CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.17998291

Available online at: http://www.iajps.com Research Article

# FORMULATION DESIGN AND *IN VITRO* EVALUATION OF TROPISETRON SUSTAINED RELEASE MATRIX TABLETS

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**Abstract:**

*Tropisetron is taken orally twice daily at a dosage of 5 mg, with a plasma half-life of 20 minutes. The optimal formulation of Tropisetron was determined to be a once-daily sustained-release pill to reduce administration frequency and enhance patient adherence. Using hydrophilic synthetic polymers like hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic synthetic polymers like Eudragit RSPO and RLPO, the current work sought to evaluate and improve sustained-release Tropisetron matrix tablets. Utilizing a USP type-II paddle type eight station dissolving device, an in vitro release investigation was carried out. The formulation $TRS_{12}$, consisting of HPMC K15M and Eudragit RSPO grades, was deemed the superior among all formulations. The TRS12 formulation was found to release the drug for up to 12 hours at a steady, regulated rate. To confirm the drug's compatibility with polymers, FTIR and DSC studies were conducted. Different pre- and post-compression characterizations of the tablet were conducted, and the results complied with pharmacopoeia requirements. Accelerated stability experiments were done to confirm the stability of the dosage formulations.*

***Key Words:*** *Tropisetron, Sustained-release, HPMC K4M, HPMC K15M, Eudragit RSPO, Eudragit RLPO*

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*Please cite this article in press* ***Lubna Nousheen*** *et al.,* ***Formulation Design And In Vitro Evaluation Of Tropisetron Sustained Release Matrix Tablets****, Indo Am. J. P. Sci, 2025; 12(11).*

## 1. INTRODUCTION

Oral drug administration is the most favored and advantageous method among all drug delivery techniques, as it enhances the medication's residence duration for absorption by offering the broadest dynamic surface area. Traditional dosage forms often lead to significant fluctuations in the drug's concentration within tissues and circulation, resulting in undesirable toxicity and ineffectiveness [1]. The aforementioned circumstances, characterized by unpredictable absorption and repeated dosing, prompted the concept of controlled drug delivery systems. Sustained or controlled delivery systems aim to reduce dose frequency or enhance therapeutic efficacy by localizing the medication to the site of action, minimizing the required dosage, or assuring consistent drug administration [2]. These dosage compositions exhibit enhanced pharmacological effects and prolonged therapeutic effectiveness. Matrix tablets are among the most commonly employed controlled-release dosage forms due to their regulated pharmaceutical release mechanism [3, 4]. Chronic illnesses such as asthma, migraines, diabetes, hypertension, and inflammation, which require stable plasma levels for maintenance therapy, can benefit from a diverse array of medicines [5].

Tropisetron is a serotonin 5-HT3 receptor antagonist mostly employed as an antiemetic to alleviate nausea and vomiting post-chemotherapy, while it has been experimentally utilized as an analgesic for fibromyalgia. Nausea is an unpleasant and challenging-to-articulate psychological feeling. Nausea is generally linked to reduced stomach motility and heightened tone in the small intestine. Additionally, reverse peristalsis frequently occurs in the proximal small intestine. Tropisetron is a powerful and selective antagonist of the 5-HT3 receptor, particularly utilized in the management of nausea and vomiting generated by chemotherapy or postoperative conditions. Tropisetron is nearly entirely absorbed from the gastrointestinal system, although experiences dose-dependent first-pass metabolism. The absolute bioavailability of oral Tropisetron rises from 0.52 at a 20 mg dose to 0.66 at a 100 mg dose, potentially attaining 1.0 at doses of 45 mg and above. Following intravenous administration, the plasma levels of Tropisetron declined swiftly, exhibiting an initial distribution half-life of around 6 minutes. The terminal half-life of Tropisetron was roughly 6 hours following both intravenous and oral dosing. The mean dose-corrected absolute bioavailability of oral Tropisetron was 0.60. The advised therapeutic dosage of Tropisetron is 5 mg orally, with a range of 2–5 mg. [6]

This study aimed to develop sustained-release Tropisetron tablets utilizing polymeric retardant materials, specifically Eudragit (RSPO and RLPO) and hydroxyl propyl methylcellulose (HPMC K4M and K15M), to reduce dosing frequency and enhance therapeutic efficacy. Various formulations of sustained release tablets were developed by integrating differing quantities of HPMC and Eudragit to improve the drug release profile of the investigated medication. The novel formulation reduces dosage frequency and enhances chronic migraine treatment, which is expected to improve patient compliance.[7]

## 2. MATERIALS AND METHODS:

### Materials

Tropisetron was acquired as a complimentary sample from Sunshine Laboratories in Mumbai, India. Samples of HPMC K4M and HPMC K15M polymers were procured from Glenmark Pharma in Nasik, India. Dr. Reddy's Laboratories in Hyderabad, India supplied complimentary samples of Eudragit RSPO and RLPO. We procured lactose monohydrate, magnesium stearate, talc, and PVP K30 from S.D. Fine Chemicals Pvt. Ltd. located in Mumbai, India. Each component was of laboratory-grade quality. A twofold distillation method was conducted in the laboratory to prepare the distilled water utilized in the study.

