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Research Article

**FORMULATION AND EVALUATION OF DOLUTEGRAVIR  
SODIUM CONTROLLED RELEASE TABLETS.**<sup>1</sup>B.Bhagya Sri, <sup>2</sup>Patnala Venkata Satya Kumari<sup>1</sup>Department of Pharmaceutics, Avanathi Institute of Pharmaceutical Sciences, Bhogapuram,  
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**Abstract:**

*This research focuses on the development of controlled-release tablets containing 200 mg of Dolutegravir sodium, a second-generation antiretroviral drug used in HIV treatment. Six formulations were designed using the direct compression method, incorporating varying concentrations of hydrophobic polymers along with different excipients as fillers. The prepared formulations were subjected to pre-compression and post-compression evaluations, along with in-vitro dissolution studies. Based on dissolution profiles, formulation F6 was identified as the optimized formulation, as it exhibited superior controlled drug release and aligned best with the desired kinetic model.*

**Keywords:** Dolutegravir (DTG), HPMC K15M, Carbopol 971G, Microcrystalline Cellulose (MCC), Controlled Release Tablets.

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## INTRODUCTION:

### Oral Drug Delivery Systems:

The term "drug delivery" encompasses a wide range of techniques used to introduce therapeutic agents into the human body. Medications are administered primarily to treat various health conditions, but they are rarely used in their pure form. Instead, they are formulated into suitable dosage forms to control the intensity and duration of their action. Among various administration routes, the oral route is the most widely preferred for drug delivery due to its convenience and patient acceptance.

### Limitations of Conventional Oral Dosage Forms:

Conventional oral drug delivery systems have several drawbacks, including:

- Poor patient compliance due to the risk of missed doses.
- Fluctuations in drug plasma concentration, leading to inconsistent therapeutic effects.
- The need for multiple doses increases the risk of toxicity and raises overall treatment costs.

### Approaches to Overcome These Limitations:

To address these challenges, researchers focus on:

- Developing novel drugs with improved safety profiles, extended half-lives, and higher therapeutic efficacy.
- Enhancing the use of existing drugs through advanced concepts and technologies in controlled and targeted drug delivery.

While the development of new drugs presents significant challenges, controlled drug delivery systems provide a viable alternative. An ideal controlled release system ensures precise drug release at a predetermined rate for a specified duration, maintaining stable plasma drug levels, minimizing toxicity, and maximizing therapeutic efficiency.

Several factors influence the design of an oral controlled release drug delivery system, including:

- The anatomy and physiology of the gastrointestinal tract (GIT).
- The pharmacokinetic and pharmacodynamic properties of the drug.
- The physicochemical characteristics of the drug and the selected delivery system.

Controlled release formulations are particularly beneficial for drugs that are rapidly eliminated, have a short half-life, or require sustained absorption in the

GIT. These dosage forms offer continuous drug release at a specific site, ensuring prolonged therapeutic effects while reducing dosing frequency and side effects.

### Objective of the Study:

The primary goal of this study is to develop a controlled-release formulation of Dolutegravir sodium that maintains a steady-state blood concentration, ensuring therapeutic efficacy. Controlled drug delivery systems are designed to enhance therapeutic outcomes, reduce dosing frequency, and improve patient compliance in the treatment of various diseases.

Dolutegravir is an antiretroviral agent used in the treatment of HIV-1. It functions by inhibiting HIV integrase, binding to its active site, and preventing the strand transfer step necessary for the integration of retroviral DNA into the host cell. This inhibition is a critical step in the HIV replication cycle and is essential for suppressing viral activity.

Considering these factors, the present study aims to develop an optimized controlled-release tablet formulation using hydrophobic polymers to achieve sustained drug release.

### Study Objectives:

Dolutegravir sodium was selected for this study due to its favorable characteristics for a controlled drug delivery system. The key objectives include:

- Enhancing bioavailability for maximum therapeutic effectiveness.
- Achieving controlled and targeted drug release.
- Minimizing first-pass metabolism through sustained release.
- Reducing drug concentration fluctuations at the local site.
- Maximizing therapeutic efficacy with prolonged drug action.
- Reducing dosing frequency to improve patient adherence.

In this study, **HPMC K15M** and **Carbopol 971G** were selected as the primary polymers for controlled drug release. These polymers were chosen for their ability to provide sustained action while maintaining stability in both acidic and alkaline conditions. Various formulation parameters were evaluated to identify the optimized and most effective formulation.

## METHOD AND METHODOLOGY:

**Pre-Formulation Studies:**

The primary objective of pre-formulation studies is to collect essential data that aids in developing a stable and bioavailable formulation. These studies help optimize formulation parameters, increasing the likelihood of producing a safe, effective, and stable dosage form. Before incorporating an active pharmaceutical ingredient (API) into a dosage form, it is crucial to analyze its physicochemical properties, including physical form, solubility, density parameters, compressibility index, angle of repose, melting point, and sieve analysis.

**Objectives of Pre-Formulation Studies:**

Pre-formulation studies were conducted on both the active pharmaceutical ingredient (API) and excipients to achieve the following objectives:

- Establishing specifications for the API.
- Evaluating compatibility between the active and inactive ingredients.
- Characterizing the reference product to ensure formulation consistency.

**Classification of Pre-Formulation Studies:**

Pre-formulation studies can be broadly classified into two categories:

1. **API Characterization** – Assessing the physicochemical properties of the active ingredient.
2. **Compatibility Study** – Evaluating interactions between the API and excipients to ensure formulation stability.

**API Characterization:****Organoleptic Properties:**

The drug's odor, taste, and color were assessed and recorded using standard descriptive terminology. These characteristics provide essential information about the physical attributes of the active pharmaceutical ingredient (API).

**Solubility:**

The solubility of the API was determined by dispersing a known quantity of the drug in a suitable solvent. The solubility classification was based on standard reference guidelines.

**Density****Bulk Density (Db):**

Bulk density is defined as the ratio of the mass of a powder to its bulk volume. It is determined by carefully pouring a known weight of the powder into a graduated measuring cylinder and recording the

volume it occupies. Bulk density is expressed in terms of mass per unit volume (g/mL).

**Angle of Repose ( $\theta$ ):**

The angle of repose ( $\theta$ ) is a measure of the flow properties of a powder and indicates the frictional forces within a loose powder sample. It is defined as the maximum angle formed between the surface of a powder pile and the horizontal plane. This parameter helps in assessing the powder's flowability, which is crucial for various pharmaceutical processes.

Where:

- $\theta$  = Angle of repose
- $h$  = Height of the powder pile
- $r$  = Radius of the base of the pile

A lower angle of repose indicates better flow properties, whereas a higher angle suggests poor flowability due to increased interparticle friction.

**FT-IR Spectral Studies:**

Fourier Transform Infrared (FT-IR) spectroscopy was performed to identify potential interactions between the drug and excipients. The spectra of pure Dolutegravir sodium and formulation excipients were recorded using a **Jasco FT-Infrared Spectrophotometer** with the potassium bromide (KBr) pellet technique (1:100). The spectra were obtained in transmittance mode within a wavenumber range of **400–4000  $\text{cm}^{-1}$**  with a resolution of **4  $\text{cm}^{-1}$** .

