Research Article

Formulation and Evaluation of Levetiracetam Extended Release Tablets

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ABSTRACT

The purpose of this study was to develop extended release tablets of levetiracetam for sustained release. Extended release dosage forms encompass a wide variety of prolonged action preparations that provide sustained release of their active constituents for a definite period of time. Levetiracetam is an anticonvulsant medication used in treatment for epilepsy in the case of partial seizures, or as an adjunctive therapy for partial, myoclonic and tonic-clonic seizures. This novel formulation may improve patient compliance with oral therapy when compared to conventional levetiracetam tablets. Extended release formulation of levetiracetam poses substantial challenges due to its cost to formulation, biocompatibility, etc. Extended release tablet of levetiracetam were formulated in different combinations of polymers in Hydroxyl propyl methyl cellulose (HPMC K4M) and PVP K-90 by wet granulation method. The formulated granules were evaluated for Density (Bulk and Tapped Density), Angle of repose, Compressibility index, Hausner Ratio, Solubility and Melting Point. The formulated tablets were subjected to Appearance, Thickness, Weight variation test, Hardness test, *in-vitro* dissolution studies, etc.

Keywords: Levetricetam, Extended release Tablets, HPMC K4M, *In vitro* dissolution studies.

INTRODUCTION

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience[1]. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma. The Immediate release drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral sustained drug delivery has some potential advantage like sustained release rate & dose maintenance in plasma. The sustained release formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate[2].
In present study, extended release tablet dosage form of Levetiracetam was formulated using various grades of HPMC. The optimized grade and combination of the formulation was then characterized for various physicochemical properties.

MATERIALS AND METHODS

Drugs and Chemicals

Levetiracetam (Dr. Reddy's.), Povidone Iodine (ISP Technology), Surelease E-7-19010 (Colorcon Pvt. Ltd.), HPMC K15M (Dow Chemical Co.), HPMC K4M (Dow Chemical Co.), Microcrystalline cellulose (FMC Biopolymer), Aerosil (Degussa), Mg. Stearate (Ferro-Belgium), Opadry® II (Colorcon Pvt. Ltd.) were used in the study.

Methods

Preformulation Study

Levetiracetam was characterized for organoleptic properties vis. State, color and odor. Solubility was determined in different media like in water, 0.1 N HCl, Acetate buffer pH 1.2 and phosphate buffer pH 6.8[3]. Particle size analysis of levetiracetam was carried out using malvern master sizer[4-6].

Interference Study

Being a new formulation it becomes mandatory to check whether the drug is compatible with all other ingredients or not.

The drug and the excipients should not be having any compatibility associated problem with each other so that a reliable, stable and safe product can be formulated. FTIR (Fourier-transformed infrared) spectra and DSC (Differential scanning calorimetry) studies were carried

out for pure drug and physical mixture of drug with the excipients in above said context. FTIR spectra were obtained by press KBr disk method (2 mg sample in 200 mg KBr) using FTIR (Shimadzu FTIR-8400 specrophotometer) keeping the scanning range 400-4000cm^{-1}. Melting behaviour spectra were obtained by crimping the drug (3mg) or drug and drug + excipients (3mg) carrying DSC (Shimadzu, DSC-67 Japan). Temperature range was kept 35°C to 225°C with continuous heating rate of 10°C per minute in an inert environment of nitrogen gas. The physical mixtures of drug with different excipients for both of the studies were prepared by triturating drug and additives in a dried mortar for 5 minutes[7-10].

Formulation of Tablets

Levetiracetam extended release oral matrix tablets were prepared by the wet granulation technique using variable concentrations of HPMC K4M and K15M. The amount of active pharmaceutical ingredient taken was kept constant to 500 mg. Ingredients except microcrystalline cellulose, Aerosil and magnesium stearate were blended in a blender uniformly. Granulation was done with sufficient binding solution of PVP K90 and isopropyl alcohol. The lubricated granules were compressed on rotary machine using 18.75 mm x 8.75 mm, oval shaped, beveled edges, plain/plain, "D" tooling and keeping average weight 700-775 mg. Batch F001-F011 were prepared by wet granulation techniques using HPMC K4M and K15M. Tablets prepared were stored in an air tight container for further studies. Compositions of various formulations are shown in Table 1.

Micromeritics Evaluation of Granules

Micromeritics properties like apparent Bulk density, Tapped Bulk density, Compressibility index, Hausner ratio, Angle of repose and Melting point were determined and compared with the flow properties of Levetiracetam pure drug.

