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Formulation and Evaluation of Levetiracetam Matrix Tablet Using Polyethylene Oxides

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ABSTRACT

The objective of work was to prepare and characterize Levetiracetam matrix tablet using Polyethylene oxides (PEO 301, PEO coagulant and PEO 303) by wet granulation technique using variable concentrations of PEO 301, PEO coagulant and PEO 303. Total 12 formulations were prepared and optimized formulation were evaluated by Differential scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and The results obtained showed that the formulations of Levetiracetam prepared with combination PEO 303 (T10) has controlled release over 12 hrs.

Keywords: Levetiracetam, matrix tablet, Polyethylene oxides, PEO coagulant

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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 (1).

Extended-release tablets and capsules are regularly taken only once or twice daily compared with equivalent conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Additionally, extended-release products present an immediate release of drug which quickly produces the wanted curative effect which then is reflected by the gradual and constant release of additional amounts of drug to control this effect over a decided period of time. The sustained plasma drug levels produced by extended-release drug products often times reduce the need for night dosing, which presents the benefit not only to the patient but to the caregiver as well (2,3). These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience (4). 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 (5).A sustained release drug system is “any drug or dosage form modification that prolongs the therapeutic activity of the drug.” Ideally, a sustained release oral dosage form is designed to rapidly release some predetermined fraction of the total dose into the gastro intensive tract (6, 7). This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then released at a constant rate (8). The rate of the drug absorption from the entire maintenance dose into the body should equal the rate of the drug removal from the

body by all the processes over the time for which the desired intensity of pharmacological response is required (9).

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 (10). 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 (Cmax) is ~ 2.4 mg/ml after dosing at 1 mg/kg. The half-life of Levetiracetam is 6-8 h (11). 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 (12). Levetiracetam has been proved to be effective in both experimental and clinical pair without causing serious side effects (13). In order to reduce the dosing frequency of administration and to improve better patient compliance, a sustained release formulation of Levetiracetam is necessary.

In this study of Levetiracetam extended-release dosage forms, various grades of polyethylene oxides (PEO 301, PEO coagulant and PEO 303) were used as a controlled release polymer and MCC (Avicel Ph 200) was used to modify the drug release and ensure that most of drug is released in a period time comparable to the gastrointestinal residence time.

MATERIALS AND METHOD

Levetiracetam was obtained as a gift sample from SD fine chemical Limited, Mumbai, India. Polyethylene oxides (PEO 301, PEO coagulant and PEO 303), Avicel & Aerosil 200 were obtained as a gift sample from S.D Fine Chemicals, Mumbai.

Formulation of Levetiracetam matrix tablets

Levetiracetam tablets are prepared using differing combinations of Polyethylene oxides. Micro crystalline cellulose was mixed similarly and the mix was incorporated with aerosol and powder ultimately lubricated up with magnesium stearate. Levetiracetam matrix Tablets were prepared by

the wet granulation technique using variable concentrations of PEO 301, PEO coagulant and PEO 303. The tablets are compressed using 16-station rotary tablet machine (Cad mach, Ahmadabad, India). (Table 1)

Table 1. Quantity of raw materials per tablet (mg)

Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Levetiracetam	500	500	500	500	500	500	500	500	500	500	500	500
PEO 301	50	75	100	125	-	-	-	-	-	-	-	-
PEO coagulant	-	-	-	-	50	75	100	125	-	-	-	-
PEO 303	-	-	-	-	-	-	-	-	50	75	100	125
Avicel ph 200	230	205	180	155	230	205	180	155	230	205	180	155
Aerosil 200	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	800	800	800	800	800	800	800	800	800	800	800	800

Characteristics of tablet formulations

The tablets were characterized by weight variation, hardness, disintegration, friability and content uniformity of dose (Table 2). The average weight was measured over 20 units, as recommended by the United State Pharmacopoeia (U.S.P), 2006. The hardness was determined in a Monsanto Hardness Tester over 10 tablets. For each formulation, the friability was tested in a Roche Friabilator over a sample of 20 tablets and the acceptance criterion was a maximum loss of 2% of initial weight (U.S.P. 2006). Levetiracetam controlled release tablets were evaluated as per the specified limit of USP to meet the quality of formulation (14). Tablets were evaluated for individual and average weight variations, thickness, hardness, assay and *in vitro* drug release. Individual and average weight variations were measured in the Single Pan electronic balance. The friability was tested using 6.0gm of tablets for 100RPM in Roche Friabilator and the limit was kept NMT 2% as per USP.