### Methods

**Formulation of sustained-release matrix tablets of Tropisetron**

Wet granulation methods were utilized to produce Tropisetron sustained release matrix tablets, with twelve distinct formulations selected based on differing polymer concentrations. Prior to incorporation into formulations, exact quantities of each component were measured and passed through sieve number 80. Exact quantities of lactose monohydrate, HPMC, Tropisetron, Eudragit RSPO, RLPO, and PVP K30 were combined and filtered through a #20 mesh for each formulation. PVP K30 served as a binder, while lactose monohydrate functioned as a diluent. A wet lump mass was formed by incorporating the requisite quantity of distilled water as a granulating agent. To reduce moisture content and prevent aggregates from adhering to the sieve during sieving, they were initially dried for ten minutes. The aggregates were passed through filter #20 to obtain granules. To reduce the moisture content to 3–5%, the granules are subjected to drying in a hot air oven maintained at 40°C for approximately 20 minutes. The formulations were evaluated for angle of repose, bulk density, and compressibility prior to compression, following lubrication with talc and magnesium stearate. The evaluated granules were

pulverized with 6 mm concave punches on a 10-station rotating tablet press to produce sustained-release matrix tablets. Tropisetron is available in a sustained-release matrix formulation, with each tablet containing 5 milligrams. The identical approach was employed for each formulation, and the compositions for the different formulations are detailed in Tables 1 and 2. Subsequently, various post-compression attributes, such as mean thickness, weight fluctuation, hardness, friability, swelling assessments, drug content, and in vitro dissolution studies, were assessed for the produced tablet formulations.[9]

**Table 1: Various excipients used in formulations and their compositions ($TSR_1$ to $TSR_6$)**

| Ingredients (mg) | $TSR_1$ | $TSR_2$ | $TSR_3$ | $TSR_4$ | $TSR_5$ | $TSR_6$ |
|---|---|---|---|---|---|---|
| **Tropisetron** | 5 | 5 | 5 | 5 | 5 | 5 |
| **HPMC K4M** | 10 | 15 | 20 | - | - | - |
| **HPMC K15M** | - | - | - | 10 | 15 | 20 |
| **Eudragit RSPO** | 20 | 15 | 10 | - | - | - |
| **Eudragit RLPO** | - | - | - | 20 | 15 | 10 |
| **Lactose monohydrate** | 52 | 52 | 52 | 52 | 52 | 52 |
| **PVP K30** | 10 | 10 | 10 | 10 | 10 | 10 |
| **Mg. stearate** | 2 | 2 | 2 | 2 | 2 | 2 |
| **Talc** | 1 | 1 | 1 | 1 | 1 | 1 |
| **Total weight** | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 2: Various excipients used in formulations and their compositions ($TSR_7$ to $TSR_{12}$)**

| Ingredients (mg) | $TSR_7$ | $TSR_8$ | $TSR_9$ | $TSR_{10}$ | $TSR_{11}$ | $TSR_{12}$ |
|---|---|---|---|---|---|---|
| **Tropisetron** | 5 | 5 | 5 | 5 | 5 | **5** |
| **HPMC K4M** | 10 | 15 | 20 | - | - | **-** |
| **HPMC K15M** | - | - | - | 10 | 15 | **20** |
| **Eudragit RSPO** | - | - | - | 20 | 15 | **10** |
| **Eudragit RLPO** | 20 | 15 | 10 | - | - | **-** |
| **Lactose monohydrate** | 52 | 52 | 52 | 52 | 52 | **52** |
| **PVP K30** | 20 | 20 | 20 | 20 | 20 | **20** |
| **Mg. stearate** | 2 | 2 | 2 | 2 | 2 | **2** |
| **Talc** | 1 | 1 | 1 | 1 | 1 | **1** |
| **Total weight** | 100 | 100 | 100 | 100 | 100 | **100** |

## 3. EVALUATION

**Drug excipients compatibility studies**

Both Fourier Transform Infrared (FTIR) and Differential Scanning Calorimetric (DSC) analysis were utilized in order to conduct drug excipient compatibility tests.

**Fourier Transform Infrared (FTIR) spectroscopy:**

In order to determine whether or not there was any kind of physical or chemical interaction between the API and the excipients that were integrated into the formulation, a Fourier transform infrared (FTIR) investigation was carried out. In order to accomplish this, the potassium bromide (KBr) pellet method was utilized. For two minutes, the samples were triturated with KBr, and the pellet was formed by setting the pressure to 100 kg/cm$^2$ for the duration of the process. Utilizing a Shimadzu FTIR 8400S, the pellet that was collected was subjected to analysis. Before the examination of the test samples, the KBr background was initially acquired. When it came to the analysis of the medicine and the excipients, the identical processes were carried out again. The FTIR tests of the pure medicine Tropisetron, HPMC, Eudragit, and the improved formulation ($TSR_{12}$) were carried out, and the presence of functional groups was compared through the spectra that were acquired.[10]

**Differential Scanning Calorimetric (DSC) analysis:**

The thermoanalytical technique known as differential scanning calorimetry, or DSC, is a method in which the difference in the amount of heat that is required to raise the temperature of a sample and a reference is measured as a function of temperature. Over the course of the experiment, the temperature of both the sample and the reference is kept at a level that is very close to being identical. An aluminum crucible was hermetically sealed with a hermetically sealed lid, and samples weighing exactly 5 to 6 mg were heated at a steady rate of 10 degrees Celsius per minute over a temperature range of 40 to 300 degrees Celsius. In order to keep the atmosphere inert, nitrogen gas was pumped through the system at a rate of 50 ml per minute. Using a Shimadzu DSC 60 from Japan, a differential scanning calorimetry (DSC) analysis was performed on Tropisetron, HPMC, Eudragit, and a physical mixture of pharmaceuticals with excipients that were utilized for formulations. The purpose of this research was to analyze any potential polymer-drug thermal interaction.[11]