Physical Evaluation of Levetiracetam ER Tablet

Extended Release tablets prepared were evaluated for the following official parameters: Weight variation, hardness, thickness, friability and drug content were measured[11].

***In-vitro* Dissolution Study**

The *in vitro* drug release studies of the matrix tablets were conducted in USP type II dissolution apparatus equilibrated at temperature 37 ± 0.5°C and 100 rpm speed. The dissolution studies were carried out for 18 hours in 900 ml of phosphate buffer pH 6.8. The dissolution samples were collected at every 1 hour interval and replaced with an equal volume of buffer to keep the volume constant. The sample solution was diluted sufficiently and analyzed at 210 nm by a HPLC (Shimadzu (LC-2010 CHT), Tokyo, Japan). The amount of drug present in the sample was calculated with the help of appropriate calibration curves constructed from reference standard of the respective drug[12-13].

Comparison of Dissolution profiles by Similarity (f2) and Dissimilarity (f1) Factors

The similarity factor (f2) was defined by CDER, FDA and EMEA as the 'logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. This was calculated to compare the test with reference release profiles.

It was calculated from the mean dissolution data according to the following equation.

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

n - No. of full points

R The reference profile at the time point t

T - The test profile at the same point.

The method is more adequate to compare dissolution profiles when more than three or four dissolution time points are available and can only be applied if average difference between Rt and Tt is less than 100. If this difference is higher than 100, normalization of data is required.

Dissimilarity Factor (f1)

Dissimilarity factor (f1) describes the relative error between two dissolution profiles. It depicts approximately the percent error between curves. The percent error is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles. Dissimilarity factor or difference factor (f1) was calculated from the following equation.

Both Similarity factor (f2) and dissimilarity factor (f1) are model independent methods to comparison *in vitro* test and reference products dissolution profiles. f1 and f2 are outlined in the SUPAC and IVIVC guidelines. Dissolution profiles are comparable when f1 value is in range of 0 to 15 and f2 value is in range of 50 to 100.

Comparison between innovators product and test batches was done by using similarity factor (f2) value, calculated from the mean dissolution data by using above equation[14-19].

Drug Release Mechanism

The kinetic models used were zero order, first order, Higuchi equation and Korsmeyer-Peppas equation[20].

Stability Study

Tablets were packed in PVDC-Al blister and charged for stability at 40°C / 75 % RH condition. Stability study was carried out for the optimized formulations. Tablets of

optimized formulation were striped packed and kept in a humidity chamber for 30 days on above mention temperature. *In vitro* drug release was determined after one month[21].

RESULTS

Preformulation Study

The drug is a white crystalline powder found to be bitter in taste and odorless. The solubility of Levetiracetam in Water, 0.1N HCl (1.2 pH) and Phosphate buffer(6.8 pH) was found to be 1.95 gm/ml, 1.98 gm/ml and 1.98 gm/ml, respectively. More than 80 % particles were below 850 µ. However, solubility of drug is very high (freely soluble) in all medias (pH 1.2 – 8.0). Therefore, particle size is not critical for bioavailability. The drug ratio in the formulation is more than 50% therefore bigger particle size was selected because smaller particle size may create problem during process. The melting point of API was found to be 118 °C-119 °C.

Interference Studies

FTIR spectra of drug and physical mixture of drug and excipients has been shown in Figure 1 and 2 respectively. The major peaks of Levetiracetam were at 2948cm^{-1}, 1250cm^{-1}, 1594cm^{-1} and 3387 cm^{-1} which are retained in the spectra of physical mixture of drug and spectra.