**Differential Scanning Calorimetry (DSC):**

Thermal analysis was carried out using a **DSC Q200 (TA Instruments, NJ, USA)** equipped with a refrigerated cooling system (RCS). The DSC compartment was purged with **50 mL/min dry nitrogen**, while the RCS was purged with **150 mL/min nitrogen**. Calibration was performed using empty pans of matched weight and three temperature standards:

- **Cyclohexane ( $T_m = 279.54 \text{ K}$ )**
- **Indium ( $T_m = 429.61 \text{ K}$ )**
- **Tin ( $T_m = 504.93 \text{ K}$ )**

Approximately **3–5 mg** of Dolutegravir sodium was placed in hermetically sealed aluminum pans and subjected to a controlled heating rate from an initial temperature to a point beyond its melting point under **50 mL/min nitrogen purging**. The resulting data was analyzed using **Universal Analysis Software (TA Instruments)**.

**Analytical Method Development for Dolutegravir Sodium:****UV Spectrophotometric Analysis**

A calibration curve for Dolutegravir sodium was prepared in the **2–10 µg/mL** concentration range at a **wavelength of 254 nm** using **pH 6.8 phosphate buffer solution**. Based on **Beer-Lambert's Law**, a graph was plotted between **absorbance and concentration**, yielding a regression coefficient ( $r^2$ ) value of **0.999** with an intercept of **0.005**, indicating good linearity.

#### Preparation of Standard Stock Solution

- **100 mg** of Dolutegravir sodium was dissolved in **100 mL** of **pH 6.8 phosphate buffer** in a **100 mL volumetric flask** and the volume was adjusted with the same buffer.
- From this solution, **1 mL** was taken and diluted to **100 mL** with **pH 6.8 phosphate buffer** to obtain the working stock solution.

#### Method for Drug Estimation

For the determination of Dolutegravir sodium in **pH 6.8 phosphate buffer**, the stock solution was **serially diluted** to obtain concentrations of **2, 4, 6, 8, and 10 µg/mL**. The absorbance was measured at **254 nm**, and a calibration curve was constructed.

#### Formulation of Dolutegravir Sodium Controlled-Release Tablets:

Dolutegravir sodium **controlled-release tablets** were formulated using the **direct compression method**.

#### Formulation of Dolutegravir sodium controlled release tablets

| Ingredients mg/tab         | Formulation |     |     |     |     |     |
|----------------------------|-------------|-----|-----|-----|-----|-----|
|                            | F1          | F2  | F3  | F4  | F5  | F6  |
| API (Dolutegravir sodium ) | 100         | 100 | 100 | 100 | 100 | 100 |
| Carbopol 971G              | 30          | 40  | 50  | --- | --- | --- |
| HPMC k15 M                 | ---         | --- | --- | 30  | 40  | 50  |
| Microcrystalline Cellulose | 64          | 54  | 44  | 64  | 54  | 44  |
| Talc                       | 2           | 2   | 2   | 2   | 2   | 2   |
| sodium Stearyl Fumarate    | 2           | 2   | 2   | 2   | 2   | 2   |
| Mg stearate                | 2           | 2   | 2   | 2   | 2   | 2   |
| Total weight (mg)          | 200         | 200 | 200 | 200 | 200 | 200 |

#### Evaluation of Dolutegravir Sodium Controlled-Release Tablets:

##### Physical Appearance:

The physical characteristics of the tablets were assessed through **visual inspection**, which includes evaluating various attributes such as:

- **Size and shape**
- **Color and surface texture**
- **Odor and taste**

Six different formulations, each containing **200 mg** of Dolutegravir sodium, were prepared using various excipient concentrations.

#### Preparation Process:

##### Weighing & Mixing

- Dolutegravir sodium was weighed accurately and mixed uniformly with polymers (**Carbopol 971G and HPMC K15M**).
- The mixture was passed through a **#40 mesh sieve** for uniform particle size distribution.
- Microcrystalline cellulose (**MCC**), used as a diluent, was also passed through a **#40 mesh sieve** and blended with the drug-polymer mixture.

##### Addition of Lubricants

- A mixture of **talc, sodium stearyl fumarate, and magnesium stearate** (1:1 ratio) was added to the powder blend and mixed thoroughly for a few minutes.

##### Compression into Tablets:

The final blend was compressed into tablets using a **stationary rotary compression machine** with an **8 mm punch size**.

- **Presence of identification markings or symbols**

These parameters ensure uniformity and aid in the identification of the formulation.

##### Weight Variation Test:

To determine uniformity in tablet weight, a **weight variation test** was conducted. The procedure involved:

1. Selecting **20 tablets** from each formulation batch.
2. Weighing each tablet individually using an **electronic balance**.
3. Calculating the **average weight** of the tablets.
4. Comparing individual tablet weights with the average weight to check for deviations within the permissible limits as per **pharmacopeial standards**.

#### Evaluation of Dolutegravir Sodium Controlled-Release Tablets:

##### 1. Thickness Measurement

The thickness of the tablets was determined using a **vernier caliper**. Five tablets from each formulation batch were selected, and the **average thickness** was recorded to ensure uniformity.

##### 2. Hardness Test (kg/cm<sup>2</sup>)

Tablet hardness, which indicates the tablet's mechanical strength, was assessed using a **Monsanto hardness tester**. Five tablets from each batch were selected, and the force required to break each tablet was measured. The average hardness was then calculated.

##### 3. Friability Test (%)

The **Roche friabilator** was used to evaluate the friability of the tablets. The procedure involved:

1. Weighing **ten tablets** initially (**W1**).
2. Placing them in the friabilator, which rotates at **25 RPM** for **100 revolutions**, causing the tablets to drop from a height of six inches with each rotation.
3. After completing the rotations, the tablets were **dedusted and reweighed (W2)**.
4. **Friability (%)** was calculated using the formula:  

$$\text{Friability}(\%) = \frac{W1 - W2}{W1} \times 100$$

A friability value of **less than 1%** was considered acceptable.

#### Evaluation of Dolutegravir Sodium Controlled-Release Tablets:

##### 1. Drug Content Analysis

To determine the amount of drug present in each tablet, the following procedure was carried out:

1. **Crushing the Tablet:** Ten tablets were selected, and each was finely crushed using a mortar and pestle.
2. **Sample Preparation:** The powdered tablet content was transferred to a **100 mL volumetric flask** and dissolved in a **pH 6.8 phosphate buffer**.

3. **Sonication:** The solution was mixed and subjected to **sonication for 5 minutes** to ensure proper dissolution.
4. **Filtration:** The solution was filtered using **Whatman filter paper** to remove any undissolved particles.
5. **Dilution:** The filtrate was diluted appropriately (**1:10 mL**) using a **pH 6.8 phosphate buffer**.
6. **UV Spectrophotometric Analysis:** The drug content was analyzed using a **validated UV spectrophotometric method** at  $\lambda_{\text{max}}$  **254 nm**.