**Evaluation of precompression parameters**
**Angle of Repose (θ)**

The angle of repose is a technique employed to assess the flow characteristics of powder and grains from the hopper to the die cavity during tablet compression. The angle of repose is the angle created between the horizontal base of the bench surface and the edge of a conical pile of grains. The funnel employed was constructed of stainless steel, featuring an orifice diameter of 10 mm and a height of 111 mm from the top of the funnel to the end of the orifice. The funnel was secured 4 cm above the bench surface. Upon constructing the cone from a 5 g sample, the height of the granules comprising the cone (h) and the radius (r) of the base were recorded.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where θ is referred to as the angle of repose, which reflects the flow qualities of granules, and h and r represent the height and radius of the granule heap, respectively. The standards stipulate that an angle of repose value below 25° signifies excellent flow, whereas a number beyond 40° denotes poor flow.[12]

**Bulk density and tapped density**
Bulk density and tapped density are typically assessed for powders and granules to ascertain the compressibility index and Hausner's ratio. The bulk and tapped densities were assessed according to the methodologies specified in the USP. Samples weighing between 9 and 13 grams were transferred through a no. 18 sieve into a pre-weighed 25 ml graduated cylinder marked in 0.5 ml increments. The bulk volume was determined following two manual taps of the cylinder on a flat tabletop surface. The tapped volume was assessed using the Electrolab ETD-1020 Tap Density Tester following increments of 500, 750, and 1250 taps at a rate of 250 drops per minute. To ascertain both the bulk density (BD) and tapped density (TD) of the manufactured Tropisetron sustained release granules across all formulations, the subsequent formulas were employed.[13]

$$BD = \frac{weight\ of\ the\ granule\ taken}{volume\ of\ the\ packing}$$

$$TD = \frac{weight\ of\ the\ granule\ taken}{tapped\ volume\ of\ the\ packing}$$

**Compressibility index (Carr's index):**

The flowability of powder can be assessed by comparing its bulk density (BD) and tapped density (TD), as well as the rate of compaction. Carr's index values between 5-15 signify excellent flow, values between 12-16 denote good flow, values between 33-38 indicate very bad flow, and values over 40 represent extremely poor flow. The compressibility index (Carr's index) of the formulated Tropisetron sustained release granules was determined using the specified formula [14]

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

**Hausner's ratio**
This is an alternative method employed to ascertain the flow parameters of granules and all formulations of the manufactured Tropisetron sustained release granules, determined using the following formula.

$$Hausner's\ ratio = \frac{TD}{BD}$$

Values below 1.25 signify good flow (20% of Carr's index), while values beyond 1.25 denote bad flow (33% of Carr's index). A glidant must be used to enhance flow within the range of 1.25 to 1.5. [15]

**Evaluation of post-compression parameters of Tropisetron SR matrix tablet formulations**
**Average thickness**
The measurement of thickness is a method employed to assess the consistency of the formulation and its physical appearance. The thickness of each tablet was measured using digital Vernier Calipers (Mitutoyo dial thickness gauge, Japan), and the results were presented as mean values of 10 readings, accompanied by standard deviations. From each formulation of Tropisetron

sustained-release pills, ten tablets were randomly selected for the assessment of thickness. The tablet thickness must be regulated within a ± 5% deviation from the standard value as per the specification. [16]

**Tablet hardness**

Tablet hardness testing is a laboratory method employed by the pharmaceutical industry to assess the breaking point and structural integrity of a tablet under conditions of storage, transportation, and handling prior to use. The fracture point of a tablet is determined by its configuration. The hardness of all formulations of the manufactured Tropisetron SR tablets was assessed using a Monsanto hardness tester (Cad Mach). As per USP requirements, hardness values ranging from 4 to 5 kg/cm² are deemed appropriate for SR tablets. The crushing strength of ten SR matrix tablets with specified weights was measured in kg/cm², and the means together with the standard deviation were computed. [17]

**Friability**

Friability refers to the propensity of a tablet to chip, crumble, or fracture during compression. This propensity is often restricted to uncoated tablets and surfaces during manipulation or subsequent storage. In the pharmaceutical sector, friability testing is a standard practice, and the device utilized for this procedure is known as a Friabilator or friability tester. For any compressed uncoated tablet, a friability loss of less than 0.1% to 0.5%, with a maximum of 1% of the tablet weight, is deemed acceptable. Ten tablets (Wi) from each batch of Tropisetron SR were previously weighed using Roche friability (Roche friability, Secor India). Following one hundred revolutions of the friabilator, the tablets were cleaned with a soft cloth to eliminate dust, and the total remaining weight (Wf) was documented. Friability was determined using the subsequent formula. [18]

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

**Weight variation test**

Weight uniformity is an in-process testing criterion that guarantees dose unit consistency during compression. All formulations of Tropisetron SR tablets were evaluated for weight variation in accordance with the USP standard. Twenty tablets from each batch were weighed both collectively and individually utilizing an electronic balance. The mean weight was determined using the percentage fluctuation of each tablet, and the procedure was repeated three times to get the standard deviation. The USP monograph stipulates that the weight variation tolerance limit for uncoated tablets is 10% for an average weight of 130 mg or less, 7.5% for an average weight between 130-324 mg, and 5% for an average weight beyond 324 mg. To be deemed acceptable, the weight of no more than two tablets must differ from the average weight by no more than 7.5%, and no individual tablet may deviate by more than 15%.[19]

