Formulation development and in vitro evaluation of oral disintegrating tablets for newer anticonvulsant agent

Abstract

Objective: The main objective of current research work is to formulate the Levetiracetam oral disintegrating tablets. Levetiracetam, a newer anti convulsant and used to treat epilepsy and chronic seizures.

Methods: The oral disintegrating tablets of Levetiracetam were prepared employing various proportions of Crospovidone and Croscarmellose sodium as a Superdisintegrants by Direct Compression technique. 9 formulations were developed and are evaluated for various finished product quality assurance methods.

Results: Results reveals that all the formulation was found to be within the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters were determined.

Conclusion: Formulation (F5) containing 37.5mg of Crospovidone and 37.5mg of Croscarmellose, is ideal formulation (similarity factor f2= 82.676, dissimilarity factor f1=2.049 & No significant difference, t=0.0456) to marketed product (SPRITAM-250). Formulation (F5) follows First order, Higuchi’s kinetics, mechanism of drug release was found to be Non-Fickian Diffusion (n=0.666).

Keywords: levetiracetam, factorial design, superdisintegrants, crospovidone, croscarmellose sodium, wetting time, disintegration time, non-fickian diffusion

Abbreviations: ODT, oral disintegrating tablet; RPM, revolutions per minute; Kg, kilogram; CP, crospovidone; CCS, croscarmellose sodium; mg, milligram; mL, milliliter; %CDR, percentage cumulative drug release; BCS, biopharmaceutical classification; UR, un released; Min, minute; ºC, degree centigrade; mm, millimeter; t1/2, half life; t10%, time taken to release 10% drug from dosage form; t50%, time taken to release 50% drug from dosage form; t75%, time taken to release 75% drug from dosage form; t90%, time taken to release 90% drug from dosage form; WT, wetting time; DT, disintegration time

Introduction

Dysphasia is a common problem of all age groups, especially geriatrics and pediatrics. Oral disintegrating tablets creates new trend in the pharmaceutical market. Fast dissolving tablets are suitable many kinds of patients. Oro dispersible tablets, rapimelts, mouth-dissolving tablets, Fast dissolving tablets, quick dissolving, melt-in mouth tablets, porous tablets were also frequently used for ODT. Many drugs candidates are suitable to formulate as ODT.1

They quickly disintegrate/dissolve in oral cavity within <1 min.2–4 FDTs are prepared by various techniques, formed ODTs may vary in sensual characteristics such as, mouth feel, taste, swallowability, mechanical strength of tablet, drug release, bioavailability and stability. Various processes involved in formulating ODTs include Lyophilization, mass extrusion, cotton candy process, molding, spray drying, and compaction (wet granulation, dry granulation, direct compression), Durasolv® technology.5

Levetiracetam is an anticonvulsant agent, used to treat epilepsy. The main aim of this study is to formulate Oral Fast Disintegrating Tablets of Levetiracetam to achieve rapid dissolution, absorption. Oral disintegrating Tablets of Levetiracetam were designed with a view to enhance the patient compliance (pediatric) and provide a quick onset of action.1–4

In the current research investigation the direct compression method was utilized to formulate tablets, due numerous advantages such as simplest and cost effective tablet production method.5

Materials and methods

Levetiracetam was a gift sample procured from Aurobindo Pharma Ltd, Hyderabad, India. Mannitol, Crospovidone, Croscarmellose sodium were procured from DME Pvt Ltd, Mumbai. Other excipients were procured from LobaChemie. Ltd., Mumbai.

Preparation of levetiracetam fast dissolving tablets

Levetiracetam Tablets were prepared by direct compression method. The formulae was presented as Table 1. All ingredients were subjected screening with the help sieve #40. All the above ingredients were subjected to uniform mixing. Lubricants were screened vis sieve #80, mix them with above powder blend. The powder blend was subjected to compression using minipress (RIMEK 8 station) using 10mm circular punches. Formed tablets were evaluated for In-process quality assurance tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Evaluation of levetiracetam fast dissolving tablets

Hardness: The hardness test was performed using Monsanto Tablet Hardness Tester.16