##### 2. In-Vitro Dissolution Studies

The in-vitro dissolution profile of the tablets was evaluated using a **USP Type II dissolution apparatus (paddle method)** [Lab India, Model: DS-8000, Mumbai].

##### Procedure:

1. **Dissolution Medium:** **900 mL** of **pH 6.8 phosphate buffer** was used as the dissolution medium.
2. **Experimental Conditions:**
  - **Temperature:** Maintained at **37 ± 0.5°C**
  - **Paddle Speed:** **100 RPM**
3. **Sampling:** **5 mL** aliquots of the dissolution medium were withdrawn at predetermined time intervals (**1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 16 hr, and 20 hr**).
4. **Filtration & Analysis:** The withdrawn samples were filtered and analyzed using a **UV spectrophotometer** at **254 nm** to determine the amount of drug released.

**RESULTS & DISCUSSION:****Results:****Identification of API****Table : Identification of API**

| S.No. | Parameters        | Standard value  | Observed value  |
|-------|-------------------|---|---|
| 1     | Solubility        | Dolutegravir Sodium is soluble in organic solvents such as Dimethoxy sulfa oxide and dimethylformamide (DMF) and slightly soluble in ethanol. | Dolutegravir Sodium is soluble in organic solvents such as Dimethoxy sulfa oxide and dimethyl formamide (DMF) and slightly soluble in ethanol |
| 2     | Appearance        | a white to light yellow in powder, crystalline form   | a white to light yellow in powder, crystalline form   |
| 3     | Melting point     | 187-189°C   | 188°C   |
| 4     | Percentage purity | 97%   | 95%   |
| 5     | $\lambda$ - max   | 254 nm  | 254 nm  |

**Pre- Formulation Parameters:****Table:Pre-formulation Parameters**

| S.No. | Parameters                 | Observations       |
|-------|----------------------------|--------------------|
| 1     | Dolutegravir Sodium        | API                |
| 2     | Angle of repose            | 35.37 <sup>0</sup> |
| 3     | Bulk density               | 0.386 gm/cc        |
| 4     | Tapped density             | 0.551 gm/cc        |
| 5     | Compressibility index %    | 13.04 %            |
| 6     | Hauser <sup>ts</sup> ratio | 1.428              |
| 7     | Drug content               | 93.5%              |
| 8     | Melting point              | 188 <sup>0</sup> c |

**Drug - Excipients Compatibility studies****Table : Physical Compatibility Results**

| Material                             | Sample Status After 1 month, kept at 25°C<br>/60%RH & 40°C/75%RH |
|--------------------------------------|--|
| Dolutegravir Sodium + HPMCK15        | No Change  |
| Dolutegravir Sodium + Carbopol 971 G | No Change  |
| Dolutegravir Sodium + SS F           | No Change  |
| Dolutegravir Sodium + MCC            | No Change  |
| Dolutegravir Sodium + Talc           | No Change  |
| Dolutegravir Sodium + Mg stearate    | No Change  |



