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# FORMULATION AND EVALUATION OF SODIUM VALPROATE SUSTAINED RELEASED TABLETS

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## ABSTRACT

Epilepsy is a periodic disarrhythmia of the brain. The aim of present research work was to develop sustained release tablet of sodium Valproate. Sodium Valproate is an anticonvulsant; it blocks the sodium channel in cell membrane and prevents the electric discharge from initiating. Sodium Valproate sustained release tablets were prepared by wet granulation method using hydrophilic polymer like Hydroxypropylmethylcellulose (HPMC). The interaction between the excipients and sodium Valproate was studied through FTIR spectroscopy. Various concentrations of polymer was used in the six proposed formulations(F1-F6) for the study of release rate retarded effect at 2.5%,5%,7.5%,10%,12.5% and 15% of total weight of tablet respectively. Then the tablets were evaluated in terms of their physical parameters (taste, disintegration time, hardness, friability, weight variation), drug content and *In vitro* released studies. All the formulations showed compliance with pharmacopeial standards. The invitro dissolution study were conducted using USP dissolution apparatus-2(paddle method) in 900ml 0.1N HCL for 2 hours and remaining 22 hours performed in 6.8 PH phosphate total period of an buffer at 100rpm for 24 hours. Based on the dissolution data comparisons with innovator product, formulation f5 was as the best formulation.

**Key Words:** Sodium Valproate, Sustained Release Tablet, HPMC, Wet Granulation, *In-vitro* dissolution.

## INTRODUCTION

Conventional oral drug delivery systems are slowly fading away in the market due to its disadvantages. These delivery systems produce fluctuation of drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level. This effect is usually totally dependent on the particular agent's biological half life, frequency of administration and release rate. Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half – life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Matrix type Sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pelletization during manufacturing and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation.

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Hydrophilic polymer matrix system are widely used for designing oral Sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The hydrophilic polymer selected for the present study was HPMC.Sodium valproate, chemically sodium-2-propyl pentanoate, is first line drug used for its unique anticonvulsant properties1. It is quite dissimilar to other established anticonvulsants such as barbiturates, hydantoins, succinamides, oxazolidin-ediones and acetylureas in that it has no nitrogen or aromatic moiety. Sodium valproate works by stabilizing electrical activity in the brain. When abnormally rapid and repetitive electrical signals are released in the brain, the brain becomes over-stimulated and normal function is disturbed. This results in fits or seizures. Sodium valproate prevents epileptic fits by preventing the excessive electrical activity in the brain. This is achieved by increasing the activity of a neurotransmitter called GABA in the brain3. Sodium valproate is thought to increase the production and prevent the breakdown of GABA in the brain. This increases the calming activity of GABA in the brain, which stabilizes the electrical nerve activity and helps prevent fits. Sodium valproate may also stabilize the electrical nerve activity by preventing sodium from entering the nerve cells when

they begin to fire rapid and repetitive electrical signals. A build up of sodium in the nerve cells is necessary for an electrical signal to build up and be passed on, so sodium valproate may also prevent fits in this way. In addition to its licensed use for treating epilepsy, sodium valproate is used off-license by specialists as a mood stabilizer for treating people with the psychiatric illness,bipolar affective disorder.

## MATERIALS AND METHOD:

Materials used in the experiment were Sodium Valproate (Lot pharmaceutical co., Ltd., Chennai), Starch (ISP Technologies., Ahmadabad), Dichloro methane (ISP Technologies., Ahmadabad), Hydroxypropyl methyl cellulose (Dow chemical's., Bangalore), Microcrystalline cellulose (Avicel. Delhi), Magnesium stearate (Nof Corporation., Ahmadabad), Talc (Shengtai Chem Co., Ltd., Chennai), PVP-K 90 (Dow chemical's., Bangalore), Isopropyl alcohol (Shell chemicals, Chennai)