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Table 1 Formule for the Preparation of Levetiracetam Fast Dissolving Tablets

| Name of Ingredients | Quantity of Ingredients per Each Tablet (mg) |
|---------------------|---------------------------------------------|
|                     | F_1 | F_2 | F_3 | F_4 | F_5 | F_6 | F_7 | F_8 |
| Levitiracetam        | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Mannitol             | 42  | 54.5| 67  | 54.5| 67  | 79.5| 67  | 92  |
| Crodospovidine       | 50  | 50  | 50  | 37.5| 37.5| 37.5| 25  | 25  |
| Croscarmellose sodium| 50  | 37.5| 25  | 50  | 37.5| 25  | 50  | 25  |
| Magnesium Stearate   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| Talc                 | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| Total Weight         | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

Friability: The friability of the tablets was determined with the help of Roche Friabilator. Weight of 20 Tablets noted as Initial weight (W_0) are dedusted in a drum for 4 min with a rotation rate of 25rpm and weight was noted as Final weight (W). Percentage friability was determined from following equation. The weight loss should not be more than 1%.^{16}

Friability (%) = (W -W_0)/W_0 x 100

Content uniformity: 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 92.5% or not more than 107.5% (100±7.5%) of the labeled drug content can be considered as the test was passed.^{17}

Assay: Select fixed number of sample on the random basis (20), comminute them to obtain powder. The powder equivalent to 100mg Levitiracetam was weighed and dissolved in 10ml of Distilled water in volumetric flask, the volume was adjusted to 100ml with Phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0ml of solution were diluted to 10ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content in was determined spectrophotometrically at 215nm.^{15}

Thickness: Thickness was determined with the help vernier calipers.^{18}

Wetting time: To measure Wetting time of the Tablet, a piece of Tissue paper folded twice was placed in a small petri dish (Internal Diameter is=6.5cm) containing 5ml of Distilled water. A Tablet placed on the paper, and the time for complete wetting of the tablet was measured in sec.\textsuperscript{19,20}

In-vitro dissolution study: Levitiracetam oral disintegrating tablets subjected to dissolution test with the help of USP XXIII type-II tablet dissolution test apparatus using 900ml of Phosphate buffer pH 6.8 operated under standard set of conditions. Withdraw samples at fixed intervals with the aid of syringe with a pre-filter, and maintain the sink condition. Absorbance’s for samples were noted at 215nm using UV Visible spectrophotometer (after suitable dilutions if necessary). The determinations were performed in triplicate (n=3).^{11}

Disintegration test: Disintegration of oral disintegrating tablets is achieved in the oral cavity owing to the impact of saliva, salivary volume is limited hence there is no proper In vitro In vivo correlation (IVIVC) was found in USP and IP. A modified method was used to determine to perform the disintegration test. A cylindrical vessel with 10 # was placed in such way that only 2ml of medium would be placed below the sieve. 6ml of medium was placed inside the vessel in such way that 4ml of the media was below the sieve and 2ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on the top of agitator. Disintegration time was recorded. Six tablets were chosen randomly from the composite samples and the average value was determined.^{18}

Kinetic modeling of drug release: The dissolution profile of all the formulations was subjected to kinetic modeling.\textsuperscript{21–25}

Results and discussion

9 Levetiracetam Oral Disintegrating Tablet formulations were prepared by direct compression method using various proportions of superdisintegrants combination as per the formulae presented in Table 1. All the formulations containing 250mg of Levetiracetam prepared tablets prepared and evaluated for various pharmacopoeial limits such as, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods. The Thickness values were found in the range from 3.45±0.7mm to 3.74±0.1mm. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches. Hardness was maintained to be within 3.11±0.12kg/cm^2 to 3.55±0.1kg/cm^2. The hardness of all batches were almost uniform and possess good mechanical strength. The study results for friability were found well within the approved range (<1%) in all the formulation. Results revealed that the tablets possess good mechanical strength.

All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5%. Average weight for all formulations was found to be in the range of 399.68±0.3-401.48±2.0mg. This is due to good flow property and compressibility of all the formulations.

From the results of wetting time and Disintegration time, it reveals that as the concentration of superdisintegrants increases the wetting time decreases (Concentration of superdisintegrants inversely proportional to wetting time).Wetting time for all the formulations varied from 12.17±1.3 to 88.03±1.2 sec. The Disintegration Time of tablets was in the range of 9.12±0.5-53.21±2.4 sec.

