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# FORMULATION AND EVALUATION OF LEVITIRACETAM MATRIX TABLETS

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**Abstract:**
*For many years the treatment of acute or chronic sicknesses were carried out normally via the transport of medication to sufferers through diverse pharmaceutical forms encompass pills, pills, creams, suppositories, drinks, ointments, aerosols and injectables. The kinds conventional oral drug delivery systems are regarded to provide delivery of the drug. Therefore to reap as well as to hold the drug awareness within the range of healing effectiveness required for the treatment. Levetiracetam matrix tablets were prepared by using different viscosity grades of Polyethylene oxides such as PEO WSR 301, PEO Coagulant and PEO 303. The matrix tablets were prepared by direct compression method. The matrix tablet formulation L-8 and L-10 which releases all the drugs in 12 hours were selected for the study of accelerated stability. All levetiracetam matrix tablets with PEO WSR 301 (L-1 to L-4) were evaluated The hardness of the tablets is in the range of 13.1-14 kg/cm2. The friability below 1% indicates clearly the good mechanical resistance of the preparations of tablets. Testing of the prepared matrix tablets was found in the range of 99.1 to 101 % clearly indicates a good uniformity of content. The thickness of the tablets is in the range of 6.18 to 6.28 mm. The weight variation of tablets was within the range and 850 mg were found in all of the tablets. The matrix tablet formulation L-8 and L-10 which releases all the drugs in 12 hours were selected for the study of accelerated stability. DSC and FTIR studies were also performed.*

**Keywords:** *Controlled release formulations, Levetiracetam matrix tablets, Polyethylene oxides.*

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## INTRODUCTION:

**Controlled Release Drug Therapy**

For many years the treatment of acute or chronic sicknesses were carried out normally via the transport of medication to sufferers through diverse pharmaceutical forms encompass pills, pills, creams, suppositories, drinks, ointments, aerosols and injectables. Even these days, those conventional dosage paperwork are the main vehicles pharmacists usually visible inside the prescription and non-prescription drug market. The kinds conventional oral drug shipping systems are regarded to provide a set off launch of the drug. Therefore to reap as well as to hold the drug awareness within the range of healing effectiveness required for the treatment, it's miles frequently vital to take this kind of drug shipping gadget several instances an afternoon. This interprets into a extensive fluctuation of the drug tiers frequently with a sub-healing and/or poisonous ranges and waste of drugs. Recently, numerous technical advances have resulted inside the development of latest drug delivery systems able to controlling the rate of shipping of medicine, preserve the period of the therapeutic activity and cognizance the delivery of medication to a tissue [1].

A controlled release of the for management of the system usage and dosage form of the oral route is designed for flexibility and attention. The design of the delivery system for oral controlled release delivery system, such as the types of considerable importance are related to each other, multiple variables in the treatment of the disease is the patient to the treatment length, and drug property.

Controlled Release of 2 means that the system is capable of some real therapeutic control to indicate whether it is the temporal or spatial nature or both. In other words, the system tries to maintain a constant concentration of active agents in the target tissue to make available. It is this kind of this system that is different from the sustained release systems

**Advantages of CONTROLLED release dosage form [3]:**

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Sustained blood levels**; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic property of drug. The use of CONTROLLED releaseproducts may maintain therapeutic concentration over prolonged period.
- **Attenuation of adverse effect**, the use of CONTROLLED release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, haemodynamic changes etc.

**Disadvantages of CONTROLLED release dosage form: [3]**

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

**The major objectives of the investigation are as follows:**

- To Prepare Controlled release tablets of Levetriacetam with different polymers.
- To construct a theoretical release profile to select the best formulations.
- To Select Dissolution media, Validation and dissolution of Controlled release dosage forms.

## *EXPERIMENTAL*

**Formulation of Controlled release tablets of Levetriacetam matrix tablets:**

Levetiracetam matrix tablets were prepared by using different viscosity grades of Polyethylene oxides such as PEO WSR 301, PEO Coagulant and PEO 303.

**Construction of theoretical release profile:**

To draw a theoretical profile mimicking the required release pattern derived from the dose calculations.