## METHOD OF PREPARATION OF SODIUM VALPROATE SUSTAINED RELEASE TABLETS:

Sodium Valproate granules were prepared by Wet granulation method. Microcrystalline cellulose, hydroxylpropylmethylcellulose, and starch were weighed &dried, and screened through a 100-mesh sieve. Then hydroxylpropylmethylcellulose and starch and half of amount of microcrystalline cellulose were mixed with sodium Valproate and were wet granules prepared by adding poly vinyl pyrolidine-K 90(4%) in isopropyl alcohol and dicloro methane as binding solution and sheared by pestle &formed as dump mass and passed through 12-mesh sieve. Granules were tray dried at 60°C using a hot air oven for 1 hrs. Dried granules were screened through 20-mesh sieve. Humidity was maintained in room around 50%RH. The bulk and tapped densities of the granules were determined using the test for apparent volume and Carr's Index was also calculated. Sodium Valproate sustained release tablet were hydroxypropylmethylcellulose based hydrophilic matrix system. Dried granules were mixed with magnesiumstearate and talcum powder and remaining half quantity of microcrystalline cellulose .Then they were compressed using single tablet punching machine.

## CALIBRATION CURVES OF SODIUM VALPROATE:

100 mg of Sodium Valproate was taken and dissolved in small amount of acidic buffer i.e, 0.1N HCl and further diluted up to 100 ml with the same buffer. This gives standard solution of Sodium Valproate (1mg/ml) which can be used for further dilutions. From the standard solution, samples of different concentrations are prepared, and analyzed spectrophoto-metrically at 213 nm. 100 mg of Sodium Valproate was taken and dissolved in small amount of phosphate buffer of pH 6.8 and further diluted up to 100 ml with the same buffer. This gives standard solution of Sodium Valproate (1mg/ml) which can be used for further dilutions. From the standard solution, samples of different concentrations are prepared, and analyzed spectrophoto-metrically at 210 nm.

## DRUG – EXCIPIENTS COMPATIBILITY STUDY

DSC studies were carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

## EVALUATION

### PRE COMPRESSION STUDIES

**Angle of Repose:**

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. **Tan θ = h/r** Where, h = height of the heap, r = Radius of the heap

Pharmacopoeial specifications for angle of repose

| ANGLE OF REPOSE | POWDER FLOW |
|---|---|
| < 25 | Excellent |
| 25 – 30 | Good |
| 30 – 40 | Passable |
| > 40 | Very poor |

**Bulk Density and Tapped density:**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas. **LBD = weight of the powder / volume of the powder and TBD = weight of the powder / tapped volume of the powder**

**Compressibility Index:**

The compressibility index of the granules was determined by Carr's compressibility index.

**Carr's index (%) = [TBD-LBD] / TBD X 100**

| % Comp.Index | Properties |
|---|---|
| 5-15 | Excellent |
| 12-18 | Good |
| 18-21 | Fair |
| 23-35 | Poor |
| 33-38 | Very poor |
| >40 | Very very poor |

### POST COMPRESSION PARAMETERS

**Weight variation:**

All prepared tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.

**Friability:**

Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020).

The percentage friability was then calculated by,

**% Friability = [(W1 – W2) / W1] × 100**

% Friability of tablets less than 1% is considered acceptable.

**Hardness:** Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester).

**Thickness:** Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

**Drug content:**

Transfer an amount of powder (from NLT 20 Tablets) to a suitable volumetric flask to obtain a nominal concentration of 1 mg/ml of Sodium Valproate. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, and pass through a suitable filter. Sample was analyzed by HPLC method and the chromatographic conditions are column – 3.9mm*15cm packed with phenyl group bonded to porous silica (4 µm), detector: UV 210nm, Flow rate: 1ml/min, injection volume: 20 µl, run time: 6min and the mobile phase composition is methanol and buffer (11:9), Adjust with phosphoric acid to a pH of 5.0. Buffer: 0.5 gm of citric acid monohydrate and 0.4 gm of dibasic sodium phosphate in 1 L of water. The actual content in sample was read by comparison with standard Sodium Valproate.

**Disintegration test:** In this process we were using distilled water as medium at 37±2$^{o}$ C at 29-32 cycles per minute; test was completed after 30 minutes.