Dissolution

Tablet dissolution was assessed in a standard USP 24 apparatus II in 900mL of mimicked gastric liquids for 24 hours. The stirring speed was 50 rpm. Temperature was maintained at 37°C±0.5°C throughout the experiment. Dissolution was monitored for 12h, samples being taken at 1,2,3,4,5,6,7,8,9,10,11 & 12. After the collection of each sample, the dissolution medium was replenished with the same volume of fresh medium. The samples were diluted to 100 mL with dilution medium and analyzed for drug content by 210 nm. The concentration of Levetiracetam was determined using a HPLC at 210 nm (15-16).

FTIR investigation of Levetiracetam network tablets arranged with Polyethylene oxides

Compatibility studies of each drug (Levetiracetam) with Polyethylene oxides were carried out using Fourier Transform Infrared (FT-IR) spectroscopy. The spectrum was scanned over the frequency range between 4000 and 600cm^{-1}and at 4 cm resolution. Appearance, disappearance or broadening of absorption band (s) on the spectra of mixture in comparison with the spectrum of drug was used to determine possible interactions between pure drugs and polymers.

(DSC) Differential Scanning calorimetric investigation of Levetiracetam network tablets arranged with Polyethylene oxides

A Mettler Toledo DSC STAR^{e} SYSTEM was used for all the DSC studies. The DSC uses Stare Software V8.10 for its operation. Samples ranging from 8 to 15 mg were used and the results were normalized using Stare software so that the results could be compared. The samples were placed in a 100 µL pan. The pans are covered with a lid and the lid is crimped into place. A pinhole is made on the lid to vent out any gas which might result while heating. The pan is then placed inside the furnace using an empty pan as a blank. The DSC was calibrated using indium (5-10 mg) with a melting onset temperature at 156 ± 0.2 ºC and zinc with a melting onset temperature of 419.6±0.7^{0}C as the standards. The two processes show a heat flow of 28.45± 0.6J/g and 107.5±3.2 J/g for indium and zinc, respectively.

RESULTS AND DISCUSSION

Evaluation of tablet formulations

The early indication showed that the Formulation T1-T12 had good hardness and other parameters meet the USP Specified limit. Table 2 summarizes the results obtained from the tests conducted on all batches. All batches met the requirement for weight variation test according to USP. The disintegration time for the tablets correlated well with their hardness (the greater the hardness of the tablet the longer was the time needed to achieve disintegration) all batches passed the test for Drug Content in Tablets which should not be less than 98.0 percent and not more than 102.0 percent. (Table 2)

Table 2. Physicochemical characteristics of prepared tablets

Formulation	Hardness (kg/cm2)	Weight Variation (mg)	Friability (%)	Drug Content (%)
T1	13.2	800	0.65	99.78
T2	13.5	800	0.75	99.17
T3	13.2	800	0.66	100.1
T4	14	800	0.5	99.87
T5	13.6	800	0.67	99.56
T6	13.8	800	0.69	99.11

T7	13.1	800	0.71	99.34
T8	13.9	800	0.55	99.56
T9	13.6	800	0.46	99.15
T10	13.9	800	0.66	99.21
T11	14	800	0.71	99.34
T12	13.2	800	0.55	99.17

In vitro drug release studies of Levetiracetam matrix tablets of all formulation

Table 3. Cumulative percent drug release and launch kinetics of formulations organized with PEO WSR 301. Every value represents mean S.D (n=3)

Time (hrs)	T1	T2	T3	T4
0	0	0	0	0
1	44	38	30	23
2	70	61	54	49
3	79	72	66	59
4	92	85	81	73
5	95	92	87	80
6	99	94	90	85
7		97	93	88
8		99	95	91
9			99	95
10				97
11				99
12				

In the above table , for formulations T1 to T4 percentage drug release was determined based on the time and also drug release was determined by kinetic models i.e zero order, first order, Higuchi Crowell's, Peppas model mentioning the release correlation coefficient.