**Evaluation of Controlled release Tablets:**

Evaluation of Controlled release tablets embodies

a) Construction of standard graph of Levetriacetam in Water, pH 6.8

Phosphate buffer, 0.1 N HCl.

b) To evaluate the prepared Controlled release tablets for

i)Weight variation.

ii)Tablet Thickness.

iii)Tablet Hardness.

iv)Friability.

c) In – vitro Drug release from the formulations in Water, using USP Paddle Apparatus II.

d) Calculation of f2 factor for the determination of similarity between the formulations.

e) To study the effect of pH, Storage temperature on Drug release.

f) To determine the Drug content of Controlled release tablets.

g)To perform stability studies as per ICH guidelines.

## MATERIALS AND METHODS:

**Levetriacetam Matrix Tablets**

**Formulation and Evaluation of Levetiracetam matrix tablets**

Levetiracetam matrix tablets are prepared by different viscosity grades of polyethylene oxides as PEO WSR 301, PEO PEO coagulant and 303. The array of tablets was prepared by direct compression method. The polymer of drugs were screened and well mixed in this Add thinner as cellulose microcrystalline cellulose and finally lubricated with lubricant. The powder mixture is mixed well by the uniformity and finally compressed using 18x 7.5 mm with a capsule, with Cadmachrotory punch compression machine. The tablets were evaluated the matrix prepared by various physicochemical properties and is described in the next section

**Formulation development of Levetiracetam matrix tablets with PEO 301**

**Table 1: Formulation composition of the prepared Levetiracetammatrix tablets withPEO WSR 301.**

| Ingredients (mg) | L-1 | L-2 | L-3 | L-4 |
|---|---|---|---|---|
| | mg/tablet | | | |
| Levetiracetam | 500 | 500 | 500 | 500 |
| PEO 301 | 75 | 100 | 125 | 150 |
| PEO Coagulant | * | * | * | * |
| PEO 303 | * | * | * | * |
| Avicel Ph 200 | 255 | 230 | 205 | 180 |
| Aerosil 200 | 7.5 | 7.5 | 7.5 | 7.5 |
| Talc | 7.5 | 7.5 | 7.5 | 7.5 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Total weight | 850 | 850 | 850 | 850 |
| | | | | |
| Hardness ($Kg/cm^2$) | 13.5 | 13.4 | 13.1 | 14 |
| Weight variation (mg) | 850 | 850 | 850 | 850 |
| Friability (%) | 0.65 | 0.75 | 0.66 | 0.5 |
| Drug Content (%) | 99.1 | 99 | 99.2 | 101 |

**Formulation development of Levetiracetam matrix tablets with PEO Coagulant**

**Table 2: Formulation composition of the prepared Levetiracetam matrix tablets withPEO Coagulant.**

| Ingredients (mg) | L-5 | L-6 | L-7 | L-8 |
|---|---|---|---|---|
| | mg/tablet | | | |
| Levetiracetam | 500 | 500 | 500 | 500 |
| PEO 301 | * | * | * | |
| PEO Coagulant | 75 | 100 | 125 | 150 |
| PEO 303 | * | * | * | |
| Avicel Ph 200 | 255 | 230 | 205 | 180 |
| Aerosil 200 | 7.5 | 7.5 | 7.5 | 7.5 |
| Talc | 7.5 | 7.5 | 7.5 | 7.5 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Total weight | 850 | 850 | 850 | 850 |
| | | | | |
| Hardness ($Kg/cm^2$) | 13.8 | 13.6 | 13.8 | 13.8 |
| Weight variation (mg) | 850 | 850 | 850 | 850 |
| Friability (%) | 0.67 | 0.59 | 0.71 | 0.55 |
| Drug Content (%) | 99.7 | 99.3 | 99.9 | 99.9 |