Results for all Post-compression parameters were tabulated or shown in Table 2-4 and plots for wetting time and disintegration were presented in Figure 1 & Figure 2. The cumulative percentage drug released by each tablet in the In Vitro Release studies were based on the mean content of the drug present in the respective tablet.

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Figure 1 Wetting Time Chart for Formulation F₁-F₉

Figure 2 Disintegration Time Chart for Formulation F₁-F₉

Table 2 Post-Compression Parameters

| S. no | Formulation Code | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Average Weight (mg) | Drug Content (%) | Wetting Time (sec) | Disintegration Time (sec) |
|-------|------------------|-------------------|----------------|----------------|---------------------|-----------------|---------------------|---------------------------|
| 1     | F₁               | 3.11±0.12         | 3.4±0.8        | 0.58±0.2       | 400.69±0.9          | 99.49±1.1       | 12.17±1.3          | 9.12±0.6                  |
| 2     | F₂               | 3.20±0.15         | 3.45±0.7       | 0.64±0.3       | 401.46±1.9          | 99.28±0.7       | 14.09±1.3          | 9.32±0.6                  |
| 3     | F₃               | 3.21±0.11         | 3.6±0.5        | 0.62±0.1       | 400.67±1.1          | 99.41±0.5       | 18.10±1.7          | 10.30±0.7                 |
| 4     | F₄               | 3.2±0.14          | 3.5±0.6        | 0.62±0.19      | 405.55±2.2          | 99.53±0.4       | 38.23±1.5          | 12.5±0.9                  |
| 5     | F₅               | 3.15±0.16         | 3.55±0.4       | 0.52±0.30      | 401.48±1.1          | 99.39±0.6       | 42.38±1.2          | 12.81±0.9                 |
| 6     | F₆               | 3.55±1.0          | 3.7±0.2        | 0.65±0.04      | 401.04±2.0          | 99.92±0.4       | 48.2±1.2           | 13.21±0.7                 |
| 7     | F₇               | 3.3±0.15          | 3.55±0.6       | 0.61±0.3       | 400.48±1.4          | 99.23±1.0       | 51.16±1.5          | 28.18±1.2                 |
| 8     | F₈               | 3.31±0.12         | 3.6±0.4        | 0.57±0.4       | 399.68±0.3          | 99.51±0.8       | 78.11±1.9          | 42.39±0.5                 |
| 9     | F₉               | 3.21±0.13         | 3.74±0.1       | 0.62±0.4       | 400.45±0.9          | 99.49±0.9       | 88.03±1.2          | 53.21±2.4                 |

Table 3 Statistical parameters

| S. no | Formulation Code | Zero order | First order | Higuchi | Korsmeyer-peppas |
|-------|------------------|------------|------------|---------|------------------|
|       |                  | a          | b          | r       | a                | b          | r       | a | b | r |
| 1     | F₁               | 49.51      | 1.150      | 0.689   | 1.678            | 0.031      | 0.948   | 24.919 | 12.157 | 0.874 | 0.730 | 0.830 | 0.746 |
| 2     | F₂               | 46.954     | 1.178      | 0.710   | 1.678            | 0.027      | 0.912   | 22.494 | 12.282 | 0.889 | 0.701 | 0.847 | 0.755 |
| 3     | F₃               | 44.34      | 1.212      | 0.733   | 1.730            | 0.026      | 0.934   | 20.077 | 12.420 | 0.903 | 0.671 | 0.861 | 0.764 |
| 4     | F₄               | 48.066     | 1.173      | 0.696   | 1.630            | 0.028      | 0.880   | 23.282 | 12.334 | 0.879 | 0.705 | 0.847 | 0.749 |
| 5     | F₅               | 45.180     | 1.242      | 0.730   | 1.777            | 0.033      | 0.969   | 20.310 | 12.735 | 0.904 | 0.666 | 0.873 | 0.761 |
| 6     | F₆               | 42.480     | 1.261      | 0.749   | 1.762            | 0.028      | 0.941   | 17.915 | 12.765 | 0.913 | 0.638 | 0.886 | 0.770 |
| 7     | F₇               | 46.381     | 1.178      | 0.710   | 1.682            | 0.025      | 0.914   | 21.993 | 12.266 | 0.888 | 0.694 | 0.849 | 0.753 |
| 8     | F₈               | 43.238     | 1.233      | 0.739   | 1.737            | 0.025      | 0.931   | 18.836 | 12.570 | 0.905 | 0.648 | 0.876 | 0.766 |
| 9     | F₉               | 42.401     | 1.217      | 0.739   | 1.725            | 0.022      | 0.906   | 18.324 | 12.406 | 0.904 | 0.644 | 0.874 | 0.766 |
| 10    | MP               | 44.978     | 1.22       | 0.730   | 1.76             | 0.031      | 0.952   | 20.44  | 12.532 | 0.899 | 0.676 | 0.861 | 0.765 |