For formulations T1, T2, T3, T4 the percentage drug release was found to be 99% at 6 hours, 99% at 8 hours, and 99% at 9hours and 99% at 11 hours respectively.

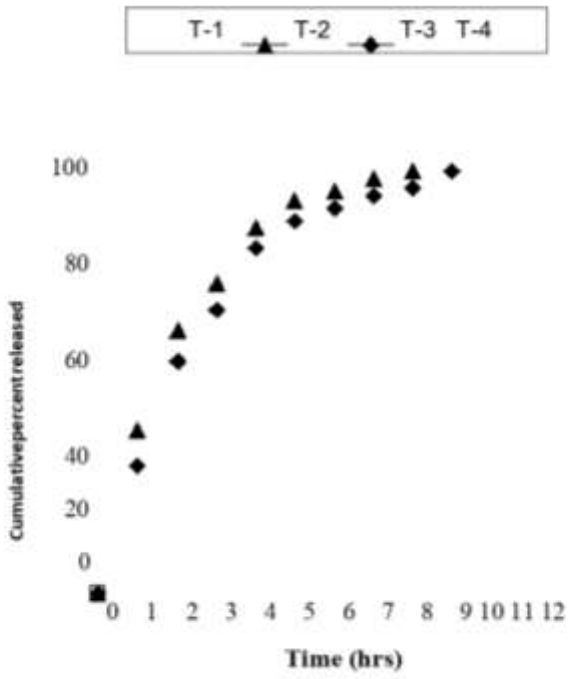

Figure 1. In vitro drug release studies of Levetiracetam matrix drugs arranged with PEO 301.

All the enumerating shows awesome properties. T-1 design containing 7.5 % Polymer put off the pharmaceutical for 6 hrs. T-2 arrange for that contains a 10 % of polymer put off the answer for 8 h, T-3 definition with 12.5 % of polymer calm release conceded by 9 hrs and T-4 enumerating with 15 % of pharmaceutical release 301 PEO conceded until 11 hours.

Table 4. Cumulative percent drug launch and release kinetics of formulations arranged with PEO Coagulant. Each value represents mean S.D (n=3)

Time (hrs)	T5	T6	T7	T8
0	0	0		0
1	38	32	25	31
2	62	56	48	44
3	69	63	59	56
4	80	75	70	67
5	88	83	81	77
6	91	87	84	81
7	96	91	88	85
8	99	94	91	87
9		97	94	90
10		99	97	93
11			99	95
12				99

In the above table , for formulations T5 to T8 percentage drug release was determined based on the time and also drug release was determined by kinetic models i.e zero order, first order, higuchi crowell's, peppas model mentioning the release correlation coefficient.

For formulations T5, T6, T7, T8 the percentage drug release was found to be 99% at 8 hours, 99% at 10 hours, and 99% at 11hours and 99% at 12 hours respectively.

