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# FORMULATION AND EVALUATION OF DIVALPROEX SODIUM CONTROL RELEASE FOR ORAL DELEIVERY

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**ABSTRACT**

The objectives of this research work are to formulation and evaluation of divalproex sodium control release for oral delivery it may decrease the dosage frequency, increase the patient compliance and minimize the dose dumping. Osmotic tablet is prepared as controlled porosity osmotic tablet which is prepared by adopting wet granulation method. In this research work we had taken the preliminary batches for selection of osmogen and pore forming agent. Sodium chloride, as an osmogen and mannitol as pore forming agent. Different batches were prepared with different concentration of osmogene to find out thr optimized batches total fout coating solutions were prepared and evaluation of them were selected for their further formulation process all evaluation parameters were evaluated for determination of optimized batch and after stability study the prepared batch of osmotic tablet was compared with marketed formulations Based on all results, T5C2 Batch had gives maximum release 99.% at 24hr it gives satisfactory results. From all the results we had conclude that by preparing osmotic tablet it may give sustained release of drug over the period of time and also gives patient compliance.

**Key Words:** Osmotic tablet, coating solutions, oral delivery

# 1. INTRODUCTION:

## 1.1 Introduction to Disease:

Epilepsy is a chronic brain disease that causes seizures, which are brief episodes of involuntary movement. Seizures can be partial, affecting one part of the body, or generalized, affecting the entire body. Epilepsy is caused by abnormal, excessive, and synchronized electrical discharge in the brain cells called neurons. Epilepsy may occur as a result of a genetic disorder or an acquired brain injury, such as a trauma or stroke. During a seizure, a person experiences abnormal behavior, involuntary movement of limbs and sensations, sometimes including loss of consciousness. Generally in between the neuronal ending in brain there is a normally passing of signal regulated by sodium, calcium and chloride channels known as action potential. During generation of action potential sodium and Calcium rushed in and release of neurotransmitter glutamate from the nerve vesicle acts as a excitatory generation of signal and on another side inhibitory neurons releases neurotransmitter GABA which binds to GABA-A receptors on excitatory neurons and allows the negatively charged chloride ions to enter in and by this way control of action potential takes place. But the Patient suffering from seizures have imbalance of the ions due to which it suffers from abnormal, excessive, and synchronized electrical discharge in the brain cells which leads to sudden episodes of contractions in body, impaired motor function and sometimes may drags to unconsciousness.[1][2][3][4][5][6]

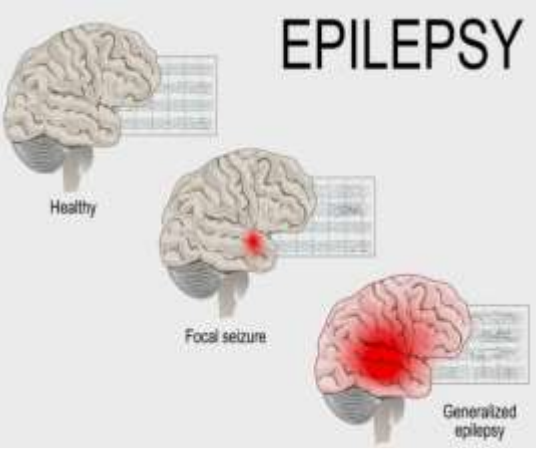


**Figure 1.1 Epilepsy Types**

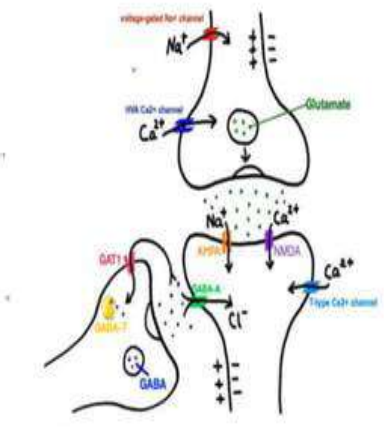


**Figure 1.2 Signal Pathways in Brain**

### 1.1.1 Causes of Epilepsy[7][8]

- Alcohol or drugs
- Infection
- Genetic factors
- Trauma to the head and brain injury

- Congenital conditions
- Brain tumor
- Drug withdrawal
- Medications

**1.1.2 Treatment of epilepsy**[9]

- **Barbiturates:** Phenobarbitone
- **Deoxy barbiturate:** Primidone
- **Hydantoin:** Phenytoin, fosphenytoin
- **Iminostilbene:** carbamazepine, Oxcarbazepine
- **Succinimide:** Ethosuximide
- **Aliphatic carboxylic acid:** Valproic acid, **Divalproex**
- **Benzodiazepines:** Clonazepam, lorazepam, Clobazam, Diazepam
- **Phenyl triazine:** Lamotrigine
- **Cyclic GABA Analogues:** Gabapentin, pregabaline
- **Newer Drugs:** Topiramate, Zonisamide, levetiracetam, Vigabatrin, Tiagabine, Lacosamide

**1.2 Introduction to Drug:**[10][11]

Divalproex generally acts by increasing brain GABA concentrations, which leads to influx of more negatively charged chloride ion into the brain and also it inhibits the sodium ion channel in brain which ultimately inhibits the excitatory impulses in brain and prevents the sudden episodes of contractions to the patient suffering from epilepsy.