***In vitro* Dissolution test**

Drug release profile was evaluated in vitro, using a dissolution test apparatus. The USP XIII Type II (paddle type) method (TDT-08L, Electro lab, Mumbai, India.) was selected to perform the dissolution profile of Sodium Valproate SR tablets .The dissolution of SR tablet is performed into 0.1 N HCl for 2 hours and then the phosphate buffer pH 6.8 for 1 hour. The temperature was maintained at 37±0.5°C and a constant paddle rotation speed of 100 rpm. Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UV Spectro Photometry.

## STABILITY STUDIES:

Stability study was done to see the effect of temperature and humidity on tablets. Tablets were evaluated periodically (initial, and after 1 month) for appearance, hardness, friability, drug content and i*n vitro* drug release.

## RESULTS AND DISCUSSION

The DSC thermograms for drug and polymer mixture are represented in Fig.2. DSC analysis of Sodium Valproate shows the endothermic peak at its melting point i.e. at 98.8ºC. The peak of Mixture of excipients with Sodium Valproate showed the little change in melting point of drug from 98.8ºC to 98.5ºC. It indicates that it may not affect the stability of formulation, so it is confirmed that drug is compatible with all excipients. The granules were prepared by Wet granulation method. Flow properties of granules were estimated by angle of repose. All the formulations showed angle of repose within the range of 25-30$^{0}$, indicates that they had good flow property (Table.2). Tapped density of granules was found in range of 0.75 – 0.9gm/ml (Table.2).Bulk density of granules were found to be less than 1gm/ml (Table.2). These values were suitable to punch the granules as compressed tablets. The hardness of the sustained release tablets was within the range of 4-5kg/cm$^{2}$ (Table.3). The friability results showed that the compressed sustained release tablets can withstand from the shocks (Table.3).The weight variation was within the limit i.e., ±5mg (Table.3).The disintegration time of all the formulations within the limits i.e 30 mins (Table.3). Thickness of all batches was in the range of 5.92– 6.1mm(Table.3). The percentage of drug content for F1 to F5 was found to 97.52% to 99.24% of Sodium Valproate, it complies with official specifications (90% – 110%). The results were shown in table 3.After 24$^{th}$ hour the percentage drug release from the formulations were 96.4%, 95.1%, 94.6%, 93.9%, 97.6%, 82.4% for the formulations containing Hydroxypropyl methyl cellulose 2.5%, 5%, 7.5%, 10%, 12.5% and 15% respectively (Table.4). Formulation F5 was identified to be the best as it matches well with the innovator (Fig.4). The results of the stability study for the optimized formulation F5 was given (Table.5). The results of stability indicated that there was no change in the formulation F5 after 1 month accelerated stability study. The prepared formulation of Sodium Valproate SR release tablet was stable.

**Table.1 Formulations of Sodium Valproate SR Tablets:**

| Ingredients(Mg) | Formula(amount per tablet) | | | | | |
|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| Sodium Valproate | 200 | 200 | 200 | 200 | 200 | 200 |
| Starch | 187.5 | 175 | 162.5 | 150 | 137.5 | 125 |
| Hydroxypropyl methyl cellulose | 12.5 **(2.5%)** | 25 **(5%)** | 37.5 **(7.5%)** | 50 **(10%)** | 62.5 **(12.5%)** | 75 **(15%)** |
| Dichloro methane | 10 | 10 | 10 | 10 | 10 | 10 |
| Microcrystalline cellulose | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| PVP-K 90 | 20 | 20 | 20 | 20 | 20 | 20 |
| Isopropyl alcohol | 10 | 10 | 10 | 10 | 10 | 10 |

