Formulation, Characterisation and Evaluation of the Ethosuximide Oral Immediate Release Tablets

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ABSTRACT

The present study is aimed to formulate, characterization, and evaluate oral immediate-release tablets of Ethosuximide. It is employed as an anti-epileptic agent used in the treatment of epilepsy, in all the age groups who were ≥ 1 year. The dosage form is formulated by directly compressing the blend and granulating the powder blend by wet granulation methods. The optimized formulation is achieved by the trial and error method by changing the concentration of lactose monohydrate and di-basic calcium phosphate dehydrate as diluents, sodium starch glycolate as Super-dis-integrant, rice Starch as an intra-granular binder, hydroxypropyl cellulose as binder talc as a lubricant. Evaluation parameters such as micromeritic properties, disintegration time along with in-vitro drug release studies were performed for characterizing the dosage form. In-vitro drug release studies were carried out using 0.1 NHCl as dissolution media with 75 rpm and temperature of 37°C ± 5°C by employing USP apparatus II (Paddle type). Estimation of the % drug release of the tablet was carried out using the UV method. The prepared formulation and the marketed formulation were tested for the in-vitro drug release profile and the prepared formulation was compared with the marketed formulation. All the evaluated result was found to be within the specifications. Therefore, from the obtained evaluation results F6 trial was selected as the best formulation.

INTRODUCTION

Epilepsy can be characterized as a neurological disorder with a tendency for recurring, unprovoked seizures (Schemann and Neunlist, 2004). A seizure is an alteration in individuals’ consciousness and behavior due to abrupt disturbances in the electric impulses in the brain (Bharucha, 2003). Epilepsy may occur due to an imbalance between inhibitory and excitatory processes in neurons or ensues abnormal and overweening cortical neuronal activity inside the brain (Groot et al., 2012). The seizures may range from short and sensible to lengthy rip snorting shaking, uncontrollable twitching, losing consciousness, muscle stiffness, unresponsive, sudden loss of muscle tone (Lowenstein, 2009; Prasad et al., 2007).

Around 50 million of the world's population are suffering from epilepsy and most of them are from a developing country (Who, 2008). An approximate population of ten (10) million in India are epileptic and many of them aren’t able to receive proper treatment due to a multitude of reasons such as poverty, cultural beliefs, and lack of knowledge, treatment
gap, stigma and shortage of healthcare professionals (Udani, 2005; Gourie-Devi et al., 2004).

The Immediate-release formulations are known for their rapid onset of action and hence are intended in the usage of treating diseases or disorders which require such action. Examples of such cases were angina, pulmonary arterial hypertension, vasoconstriction and pain (Chien, 1983). It also possess a broad spectrum of advantages such as enhanced oral bioavailability because of the pre-gastric absorption, convenience in administration to nauseous patients, geriatrics, and expansion in business (Ghosh, 2005).

Numerous formulations come under conventional immediate release which includes fast disintegrating tablets, effervescent tablets and granules, fast dissolving films (Allen et al., 2005). Trending technology employed in the manufacturing of fast-dispersing dosage forms a multitude of equipment such as modified tableting systems, floss or shear form technology (Syed, 2011).

**MATERIALS AND METHODS**

Ethosuximide was purchased from the TCI chemicals and all the other excipients like lactose monohydrate, sodium starch glycolate, dibasic calcium phosphate dehydrate, hydroxypropyl cellulose, rice starch, talc were procured from Loba chemicals.

**Pre-formulation Studies**

**Identification of Active Pharmaceutical Ingredient**

**Preparation of standard curve for API**

The drug was weighed accurately to 100mg and dissolved and the solution obtained was diluted with water to 100ml in a volumetric flask.

The above solution was the primary stock solution, having a concentration of 1000μg/ml. From this solution, accurately pipette out 1ml into 10ml volumetric flask, having 100μg/ml of concentration which was the secondary stock solution.

From secondary stock solution pipette out 1, 2, 3, 4, and 5ml into individual 10ml volumetric flask and water was used to make up the volume to 10ml. All the obtained samples were measured at 264nm and the data is mentioned in Table 1 and the calibration curve obtained by the values is mentioned in Figure 1 (Shaik, 2012).