Divalproex when administered by patients orally, it gets dissociated in the stomach and converted valproic acid, it transfers to the blood by passive diffusion with high protein binding affinity (87-95%), generally valproic acid uses the monocarboxylic acid carrier in order to cross the blood brain barrier (BBB) and the neural cell plasma membranes and shows its effect on GABA and sodium ion channels. By this Divalproex sodium oral tablet is used to treat certain types of seizures, to treat manic episodes of bipolar disorder, and to prevent migraine headaches. The most common side effects observed by using Divalproex are drowsiness, dizziness, nausea, vomiting, indigestion, diarrhea, weight loss. The most serious side effects due to valproic acid are liver injury, pancreatitis and abnormal bleeding.

Divalproex available in various orally administered formulation such as extended release, Delayed release generally for the treatment of epilepsy.

**1.3 Introduction to Osmotic Drug Delivery System:**[12]

An osmotic drug delivery system, also known as an osmotic pump, is a system that releases drugs over time through a semi permeable membrane that contains one or more ports. The system is made up of a core containing a drug and an osmogen, which is coated with the membrane. The osmogen absorbs water from the surrounding medium through the membrane, which

is permeable to water but impermeable to the drug. The drug is released as a solution or suspension over time.

Osmotic drug delivery systems are a promising strategy for controlled drug delivery. The system is independent of gut factors and is regulated only by the nature of the formulation. Most drugs used in this type of system have a short half-life, are very potent, and require to be used over long durations.

**1.3.1 Principle of Osmotic Drug Delivery System (ODDS):**[13]

ODDS use osmotic pressure to control the release of the drug. The movement of the water across the semi permeable membrane, driven by a difference in osmotic pressure. The membrane is non extensible and the increase in volume due to imbibitions of water raises the hydrostatic pressure inside the tablet. The pressure forces the drug solution out through small pores or channels, controlling the rate of release. Adjusting the porosity of the membrane allows for the release rate of the drug, offering sustained and controlled over an extended period.

**1.3.2 Components of the Controlled Porosity Osmotic drug delivery system:**[14][15][16]

**1. Core Tablet or Capsule:**

This contains the drug to be delivered. It can be solid tablet or a capsule. Drugs that are indicated for the prolonged treatment of diseases with a biological half-life in the range of 1–6 h are best suited for osmotic systems. Drugs with a biological half-life shorter than 1 h are not good candidates, and, similarly, drugs with a half-life greater than 12 h are also not good candidates for controlled release in an osmotic pump system.

**2. Semi-Permeable Membrane with controlled Porosity:**

Surrounding the core, this membrane allows the passage of water but not the drug molecule. It's typically made up of cellulose acetate, cellulose acetate butyrate or other similar materials. The membrane in a CPODDS contains pores or channels of controlled size and distribution. These pores allow water to enter the core but also regulate the rate of drug release by controlling the flow of the dissolved drug molecules.

**3. Osmotic Agent:**

This is usually water soluble compound such as sodium chloride or sucrose, contained within the core. When the system comes into contact with water the osmotic agent creates an osmotic pressure gradient, driving water into the core.

**4. Delivery Port:**

A small hole or pores in the membrane through which the drug solution is delivered. It's often covered with a semi-permeable or a material that dissolves at a controlled rate.

**5. Optional Controlled-release Coating:**

Additional coatings may be applied to further regulate the drug release rate.

The controlled Porosity of the membrane allows for more precise control over the release kinetics of the drug, making CPODDS useful for delivering drugs with specific dosing requirements or that those need to be released gradually over an extended period.

