

# Formulation and *in vitro* Evaluation of Sustained Release Matrix Tablets of Levetiracetam for Better Epileptic Treatment

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**Abstract**—The objective of the present study was to develop sustained release oral matrix tablets of anti epileptic drug levetiracetam. The sustained release matrix tablets of levetiracetam were prepared using hydrophilic matrix hydroxypropyl methylcellulose (HPMC) as a release retarding polymer by wet granulation method. Prior to compression, FTIR studies were performed to understand the compatibility between the drug and excipients. The study revealed that there was no chemical interaction between drug and excipients used in the study. The tablets were characterized by physical and chemical parameters and results were found in acceptable limits. *In vitro* release study was carried out for the tablets using 0.1 N HCl for 2 hours and in phosphate buffer pH 7.4 for remaining time up to 12 hours. The effect of polymer concentration was studied. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. The drug release data fit well to zero order kinetics. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.

**Keywords**—Levetiracetam, sustained-release, hydrophilic matrix tablet, HPMC grade K 100 MCR, wet granulation, zero order release kinetics.

## I. INTRODUCTION

LEVETIRACETAM, chemically (S)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide derivative, is an anti seizure drug indicated as an adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy to treat myoclonic partial onset or tonic clonic seizures in children and adults. Levetiracetam appears to act via an unknown specific binding site in brain. This novel binding site is the synaptic vesicle protein, SV2A, which is an integral membrane protein present on synaptic vesicles and some neuroendocrine cells. Levetiracetam is rapidly and almost completely absorbed after oral absorption. The peak concentration (C<sub>max</sub>) is ~ 2.4 mg/ml after dosing at 1 mg/kg. The half-life of levetiracetam is 6-8 h [1]. Study state plasma concentration is reached after ~2 days of twice daily dosing. The major route of levetiracetam elimination is renal excretion, approximately 70% of the administered dose is excreted unchanged in urine. Consequently, sustained release tablets are formulated. Long term treatment with sustained release levetiracetam has the potential to provide patients increased

control over the management of epilepsy having fewer side effects. The initial dose when used as adjunct is 1 g on the first day of treatment. There after the daily dose can be increased up to a maximum dose of 3 g daily [2]. Levetiracetam has been proved to be effective in both experimental and clinical pair without causing serious side effects [3]. In order to reduce the dosing frequency of administration and to improve better patient compliance, a sustained release formulation of levetiracetam is necessary.

## II. OBJECTIVE

The objective of the present investigation is to formulate a sustained release tablets of levetiracetam using hydrophilic matrix system formed by HPMC as a release retarding polymer and to evaluate *in vitro* drug release profile and to determine various release kinetic models.

## III. EXPERIMENTAL DESIGN

### A. Preparation of Sustained Release Tablets of Levetiracetam

Levetiracetam SR tablets were prepared by the wet granulation method. All the composition, with the exception of magnesium stearate and talc, were mixed thoroughly using a tumbling mixer for 5 min and wetted in a mortar with isopropyl alcohol. The wet mass was sieved (16 mesh) and the granules so obtained were dried at 60 °C for 2 h. Further, the dried granules were sieved (22 mesh) and lubricated with a mixture of magnesium stearate and talc (2:1). Levetiracetam sustained release tablets were prepared using 16 station rotary punching machine. Each batch of experimental design consisted of 30 tablets (drug content in the tablet was 500 mg). Six batches were prepared for each formulation and the compositions of different batches of levetiracetam SR are given in Table I. The various granular characteristics and tablet pharmacotechnical parameters including its average weight and weight variation, thickness, diameter, drug content & content uniformity, hardness, friability and *in vitro* drug release behaviour were evaluated (Tables III, IV).