**Solubility profile**

100mg of the active pharmaceutical ingredient was taken in four different solvents of volume 100ml each for the solubility analysis and observed for clarity of the solution. The solvents used were water, ethanol, ether, and chloroform and dimethyl sulfoxide.

**Preformulation studies of blend**

Preformulation studies for the blend are carried out and the results of the study are mentioned in the Table 2 (Lachman et al., 2009).

| Concentration (μg/ml) | Absorbance |
|-----------------------|------------|
| 10                    | 0.238      |
| 20                    | 0.378      |
| 30                    | 0.523      |
| 40                    | 0.647      |
| 50                    | 0.723      |

**Figure 1: Calibration Curve of Ethosuximide**

**Bulk Density**

To calculate bulk density, granules were weighed initially and transferred to graduated measuring cylinder and the occupied volume of the granules were noted. By substituting these values as in the formula mentioned below,

\[
\text{Bulk density} = \frac{\text{Mass}}{\text{Apparent volume (V0)}}
\]

It was expressed in grams per milli liters or kilograms per cubic meter.

**Tapped density**

To calculate tapped density, granules were weighed and calculated by tapping the measuring cylinder with granules that remained unaffected after tapping.

\[
\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume (Vt)}}
\]

**Carr’s Compressibility Index**
Table 2: Preformulation studies of Blend

| Formulation Batch | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr’s Index % | Hausner’s ratio |
|-------------------|----------------------|------------------------|----------------|----------------|
| F1                | 0.332                | 0.346                  | 33.43          | 1.04           |
| F2                | 0.467                | 0.734                  | 17.42          | 1.57           |
| F3                | 0.563                | 0.732                  | 16.43          | 1.30           |
| F4                | 0.537                | 0.683                  | 17.74          | 1.27           |
| F5                | 0.585                | 0.724                  | 18.92          | 1.23           |
| F6                | 0.571                | 0.687                  | 18.38          | 1.20           |

Table 3: Sieve Analysis

| Sieve no | F2 % cumulative retained | F3 | F4 | F5 | F6 |
|----------|--------------------------|----|----|----|----|
| #20      | 12.93                    | 7.14 | 11.52 | 13.46 | 9.76 |
| #40      | 34.73                    | 17.98 | 31.76 | 18.34 | 27.16 |
| #60      | 42.81                    | 31.36 | 35.78 | 17.38 | 31.52 |
| #80      | 53.47                    | 44.87 | 40.34 | 29.58 | 44.35 |
| #120     | 64.32                    | 57.33 | 49.97 | 42.31 | 57.27 |

Carr’s Index of granules was calculated through the application of the formula.

\[
Carr's compressibility Index (\%) = \left(\frac{V_0 - vt}{V_0}\right) \times 100
\]

Hausner’s Ratio

Hausner ratio can be obtained as

\[
Hausner's ratio = \frac{Tapped\ density}{Bulk\ density}
\]

Sieve analysis

The set of sieves were placed on a vibrating sifter with the largest sieve size on top. 5gms of granules were accurately weighed and were passed through the set of sieves for a set time. Upon completion, the material was collected from each individual sieve and weighed and the percent cumulative weight retained was determined and the data obtained is mentioned in the Table 3.

Evaluation of Tablets

Following Evaluation tests were performed for the formulations (Syed, 2011).

Formulation development

The active and inactive ingredients were weighed and sifted through #20 sieve. The ingredients like sodium starch glycolate and rice starch were sifted through #40 sieve. After sifting, whole ingredients were mixed for 15mins.

F1 was directly compressed by adding the required excipients such as lactose monohydrate as both filler and binder, talc as a lubricant.

Hydroxypropyl cellulose was taken in distilled water, used as a binder for wet granulation and used for the formulation of F2 to F6 by changing the concentrations of hydroxypropyl cellulose, sodium starch glycolate, rice starch, lactose monohydrate.