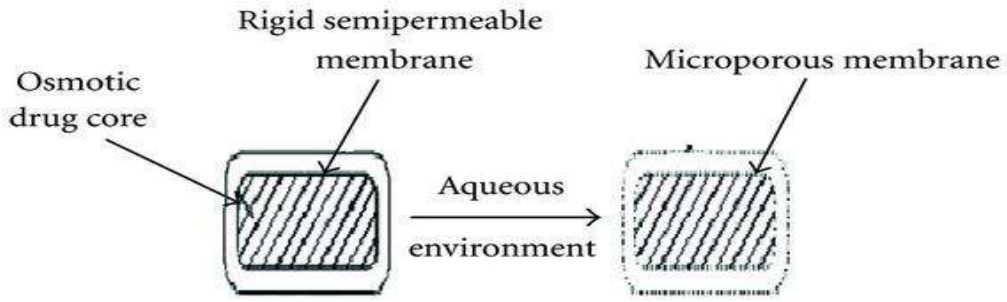


**Figure 1.3 Controlled Porosity Osmotic DDS**

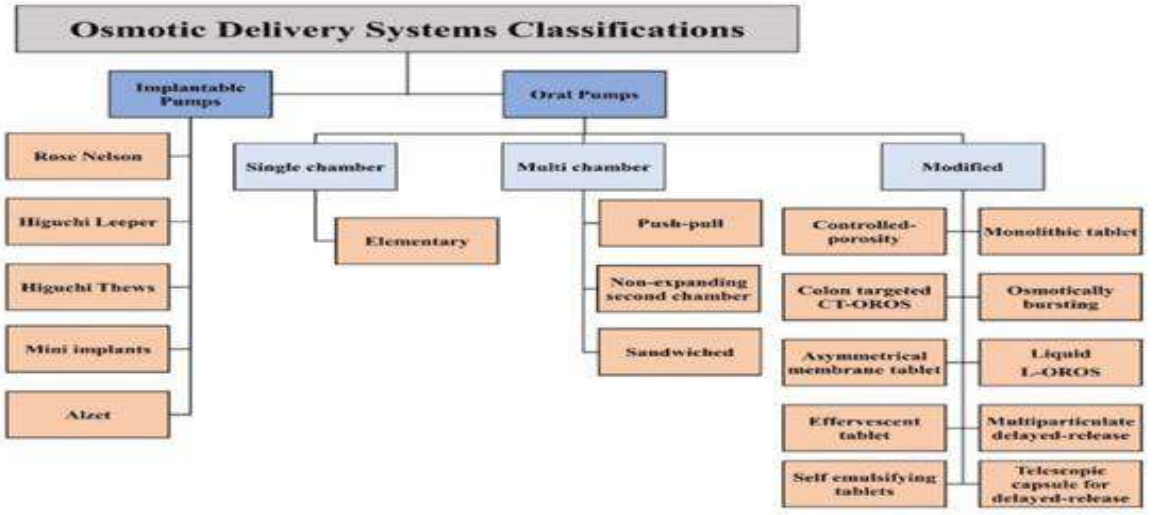


**Figure 1.4 Types of ODDS**

### 1.3.3 Mechanism of Controlled Porosity Osmotic Drug Delivery System:[16]

**1. Semi-permeable membrane:**

The drug formulation is enclosed with in a semi permeable membrane which allows the passage of water but restricts the passage of drug molecules.

**2. Osmotic Pressure:**

When the drug delivery system comes into a contact with aqueous environment (e.g gastrointestinal fluids), water permeates through the semi-permeable membrane into the core of the system due to osmotic presssure differences.

**3. Core Composition:**

The core of the system typically contains the drug along with the osmotic agents such as salts or sugars. These agents increase the osmotic pressure inside the core relative to the surrounding environment.

**4. Water Uptake:**
As water enters the core through the semi permeable membrane, it dissolves the osmotic agents, creating a hypertonic solution. This leads to influx of more water into the core.
**5. Pressure Build-up:**
The influx of water creates pressure inside the drug delivery system, causing it to swell.
**6. Drug release:**
The increased pressure forces the drug solution to be pushed out through the pores or channel in the semi permeable membrane. The drug molecules are released into the surrounding environment in controlled manner.
**7. Control Parameters:**
The rate of drug can be controlled by adjusting various parameters such as the size and number of the pores in the membrane, the osmotic pressure gradient, and the solubility characteristics of the drug.
By this carefully designing the formulation and membrane properties, controlled porosity drug delivery system can be achieve precise and sustained release drug over extended periods, offering advantages such as reduced dosing frequency and improved patient compliance.

**1.3.4 Advantages of Controlled Porosity osmotic drug delivery system over extended conventional drug delivery:**[17]
**1. Zero-order Release kinetics:**
CPODDS provide a consistent release rate of the drug over time, ensuring uniform drug plasma levels. This contrasts with the extended-release tablets, which may exhibit variable release kinetics depending on factors like gastrointestinal pH and food intake.
**2. Reduced Variability:**
CPODDS minimize the impact of physiological factors on drug release, leading to decreased inter- and intra-subject variability in drug absorption compared to conventional tablets. This can result in more predictable therapeutic outcomes.

3. **Minimized Dose Dumping**
This are designed to release drug molecules gradually, minimize the risk of dose dumping (the rapid release of a large amount of drug at once) which can occur with some extended release formulations particularly in the presence of alcohol or food.
4. **Enhanced Bioavaibility and reduced side effects:**
By maintaining the steady state concentration peak and independent drug release without depending upon physiological conditions, CPODDS

enhances the bioavaibility and reduced the side effect of the drug that can occurred due to fluctuations in drug plasma levels.

**5. Improved Patient compliance**

They require less frequent dosing intervals compared to conventional tablets, leading to improved patient compliance. Additionally, the consistent release profile of osmotic pump may simplify dosing regimens, reducing the likelihood of missed doses.

**6. Protection from Environmental factors:**

The semi permeable membrane of CPODDS provides protection against environmental factors such as pH changes, enzymatic degradation, and gastric emptying rates which can affect drug release from conventional tablets. Overall, controlled porosity osmotic drug delivery systems offers advantages in terms of consistent drug release, reduced variability, enhanced bioavaibility, improved patient compliance and protection against dose dumping and environmental factors making them attractive option for extended release drug delivery.