**Content uniformity studies**

To ascertain the content uniformity of all formulations of Tropisetron SR tablets, twenty tablets from each batch were triturated to produce a powder. One tablet's equivalent powder was dissolved in 100 cc of HCl buffer at pH 1.2 and heated at 37°C for 60 minutes with continuous stirring. The solution was chilled, filtered, and further diluted, following which the Tropisetron content was quantified using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 234 nm. All measurements were conducted in triplicate, and the mean drug content for each formulation was determined. [20]

**Swelling Index (*SI*)**

The swelling behavior of all formulations of Tropisetron SR tablets was assessed by examining their weight growth in the dissolution medium under investigation. The swelling index was assessed by positioning the tablets in the basket of the dissolution equipment, which contained 100 cc of phosphate buffer at pH 6.8, maintained at a temperature of 37 ± 0.5 °C. At each one-hour interval, up to a total of 12 hours, each dissolution basket containing a tablet was removed, blotted with tissue paper to eliminate excess water, and weighed using an analytical balance (Shimadzu, Ax 120). The experiment was conducted in duplicate for every time point. The swelling index was determined using the subsequent formula: [21]

$$Swelling\ Index\ (SI) = \frac{Wf - Wi}{Wi} \times 100$$

$W_f$ and $W_i$ are wet and dry weights of the tablet respectively.

***In vitro* drug release study**

In vitro release tests were performed for all Tropisetron SR matrix tablet formulations utilizing an eight-station USP dissolving rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India), maintained at 37 ± 0.5 °C. The initial two hours of dissolution were conducted in 900 ml of simulated gastric fluid (SGF, containing 3.2 mg/ml pepsin in 0.05M HCl, pH 1.2), followed by the remaining duration in 900 ml of simulated intestinal fluid (SIF, comprising 10 mg/ml pancreatic fluid in phosphate buffer, pH 6.8). Aliquots were extracted and evaluated for drug concentration at regular one-hour intervals using a UV-visible spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at $\lambda_{max}$ 234 nm for both HCl buffer pH 1.2 and phosphate buffer pH 6.8. Following

each sampling, an equivalent volume of fresh dissolution medium was introduced to the dissolution solution. All dissolution investigations were conducted three times, and the mean and standard deviation were computed. The calculated mean percentage of cumulative medication release was graphed against time. [22]

***In vitro* drug release kinetic studies**

The release rate and mechanism of Tropisetron from the formulated SR tablets were evaluated by using exponential equations to the dissolving data of the improved formulation ($TSR_{12}$).

Zero order release equation is calculated by the following equation.

$$Q = K_0 \, t$$

Where Q is the amount of drug released at time t and $K_0$ is the zero order release rate constant.

The first-order equation is calculated by following the equation.

$$\log(100 - Q) = log100 - \frac{K_1 t}{2.303}$$

Where $K_1$ is the first order release rate constant. When the data are plotted as logarithm of cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first order kinetics. The constant $K_1$ can be obtained by multiplying 2.303 with the slope.

The dissolution data was fitted to the following Higuchi's equation.

$$Q = K_2 t^{1/2}$$

Where $K_2$ is the diffusion rate constant. When the data are plotted as accumulative drug released versus square root of time, it yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to $K_2$.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems.

$$\log\left(M_t/M_\infty\right) = \log K + n \, logt$$

Where *Mt* is the amount of drug released at time *t*, *M*∞ is the amount of drug released after infinite time, K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi-fickian diffusion (If $n = 0.5$ then fickian diffusion and if the value is $0.5 < n < 1$, then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and $n > 1$ non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that the area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where *Wo* is the initial amount of drug, *Wt* is the remaining amount of drug in dosage form at time *t*, and $K_S$ is a constant incorporating the surface volume relation. The graphs are plotted as the cube root of the percent drug remaining versus time. [23]

**Stability studies of optimized formulation**

Stress testing of the active pharmaceutical ingredient can detect potential degradation products, thereby elucidating degradation pathways, assessing the intrinsic stability of the molecule, and validating the efficacy of the analytical methods employed. The selected accelerated condition for the stability research was 40 °C ± 2 °C and 75% ± 5% relative humidity (Climatic Zone III condition for accelerated testing), utilizing the NEC 210R10 humidity control oven (Newtronic Instruments, India) for a duration of 90 days. The tablets from the improved batch ($TSR_{12}$) were enclosed in airtight bottles and underwent accelerated stability testing in accordance with ICH recommendations. The sample was extracted from the humidity control oven on the 30th, 60th, and 90th days for the assessment of physicochemical parameters, including physical appearance, weight fluctuation, hardness, friability, swelling index, drug content, and in vitro drug release characteristics. [24, 25]

## 4. RESULTS AND DISCUSSION:

### 4.1 Drug and Polymers Compatibility Studies

**FTIR Analysis:**

Figures 1 and 2 display the FTIR spectra of Tropisetron in its purest form as well as Tropisetron combined with polymers.