Hardness test

Hardness was the mainly required element to maintain the friability stand against mechanical shocks during the period of manufacturing, packing, and shipping. The hardness tester was used to check the hardness. Three tablets from every batch were used for the evaluation and the results obtained are mentioned in Table 5.

The unit used to measure the hardness was Kp.

Thickness

Vernier calliper’s instrument was used to measure the thickness and diameter. The values were expressed in mm. The test was carried out for all formulations and data is mentioned in Table 4.

Table 4: Weight variation and thickness of the tablets

| Batch no | Weight variation | Thickness |
|----------|------------------|-----------|
| F2       | Pass             | 5.93 ± 0.10 |
| F3       | Pass             | 6.17 ± 0.10 |
| F4       | Pass             | 5.61 ± 0.10 |
| F5       | Pass             | 5.73 ± 0.10 |
| F6       | Pass             | 5.69 ± 0.10 |

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Table 5: Hardness of the tablets

| Formulation | Maximum hardness (N) | Optimum hardness (N) | Friability (%w/w) |
|-------------|----------------------|----------------------|-------------------|
| F2          | 80                   | 60-80                | 0.02              |
| F3          | 90                   | 75-90                | 0.01              |
| F4          | 175                  | 155-175              | 0.04              |
| F5          | 188                  | 176-188              | 0.03              |
| F6          | 190                  | 175-190              | 0.01              |

Table 6: Disintegration Time of the Formulations

| Formulation | Medium                                      | Disintegration time (minutes) |
|-------------|---------------------------------------------|-------------------------------|
| F2          | Purified water with the temperature maintained at 37°C | 7-8                           |
| F3          | 7-9                                         |
| F4          | 5-6                                         |
| F5          | 7-9                                         |
| F6          | 6-8                                         |

Weight variation test and content uniformity

20 tablets from each batch were randomly selected and weighed to calculate the weight variation, content uniformity and standard deviation of the tablets and the results are mentioned in Table 4. The content uniformity is calculated by UV method and the results are mentioned in the Table 7.

Friability test

Initially, 20 tablets were selected randomly and weighed. These tablets were transferred into the Friabulatordisk. The RPM of the disk was set to 25 and the disk was allowed to rotate for 4 minutes. The tablets were collected after the completion of rotations and were weighed. The initial weight and final weight were incorporated in the below formula and the results obtained are mentioned in Table 5.

\[
\%\text{Friability} = \left( \frac{\text{Initial weight} - \text{final weight}}{\text{final weight}} \right) \times 100
\]

Table 7: Content Uniformity

| Formulation | Drug Content (%) |
|-------------|------------------|
| F2          | 96.89            |
| F3          | 97.34            |
| F4          | 98.18            |
| F5          | 98.53            |
| F6          | 98.79            |

Stability Studies

Disintegration test

3 tablets from each formulation were collected and placed separately in disintegration apparatus filled with distilled water. The complete disintegration time of the tablet was noted and mentioned in Table 6.

In-vitro drug release test

The vessels in the paddle apparatus were filled completely with 0.1N HCl and each tablet was placed in each vessel, maintaining temperature at 37 ± 0.5°C temperature and the rpm at 75. The samples were collected at 2, 4, 6, 8, 10, 12, 14 and 16 hours and analysed by UV spectroscopy at 264 nm against the respective dissolution medium as blank. The results are mentioned in the Table 8 and the criteria for selection of optimized formulation are mentioned in Table 9. The percentage drug release of all the formulations along with the marketed formulation which is taken as reference is noted and the graph drawn by plotting the points is mentioned in the Figure 2.