**Formulation development of Levetiracetam matrix tablets with PEO WSR 303**

**Table 3: Formulation composition of the prepared Levetiracetam matrix tablets with PEO WSR 303.**

| Ingredients (mg) | L-9 | L-10 | L-11 | L-12 |
|---|---|---|---|---|
| | mg/tablet | | | |
| Levetiracetam | 500 | 500 | 500 | 500 |
| PEO 301 | * | * | * | * |
| PEO Coagulant | * | * | * | * |
| PEO 303 | 75 | 100 | 125 | 150 |
| Avicel Ph 200 | 255 | 230 | 205 | 180 |
| Aerosil 200 | 7.5 | 7.5 | 7.5 | 7.5 |
| Talc | 7.5 | 7.5 | 7.5 | 7.5 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Total weight | 850 | 850 | 850 | 850 |
| | | | | |
| Hardness ($Kg/cm^2$) | 13.6 | 13.7 | 13.6 | 13.1 |
| Weight variation (mg) | 850 | 850 | 850 | 850 |
| Friability (%) | 0.46 | 0.66 | 0.71 | 0.45 |
| Drug Content (%) | 99.4 | 99.6 | 99.3 | 99.6 |

**Determination of stability of the prepared Levetiracetam matrix tablets prepared with PEO coagulant and PEO 303.**

The matrix tablet formulation L-8 and L-10 which releases all the drugs in 12 hours were selected for the study of accelerated stability. The tablets were prepared in containers full of HDPE and stored in the following conditions as 40℃/75% RH for about 6 months, according to ICH guidelines. The samples were characterized by cent of drug content.

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

Thermal properties of pure drug was evaluated by means of differential analysis (DSC) caloriemetry using a diamond (DSC) (Mettler star SE 8.10). Exactly heavy 5-6 mg samples were hermetically sealed in aluminum pots and heated at a rate of 50 $^{O}$C/min from 500C to 300 $^{0}$C temperature ranges under nitrogen at a rate of 25 ml/min. DSC thermogram is given in figure

**FTIR study of Levetiracetam matrix tablets prepared with Polyethylene oxides.**

The FT-IR spectra acquired were taken from dried samples.

The characteristic band peaks acquired were taken from the prepared coated granules. The interaction study between drug and polymer was evaluated. FTIR spectra of pure Levetiracetam matrix tablets is given in the figure

**Differential scanning calorimetry (DSC) study**

Differential scanning calorimetry (DSC) study of drug loaded coated granules was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug-excipient compatibility study. The analysis was performed at a rate 5 $^{0}$C min$^{-1}$ from 50 $^{0}$C to 200 $^{0}$C temperature range under nitrogen flow of 25 ml min$^{-1}$. DSC thermogram is given in the figure

**Fourier Transform Infrared spectroscopy (FT-IR)**

The FT-IR spectra acquired were taken from dried samples.

The characteristic band peaks acquired were taken from the prepared coated granules. The interaction study between drug and polymer was evaluated. FTIR spectra of pure Levetiracetam is given in the figure

## RESULTS AND DISCUSSION:

**LEVETIRACETAM MATRIX TABLETS**

**In vitro drug release studies of Levetiracetam matrix tablets prepared with PEO WSR 301**

**Table 4: Cumulative percentage drug release and release kinetics of formulations prepared with PEO WSR 301. Each value represents mean + S.D (n=3)**

| Time (Hrs) | L-1 | L-2 | L-3 | L-4 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 44.4 | 38.4 | 30.1 | 24.4 |
| 2 | 70.3 | 61.6 | 54.5 | 49.8 |
| 3 | 79.6 | 72.8 | 66.3 | 60.6 |
| 4 | 92.5 | 85.7 | 81 | 73.8 |
| 5 | 95.3 | 92 | 87.1 | 80.6 |
| 6 | 99 | 94.3 | 90.3 | 85.7 |
| 7 | | 97 | 93 | 88 |
| 8 | | 99 | 95 | 91 |
| 9 | | | 99 | 95 |
| 10 | | | | 97 |
| 11 | | | | 99 |
| 12 | | | | |

| Release Kinetics | | | | |
|---|---|---|---|---|
| Zeroorder | 0.8551 | 0.8454 | 0.8513 | 0.8483 |
| Firstorder | 0.9774 | 0.9645 | 0.988 | 0.9942 |
| Higuchi | 0.9421 | 0.9371 | 0.9411 | 0.9393 |
| Peppas | 0.9564 | 0.9409 | 0.9315 | 0.9145 |
| peppas[n] | 0.4314 | 0.4725 | 0.5462 | 0.6246 |