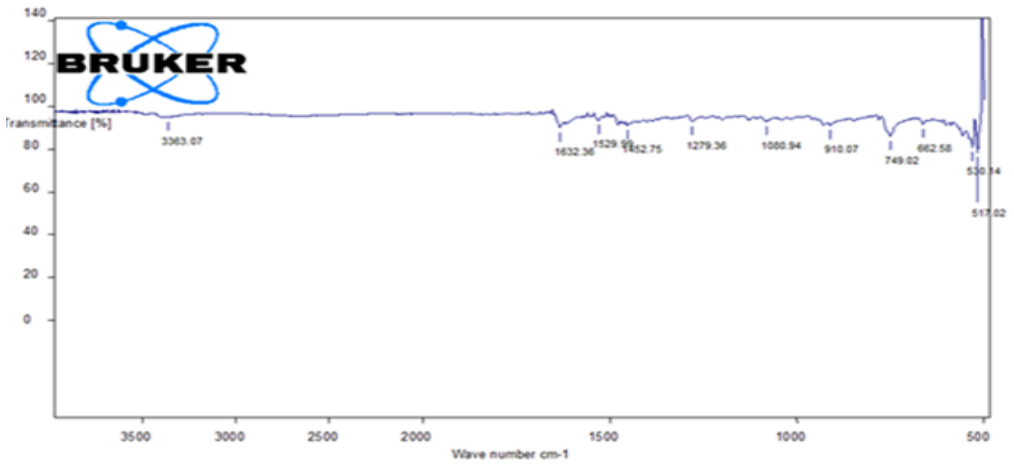


**Fig. 1: A Pure Tropisetron Drug's FTIR Spectra**

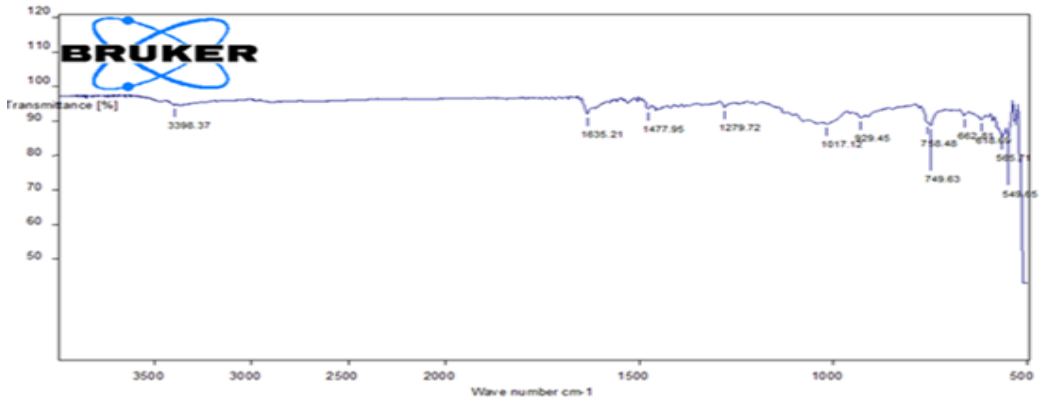


**Fig. 2: Tropisetron FTIR Spectra with Polymers**

To ascertain the compatibilities of the drug and polymers utilized in the various formulations of Tropisetron SR tablets, FTIR spectra of the pure drug and the physical mixture of the drug and polymer employed in the formulations were acquired. The aforementioned experiments revealed that there was no displacement of the principal peaks, indicating the absence of interaction between Tropisetron and the various components utilized in the formulation of distinct preparations. Consequently, the medication and excipients exhibit compatibility, facilitating the formation of stable formulations under investigation.

**DSC Analysis:**

Figure 3 & 4 DSC thermogram of Tropisetron pure Drug and physical mixture of excipients and the Tropisetron pure API used for preparation of SR tablets.

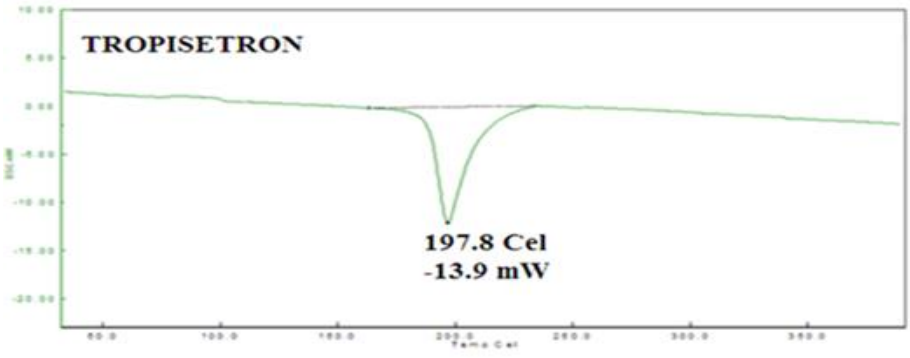


**Fig. 3: DSC thermogram of Tropisetron Pure Drug**

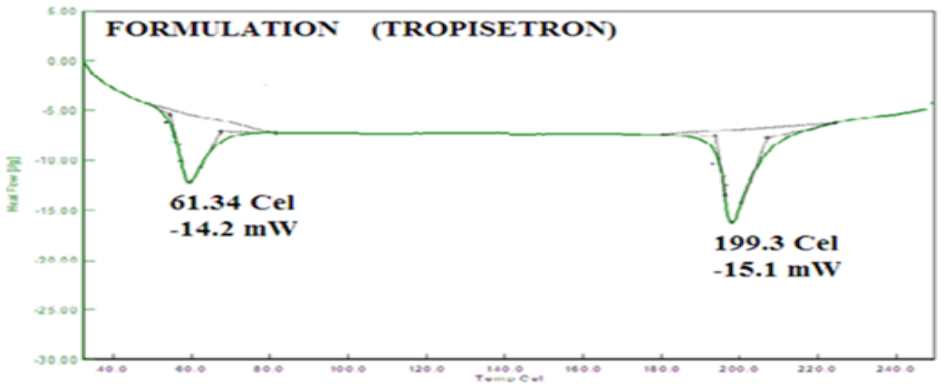


**Fig. 4: DSC thermogram of Tropisetron with polymers**

The DSC thermogram of pure Tropisetron and the physical mixture of the polymer utilized in the optimized formulation revealed an endothermic peak between 197.8 °C and 199.3 °C, indicating that the physical mixture of the optimized formulation is thermodynamically stable due to the incorporation of Tropisetron. The DSC measurements indicated that the formulation is thermodynamically stable, although it necessitated slightly more heat than the pure drug due to the presence of several excipients with the medication. No transition of peaks from endothermic to exothermic was observed. Figures 4.5 and 4.6 illustrate the DSC thermogram of Tropisetron and the physical mixture of the polymer utilized for the optimum formulation.