**Table.2 Pre-formulation Characteristics:**

| S.No | Formulations | Angle of Repose (°) | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Compressibility Index (%) |
|---|---|---|---|---|---|
| 1 | F1 | 28.7 | .72 | 0.86 | 16.27 |
| 2 | F2 | 26.4 | .78 | .89 | 12.35 |
| 3 | F3 | 27.3 | 0.74 | 0.86 | 13.95 |
| 4 | F4 | 25.9 | 0.71 | 0.87 | 18.39 |
| **5** | **F5** | **28.1** | **0.72** | **0.84** | **14.28** |
| 6 | F6 | 26.5 | 0.73 | 0.85 | 14.11 |

**Table.3 Evaluation Parameters:**

| S.No | Formulation | Hardness ($Kg/cm^2$) | Friability | Weight variation (Mg) | Disintegration time | Thickness (mm) | Drug Content (%) |
|---|---|---|---|---|---|---|---|
| 1 | F1 | 4.6 | 0.04 | 498.16 | 25min 13sec | 5.98 | 98.70 |
| 2 | F2 | 4.8 | 0.07 | 499.86 | 27min 38 sec | 5.99 | 98.25 |
| 3 | F3 | 4.2 | 0.06 | 497.42 | 28 min 23 sec | 6.0 | 98.42 |
| 4 | F4 | 4.5 | 0.04 | 500.11 | 25 min 42 sec | 6.1 | 97.52 |
| **5** | **F5** | **4.2** | **0.07** | **497.54** | **28 min 6 sec** | **5.95** | **99.24** |
| 6 | F6 | 4.8 | 0.05 | 498.37 | 26 min 9 sec | 5.92 | 98.63 |

**Table.4 Dissolution Studies:**

| S.No | Dissolution Time(hr) | Percentage Drug Release (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | Innovator |
| 1 | 1 | 28.4 | 23.4 | 21.9 | 18.8 | **18.4** | 11.4 | **18.6** |
| 2 | 2 | 40.8 | 39.4 | 36.5 | 33.2 | **30.6** | 27.4 | **31.4** |
| 3 | 4 | 59.3 | 57.3 | 54.1 | 49.3 | **45.2** | 40.1 | **45.6** |
| 4 | 8 | 73.9 | 72.6 | 69.4 | 58.3 | **55.4** | 52.2 | **56.1** |
| 5 | 12 | 89.6 | 87.4 | 85.8 | 85.6 | **73.9** | 75.1 | **74.2** |
| 6 | 24 | 96.4 | 95.1 | 94.6 | 93.9 | **97.6** | 82.4 | **98.1** |

**Table.5 Stability Study of Optimized Formulation (F5) at Accelerated (40 ± 2°C & 75 ± 5% RH)**

| Test | Initial | After 1month |
|---|---|---|
| Appearance | White colour, Capsule shaped biconvex tablet | No change In appearance |
| Hardness (Kg/cm2) | 4.2 | 4.4 |
| Friability | 0.07 % | 0.05% |
| Drug content (%) | 99.24 | 98.99 |
| *In vitro* drug release (%) | 97.6 | 97.2 |

**Fig.1 (a) Standard curve of Sodium Valproate in Acidic Buffer**

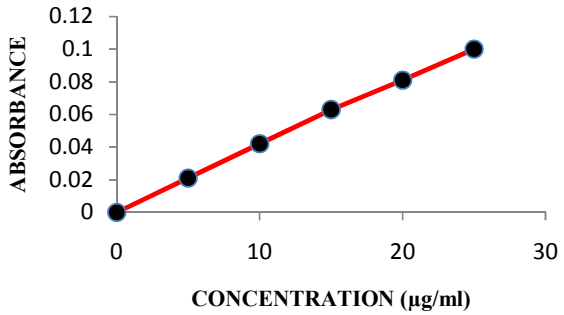
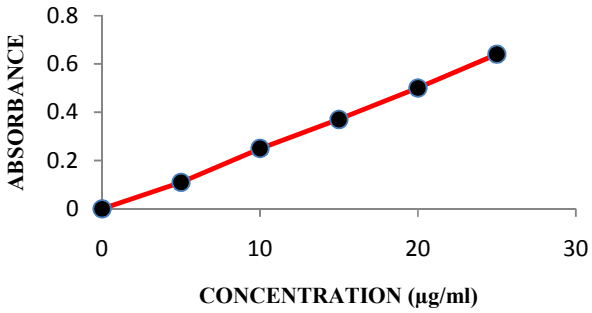