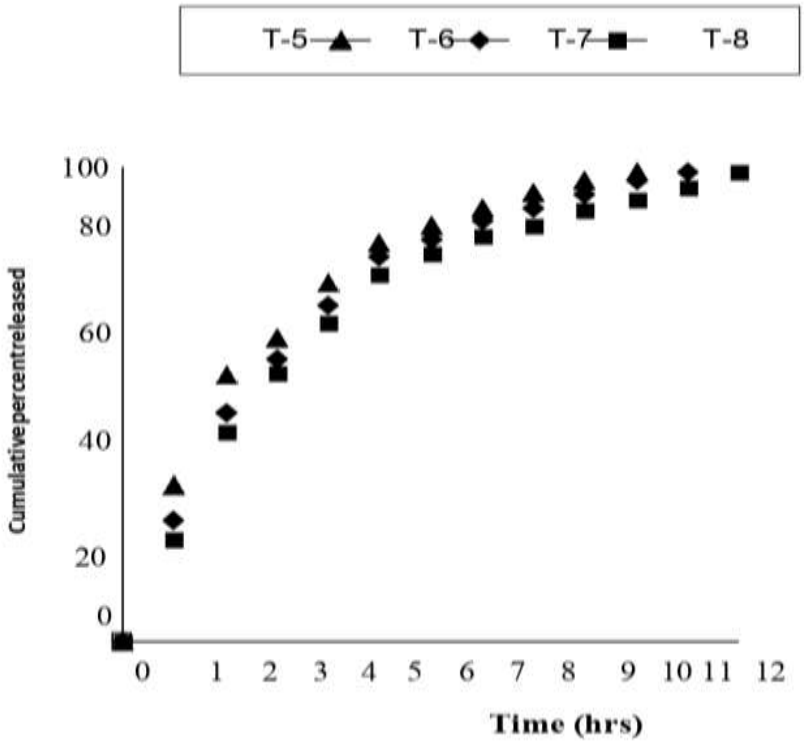

Figure 2. Aggregate percent sedate dispatch and discharge energy of details arranged with PEO Coagulant.

The results exhibited that as the polymer gathering of polyethylene oxide coagulant grows, the medicine dispatch charge changed into blocked. All the definition shows extraordinary properties. T-5 itemizing containing 7.5 % polymer ruined the prescription for 8 hrs. T-6 definition containing 10 % of polymer thwarted the medicine for 10 hrs, T-7 design with 12.5 % polymer obstructed drug release for 11 hrs and T-8 specifying with 15 % of PEO 301 ruined sedate release up to 12 hours.

Table 6. Cumulative percent drug release and release kinetics of formulations organized with PEO WSR 303. Each value represents mean +S. D (n=3)

Time (hrs)	T9	T10	T11	T12
0	0	0		0
1	33	28	22	16
2	55	50	45	41
3	64	61	55	51

4	74	71	68	62
5	83	78	74	71
6	86	83	80	77
7	92	88	85	81
8	93	90	87	83
9	96	93	90	87
10	98	96	92	89
11	99	97	94	91
12		99	97	93

In the above table , for formulations T9 to T12 percentage drug release was determined based on the time and also drug release was determined by kinetic models i.e zero order, first order, higuchi crowell's, peppas model mentioning the release correlation coefficient.

For formulations T9, T10, T11, T12 the percentage drug release was found to be 99% at 11 hours, 99% at 12 hours, and 97% at 12 hours and 93.1% at 12 hours respectively.

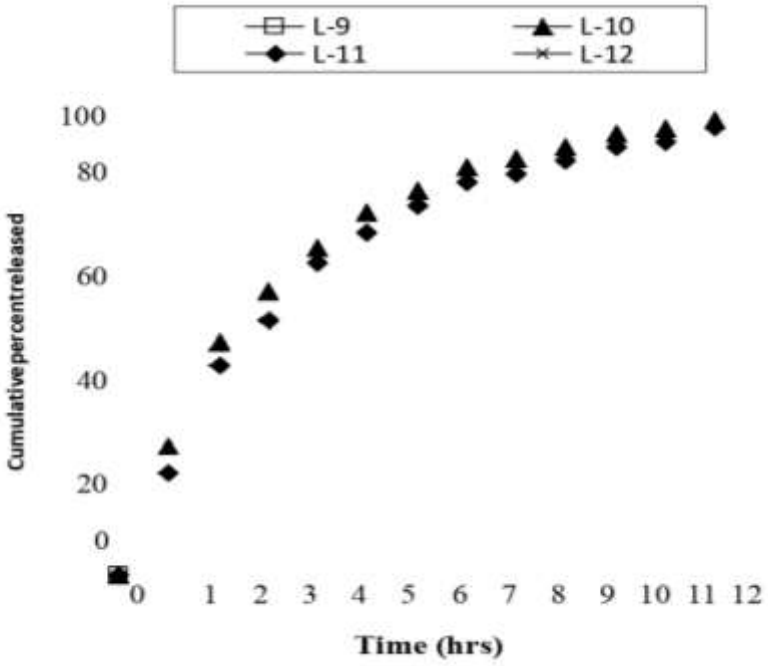

Figure 3. Combined percent tranquilize discharge and discharge energy of definitions composed with PEO 303.