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TABLE I  
COMPOSITION OF LEVETIRACETAM SR TABLETS

S.No	Ingredients	F1 (5%)	F2 (10%)	F3 (15%)	F4 (20%)	F5 (25%)	F6 (30%)
1	Levetiracetam	500	500	500	500	500	500
2	HPMC K100 MCR	40	80	120	160	200	240
3	MCC	216	176	136	96	56	16
4	PVP (2.5%)	20	20	20	20	20	20
5	Magnesium stearate (2%)	16	16	16	16	16	16
6	Talc (1%)	8	8	8	8	8	8
Total weight (mg)		800	800	800	800	800	800

\*F-Code of formulations

#### B. Powder Characteristics [4]

- **Angle of Repose ( $\theta$ ):** The granules were evaluated for its angle of repose using a fixed funnel method, where the funnel is fixed at a definite height (h). The angle of repose was calculated by measuring the height and radius of the heap of powder formed using

$$\theta = \tan^{-1} (h / r) \quad (1)$$

where,  $\theta$  = angle of repose, h = height (cm), r = radius (cm)

- **Bulk density:** It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight quantity of the pure drug into a measuring cylinder and initial weight was noted. It is expressed in g/ml and calculated using

$$Db = M / Vb \quad (2)$$

where, M - Mass of powder Vb - Bulk volume of the powder.

- **Tapped density:** It is the ratio between the total mass of the powder to its the tapped volume. Volume was measured by tapping the powder containing measuring cylinder for 100 times using the bulk density apparatus. It is expressed in g/ml and given by

$$Dt = M / Vt \quad (3)$$

where, M-mass of powder, Vt is the tapped volume of the powder.

- **Carr's index (or) % Compressibility:** It indicates powder flow properties. It is expressed in percentage and is given by,

$$CI = \frac{Dt - Db}{Dt} \times 100 \quad (4)$$

where, Dt-tapped density of the powder, Db-bulk density of the powder.

- **Hausner ratio:** Hausner ratio is an indirect index of ease of powder flow. It is calculated by

$$\text{Hausner ratio} = Dt/Db \quad (5)$$

where, Dt is the tapped density, Db is the bulk density

#### C. Evaluation of Tablets [5]

The prepared tablets were evaluated for the following properties such as hardness, friability, weight variation, drug content, *in vitro* release studies and determination of release kinetics.

- **Hardness:** The hardness of a tablet is indication of its strength and it is tested using Monsanto hardness tester. The hardness of 6 tablets was measured and the hardness was calculated.
- **Friability:** Friability is loss of weight of tablets in the container, due to removal of fine particles from their surfaces. Six tablets were weighed accurately and placed in the chamber of the apparatus. After 100 rotations, the tablets were removed from the apparatus, re-dusted and weighed. Percentage friability was determined by using:

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} \times 100 \quad (6)$$

where  $W_1$  = weight of the tablets before test  $W_2$  = weight of the tablets after test.

- **Weight variation test:** To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius India, Ltd), and the test was performed according to the Indian pharmacopoeia.
- **Drug content:** Five tablets were weighed individually; an amount equivalent to 500 mg of drug (800 mg of powder) was extracted with 100 ml of pH 6.8 buffer and sonicated for 15 minutes. The solution was then filtered through 0.45  $\mu\text{m}$  membrane, properly diluted with same pH 6.8 buffer and drug content was measured at 210 nm using UV spectrophotometer.
- ***In vitro* release studies:** The release characteristics of the marketed formulation (conventional dosage form) and the developed formulation (SR) for levetiracetam was determined using USP apparatus type II, paddle (Electrolab, Mumbai, India) at 50 rpm. The dissolution media used for the levetiracetam was 0.1 N HCl at pH 1.2 and a volume of 700 ml for the first 2 hours after which 200 ml of 0.2 M tribasic sodium phosphate was added to give a final pH of 7.4 for subsequent 12 h maintained at  $37 \pm 0.5$  °C. Dissolution tests were conducted in triplicate and mean values was plotted versus time. 5 ml of the samples were withdrawn at predetermined time intervals of 0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10 and 12.0 h. 5 ml of the dissolution medium was replaced to the dissolution jar after each sampling. Percentage drug release and cumulative release at various time intervals were calculated and compared. The marketed conventional tablets are evaluated for *in vitro* drug release profile and compared with that of the prepared sustained release behavior.

#### D. Data Analysis [6], [7]

To understand the release mechanism of drug from the system, the *in vitro* data's are fitted in to various kinetic models, such as zero order (7), first order (8) Higuchi's model (9) and Peppas's model (10):

$$Q_t = k_0 t \quad (7)$$

where,  $Q$  is the amount of drug release in time 't' and ' $k_0$ ' is the zero order rate constant and 't' is the time in hours.

$$\ln Q_t = \ln Q_0 - k_1 t \quad (8)$$

where  $Q_0$  is initial concentration of drug and  $k_1$  is the first order rate constant

$$Q_t = k_2 t_{1/2} \quad (9)$$

where  $k_2$  is the rate constant of Higuchi equation [6]. Hence, drug release rate is proportional to the reciprocal of the square root of time.