**Fig.1 (b) Standard curve of Sodium Valproate in Phosphate Buffer**




**$\lambda_{max}$ : 210nm**
**Medium : $\lambda_{max}$ : 210nm and Medium : 0.1N HCl**

**Fig.2 DSC Graph of (A) Sodium Valproate and (B) Sodium Valproate with other Excipients:**

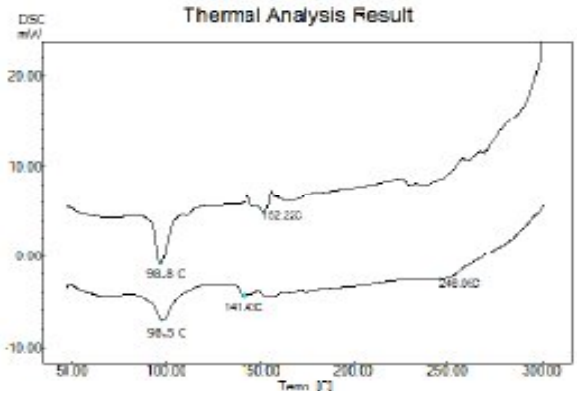



**Fig.3 Dissolution Profile of All Formulations:**

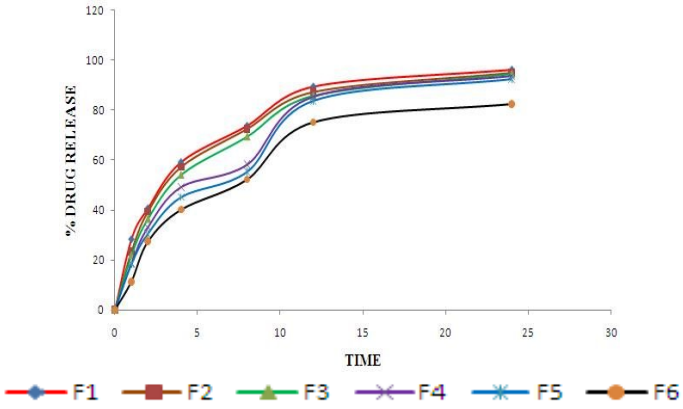
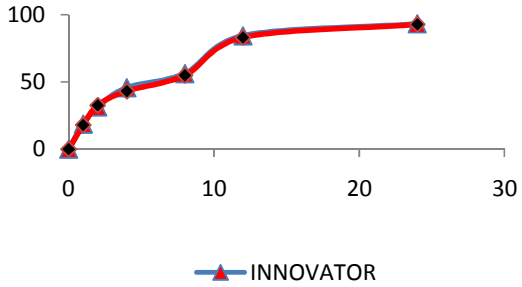



**Fig.4 Dissolution Profile of Best Formulation (F5) & Innovator:**



## CONCLUSION

Epilepsy is a periodic disarrhythmia of the brain. Sodium Valproate blocks the sodium channel located in cell membrane prevents the electrical discharges from initiating. The present work aimed at developing sustained release sodium Valproate tablets by wet granulation. Angle of repose, tapped density, bulk density values for the formulations where within the range which indicate that granules prepared by wet granulation were satisfactory for further studies. After 24$^{th}$ hour the percentage drug release from the formulations were 96.4%, 95.1%, 94.6%, 93.9%, 97.6%, 82.4% for the formulations containing Hydroxypropyl methyl cellulose 2.5%, 5%, 7.5%, 10%, 12.5% and 15% respectively (Table.6). Formulation F5 was identified to be the best as it matches well with the innovator (Fig.4). Accordingly, it can be concluded that the F5 (12.5%w/w HPMC) is robust one. The results of stability indicated that there was no change in the formulation F5 after 1 month accelerated stability study. The prepared formulation (F5) of Sodium Valproate SR release tablet was stable.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