The results demonstrate that the Concentration of polyethylene oxide polymer coagulant manufactures, the rate of drug dispatch was conceded. All the definition exhibits extraordinary properties. T-9 design containing 7.5 % Polymer concede the prescription in the midst of 11 hours. T-10 definition that contains a 10 % of polymer put off the medicine in the midst of 12 hours, T-11 design with 12.5 % of polymer sedate release conceded for 12 hours disseminated the 97 % and

the T-12 specifying with 15 % of drug release 301 PEO conceded up to 12 hours and anything is possible from that point.

Differential scanning calorimetric (DSC) study of Pure Levetiracetam.

Warm properties of unadulterated medication turned into assessed by means of differential filtering calorimetry (DSC) the utilization of a precious stone (DSC) (Mettler star SW 8.10). Fittingly measured 5-6 mg tests were thematically fixed in aluminum skillet and warmed at a charge 50^{o}C/min from 500c to 300 ^{0}c temperature assortment underneath nitrogen drift of 25 ml/min.

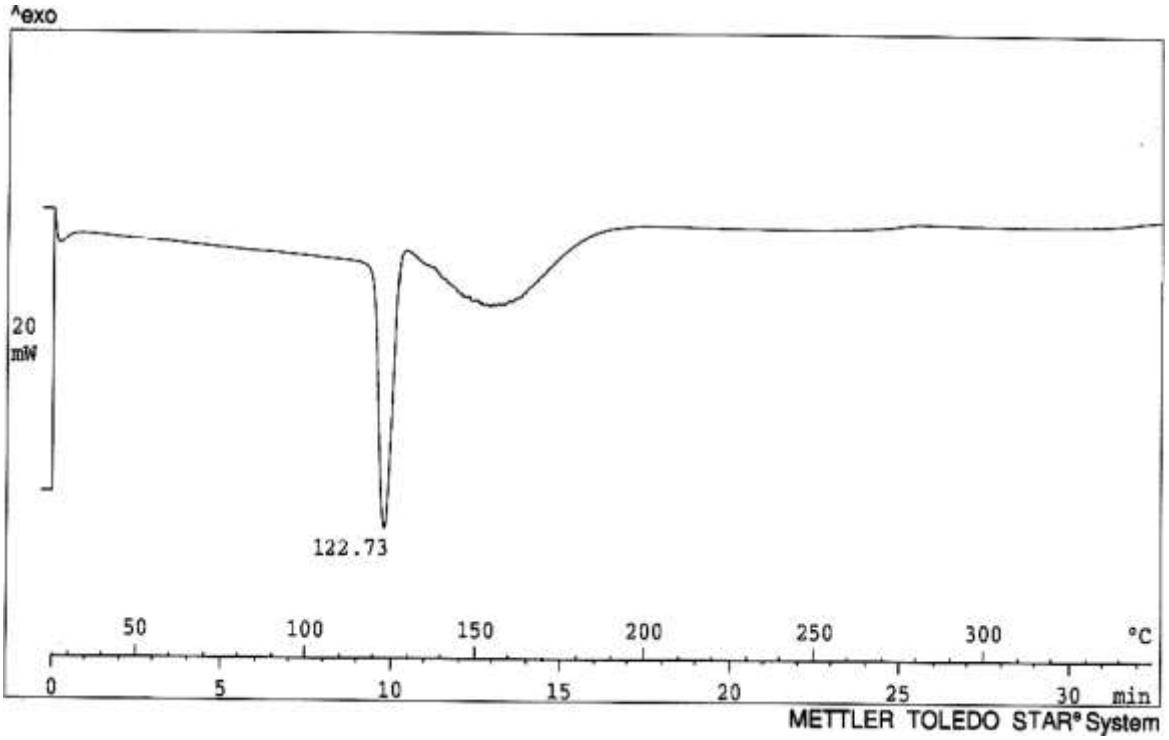

Figure 4. DSC thermogram of pure Levetiracetam.

Figure 4. Results of DSC thermogram of pure Levetiracetam shows sharp endothermic peak at 122.73 ^{O}C confirms the crystalline nature of the Levetiracetam.