The dissolution data were also fitted to the well-known exponential equation

$$M_t/M_\infty = k t^n \quad (10)$$

$M_t/M_\infty$  is the fraction of drug release at time t, and k is the kinetic constant; n is the release exponent (indicating release mechanism). *In vitro* drug release profiles were plotted according to zero order, first-order, Higuchi and Peppas's equations to understand the mechanism of drug release and to compare the differences in the release profile of optimized batch of levetiracetam sustained release tablets.

#### IV. RESULTS

Precompressional parameters of granules are given in Table II, angle of repose (24.85-27.71°) which indicates good flow properties. The LBD of granules (0.20-0.44 g/cm<sup>3</sup>). TBD of granules (0.25-0.5 g/cm<sup>3</sup>). % compressibility index (8-25%). Hausner ratio (1.08-1.33) is in the range given in official standards.

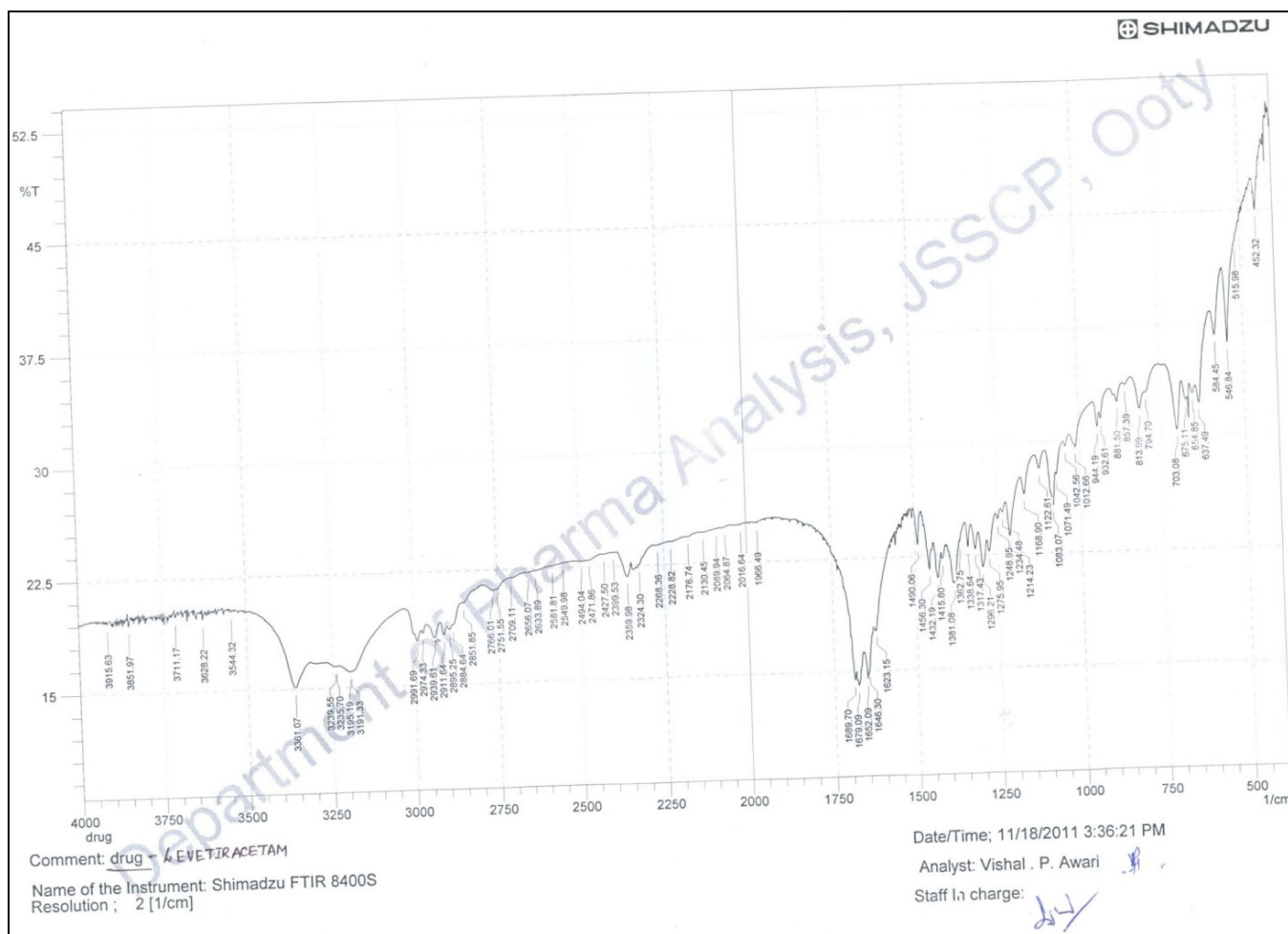


Fig. 1 FTIR Spectra of levetiracetam



TABLE IV  
EVALUATION OF LEVETIRACETAM SR TABLETS

Parameters	F1	F2	F3	F4	F5	F6
Average Wt (mg) n=20	800.2 ± 1.78	800.53 ± 1.32	800.86 ± 1.22	800.2 ± 1.10	801.06 ± 1.09	801.76 ± 1.09
Drug content (%) n=5	98.75 ± 1.7	98.25 ± 1.87	99.75 ± 1.63	98.63 ± 1.05	97.46 ± 1.11	101.3 ± 1.34
Hardness (kg/cm <sup>3</sup> ) n=6	7.0 ± 0.05	6.16 ± 0.09	7.5 ± 0.12	7.0 ± 0.22	6.5 ± 0.17	6.0 ± 0.21
Friability (%) n=6	0.74 ± 0.054	0.67 ± 0.02	0.328 ± 0.03	0.95 ± 0.041	0.95 ± 0.022	0.95 ± 0.022
Thickness (mm) n=5	5.0 ± 0.02	5.0 ± 0.018	5.0 ± 0.014	5.0 ± 0.016	5.0 ± 0.019	5.0 ± 0.02