Stability studies of optimized formulation

The shelf life of optimized formulation was performed with accelerating storage conditions such as...
### Table 8: In-vitro Release Profile

| Dissolution Media | Sl. No | Time (hrs) | RLD | F2 | F3 | F4 | F5 | F6 |
|-------------------|--------|------------|-----|----|----|----|----|----|
| 0.1 N Hcl         | 1      | 2          | 27.1| 16.9| 19.3| 21.3| 23.7| 25.3|
|                   | 2      | 4          | 40.5| 24.5| 25.7| 36.7| 35.9| 39.4|
|                   | 3      | 6          | 56.7| 43.6| 44.8| 45.8| 47.3| 54.7|
|                   | 4      | 8          | 69.7| 52.3| 53.4| 61.2| 65.4| 68.3|
|                   | 5      | 10         | 79.3| 65.7| 65.7| 70.9| 76.9| 78.6|
|                   | 6      | 12         | 89.4| 76.8| 71.7| 77.1| 82.7| 87.9|
|                   | 7      | 14         | 95.7| 79.4| 82.3| 81.8| 91.5| 94.8|
|                   | 8      | 16         | 98.7| 87.3| 85.1| 92.5| 94.6| 97.8|

### Table 9: Criteria for selection of Optimized Formulation

| Sl.NO | Time (hrs) | RLD (R) | Optimized Formulation F6 (T) | /R-T/ | /R-T/2 | f2 value | f1 value |
|-------|------------|---------|------------------------------|-------|--------|----------|---------|
| 1.    | 2          | 22.1    | 21.2                         | 0.60  | 0.36   | 89       | 1.779   |
| 2.    | 4          | 39.2    | 38.5                         | 0.70  | 0.49   |          |         |
| 3.    | 6          | 51.7    | 49.5                         | 2.20  | 4.84   |          |         |
| 4.    | 8          | 69.4    | 68.2                         | 1.20  | 1.39   |          |         |
| 5.    | 10         | 76.9    | 75.6                         | 1.30  | 1.69   |          |         |
| 6.    | 12         | 84.7    | 83.5                         | 1.20  | 1.39   |          |         |
| 7.    | 14         | 93.05   | 92.8                         | 0.25  | 0.0625 |          |         |
| 8.    | 16         | 99.6    | 97.5                         | 2.1   | 4.41   |          |         |
| Total |            | 536.65  | 526.8                        | 9.55  | 14.73  |          |         |

### Table 10: Stability data for the optimized formulation (F6).

| Tests                             | Initial Values | 25 C/60% RH | 40 C/75% RH |
|-----------------------------------|----------------|-------------|-------------|
| Appearance                        | White-colored circular tablets with scoreline. |             |             |
| Thickness (mm)                    | 5.69± 0.10     | 5.69± 0.10  | 5.69± 0.10  |
| Hardness (N)                      | 175-190        | 176-190     | 176-190     |
| Disintegration Time               | 6-8 minutes    | 6-8 minutes | 7-9 minutes |
| Dissolution Studies (0.1 N HCl)   | In 16 hours = 98.5 | In 16 hours = 96.9 | In 16 hours = 94.3 |
| Water Assay                        | Not less than 90.0% w/w to 110.0% of Ethosuximide 250 mg per Tablet | 100.25 | 98.90 | 98.72 | 97.5 | 99.58 |

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relative humidity and temperature which can result in decomposition or a degradation reaction of active moiety if the formulation was not stable and results in a decrease in active moiety over time. Samples of the final formulation were packed in a High-Density Polyethylene bottle with screw capping with some desiccants in it for 90 days at 25 ± 2 °C and 60 ± 5% RH and 40 ± 2 °C and 75 ± 5% RH. The samples were obtained and analysed and the results are mentioned in the Table 10, (ICH, 2003).

RESULTS AND DISCUSSION

The solubility of the drug was examined and it has been found that the calibration curve values fall under 200-800 μg/ml in water. Among all the trails that have been done, the F1 (direct compression) was found to be not falling under the satisfying results, hence F1 has not been studied further.

Formulations from F2 to F4 showed satisfactory results and meets all the requirements but the dissolution profile was not satisfactory when compared to the marketed formulation. Formulation F5 and F6 showed promising dissolution results when compared to the marketed formulation. The dissolution results of F6 were almost similar to the marketed formulation and has better disintegration time when compared to that of the F5 and also has less surface area.

Summary

The present research was aimed to prepare oral disintegrating tablets of Ethosuximide which is an anti-epileptic drug. A total of six formulations has been prepared by trial and error method using various concentrations of excipients such as lactose monohydrate and dibasic calcium phosphate dehydrate as diluents, sodium starch glycolate as Superdisintegrant, rice Starch as an intragranular binder, hydroxypropyl cellulose as binder talc as lubricant with an average tablet weight of 400 mg were developed.