## FT-IR REPORTS:

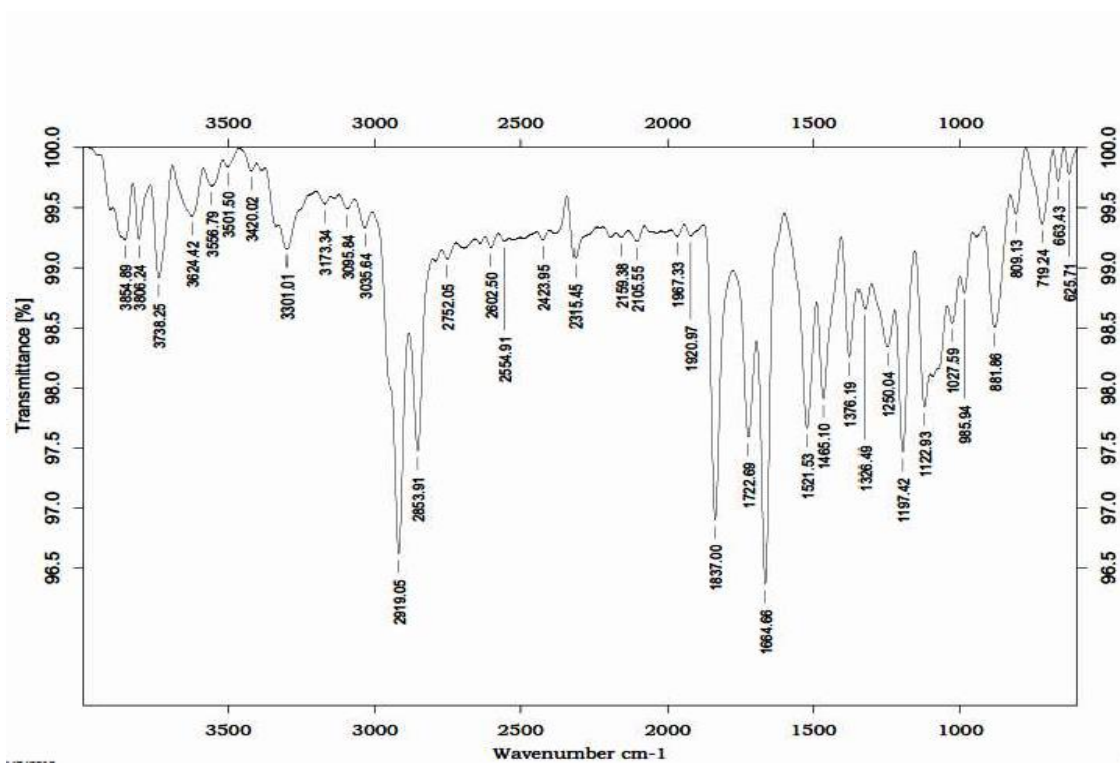


Fig : FT-IR Reports of Dolutegravir Sodium

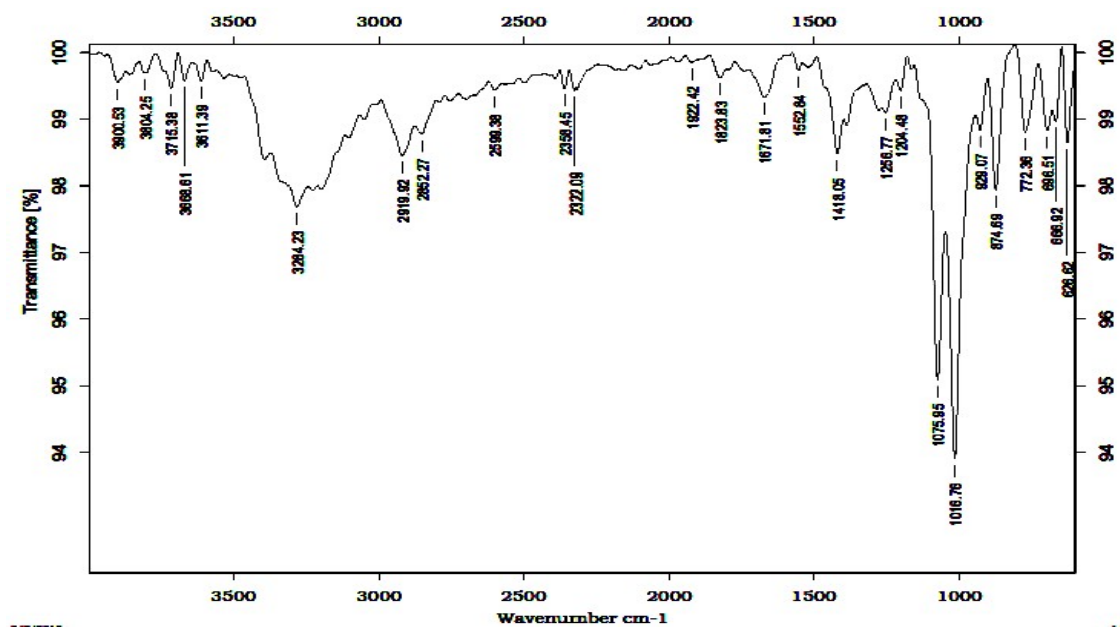
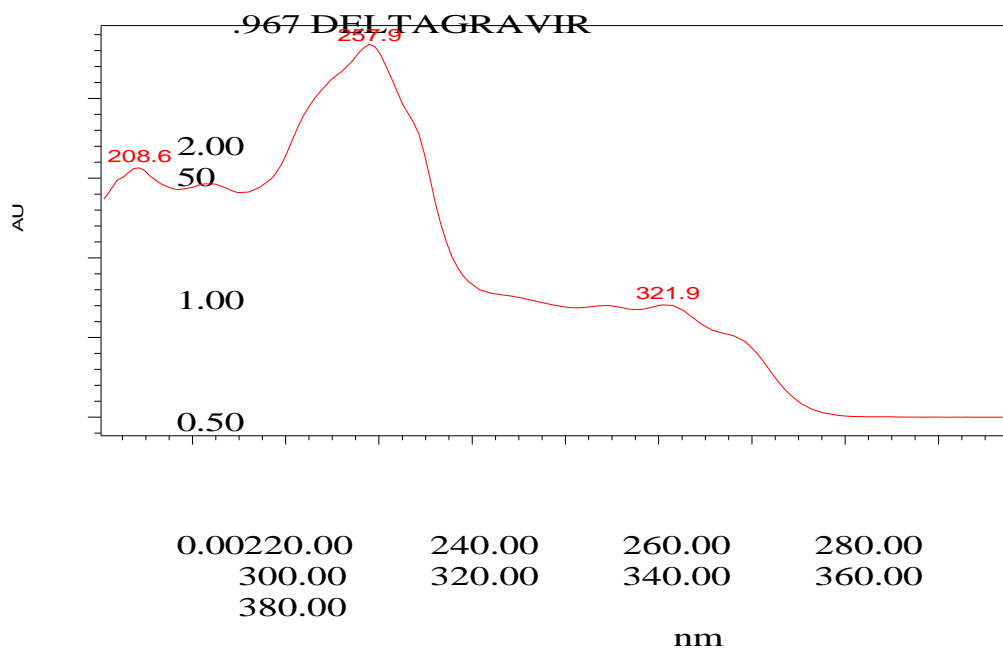
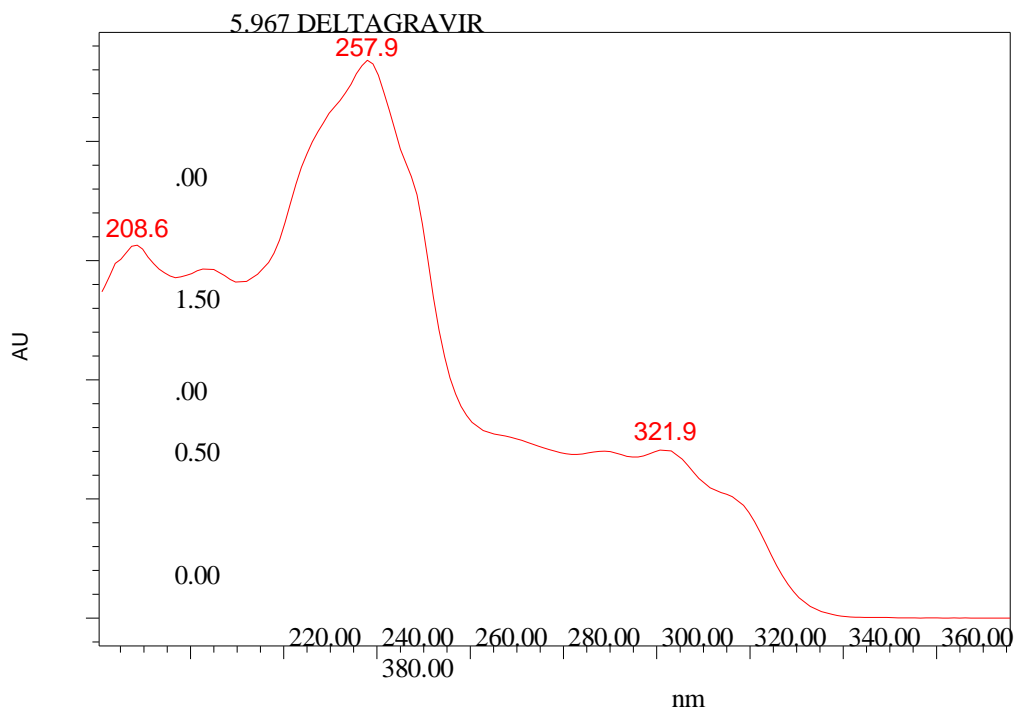


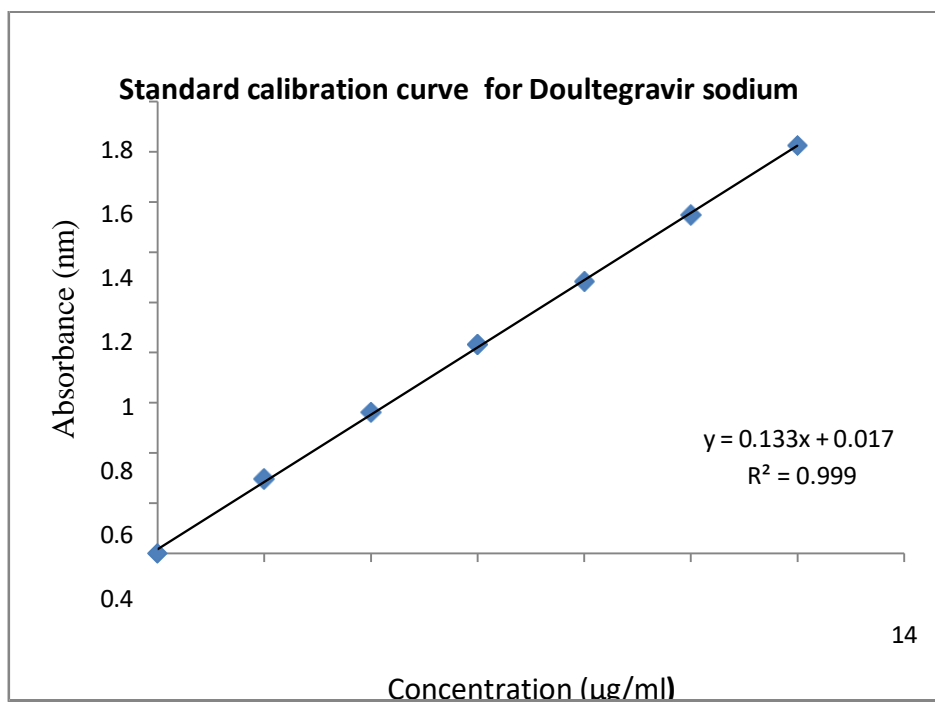
Fig : FT-IR Reports for optimized formula