**Pre-compression Parameters**

Precompression factors, including bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose, were assessed to elucidate the flow properties of granules for the facilitation of tablet formulation production. This illustrated the granules' efficient packing capability. The density of granules is determined by particle packing and fluctuates when the granules consolidate, according to studies of bulk and tapped densities. When Carr's index is below 16%, it generally indicates that all formulations possess satisfactory flow characteristics. Elevated Carr's index values may be ascribed to formulations including a greater proportion of fine particles and heterogeneous particle sizes. A rapid and straightforward method to assess the flow characteristics and evaluate the cohesiveness of a granule column is to utilize the Hausner ratio. Hausner's ratios for all Tropisetron SR tablet formulations were low, indicating excellent granule flowability. Granules with a Hausner's ratio below 1.25 demonstrate superior flow qualities, which was true for all formulations of Tropisetron SR granules examined. The pertinent phenomenon for evaluating the flow characteristics of particles over 150 micrometers is the angle of repose. Angles of repose of 25° indicate that the material is flowing freely, whereas 40° implies that the material is not flowing effectively. All formulations exhibited angles of repose below 25°. The granules for the Tropisetron SR tablet demonstrated outstanding flow properties and were effective for tablet compression. Table 3 presents the precompression parameter outcomes for all formulations of Tropisetron sustained-release tablets.

**Table 3: Result of precompression parameters of Tropisetron SR granules**

| F. No. | Bulk density (gm/cc) | Tapped density (gm/cc) | Angle of repose | Carr's index | Hausner's ratio |
|---|---|---|---|---|---|
| $TSR_1$ | 0.341±0.01 | 0.390±0.02 | 21.34±0.12 | 12.974 | 1.14 |
| $TSR_2$ | 0.373±0.02 | 0.411±0.02 | 22.73±0.10 | 09.704 | 1.12 |
| $TSR_3$ | 0.382±0.02 | 0.426±0.02 | 20.42±0.24 | 10.521 | 1.10 |
| $TSR_4$ | 0.387±0.02 | 0.433±0.01 | 22.61±0.16 | 10.822 | 1.11 |
| $TSR_5$ | 0.332±0.01 | 0.371±0.02 | 22.67±0.12 | 09.947 | 1.12 |
| $TSR_6$ | 0.371±0.02 | 0.416±0.03 | 19.35±0.13 | 11.265 | 1.11 |
| $TSR_7$ | 0.363±0.02 | 0.401±0.02 | 21.50±0.15 | 09.940 | 1.12 |
| $TSR_8$ | 0.342±0.01 | 0.387±0.01 | 23.41±0.12 | 11.564 | 1.12 |
| $TSR_9$ | 0.351±0.02 | 0.403±0.03 | 22.43±0.13 | 13.071 | 1.14 |
| $TSR_{10}$ | 0.373±0.02 | 0.422±0.02 | 21.41±0.11 | 11.120 | 1.12 |
| $TSR_{11}$ | 0.382±0.01 | 0.427±0.01 | 20.52±0.12 | 10.467 | 1.13 |
| $TSR_{12}$ | 0.363±0.02 | 0.394±0.02 | 21.36±0.12 | 08.830 | 1.11 |

**All values are expressed as mean± SD; (n=3)**

**Post-Compression parameters:**

All physical characteristics of the Tropisetron SR matrix tablets were considered satisfactory. All tablets from the formulations exhibited a consistent, white, circular shape and a smooth surface morphology. There were no symptoms of the typical tablet anomalies such as capping, picking, or chipping. The average thickness of all Tropisetron SR matrix tablet formulations ranged from 3.21±0.13 mm to 3.78±0.12 mm. The deviations from the mean value were approximately 5% and within permissible limits. The granule flow, applied force, and granule depth fill within the die cavity remained similar during the tablet production process, as seen by the uniform tablet thickness. The weight fluctuation range for different formulations was 3.39±0.34% to 3.80±0.31%. All formulations fall within the permissible 5% range for the standard percentage variation of tablet formulations weighing 100mg. The average percentage variation of all pill formulations was determined within the specified dates. Consequently, all formulations conformed to the regulatory standard for weight uniformity by successfully completing the test. The weight variation tolerance limit shown consistency in tablet compression, hence ensuring uniform medicinal content across all formulations within the specified limits. The tablets must be robust to withstand harm from transportation. The hardness of all Tropisetron SR tablet formulations varied from 5.23±0.1 to 5.78±0.2 kg/cm², indicating excellent handling and transportation characteristics. Increased homogeneity in the compression force applied during tablet punching is indicated by reduced variability in tablet hardness. The percentage of losses that occur during packaging and shipment is commonly measured using the physical condition of a tablet known as friability. The range of all formulas' percentage friability was 0.66±0.03% to 0.57±0.02%. The percentage of friability in the current studies was within the permitted levels for all formulations, suggesting that the product is resistant to harm from handling and transportation. To keep the formulations' bioequivalency, tablets' medication contents must be consistent from one to the next. The drug content percentages for the formulation of Tropisetron SR tablets ranged from 98.42±1.1% to 101.62±1.1%, exhibiting a variation of 4%, which was within acceptable limits. The value ensures even distribution of the tablet's pharmaceutical substance. Table 4 enumerates the physicochemical characteristics of the several Tropisetron SR tablet formulations.