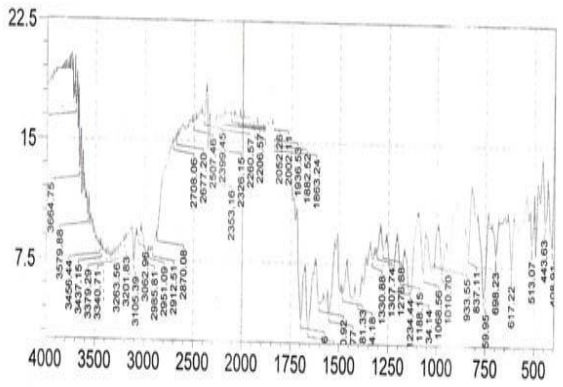

Figure 1: FTIR Spectra of Standard Levetiracetam

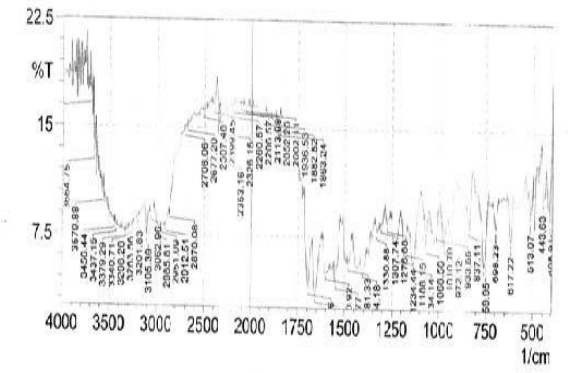

Figure 2: FTIR spectra of Test Levetiracetam

DSC spectra illustrated in Figure 3, pure drug levetiracetam exhibited an endothermic peak at about 123.10°C, which started to melt at 119.4°C, the range of which corresponded to the melting point of the drug (117-119°C). The physical mixture of drug levetiracetam and excipients exhibited an endothermic peak at about 120.15°C, which corresponded to the melting point of the drug (117-119°C), as illustrated in Figure 4, ruling out any interaction between the drug and the polymer.

Levetiracetam

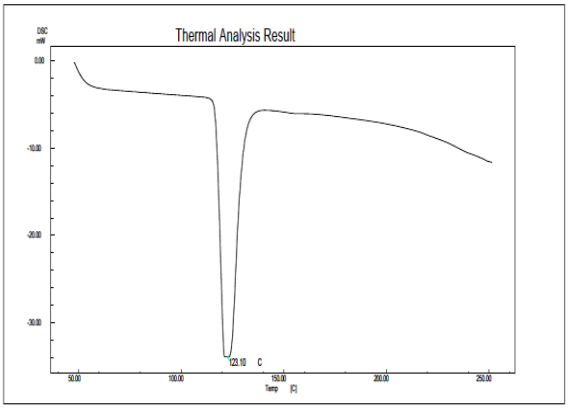

Figure 3: DSC Graph of Levetiracetam

Mix (Levetiracetam + Excipients)

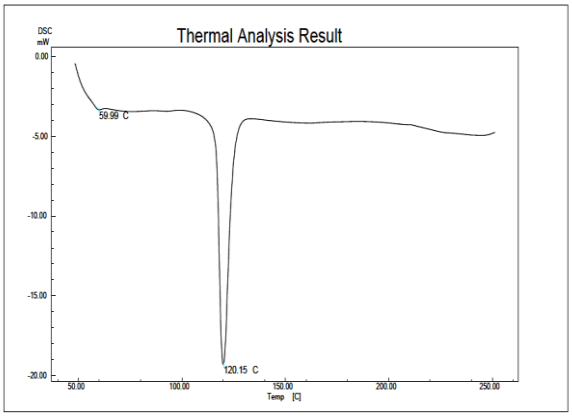

Figure 4: DSC Graph of Mixture (One Month, 40 °C / 75 % RH)

Micromeritics Evaluation of Levetiracetam Granules

The observation of evaluation of flow of granules is presented in Table 2. The flow properties of granules ready for compression were compared with that of pure drug.

The result suggested that there is a little enhancement in the flow properties when drug in converted into granules by adding all other excipients.

Physical Evaluation of the Tablets

The weight of all the batches was found to be in the range of 702.3-705.21, 726.41-729.77 and 778.09-776.65 mg respectively.

The thickness was in the range of 5.4-6.3 mm. The hardness obtained was in the range of 9-14 Kiloponds. The % friability was observed in the range of 0.114-0.2.

***In vitro* Dissolution of Levetiracetam ER tablets**

The result of *in vitro* drug release is summarized in Table 3.

F001 to F011 batches were prepared using different excipients and their different ratios.

Release profile of all these batches was compared. Batch F009 and F010 were only the batches showed release of drug extended upto 18 hrs.

Now these batches were compared to marketed tablet of same drug for similarity factor.

Similarity (f2) and Dissimilarity (f1) Result

The values of dissimilarity factor (f1) of batch F010 and F011 were found to be 2.85% and 3.37%, respectively and similarity factors (f2) were 89.09% and 87.78%, respectively.

The release pattern of batch F010 and F011 was found to be similar **to KEPPRA® XR** tablet.

Similarity factor (f2) and dissimilarity factor (f1) both were observed under the official range.

Mechanism of Drug Release

The release data of the optimized batch F010 was fitted into according to zero-order, first-order, Higuchi and Korsmeyer models to find the kinetics behavior of the drug.

The regression values of Zero order, First order, Higuchi and Korsemeyer-Peppas were 0.968, 0.877, 0.986 and 0.727.