**1.3.5 Disadvantages of CPODDS:**

1. Complex manufacturing process which may result in higher production costs and require specialized equipment and expertise.
2. Not all drugs can be suitable for osmotic drug delivery because of its low solubility and undergoes extensive first pass metabolism.
3. The semi permeable membrane may be susceptible to mechanical damage or manufacturing defects, leading to compromised drug release profile or system failure.
4. Risk of Osmotic imbalance and Limited Control over drug release rate.

**Marketed formulation of Divalproex**[18]


**Figure 1.5 Details on marketed formulation of Divalproex Sodium**

## 2. MATERIAL AND METHODS :

Drug Divalproex sodium and excipient Sodium chloride ( NaCl ) , Mannitol, Microcrystalline cellulose , PVP K30, Sodium lauryl sulphate Magnesium stearate , Talc, Cellulose acetate, Plastisizer

**Core Tablet:** Pre-formulation testing is the first stage in developing for a pharmaceutical product. The assessment of a pharmacological substance's chemical and physical characteristics, both in isolation and in combination with excipients, is known as pre-formulation research. It also includes information about the nature of the drug ingredient so that a plan can be created for mixing the medication with excipients in the dosage form.

**Coating of core tablet:**

Controlled porosity Osmotic coating

Three coating solutions of cellulose acetate in a mixture of acetonecontaining different levels (0%, 10% and 20% w/v) of pore-forming agent (manitol) were prepared for semi permeable membrane coating. The composition of coating solutions is given in Table. PEG 400 acted as a hydrophilic plasticizer and was added to enhance the physical and mechanical property of cellulose acetate membrane.

The coating conditions were as follows:

- Stainless steel pan with 200mm diameter
- Rotation rate of the pan - 40 rpm
- Nozzle diameter of spray gun - 1 mm
- Spray rate - 3 ml/min
- Drying temperature – 40oC

After coating, the tablets were dried at 50oC to remove residual solvent

The formulation of the controlled porosity osmotic tablet of divalproex sodium is carried out and the content of different compounds in the tablets are given in the teble below. There are total 6 different batches are prepared udsing different concentration of osmotic agent ( sodium chloride ) in batch T1 the 10 mg sodium chloride is taken in batch T2 20mg of sodium chloride is used similarly 30 mg ,40mg , 50mg and 60 mg of sodium chloride is used for batches T3 , T4 , T5 , and T6 batches respectively to find out the optimized batch .

**Table 2.1 Selection of Osmoge n and their concentration**

| Ingridents | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|
| Divalproex sodium | 125 | 125 | 125 | 125 | 125 | 125 |
| Sodium chloride | 10 | 20 | 30 | 40 | 50 | 60 |
| Microcrystalline cellulose | 121 | 111 | 101 | 91 | 81 | 71 |
| SLS | 8 | 8 | 8 | 8 | 8 | 8 |
| PVPK30 | 6 | 6 | 6 | 6 | 6 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| IPA | qs | qs | qs | qs | qs | qs |
| Magenisum sterate | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 |
| Total | 275 | 275 | 275 | 275 | 275 | 275 |

**Table 2.2 for coating solution**

| Ingridents | C1 | C2 | C3 | C4 |
|---|---|---|---|---|
| Cellolose acetate | 25 | 30 | 25 | 30 |
| Mannitol | 2.5 | 3 | 5 | 6 |
| PEG 4000 | 10 | 10 | 10 | 10 |
| Acetone(ml) | 1000 | 1000 | 1000 | 1000 |
| | | | | |

## 3. EVALUATION PARAMETERS:

### 3.1 Organoleptic characterization

Received sample of Divalproex sodium was evaluated for color, odour and taste.

### 3.2 Melting point determination

end heated and sealed is filled with a little amount of the medication, which is then dipped into a beaker of liquid paraffin and heated on flame and temperature is measured using thermometer. The drug's Divalproex sodium's melting point was measured using the capillary rise method capillary with one characteristics can be altered by temperature changes, therefore knowing the drug's melting point helps to ensure that it is handled and stored properly

### 3.3 Solubility study

Solubility of drug tested in different solvents by adopting saturation method. Take 1ml of solvent, add drug into it and shake thoroughly completely dissolve the drug with solvent. Drug added until saturation occurs and particles are seen in the solvent.

### 3.4 FTIR Studies

FTIR studies gives idea about the purity of drug. FTIR examinations using functional group detection were utilised to verify the purity of the Divalproex Sodium. Spectral peaks were used to evaluate Divalproex Sodium. Selection of excipient most important step in the development of a formulation. When drugs and excipients are not compatible, it can lead to

drug degradation and product failure. Therefore, drug excipient compatibility studies were conducted first

**Method of FTIR Study**

A little quantity of drug with KBr triturate in mortar with pestle. Sample were put in a holder and scanned the spectra and observed the peak of various functional group.