### V. CONCLUSION

A sustained release matrix tablets were formulated using Hydrophilic matrix forming polymer HPMC grade K 100 MCR by wet granulation technique. The effect of the drug to polymer ratio on the in vitro release behavior was significant. In general an increase in the polymer ratio retarded the drug release to a greater extent.

The release of drug follows non-fickian diffusion obeying zero order kinetics. Based on these observations it is concluded that the formulated matrix tablets levetiracetam using HPMC K 100 MCR is capable of exhibiting sustained release properties. There by decreasing the dosing frequency, minimize the blood level oscillations, dose related side effects and cost effective therapy. Hence, ultimately it may improve the patient compliance in the therapeutic management of epilepsy. It can also overcome the disadvantages associated with conventional dosage form.

TABLE V  
RELEASE KINETICS PROFILE OF LEVETIRACETAM SR TABLETS USING DIFFERENT KINETIC MODELS

Formulation code	Zero order (r <sup>2</sup> )	First order (r <sup>2</sup> )	Higuchi (r <sup>2</sup> )	Peppas's (r <sup>2</sup> )	Peppas's (n)
F1	0.9869	0.9869	0.9576	0.9614	0.5995
F2	0.9639	0.9639	0.9869	0.9937	0.6094
F3	0.9473	0.9473	0.9715	0.9794	0.666
F4	0.8802	0.8802	0.9903	0.9892	0.398
F5	0.8749	0.8749	0.9791	0.9655	0.353
F6	0.9402	0.9402	0.9822	0.9676	0.427

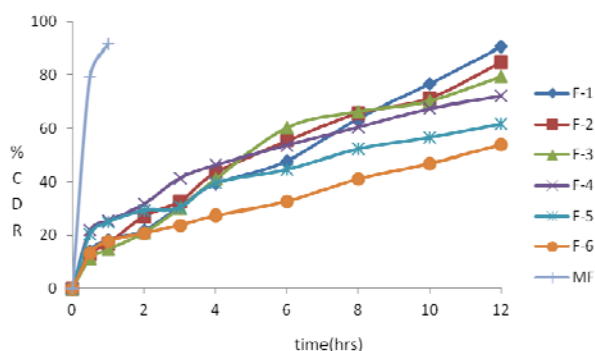


Fig. 3 In vitro drug release of different batches of levetiracetam SR tablets

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