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Cumulative % Drug release for $F_1$-$F_9$ at 60min were found to be in the range of 95.35-99.25%. Dissolution profiles of Levetiracetam oral disintegrating formulations was subjected to goodness of fit test by linear regression analysis according to kinetic modeling to ascertain the drug release mechanism. The statistical parameters for kinetic models were determined and data present as Table 3 and plots represented as fig.3-6. From the results it was clearly understood that data well for First order kinetics with $R^2$ values in the range of 0.880-0.969. The values of $r$ for formulations regarding Higuchi’s kinetics within a range of 0.874-0.913, Kinetic data also treated for Peppas equation, the slope ($n$) values ranges from 0.638-0.730 that shows Non-Fickian diffusion mechanism. Formulation $F_5$ containing 37.5mg of Crospovidone, 37.5mg of Croscarmellose sodium exerted promising dissolution parameter (Wetting time=42.38±1.2 sec, Disintegrating time=12.81±0.89 sec, t50%=8.670 min, t90%= 28.821 min) (Figure 3-6). Results for Kinetic parameters were presented in Table 4. The final best Formulation $F_5$ is compared with Marketed product SPRITAM-250 tablets and Comparative Dissolution profiles shown in Figure 7. Which shows similarity ($f_2$=82.676, $f_1$=2.049).

![Figure 3](image3.png) Comparative Zero order plots for Formulation $F_1$-$F_9$.

![Figure 4](image4.png) Comparative First order plots for Formulation $F_1$-$F_9$.

![Figure 5](image5.png) Comparative Higuchi plots for Formulation $F_1$-$F_9$.

![Figure 6](image6.png) Comparative Korsmeyer-Peppas plots for Formulation $F_1$-$F_9$.

![Figure 7](image7.png) Comparative In-vitro Dissolution Profiles of $F_5$, SPRITAM.

| S.NO | Formulation code | Kinetic parameters |
|------|------------------|--------------------|
|      |                  | $t_{10\%}$ (Min)  | $t_{50\%}$ (Min)  | $t_{75\%}$ (Min)  | $t_{90\%}$ (Min)  |
| 1    | $F_1$            | 1.463              | 9.630              | 19.260             | 32.001             |
| 2    | $F_2$            | 1.724              | 11.344             | 22.687             | 37.695             |
| 3    | $F_3$            | 1.784              | 11.739             | 23.479             | 39.010             |
| 4    | $F_4$            | 1.652              | 10.870             | 21.740             | 36.121             |
| 5    | $F_5$            | 1.320              | 8.670              | 17.345             | 28.821             |
| 6    | $F_6$            | 1.648              | 10.841             | 21.682             | 36.024             |
| 7    | $F_7$            | 1.832              | 12.051             | 24.101             | 40.044             |
| 8    | $F_8$            | 1.805              | 11.872             | 23.744             | 39.451             |
| 9    | $F_9$            | 2.092              | 13.762             | 27.525             | 45.732             |
| 10   | MP               | 1.526              | 10.042             | 20.084             | 33.370             |

**Conclusion**

The current research investigation focuses about influence of utilization of superdisintearnts such as Crospovidone and Croscarmellose sodium in the formulation development of oral disintegrating tablet formulations of Levetiracetam. Results reveals that quantities of Supersdisintegrant shows good impact on release of drug from formulation (directly proportional) The optimized
formulation followed Higuchi’s kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type. On the basis of evaluation parameters, the optimized formulation F3 may be used for the effective management of Epilepsy, convulsions. This may improve the patient compliance by showing rapid action via disintegration without difficulty in swallowing and side effects which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

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Conflicts of interest
The author declares that there is no conflicts of interest.

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