3.5 **DSC Study**

Differential scanning calorimetry studies in which we identify the drug by its melting point. The difference in heat flow to a sample and to a reference are measured during predefined temperature program.

3.6 **Pre Formulation**

The evaluation parameters of Osmotic tablet are given below.
**1. Flow properties ( 1 ) Bulk density** Put 5g ofpowder into a 20ml graduated measuring cylinder that is attached to a bulk density tester. The bulk density of the powder will be provided by the apparatus. Bulk density formula given below Bulk density = weight of powder / bulk volume of powder
The entire process repeats 3 times.
**(2) Tapped density** A 20 ml graduated measuring cylinder with a tapped density tester attached is filled with 5 g of powder. The apparatus provides the mass of powder's tapped density. By adding powder to a cylinder and dropping the cylinder 300 times from a height of one inch at intervals of every two seconds, one can manually determine the tapped density. Tapped density formula given below
Tapped density = weight ofpowder (g)/ volume ofpowder
Entire process repeats 3 times.
**(3) Carr's compressibility index**
Carr's compressibility index = Tapped density – bulk density * 100/ Tapped density
**(4) Hausner's ratio**

Hausner's ratio = Tapped density/ Bulk density
**(5) Angle of repose**
The funnel is used to pour the powder, creating a mound. To ensure that the funnel tip stays near the pile's tip, it should be adjusted. Pour the powder just until the pile reaches a certain height. Divide the height by the cone's circle radius and use the inverse tangent to find the angle of repose
tan ɵ = Height of pile/ radius of base of pile

**Post compression parameters**

**3.7 Weight variation** The weight variation test is performed to confirm that each tablet in a batch contains the appropriate quantity of the active pharmaceutical ingredient (API). This is especially important because even minor discrepancies in weight can lead to dose inaccuracy, potentially impacting therapeutic effectiveness and safety. To conduct the weight variation test, a random sample of tablets (usually around 20 tablets) is selected from each batch. Each tablet is weighed individually using a precision balance. The average weight of the sample is then calculated, and the deviation of each tablet's weight from this average is determined. The United States Pharmacopeia (USP) and other regulatory guidelines specify permissible limits for weight variation, which typically depend on the average weight of the tablet:

**3.8 Thickness**

**Definition**: The thickness test measures the physical dimension of the tablet, specifically its thickness, to ensure uniformity. Tablet thickness can impact dosage uniformity, packaging, and appearance. Any significant variation in thickness could indicate issues with the compression process or formulation.

**Procedure**: A sample of around 10 tablets is usually selected for thickness testing. Using a calibrated instrument, such as a vernier caliper or automated thickness gauge, each tablet's thickness is measured, typically in millimeters. According to pharmacopoeial standards, the allowable deviation in thickness is generally ±5% of the target thickness. Any deviation beyond this range may require adjusting the compression settings or modifying the formulation to achieve consistent thickness

**3.9 Hardness**

**Definition:** The hardness, or crushing strength, test assesses the tablet's mechanical strength, which is essential for ensuring the tablet can withstand handling, transportation, and packaging. The hardness test is crucial because a tablet that is too hard may not disintegrate as required for drug release, while one that is too soft may break apart during handling.

**Procedure:** The test is conducted using a hardness tester, such as a Monsanto, Pfizer, or Schleuniger tester, which applies increasing pressure to the tablet until it fractures. The force needed to break the tablet, usually measured in kilograms per square centimeter ($kg/cm^2$) or newtons (N), is recorded. Acceptable hardness typically ranges from 4 to 8 $kg/cm^2$, depending on the tablet type. Adjustments to the formulation or compression force may be required if the hardness is outside the desired range.

3.10 **Friability**

**Definition**: The friability test evaluates the ability of tablets to resist abrasion and mechanical stress without crumbling or breaking. Friability is essential for ensuring tablets can withstand handling during packaging, transportation, and use without breaking into smaller pieces.

**Procedure**: In this test, a specific number of tablets (usually 10 ) if the weight of tablet is more than 650mg and if it is less than 650 mg then 6.5 gram of tablet is weighed accurately and then placed in a friabilator, a rotating drum that subjects the tablets to abrasion. The friabilator rotates for 100 revolutions at a set speed, typically 25 rpm. Afterward, the tablets are weighed again, and the percentage weight loss is calculated as follows:
Tablets are generally acceptable if they lose less than 1% of their weight. Excessive weight loss may indicate the need to adjust the formulation or compression process to improve tablet cohesion and durability. **(3).**

### 3.11 Drug content

According to USP method unit dosage are individually assayed for drug content according to method describe in individual monograph. The standards for content uniformity are satisfied, unless otherwise specified in the monograph, ifthe amount ofactive ingredient in each dosage unit falls between 85 and 115% ofthe label claim and the standard deviation is less than 6%.