***In vitro* drug release studies of Levetiracetam matrix tablets prepared with PEO coagulant**

**Table 5: Cumulative percentage drug release and release kinetics of formulations prepared with PEO Coagulant. Each value represents mean + S.D (n=3)**

| Time (Hrs) | L-5 | L-6 | L-7 | L-8 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 38.2 | 32.9 | 25.5 | 21.5 |
| 2 | 62.2 | 56.3 | 48 | 44.3 |
| 3 | 69.2 | 63.9 | 59.5 | 56.5 |
| 4 | 80.6 | 75.5 | 70.7 | 67.1 |
| 5 | 88.6 | 83.8 | 81 | 77.4 |
| 6 | 91.6 | 87.5 | 84.8 | 81.7 |
| 7 | 96 | 91.1 | 88.6 | 85.4 |
| 8 | 99 | 94.7 | 91.1 | 87.6 |
| 9 | | 97 | 94.3 | 90.9 |
| 10 | | 99 | 97 | 93 |
| 11 | | | 99 | 95.8 |
| 12 | | | | 99 |

| Release Kinetics | | | | |
|---|---|---|---|---|
| Zeroorder | 0.8961 | 0.8719 | 0.8594 | 0.8509 |
| Firstorder | 0.9346 | 0.9567 | 0.9511 | 0.9211 |
| Higuchi | 0.9606 | 0.9507 | 0.9448 | 0.9403 |
| Peppas | 0.9656 | 0.9564 | 0.945 | 0.9312 |
| peppas(n) | 0.9444 | 0.4575 | 0.5348 | 0.5634 |

***In vitro* drug release studies of Levetiracetam matrix tablets prepared with PEO WSR 303**

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

| Time (Hrs) | L-9 | L-10 | L-11 | L-12 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 33.8 | 28 | 22.1 | 16.8 |
| 2 | 55.3 | 50.8 | 45.7 | 41.6 |
| 3 | 64 | 61.7 | 55.6 | 51 |
| 4 | 74.9 | 71.1 | 68 | 62.9 |
| 5 | 83 | 78.9 | 74.6 | 71.6 |
| 6 | 86.3 | 83.5 | 80.2 | 77.2 |
| 7 | 92 | 88.6 | 85.3 | 81 |
| 8 | 93.7 | 90.6 | 87.1 | 84.8 |
| 9 | 96 | 93.1 | 90.1 | 87.3 |
| 10 | 98 | 96 | 92.9 | 89.6 |
| 11 | 99 | 97 | 94.2 | 91.1 |
| 12 | | 99 | 97 | 93.1 |

| Release Kinetics | | | | |
|---|---|---|---|---|
| Zeroorder | 0.8551 | 0.8454 | 0.8513 | 0.8483 |
| Firstorder | 0.9774 | 0.9645 | 0.988 | 0.9942 |
| Higuchi | 0.9432 | 0.9371 | 0.9411 | 0.9393 |
| Peppas | 0.9564 | 0.9409 | 0.9315 | 0.9145 |
| peppas(n) | 0.4314 | 0.4725 | 0.5462 | 0.6246 |

**Determination of stability of the prepared Levetiracetam matrix tablets prepared with PEO coagulant and PEO 303.**

**Table 7: Estimation of % drug content of accelerated stability study samples of Levetiracetam matrix tablets at 40°C/75% RH**

| **Formulation** | **L-8** | **L-10** |
|---|---|---|
| Estimated (%) | **% Drug content** | |
| Initial | 99.9 | 99.6 |
| 40℃/75% RH 1 M | 98.23 | 99.12 |
| 40℃/75% RH 2 M | 98.89 | 99.08 |
| 40℃/75% RH 3 M | 99.11 | 99.11 |
| 40℃/75% RH 6 M | 98.99 | 98.98 |

In vitro dissolution of stability samples were performed according to the methods described in the dissolution of the routine analysis of levetiracetam. There is not much difference in the initial and after 6 months of stability in accelerated conditions. This clearly indicates the nature of the drugaccelerated test of study have given similar results between initial 1 month, 2 months, 3 months and 6 months. This confirms the stable nature of the drug in the matrix prepared from tablets of levetiracetam.