**Differential scanning calorimetry:****Fig : DSC Reports for Dolutegravir Sodium****Fig : DSC Reports for Dolutegravir Sodium optimized**



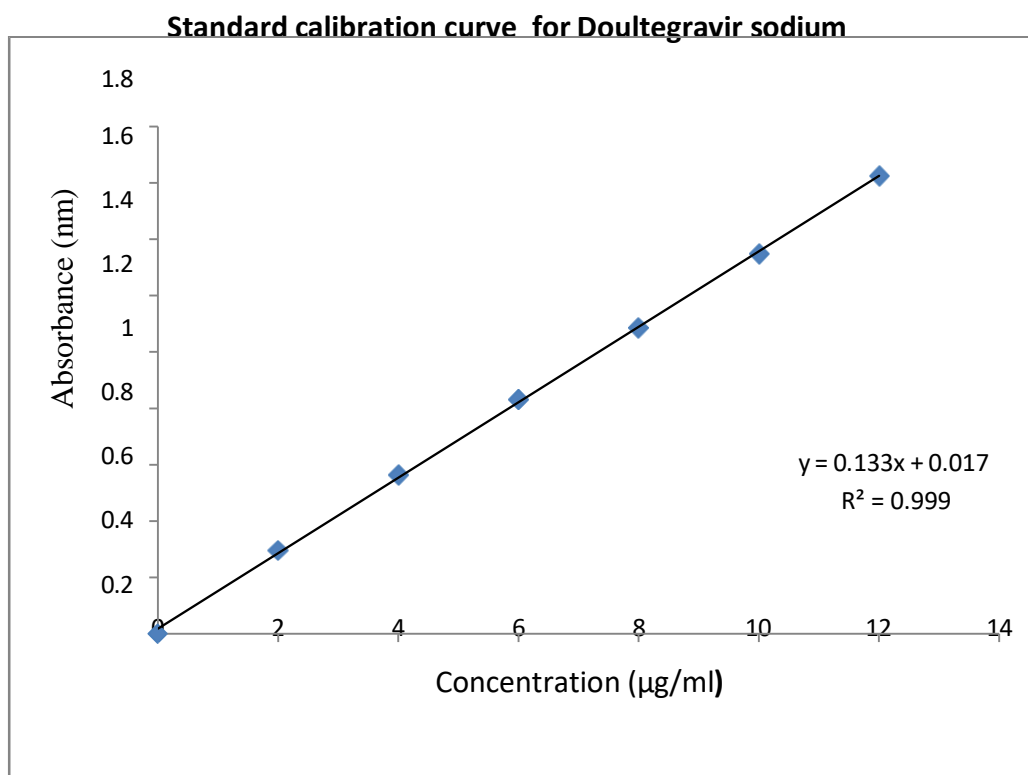
**Analytical Method for Estimation of Dolutegravir Sodium by U.V Spectrophotometer.****Table : Standard Calibration Data of Dolutegravir Sodium in 0.1N HCl**

| Concentration ( $\mu\text{g/ml}$ ) | Absorbance (nm) |
|------------------------------------|-----------------|
| 0                                  | 0               |
| 5                                  | 0.129           |
| 10                                 | 0.261           |
| 15                                 | 0.384           |
| 20                                 | 0.512           |
| 25                                 | 0.631           |
| 30                                 | 0.763           |

**Fig : Calibration curve of Dolutegravir Sodium 0.1N HCl**

**Table No: Standard Calibration Curve for the Dolutegravir Sodium in 6.8 pH phosphate buffer.**

| S. No | Concentration ( $\mu\text{g/ml}$ ) | Absorbance(nm) |
|-------|------------------------------------|----------------|
| 1     | 2( $\mu\text{g/ml}$ )              | 0.102          |
| 2     | 4( $\mu\text{g/ml}$ )              | 0.206          |
| 3     | 6( $\mu\text{g/ml}$ )              | 0.311          |
| 4     | 8( $\mu\text{g/ml}$ )              | 0.424          |
| 5     | 10( $\mu\text{g/ml}$ )             | 0.538          |



**Fig : Standard Calibration Curve for the Dolutegravir Sodium in 6.8 pH phosphate buffer**

Pre – compression parameters:

Table : Micromeritic properties of the granules of Dolutegravir Sodium formulation

| Formulation code | Bulk density (g/ml) | Tapped density (g/ml) | Hausner's ratio | Angle of repose( $\theta$ ) | Compressibility Index (%) |
|------------------|---------------------|-----------------------|-----------------|-----------------------------|---------------------------|
| F1               | 0.510               | 0.634                 | 1.31            | 23.01                       | 18.20                     |
| F2               | 0.491               | 0.626                 | 1.32            | 24.18                       | 18.30                     |
| F3               | 0.500               | 0.622                 | 1.29            | 25.11                       | 20.57                     |
| F4               | 0.510               | 0.632                 | 1.28            | 23.23                       | 21.42                     |
| F5               | 0.508               | 0.640                 | 1.27            | 25.17                       | 22.80                     |
| F6               | 0.509               | 0.636                 | 1.22            | 23.15                       | 23.75                     |