### 3.12 *In-vitro* drug release studies :

Dissolution study was performed by using USP Type II paddle apparatus. Condition required for dissolution studies are given below. **Dissolution medium:** 1.2 pH buffer (2 hr), after phosphate buffer pH 6.8 **Paddle speed:** 100 rpm **Temperature:** 37 ± 0.5 ˚C **Sample volume:** 5ml **Time interval for sampling:** 2hrs **Wavelength of scanning:** 210nm Three tablets taken for dissolution.

### 3.13 Stability:

The optimized formulation tablets were stored in blister packs within stability chambers set at 40°C ± 2°C and 75% ± 5% RH for three months due to lack of time, as recommended by the ICH Q1A(R2) Guideline on "Stability Testing of New Drug Substances and Products." This guideline specifies such accelerated testing conditions to simulate longer-term storage in a shorter period, allowing for a quicker assessment of product stability. After three months, samples were analyzed for physical appearance, drug content, and in vitro release profile. These tests helped confirm that the tablets retained their quality, strength, and release characteristics under the accelerated conditions, supporting the reliability and robustness of the formulatio

## 4. RESULTS AND DISCUSSION:

**4.1 Organoleptic characterization** Various organoleptic characterization of Divalproex sodium is given below.

**Table 4.1 Organoleptic characterization of Divalproex sodium**

| Sr.No | Characterization | observation |
|---|---|---|
| 1 | apperance | White to off powder |
| 2 | odour | Odourless |
| 3 | taste | - |

## 4.2 Melting point determination

**Table 4.2 Melting Point of Divalproex sodium**

| Refrence melting point | Observed melting point |
|---|---|
| 98 - 104 °C | 102 – 106 ° C |

It confirms the purity of the experimental drug because the observed melting point is determined to be within the range of the reference drug.

## 4.3 solubility studies

**Table 4.3 solubility studies**

| Sr no | Drug name | solvent | Result |
|---|---|---|---|
| **1** | Divalproex sodium | water | Soluble |
| **2** | Divalproex sodium | toluene | Insoluble |
| **3** | Divalproex sodium | Phosphate buffer 6.8 | Soluble |
| **4** | Divalproex sodium | Acidic buffer 1.2 | Soluble |

## 4.4 FTIR Studies

Pure Divalproex sodium was the subject of FTIR analyses in the 4000 to 500 cm-1 wave number range. Based on the functional group that the medication contains, all necessary peaks are determined.

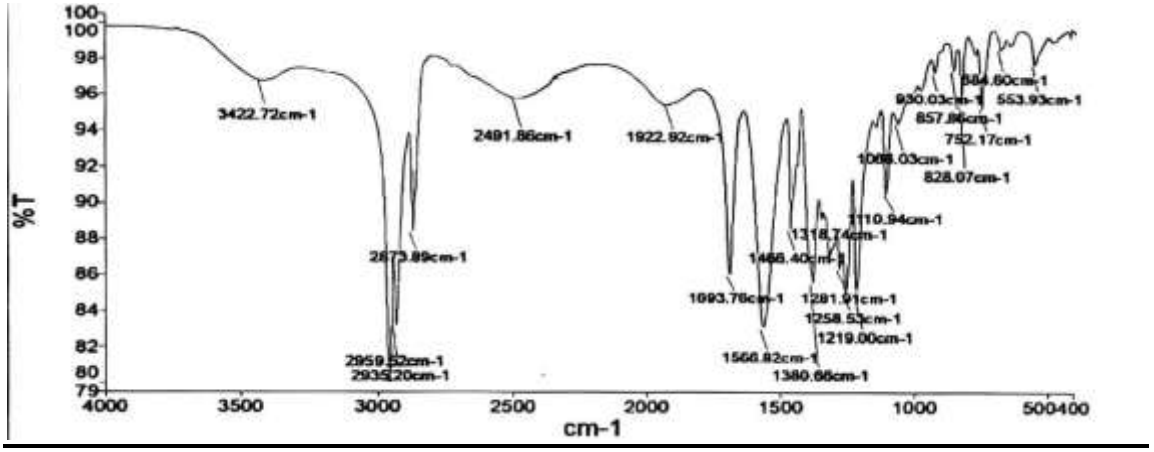


**Figure 4.4 FTIR of Divalproex sodium**

## 4.5 DSC studies

The DSC analysis wasperformed on the pure drug sample of divalproex sodium to study its thermal behavior . the sample displays an endothermic peak at approximately 102oC .which corresponds to the melting point of the drug. The finding aligns with the expected thermal profile for divalproex sodium and helps confirm its identity and purity.