It may be concluded that the drug release from Levetiracetam tablet is best fit in Higuchi model.

Table 1: Composition for Formulations F001 to F011

Ingredients	F001 (mg)	F002 (mg)	F003 (mg)	F004 (mg)	F005 (mg)	F006 (mg)	F007 (mg)	F008 (mg)	F009 (mg)	F010 (mg)	F011 (mg)
Levetiracetam	500	500	500	500	500	500	500	500	500	500	500
HPMC K4M	150	100	65	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	100	150	100	100	150	150	175	175
Surelease	-	-	-	-	-	-	-	-	-	40	40
Povidone K90	14	14	14	-	-	14	28	14	28	28	28
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
MCC	26	76	111	90	40	76	62	26	12	27	27
Aerosil	5	5	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5	5	5
Opadry	-	-	-	25	25	25	25	25	25	25	25
Total Weight	700	700	700	725	725	725	725	725	725	775	775

Table 2: Evaluation of Powder Blend Ready for Compression

Batch No.	Bulk	Tapped	% Carr's index	Hausner's Ratio
API	0.404 ± 0.09	0.469 ± 0.11	16.08 ± 0.19	1.16 ± 0.09
F001	0.432 ± 0.12	0.476 ± 0.11	10.18 ± 0.14	1.10 ± 0.09
F002	0.413 ± 0.13	0.478 ± 0.09	15.73 ± 0.19	1.15 ± 0.11
F003	0.424 ± 0.21	0.469 ± 0.19	10.61 ± 0.12	1.10 ± 0.12
F004	0.415 ± 0.19	0.472 ± 0.16	13.73 ± 0.14	1.13 ± 0.12
F005	0.422 ± 0.11	0.489 ± 0.09	15.87 ± 0.14	1.15 ± 0.13
F006	0.431 ± 0.09	0.481 ± 0.17	11.60 ± 0.13	1.12 ± 0.09
F007	0.43 ± 0.11	0.488 ± 0.11	13.48 ± 0.14	1.13 ± 0.17
F008	0.417 ± 0.17	0.475 ± 0.12	13.90 ± 0.11	1.13 ± 0.17
F009	0.411 ± 0.09	0.477 ± 0.11	16.05 ± 0.09	1.16 ± 0.12
F010	0.435 ± 0.12	0.486 ± 0.12	11.72 ± 0.11	1.11 ± 0.16
F011	0.42 ± 0.09	0.485 ± 0.09	15.47 ± 0.12	1.15 ± 0.12

Note: values are mean of three observations (n=3) ± SD

Table 3: Percentage Cumulative Drug Release

Time (Hrs)	% Cumulative Drug Released											
	KEPPRA® XR	F001	F002	F003	F004	F005	F006	F007	F008	F009	F010	F011
0	0	0	0	0	0	0	0	0	0	0	0	0
1	15.47±1.02	27.56±0.78	33.29±0.93	46.53±0.69	30.14±1.03	27.53±0.83	27.48±0.95	28.45±1.12	26.64±0.79	25.83±0.42	16.43±1.21	17.47±1.01
2	25.74±0.98	40.67±0.82	48.65±1.04	61.79±0.77	40.71±0.90	35.71±0.91	38.59±0.81	39.73±0.98	34.93±1.07	33.76±1.18	23.46±1.09	26.82±1.05
4	38.43±0.96	59.57±0.76	69.78±1.07	82.46±0.91	53.64±0.94	47.28±1.14	52.75±1.03	51.93±1.06	45.94±1.11	46.74±1.04	37.69±1.11	37.38±0.66
6	51.93±1.20	72.95 ±1.16	83.63±0.88	90.14±0.75	69.78±0.76	64.72±0.66	70.85±0.97	68.94±0.93	64.85±0.89	62.14±0.78	53.14±0.91	50.06±1.04
8	62.27±0.75	82.47±1.02	91.31±0.93	94.32±0.86	84.21±0.97	77.26±1.11	83.86±1.02	81.37±0.65	78.37±0.95	75.58±1.07	61.83±1.06	63.27±0.76
10	71.88±1.12	88.76±1.16	95.45±0.78	96.47±0.92	94.64±1.07	85.44±1.22	95.89±1.15	92.65±0.92	87.57±0.59	86.64±1.20	69.93±1.06	73.83±1.16
12	82.51±0.82	93.74±0.98	97.56±0.82	97.39±0.65	102.45±0.66	98.41±0.74	100.73±0.88	99.68±1.09	98.26±0.99	96.35±0.92	81.05±0.86	83.38±1.09
14	92.13±0.88	100.74±0.86	99.94±1.12	98.28±0.99	102.47±1.05	100.15±0.84	101.38±0.78	99.79±1.01	98.42±1.16	99.62±1.05	90.89±0.99	94.18±0.74
16	99.93±0.98	100.87±1.12	100.48±1.19	98.49±0.87	102.740.65	100.32±0.94	101.48±1.07	99.95±1.04	99.03±0.75	99.92±1.02	98.04±0.78	102.21±0.60
18	100.12±1.16	101.35±1.05	100.75±1.09	99.04±0.75	102.85±1.15	100.68±1.05	101.97±1.18	99.98±1.08	99.27±0.82	100.68±1.12	101.34±0.86	102.37±1.09