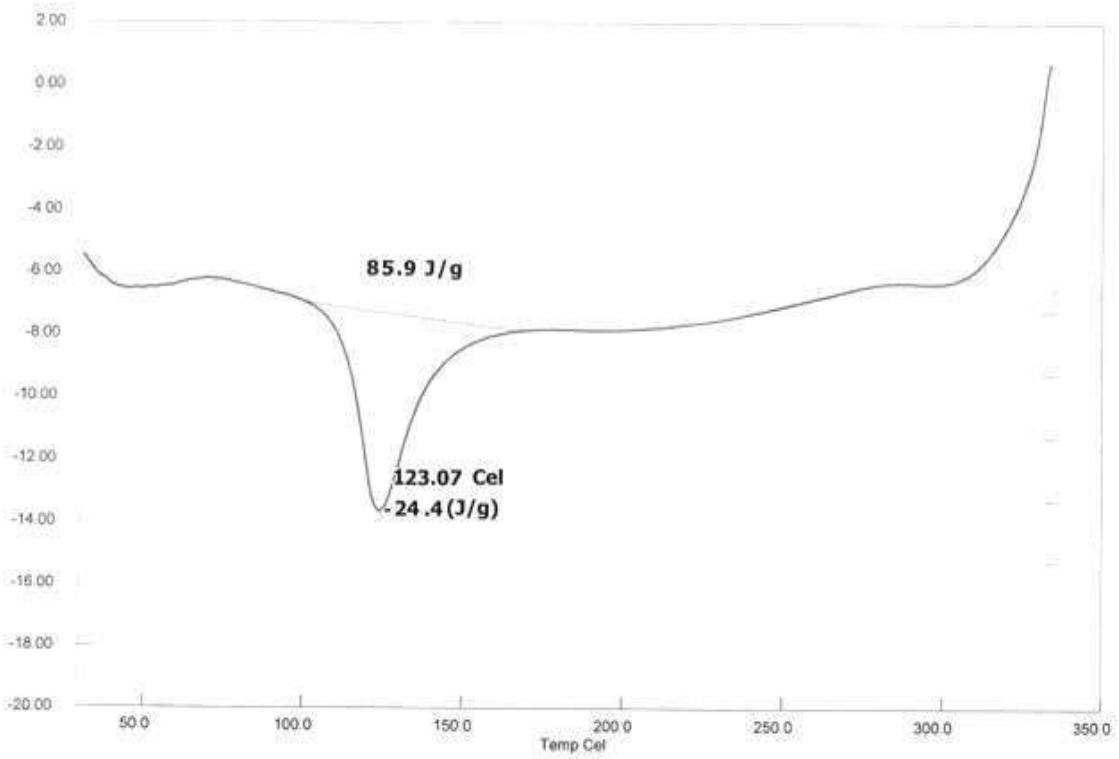

Figure 5. DSC thermogram of the Levetiracetam matrix tablet prepared with PEO

Differential scanning calorimetric (DSC) study of Levetiracetam matrix tablets prepared with Polyethylene oxides.

Results of DSC thermogram of pure Levetiracetam show sharp endothermic peak at 122.73 ^{O}C confirms the pure Levetiracetam. Similar sharp endothermic peaks at 123.07 ^{O}C was observed for the matrix tablet prepared with the polyethylene oxide clearly indicates the no drug polymer interaction.

FTIR study of Pure Levetiracetam.

The infrared spectra of Levetiracetam pure drug, was recorded at a range of 400– 4000 cm^{-1} on Perkin Elmer FTIR. The FTIR spectra of the pure Levetiracetam show spectrum peak points at 3362 cm^{-1} amide (NH2) group, 1678 cm^{-1} for CONH 2 group and 1491 cm^{-1} methylene CH bend.