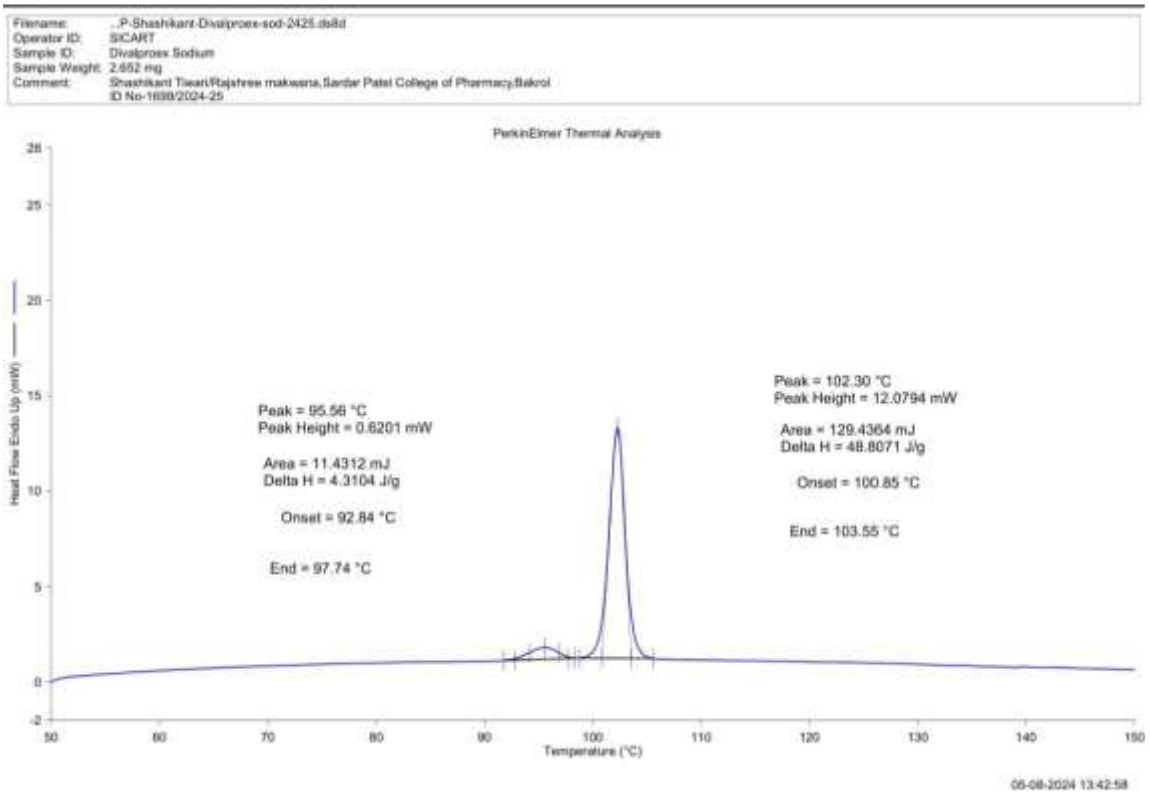


**Figure 4.5 DSC of pure drug**

From the above data we conclude that no interaction seen between the Divalproex sodium an all excipients. So, the composition of these all excipients is used for further formulation

### 4.6 Precompression evaluation

**Table 4.6 Precompression evaluation of the granules**

| Sr no | Formulation | Carr's index | Hausners ratio | Angle of repose |
|---|---|---|---|---|
| **1** | **T1** | 10.62 + 0.21 | 1.06 ± 0.03 | 21.43 ±0.16 |
| **2** | **T2** | 12.69 + 0.22 | 1.15 ± 0.07 | 19.84 ±0.64 |
| **3** | **T3** | 10.35 + 0.28 | 1.17 ±0.05 | 17.45 ± 0.41 |
| **4** | **T4** | 10.29 + 0.34 | 1.12 ± 0.09 | 22.26 ±0.32 |
| **5** | **T5** | 12.82 + 0.27 | 1.14 ± 0.07 | 20.47 ±0.17 |
| **6** | **T6** | 13.02 + 0.31 | 1.18 ±0.06 | 21.34 ± 0.24 |

The angle of repose of the blend was ramged from 17.45 to 21.43 and The hausners ratio was found between 1.06 to 1.18 the flow property of granules is excellent

**4.7 Evaluation of weight**

**Table 4.7 Evaluation of weight in gram**

| Sr no | Formulations | Weight in grams |
|---|---|---|
| **1** | **T1** | 0.275 ± 0.002 |
| **2** | **T2** | 0.276 ±0.001 |
| **3** | **T3** | 0.275 ±0.002 |
| **4** | **T4** | 0.275 ±0.003 |
| **5** | **T5** | 0.274 ±0.003 |
| **6** | **T6** | 0.275 ±0.001 |

The angle of repose of the blend was ramged from 17.45 to 21.43 and The hausners ratio was found between 1.06 to 1.18 the flow property of granules is excellent

**4.8 Evaluation of of thickness**

**Table 4.8 Evaluation of thickness ( in mm)**

| Sr no | Formulations | Thickness in mm |
|---|---|---|
| 1 | T1 | 4.17 ± 0.0 |
| 2 | T2 | 4.14 ±0.0 |
| 3 | T3 | 4.20 ±0.0 |
| 4 | T4 | 4.16 ±0.0 |
| 5 | T5 | 4.20 ±0.0 |