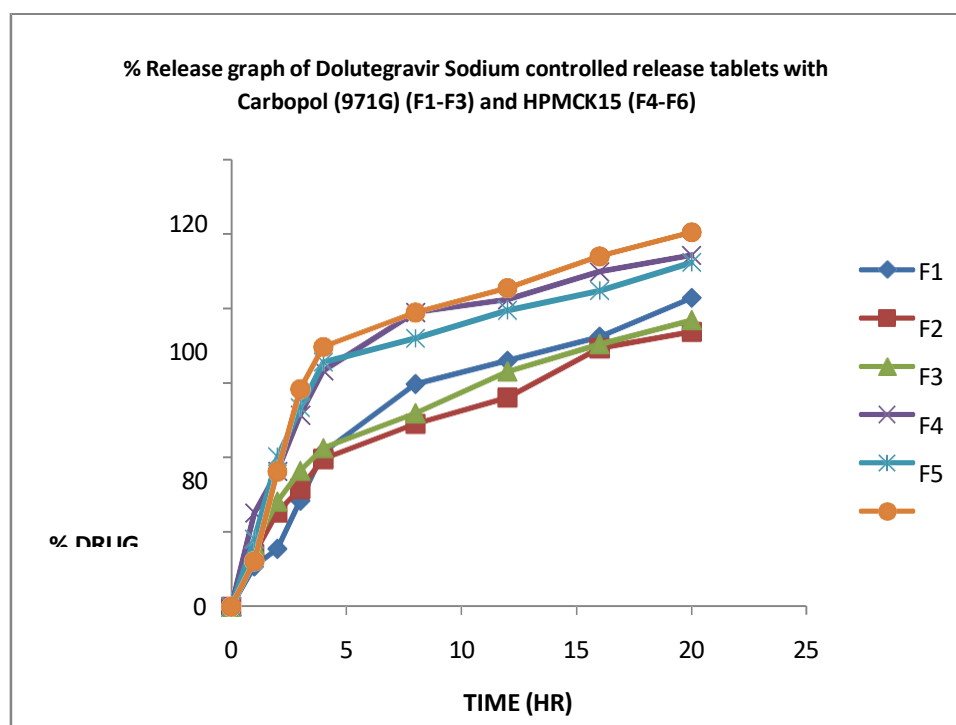
Post – compression parameters:

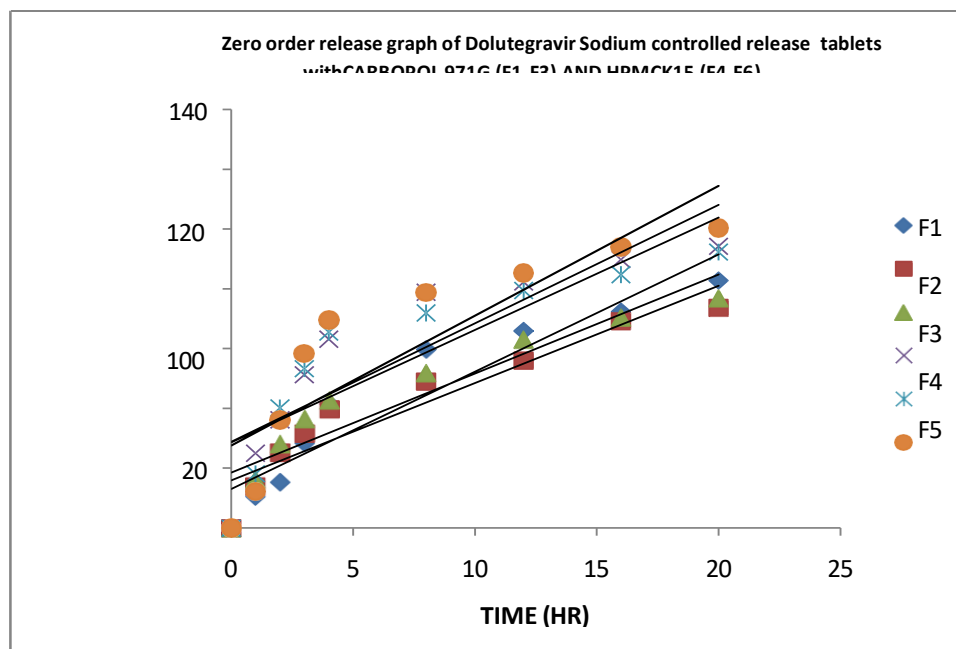
Table: Post compression parameters of Dolutegravir Sodium controlled release tablets

| Formula | Weight Variation (mg) | Thickness (mm) | Hardness (kg/cm <sup>2</sup> ) | % Friability (% loss) |
|---------|-----------------------|----------------|--------------------------------|-----------------------|
| F1      | 203.1                 | 2.00           | 3.6                            | 0.352                 |
| F2      | 204.1                 | 2.10           | 3.9                            | 0.172                 |
| F3      | 202.1                 | 2.35           | 3.8                            | 0.101                 |
| F4      | 199.5                 | 2.21           | 3.7                            | 0.132                 |
| F5      | 198.3                 | 2.13           | 3.2                            | 0.142                 |
| F6      | 202.3                 | 2.28           | 3.3                            | 0.122                 |

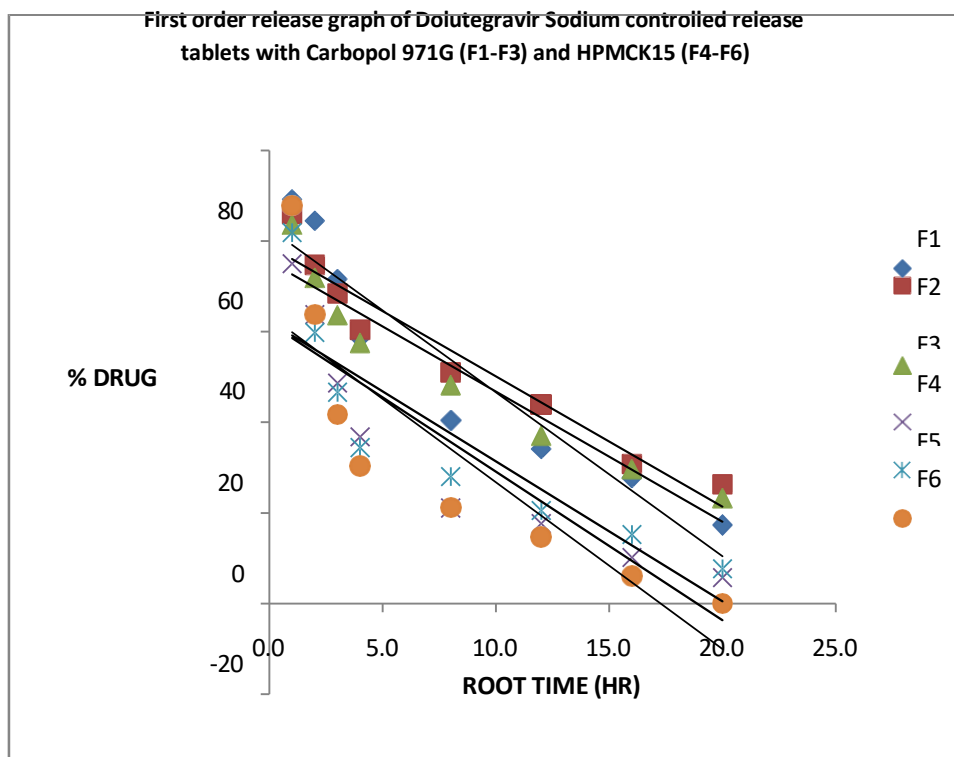
***In-vitro* dissolution studies:****Table: Dissolution studies for Dolutegravir Sodium controlled release tablets**