Note: values are mean of three observations (n=3) ± SD

Stability Study

The results of accelerated stability studies after 1 Month, 2 Month and 3 Months were tabulated as table 4. It was found that there is no change in % cumulative release of optimized F010 batch after three consecutive Months.

There was no any remarkable change after the above said period. These all evidences indicate that the tablet formulated is stable enough.

Table 4: Stability Result of Formulation

Time (h)	% Cumulative Drug Release			
	Initial	1 Month	2 Months	3 Months
0	0	0	0	0
1	16.28	17.47	16.43	15.53
2	24.59	26.82	23.46	26.05
4	33.53	37.38	39.54	35.36
6	50.34	50.06	53.14	51.83
8	61.84	63.27	61.83	62.75
10	68.86	73.83	69.93	70.57
12	81.48	83.38	81.05	83.37
14	92.52	94.18	90.89	91.76
16	100.19	102.21	98.04	99.58
18	100.53	102.37	101.34	100.89

Note: values are mean of three observations (n=3) ± SD

DISCUSSION

Levetiracetam is an Antiepilepsy or Anticonvulsant Drug and it binds to a synaptic vesicle protein, SV2A. This is believed to impede nerve conduction across synapses. Levetiracetam was having extensive 1st pass metabolism and associated with frequent dosing of conventional dosage form makes it a suitable candidate for extended release dosage form for patient compliance.

Hypromellose is one of the most widely used polymer and easily available in all the grades for preparation of extended release formulations. So for present work, Hypromellose having different grades like HPMC K15M, HPMC K4 M were selected as release retarding agent. In present study, extended release tablet dosage form of Levetiracetam was prepared using optimized combination of various grades of HPMC.

Matrix system of Levetiracetam based on hydrophilic polymer (HPMC K15M) was tried individually and Surelease was used as Granulating agent.

Finally core tablets were coated using Opadry®II White as a film coating.

The optimized proportion of HPMC K15M was decided based on trial and error methods and depending upon the dissolution profile.

Lastly, one optimized batch F010 and F011 was prepared using the final formula to check the reproducibility and matching the dissolution profile with that of Innovator.

Batch F010 was charged for the stability study with packing PVC-Alu at 40°C/75% RH for 3 months.

The results obtained after the stability period were not having any change than the initial results.

Final optimized batches obtained fulfilled the criteria for optimized batch and significantly retard the release up to 16 h with initial loading dose release, the batches F010 and F011 were considered as the optimized batches for once a day extended release tablet formulation containing Levetiracetam.

Finally, Innovator obtained from the market and the dissolution profile of the batches F010 and F011 were matched with the innovator's dissolution profile.

CONCLUSION

Present work was directed towards the development and evaluation of extended release tablet dosage form of Levetiracetam.

Criteria for optimized batches were defined. For *in vitro* dissolution the release pattern was selected depending upon the Innovator's dissolution profile.

Initially different HPMC K4M was tried as matrix agent and Ethylecellulose was used as film coating material in different proportion.

All the batches were failed to achieve desired extende release profile.

The possible reason for getting this type of result is insufficient amount of release retarding agent or polymer is not able to sustain the release of the drug.

Therefore further trials were carried out with HPMC K15M as matrix agent and Ethylcellulose as a granulator or binder using the different proportion.

Based on F2 value, Batches F010, F011 had desired *in vitro* dissolution profile and fulfill the release criteria for 16 h and matched with reference product drug release pattern with reproducibility.

So we can say that HPMC K15M in intragranulation as a matrix system and Ethylcellulose as a granulating agent successfully retard drug release from the tablets.

After stability study we can say that formulation composition of batch F010 was satisfactory optimized Composition.

With this formulation, all process parameters involved in the development of product were successfully optimized at pilot plant-scale up level.

Finally we can say that Levetiracetam Extended Release Tablet Product was successfully developed.

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