**4.9 Evaluation of of Hardness**

**Table 4.9 Evaluation of hardness ( kg / cm2)**

| Sr.No | Formulations | hardness in kg / cm2 |
|---|---|---|
| **1** | T1 | 7.2± 0.0 |
| **2** | T2 | 6.8±0.0 |
| **3** | T3 | 7.4 ±0.0 |
| **4** | T4 | 7.1±0.0 |
| **5** | T5 | 6.9±0.0 |
| **6** | T6 | 7.1±0.0 |

**4.10 Evaluation of friability**

**Table 4.10 Evaluation of friability**

| Sr.No | Formulations | Friability |
|---|---|---|
| **1** | T1 | 0.23± 0.01 |
| **2** | T2 | 0.25±0.02 |

| | | |
|---|---|---|
| **3** | T3 | 0.24 ±0.01 |
| **4** | T4 | 0.21±0.01 |
| **5** | T5 | 0.19±0.03 |
| **6** | T6 | 0.21±0.02 |

**4.11 Evaluation of drug content**

**Table 4.11 table for drug content**

| **Sr.No** | **Formulations** | **Drug content (% w/w)** |
|---|---|---|
| 1 | T5C2 | 99.21±0.2 |

**4.12 In vivo release study of the tablets.**

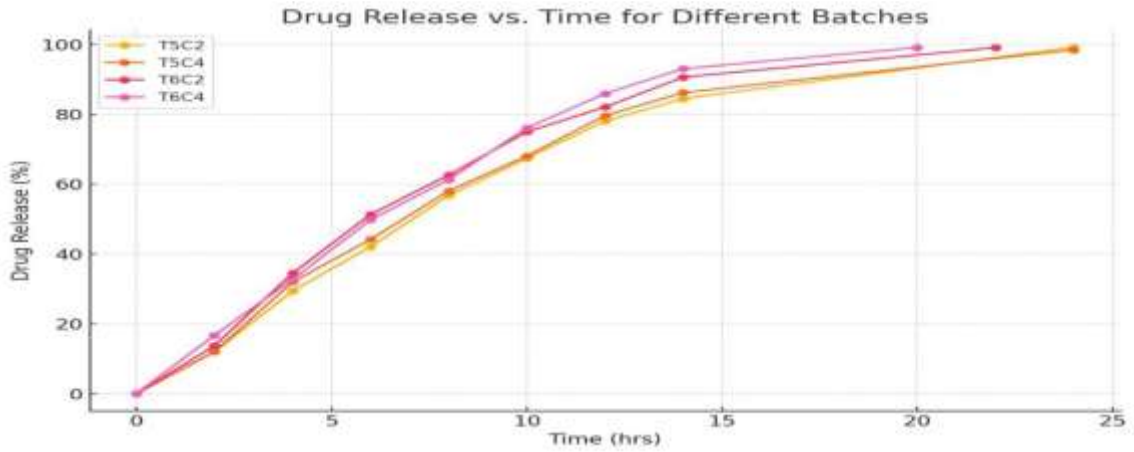


**Figure 4.12 Commulativwe percentage drug release**

**4.13 Stability study of optimized Batch**

Prepared osmotic tablet was subjected to 1 month accelerated stability study under 40°C±2°C/ 75 %RH ± 5% RH. Evaluation of film after 1 month was done which is given below

**Table 4.13 Stability Study of optimized batch Batch**

| **Sr.No** | parameters | Initial | After 1 months |
|---|---|---|---|
| **1** | apperance | White biconvex tablet plain on both side | White biconvex tablet plain on both side |
| **2** | Diameter | 9.53±0.02 | 9.49±0.03 |
| **3** | Thickness | 4.24±0.07 | 4.19±0.09 |
| **4** | Hardness | 8.76±0.0 | 8.20±0.0 |
| **5** | Drug content | 99.33±0.26 | 99.18±0.12 |
| **6** | % drug release in 24 hours | 99.18±0.54 | 98.44±0.98 |

## 5. SUMMARY & CONCLUSION:

The formulation and evaluation of an intranasal nanoemulsion of divalproex sodium is a multi-faceted process aimed at optimizing drug delivery and therapeutic efficacy. The evaluation phase encompasses a comprehensive assessment of various parameters. Physicochemical characterization involves determining properties such as droplet size, zeta potential, viscosity, and drug content uniformity, all of which influence the nanoemulsion's performance. Additionally, evaluating in vitro release profiles, permeation studies, and assessing the nasal mucosa's compatibility are critical to understanding drug release kinetics and the formulation's potential for effective intranasal delivery.The outcomes of these evaluations shed light on the nanoemulsion's ability to overcome barriers like poor drug solubility, stability, and bioavailability associated with conventional delivery methods. The enhanced drug solubilization and improved permeation across the nasal mucosa showcased by the nanoemulsion indicate its potential as an efficient drug delivery system for divalproex sodium.In conclusion, the formulation and meticulous evaluation of this intranasal nanoemulsion of divalproex sodium highlight its potential to revolutionize drug delivery systems, advancing pharmaceutical science and potentially improving patient care in the near future.

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