| Dissolution with pH 6.8 phosphate buffer, 900ml, RPM 100, $\lambda$ max 254 nm |           |       |       |       |       |       |        |
|--|-----------|-------|-------|-------|-------|-------|--------|
| % Cumulative Drug Release  |           |       |       |       |       |       |        |
| S.NO   | Time (hr) | F1    | F2    | F3    | F4    | F5    | F6     |
| 1.   | 0         | 0     | 0     | 0     | 0     | 0     | 0      |
| 2.   | 1hr       | 10.79 | 14.07 | 16.43 | 25.05 | 18.15 | 12.20  |
| 3.   | 2hr       | 15.50 | 25.24 | 28.14 | 36.24 | 40.20 | 36.21  |
| 4  | 3hr       | 28.39 | 31.55 | 36.40 | 51.33 | 53.35 | 58.36  |
| 5  | 4hr       | 41.35 | 39.57 | 42.50 | 63.21 | 65.57 | 69.61  |
| 6  | 8hr       | 59.63 | 48.96 | 51.82 | 78.90 | 71.96 | 78.83  |
| 7  | 12hr      | 65.89 | 56.02 | 62.98 | 82.32 | 79.46 | 85.39  |
| 8  | 16hr      | 72.28 | 69.19 | 70.34 | 89.81 | 84.76 | 93.88  |
| 9  | 20 hr     | 82.71 | 73.61 | 76.77 | 94.23 | 92.30 | 100.35 |

**Fig : %Release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)**



**Fig : Zero order release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)**



**Fig : First order release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)**

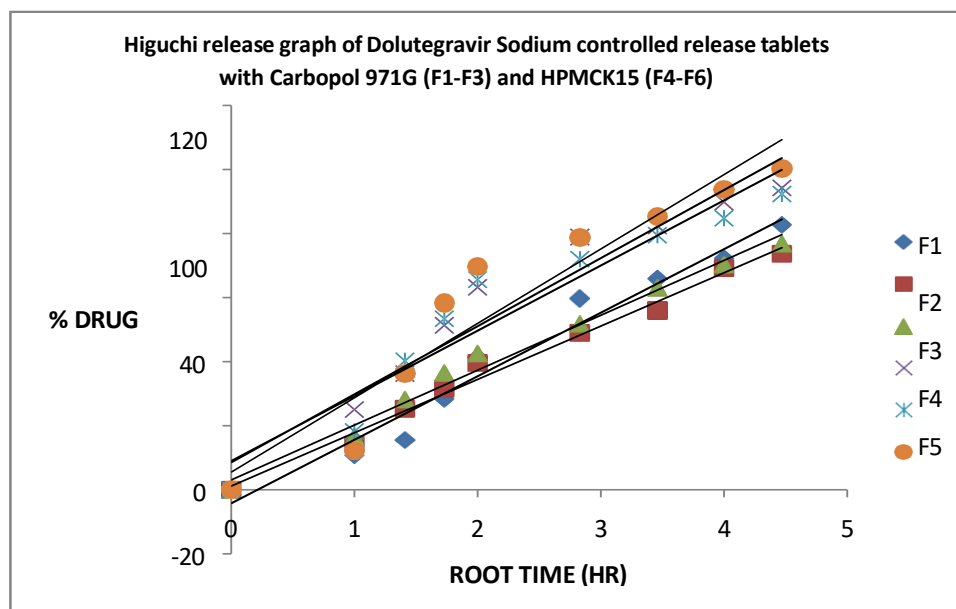


Fig : Higuchi release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

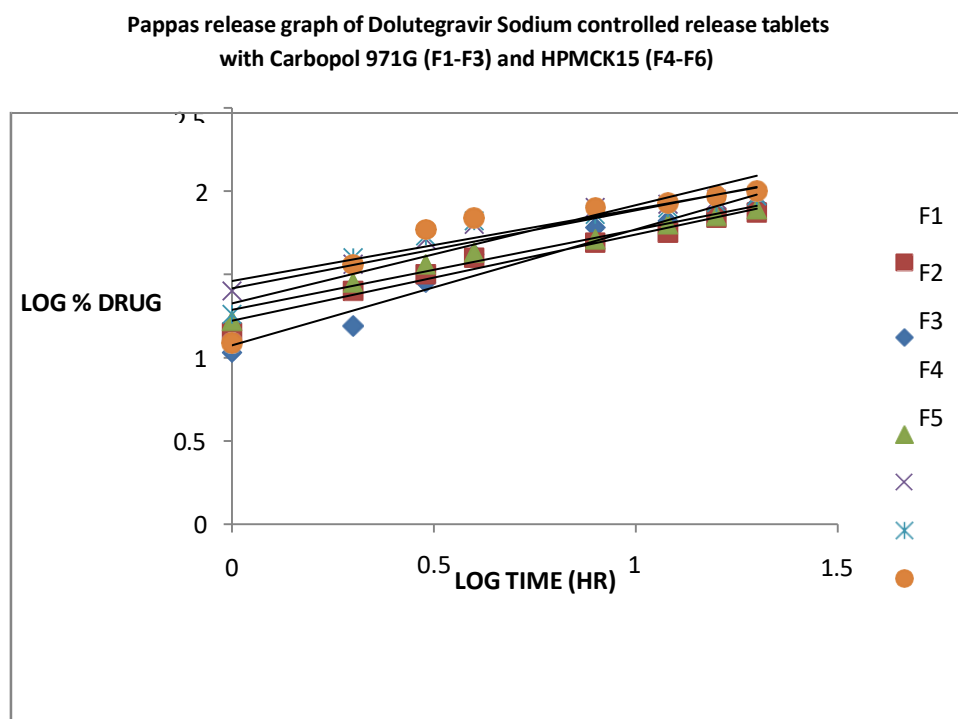


Fig : Pappas release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

Table : Drug Release Rate Kinetics

| Correlation co-efficient |            |             |         |        |
|--------------------------|------------|-------------|---------|--------|
| Formulation              | Zero order | First order | Higuchi | Pappas |
| F1 (C-917 G)             | 0.963      | 0.892       | 0.969   | 0.946  |
| F2 (C-917 G)             | 0.981      | 0.889       | 0.988   | 0.969  |
| F3 (C-917 G)             | 0.981      | 0.866       | 0.985   | 0.970  |
| F4 (HPMC K15)            | 0.920      | 0.770       | 0.941   | 0.936  |
| F5 (HPMC K15)            | 0.877      | 0.738       | 0.915   | 0.854  |
| F6 (HPMC K15)            | 0.859      | 0.749       | 0.909   | 0.804  |

**DISCUSSION:****Pre-formulation Studies:****Identification of Dolutegravir Sodium Pure Drug:****Solubility:**

The solubility studies confirmed that Dolutegravir Sodium is **soluble in organic solvents** such as **DMSO and dimethylformamide (DMF)** and **slightly soluble in ethanol**.

**Angle of Repose:**

The angle of repose for Dolutegravir Sodium was found to be **35.37°**, indicating **poor flow properties**.

**Density:**

The **bulk density** and **tapped density** of Dolutegravir Sodium were determined to be **0.386 g/cc** and **0.551 g/cc**, respectively.

