
12.	5.5	-	95.8
13.	6	-	98.1
14.	6.5	-	98.6
15.	7	-	99.8

CONCLUSION

Chronotherapeutic systems being smart and efficient dosage forms satisfy the needs of patients and offer interesting options for intelligent life cycle management and may be great help to

number of patients in near future. Henceforth the present research work may provide a platform for the efficient management of nocturnal epilepsy and in turn prevent the occurrence of day time seizures. However, the validity of the current choronotherapeutic formulation of levetiracetam have to be confirmed with reproducible *in-vitro* and *in-vivo* results in animals and humanbeings.

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