Formulation F1 was formulated from the direct compression method and formulation F2 to F6 was formulated from the wet granulation method. The prepared immediate-release tablets were evaluated for post-compression evaluation studies like thickness, hardness, weight variation, friability, drug content uniformity, in-vitro dissolution studies. F6 formulation showed good evaluation studies and a good drug release. Finally, the dissolution profile of optimized sample F6 was matched with the RLD (innovator sample) obtained from the market. From the dissolution profile, f1 & f2 value was calculated and from that value optimize trial F6 was selected. The stability of the formulation (F6) was conducted by “Accelerated stability testing” by packing the tablets in an HDPE bottle with screw capping with some desiccants in it for 90 days at 25 ± 2 °C and 60 ± 5% RH and 40 ± 2 °C and 75 ± 5% RH and sample were obtained and analysed.

CONCLUSIONS

In formulation F1 the flow characterization was not an acceptable range for compression due to which specified weight was not achieved. Formulation F2 to F4 showed good flow property but the in-vitro dissolution studies were found to be slow when compared with the innovator sample. Formulation F5 showed good flow property and the drug release was also found satisfactory but the surface area of tablets was more compared to RLD hence a formulation F6 was planned to reduce the tablet weight by reducing the tablet filler which doesn’t impact the formulation. Formulation F6 showed good flow property and the dissolution profile was found satisfactory when compared with the innovator sample and the occupancy was also matching with the RLD.

REFERENCES

Allen, L. V., Nicholas, G., Popovich, H. C. A. 2005. Ansel’s Pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins, Baltimore, Md. P. 227-260.

Bharucha, N. E. 2003. Epidemiology of Epilepsy in India. Epilepsia, 44:9–11.

Chien, W. Y. 1983. Potential Development and New Approaches in Oral Controlled-Release Drug Delivery Systems. Drug Development and Industrial Pharmacy, 9(7):1291–1330.

Ghosh, T. K. 2005. Drug Delivery to the Oral Cavity. In: Swarbeick, J. Drugs and the pharmaceutical sciences. Informa Healthcare, pages 1–3.

Gourie-Devi, M., Gururaj, G., Satishchandra, P., Subbakrishna, D. K. 2004. Prevalence of Neurological Disorders in Bangalore, India: A Community-Based Study with a Comparison between Urban and Rural Areas. Neuroepidemiology, 23(6):261–268.

Groot, M. D., Reijneveld, J. C., Aronica, E., Heimans, J. J. 2012. Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment. Brain, 135(4):1002–1016.

ICH 2003. Stability testing of new drug substances and products. ICH Harmonized Tripartite Guidelines.

Lachman, L., Herbert, A. L., Joseph, L., Kanig 2009.
The Theory and practice of industrial pharmacy. 171:293–293. 3rd Edition.

Lowenstein, D. H. 2009. Epilepsy after head injury: An overview. Epilepsia, 50:4–9.

Prasad, K., Krishnan, P. R., Al-Roomi, K., Sequeira, R. 2007. Anticonvulsant therapy for status epilepticus. British Journal of Clinical Pharmacology, 63(6):640–647.

Schemann, M., Neunlist, M. 2004. The human enteric nervous system. Neurogastroenterology and Motility, 16(s1):55–59.

Shaik, M. 2012. Development and validation of new analytical methods for the estimation of rufinamide in bulk and pharmaceutical dosage form. Rajiv Gandhi University of Health Sciences, pages 41–42. Bharathi College of Pharmacy.

Syed, A. 2011. Immediate release drug delivery system: A Review. International Journal of Biopharmaceutical & Toxicological Research, 1(1):9–31.

Udani, V. 2005. Pediatric epilepsy - an Indian perspective. The Indian Journal of Pediatrics, 72(4):309–313.

Who 2008. Neurological Disorders: Public Health Challenges. Archives of Neurology, 65(1).