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

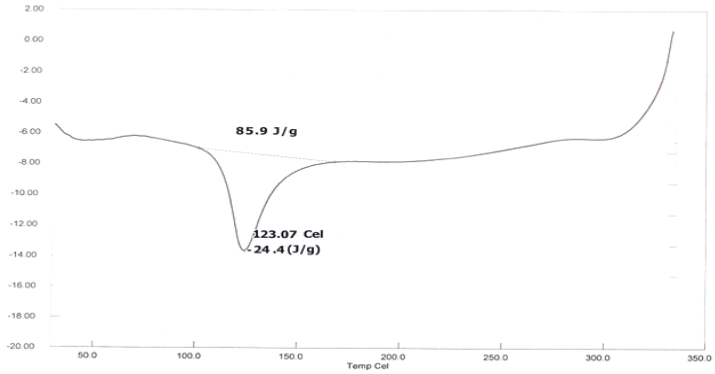


**Fig.1: DSC thermogram of the Levetiracetam matrix tablet prepared with PEO**

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 Levetiracetam matrix tablets prepared with Polyethylene oxides.**

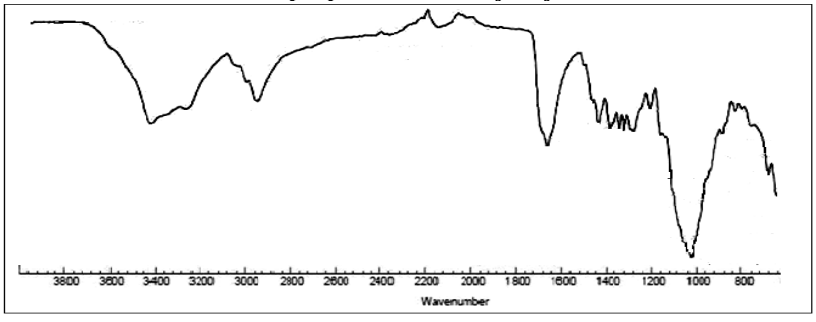


**Fig.2: FTIR spectrum of the Levetiracetam matrix tablet prepared with Polyethylene oxides**

FTIR spectra of pure Levetiracetam show spectrum points peak in 3362 cm-1amida (NH≥2) group, 1678 cm-1 for the group CONH2 and 1491 cm-1 CH methylene bending. Similar peaks were observed in the coating is prepared with polyethylene oxide confirms that there is no medicine in the interaction matrix tablets prepared polymer and good compatibility.

## SUMMARY AND CONCLUSION:

The present project is to formulate and assess Levetiracetam matrix tablets are prepared by different viscosity grades of polyethylene oxides as PEO WSR 301, PEO PEO coagulant and 303. The array of tablets were prepared by direct compression method. The polymer of drugs were screened and well mixed in this Add thinner as cellulose microcrystalline cellulose and finally lubricated with lubricant. The powder mixture is mixed well by the uniformity and finally compressed using 18x 7.5 mm with a capsule, with Cadmachrotory punch compression machine. The tablets were evaluated the matrix prepared by various physicochemical properties and is described in the next section

All levetiracetam matrix tablets with PEO WSR 301 (L-1 to L-4) were evaluated by various physico-chemical parameters such as variation in weight, hardness, thickness, friability and drug content. The hardness of the tablets is in the range of 13.1-14 kg/cm2. The friability below 1% indicates clearly the good mechanical resistance of the preparations of tablets. Testing of the prepared matrix tablets was found in the range of 99.1 to 101 % clearly indicates a good uniformity of content. The thickness of the tablets is in the range of 6.18 to 6.28 mm. The weight variation of tablets was within the range and 850 mg were found in all of the tablets.

The in vitro dissolution studies of levetiracetam formulation marketed was performed using USP Dissolution apparatus of type II at 50 rpm. Of 500 mg of levetiracetam is weighed and fell in the middle of dissolution. The Dissolution Medium (900ml) was involved in the water up to 45 minutes, which is maintained at 37 ± 0.5 ℃. An aliquot (5 mL) was removed at specific time intervals and the drug content was determined by the HPLC method RP to 212 Nm as described above.

The matrix tablet formulation L-8 and L-10 which releases all the drugs in 12 hours were selected for the study of accelerated stability.

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