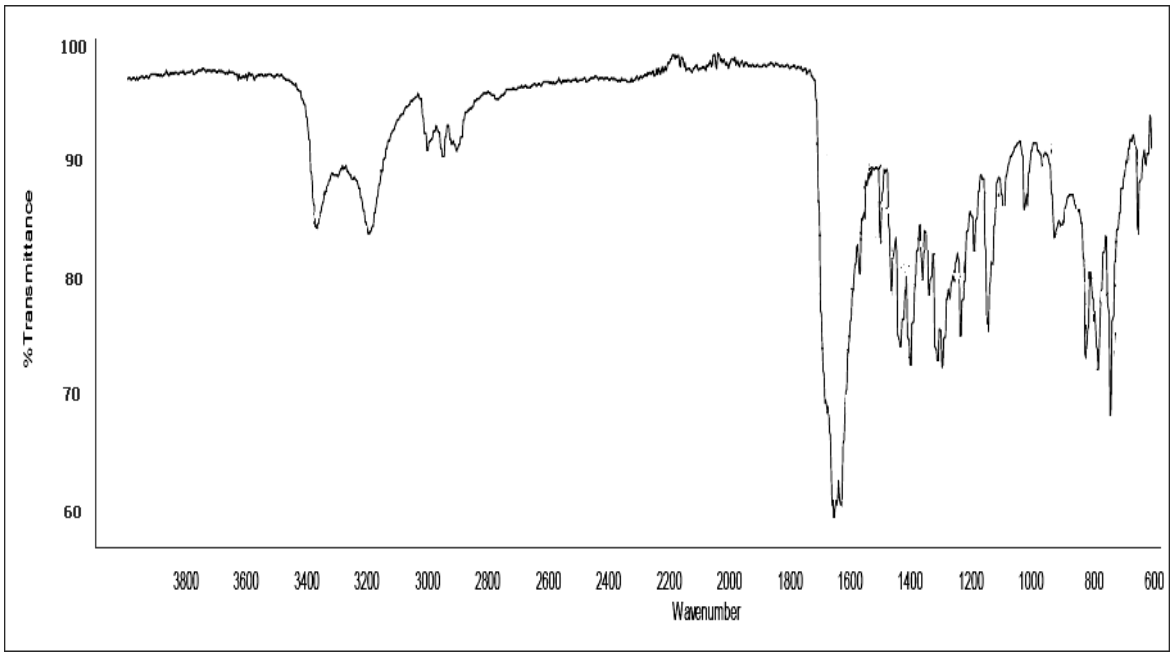

Figure 6. The FTIR spectra of the pure Levetiracetam

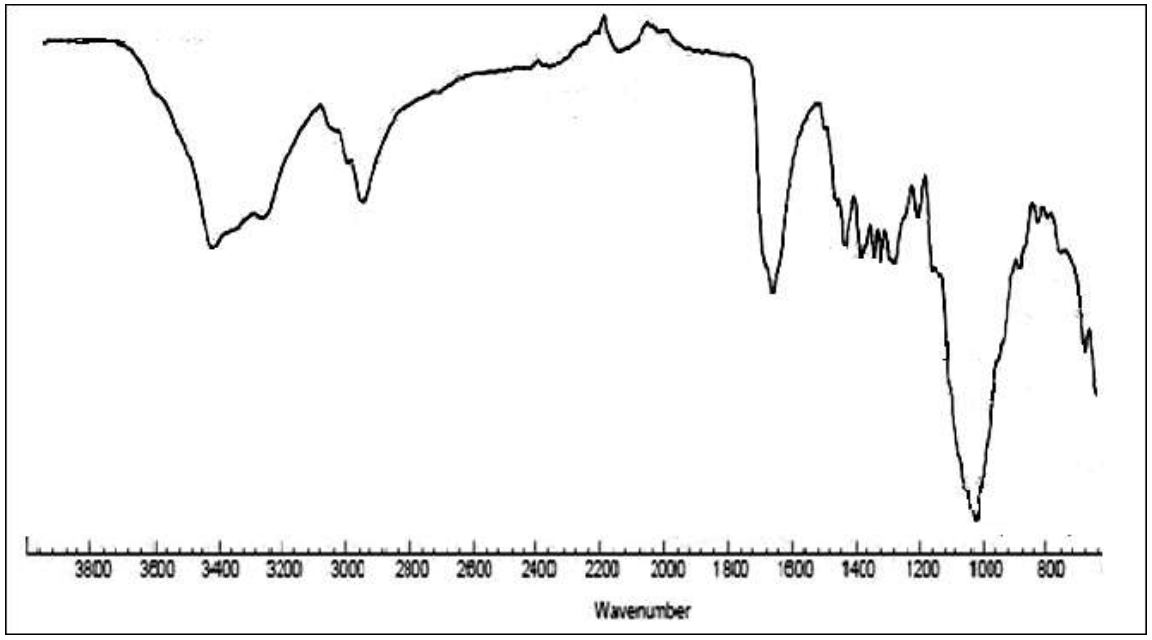

Figure 7. FTIR range of the Levetiracetam framework tablet arranged with Polyethylene oxides