**Table 4: Evaluation of post-compression parameters of Tropisetron sustained release matrix tablets**

| F. No. | Hardness ($kg/cm^2$) | Weight Variation (%) | friability (% w/w) | Thickness (mm) | Content uniformity (%) |
|---|---|---|---|---|---|
| $TSR_1$ | 5.23±0.1 | 3.42±0.32 | 0.66±0.03 | 3.42±0.10 | 99.50±1.0 |
| $TSR_2$ | 5.44±0.2 | 3.67±0.23 | 0.60±0.02 | 3.35±0.12 | 98.42±1.1 |
| $TSR_3$ | 5.51±0.2 | 3.48±0.26 | 0.59±0.01 | 3.28±0.11 | 101.60±1.2 |
| $TSR_4$ | 5.47±0.1 | 3.55±0.25 | 0.64±0.02 | 3.38±0.12 | 99.42±1.2 |
| $TSR_5$ | 5.78±0.2 | 3.63±0.33 | 0.62±0.02 | 3.40±0.13 | 98.61±1.1 |
| $TSR_6$ | 5.50±0.2 | 3.58±0.52 | 0.57±0.02 | 3.39±0.11 | 100.56±1.2 |
| $TSR_7$ | 5.30±0.1 | 3.37±0.35 | 0.64±0.01 | 3.35±0.14 | 99.72±1.1 |
| $TSR_8$ | 5.42±0.2 | 3.80±0.31 | 0.57±0.02 | 3.78±0.12 | 98.50±1.2 |
| $TSR_9$ | 5.35±0.2 | 3.39±0.34 | 0.60±0.02 | 3.56±0.12 | 99.81±1.1 |
| $TSR_{10}$ | 5.46±0.3 | 3.60±0.20 | 0.62±0.01 | 3.21±0.13 | 98.63±1.2 |
| $TSR_{11}$ | 5.57±0.2 | 3.55±0.34 | 0.57±0.02 | 3.65±0.10 | 99.82±1.3 |
| $TSR_{12}$ | 5.38±0.2 | 3.67±0.24 | 0.62±0.02 | 3.30±0.11 | 101.62±1.1 |

**All values are expressed as mean± SD; (n=3)**

**Swelling study**

The swelling index of any matrix type-controlled release formulation, which defines the medication's release from a controlled dose form, is a critical physical feature. An elevated swelling index often signifies that the drug was released from the matrix formulation by diffusion over an extended duration. A swelling study was undertaken for all Tropisetron SR matrix tablet formulations ($TSR_1$ to $TSR_{12}$) over a duration of 12 hours. Formulations with elevated concentrations of HPMC K4M and HPMC K15M exhibited larger swelling indices due to the polymers' enhanced hydrophilicity, which facilitated greater water absorption. Conversely, formulations containing elevated proportions of Eudragit RSPO and RLPO, being hydrophobic

polymers, have the contrary effect. A swelling research was undertaken for all Tropisetron SR matrix tablet formulations ($TSR_1$ to $TSR_{12}$) over a duration of 12 hours. Formulations with elevated concentrations of HPMC K4M and HPMC K15M exhibited larger swelling indices due to the polymers' enhanced hydrophilicity, which resulted in greater water absorption. Conversely, formulations with elevated concentrations of Eudragit RSPO and RLPO, being hydrophobic polymers, exhibit the opposite effect. Although the formulations containing solely HPMC of various grades exhibited a superior swelling index compared to other formulations, the peak swelling did not occur within 9 to 10 hours. Hydrophobic polymers such as Eudragit RSPO and RLPO were required to preserve the swelling characteristics for a duration of up to 12 hours. The formulations that incorporated both HPMC grades in an equal ratio exhibited an enhanced swelling index. $TSR_{12}$, including 20% HPMC K15M and 10% Eudragit RSPO, had superior performance in swelling index compared to all other formulations. Formulations $TSR_1$, $TSR_4$, $TSR_7$, and $TSR_{10}$, which contain higher percentages of the hydrophobic polymer Eudragit, exhibited reduced swelling indices compared to other formulations. Figures 5 to 8 illustrate histograms of the swelling indices with time for all formulations of Tropisetron sustained-release matrix tablets.