**Compressibility Index:**

Dolutegravir Sodium showed a **compressibility index of 13.04**, which indicates **poor flow characteristics**.

**Hausner's Ratio:**

The Hausner's ratio for Dolutegravir Sodium was calculated as **1.428**, further confirming **poor flow properties**.

**FT-IR Studies:**

The FT-IR spectra indicated that the characteristic peaks of Dolutegravir Sodium remained **unaltered** in combination with **excipients such as Carbopol 971G and HPMC K15**. This suggests that **no significant chemical interactions** occurred between the drug and the excipients used in the formulation.

**Differential Scanning Calorimetry (DSC):**

DSC analysis demonstrated that Dolutegravir Sodium exhibited **good stability** in the presence of **hydrophobic polymers**. The study also revealed **amorphization and entrapment of the drug within**

**the polymer matrix**, which contributes to controlled drug release.

**Analytical Method Development:**

Dolutegravir Sodium was **quantified using UV-Vis spectrophotometry**, and its **standard absorbance at 254 nm** was determined to be **0.311 µg/mL**.

**Preparation of Dolutegravir Sodium Controlled-Release Tablets:**

Dolutegravir Sodium controlled-release matrix tablets were formulated using the **direct compression method**. Six formulations (**F1–F6**), each containing **200 mg of Dolutegravir Sodium**, were developed.

**Procedure:**

- The drug was mixed with **Carbopol 971G and HPMC K15M** in varying concentrations.
- Microcrystalline cellulose was used as a **diluent**, and **talc, sodium stearyl fumarate, and magnesium stearate** were added as **lubricants** in a **1:1 ratio**.
- The mixture was passed through a **#40 mesh sieve** to ensure uniformity before compression.
- The final blend was compressed into tablets using a **rotary compression machine** with an **8 mm punch size**.

**Evaluation of Post-Compression Parameters:****Weight Variation:**

The weight of **20 tablets** from each formulation was recorded. The average weight ranged from **198 ± 3 mg** to **203 ± 1 mg**, complying with **IP standards**.

**Tablet Thickness**



The thickness of the formulations was found to be  $2.00 \pm 0.06$  mm to  $2.28 \pm 0.06$  mm.

#### Tablet Hardness

The hardness of the formulated tablets was  $3.6 \pm 1.0$  kg/cm<sup>2</sup>, ensuring sufficient mechanical strength.

#### Friability:

The friability of the tablets ranged from **0.101% to 0.352%**, which is within the **acceptable limit (<1%)** as per **IP standards**.

#### Drug Content:

The drug content was found to be **93.5%**, indicating uniform distribution of Dolutegravir Sodium in the formulations.

#### In-Vitro Dissolution Studies:

The in-vitro drug release study was performed using a **USP Type II dissolution apparatus (paddle method)** at **100 RPM**. The dissolution medium consisted of **900 mL of pH 6.8 phosphate buffer**, maintained at **37 ± 0.5°C**.

#### Drug Release Profile:

| Formulation | Polymer Used  | % Drug Released in 20 Hours |
|-------------|---------------|-----------------------------|
| F1          | Carbopol 971G | 82%                         |
| F2          | Carbopol 971G | 73.61%                      |
| F3          | Carbopol 971G | 76%                         |
| F4          | HPMC K15      | 94.23%                      |
| F5          | HPMC K15      | 92.30%                      |
| F6          | HPMC K15      | 100.35%                     |

- Carbopol-based formulations (F1–F3) showed **moderate drug release (73–82%) over 20 hours**.
- HPMC K15-based formulations (F4–F6) exhibited **higher drug release (94–100.35%) over 20 hours**, making them more suitable for sustained release.
- The optimized formulation, **F6 (containing HPMC K15)**, achieved **100.35% drug release in 20 hours**, confirming **effective sustained-release behavior**.

#### Curve-Fitting Analysis:

To determine the **drug release kinetics**, different mathematical models were applied:

- Zero-order kinetics
- First-order kinetics
- Higuchi model
- Korsmeyer-Peppas model

The **optimized formulation (F4)** demonstrated a **high correlation coefficient ( $R^2 = 0.978$ ) for the zero-order model**, suggesting that the drug release follows **zero-order kinetics**.

Furthermore, the **Korsmeyer-Peppas model** showed an "**n**" value of **1.742**, indicating a **non-Fickian (anomalous) diffusion mechanism**. This suggests that the drug release is controlled by **both diffusion and polymer erosion mechanisms**.

The study successfully developed **Dolutegravir Sodium controlled-release tablets with optimized formulation (F6) demonstrating complete drug release (100.35%) in 20 hours**. The drug release followed **zero-order kinetics with a non-Fickian diffusion mechanism**, making it a suitable candidate for **sustained drug delivery applications**.

#### Summary

Dolutegravir Sodium was selected as the model drug for this study due to its **high lipid solubility, effectiveness at low plasma concentrations, and significant first-pass metabolism**, making it an ideal candidate for a controlled drug delivery system.

The tablets were formulated using the **direct compression method** and evaluated for **pre-compression and post-compression parameters**, as well as **in-vitro dissolution studies**. Among the formulations developed (F1–F6), the **F6 formulation demonstrated optimal sustained release**, achieving **100.35% drug release at the end of 20 hours**.

Kinetic modeling revealed that **F6 followed zero-order release kinetics** with an  **$R^2$  value of 0.978**, indicating a controlled drug release profile. Furthermore, the drug release mechanism was best described by the **Higuchi equation** and the **Korsmeyer-Peppas model**, with an **n value of 1.742**, suggesting an **anomalous (non-Fickian) diffusion mechanism** controlled by **both diffusion and polymer erosion**.

## CONCLUSION:

Based on the findings of this study, the following conclusions were drawn:

- **Drug-excipient compatibility studies** (FT-IR analysis) confirmed that **Dolutegravir Sodium and the selected polymers (HPMC K15M, Carbopol 971G) were compatible**, with no significant chemical interactions.
- **Micromeritic studies** showed that the formulated granules exhibited **satisfactory flow properties**, ensuring uniform tablet compression.
- **Post-compression evaluation** confirmed that all formulated tablets met **IP standards for weight variation, hardness, friability, thickness, and drug content**.
- **In-vitro dissolution studies** demonstrated that **F6 (containing HPMC K15M) provided sustained drug release (100.35%) over 20 hours**, proving its suitability for controlled-release formulations.
- **Kinetic analysis** indicated that the drug release followed **zero-order kinetics** and was governed by a **non-Fickian diffusion mechanism**, as evidenced by the **Higuchi and Korsmeyer-Peppas models**.
- The study successfully formulated **Dolutegravir Sodium controlled-release tablets** using **HPMC K15M as the primary polymer**, confirming its effectiveness in sustaining drug release for **20 hours**.

## Final Remark:

This investigation successfully demonstrated the feasibility of **formulating controlled-release tablets of**

**Dolutegravir Sodium** using **HPMC K15M** as a **rate-controlling polymer**. These findings support the potential **clinical application** of this formulation for **improved therapeutic efficacy and patient compliance** in long-term HIV treatment.

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