FTIR study of Levetiracetam matrix tablets set with Polyethylene oxides. FTIR spectra of unadulterated Levetiracetam exhibit go centers top in 3362 cm-1amida (NH≥2) gathering, 1678 cm-1 for the social event CONH2 and 1491 cm-1 CH methylene winding. Relative zeniths were found in the concealing is set with polyethylene oxide insists that there is no solution in the affiliation system tablets masterminded polymer and extraordinary comparability.

CONCLUSION

The proposed techniques for the formulation of the selected anti-epileptic drug in the form of matrix tablets are by wet granulation method. Levetiracetam matrix tablets were prepared by using different grades of Polyethylene oxides (PEO 301, PEO coagulant and PEO 303). All the formulations were evaluated and the optimized formulation was subjected to stability studies. Results of the present study demonstrated that combinations of Polyethylene oxides (PEO 301, PEO coagulant and PEO 303) could be successively employed for formulating extended release matrix tablets, diffusion coupled with erosion might be the mechanism for the drug release from matrix tablets which can be expected to reduce the frequency of administration and decrease the dose dependent side effect associated with repeated administration of conventional Levetiracetam tablets.

REFERENCES

1. Himanshu Paliwal*1, Sachin Goyal1, etal. Formulation and evaluation of levetiracetam extended release tablets. Int. J. Pharm. Sci. Rev. Res., 41(1), November - December 2016; Article No. 48, Pages: 260-266.
2. Plosker GL, Clissold SP (1992) Controlled release metoprolol formulations A review of their Pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. Drugs 43: 382- 414.
3. De Haan P, Lerk CF (1984) Oral controlled release dosage forms A review. Pharm Weekbl Sci 6: 57-67.
4. Gupta M.M., Brijesh R. “A Review on: Sustained Release Technology”, International Journal of Therapeutic Applications, Volume 8, 2012, 18–23.
5. Bhowmik D, Gopinath H, Kumar B. Pragati, Duraivel S., Kumar K. P. Sampath. “Controlled Release Drug Delivery Systems”, The Pharma Innovation, Vol. 1, No. 10, 2012, 25.
6. Lachman L (1987). The Theory and Practice of Industrial Pharmacy. 3rd ed., pp 336- 413.
7. Remington (2000). The science and Practice of Pharmacy, 19th ed. 1660, pp 1676-1995.
8. Daniel C (1976). Applications of Statistics to Industrial Experiments, 2nd ed. New York, Wiley.
9. Davies OL (1978). The Design and Analysis of Industrial Experiments, 2nd ed. New York, Longman Group, pp 259-261.

10. Nagasamy Venkatesh Dhandapani. Formulation and *in vitro* evaluation of sustained release matrix tablets of levetiracetam for better epileptic treatment. International Scholarly and Scientific Research & Innovation 10(12) 2016.
11. Carol M Ulloa et al., Review of levetiracetam, with a focus on the extended release formulation, as adjuvant therapy in controlling partial onset seizures. Neuropsychiatric Disease and Treatment, 2009: 467–476.
12. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia; 2000; 41: 1179–1186.
13. Radtke RA. Pharmacokinetics of levetiracetam. Epilepsia, 2001; 42(4): 24–27.
14. Berner B, Dinh SM. *"Fundamental Concepts in Controlled Release" in "Treatise on Controlled Drug Delivery"*. New York, USA: Marcel Dekker Publication; 1992. p. 1–4.
15. Gilbert S Banker, Modern Pharmaceutics, 4 th edition, published by: Marcel Dekker; 297-321.
16. Lalla JK, Gurnancy RA, Polymers for mucosal delivery-swelling and mucoadhesive evaluation, Indian Drugs, 39(5), 270-276, 2002.

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