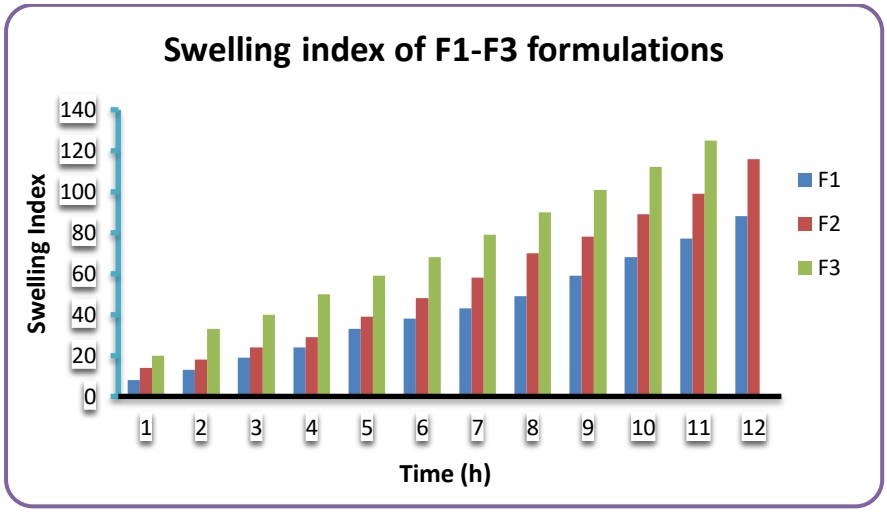


**Fig. 5: Histogram displaying the swelling index for the formulations of Tropisetron SR tablets ($TSR_1$ to $TSR_3$)**

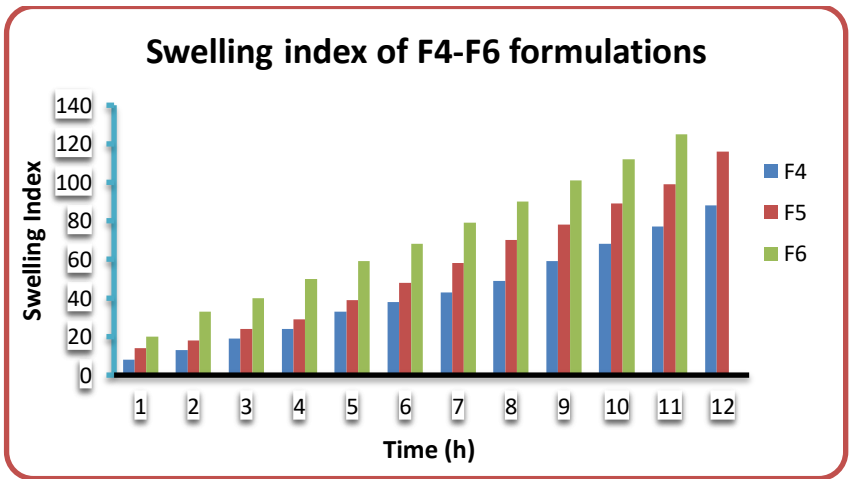


**Fig. 6: Histogram displaying the swelling index for the formulations of Tropisetron SR tablets ($TSR_4$ to $TSR_6$)**

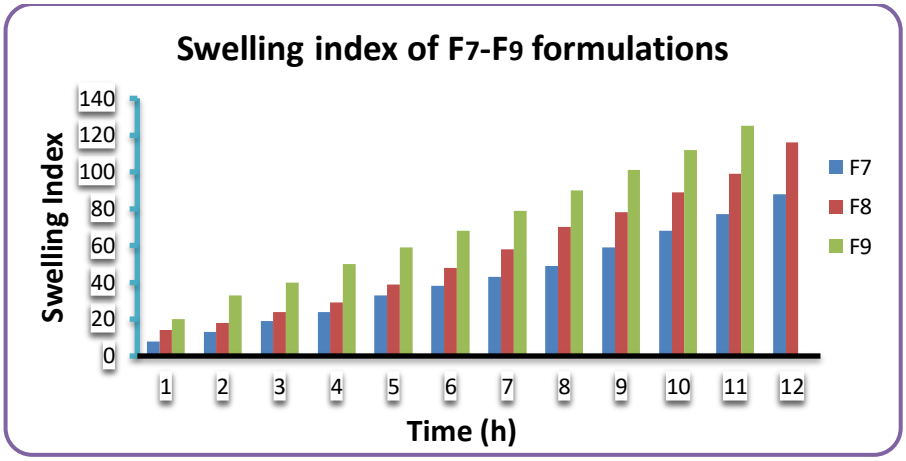


**Fig. 7: Histogram displaying the swelling index for the formulations of Tropisetron SR tablets ($TSR_7$ to $TSR_9$)**

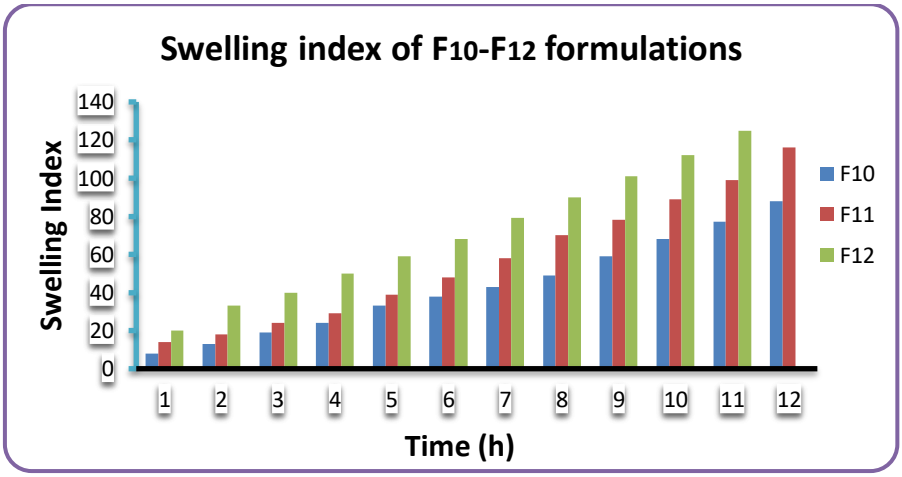


**Fig. 8: Histogram displaying the swelling index for the formulations of Tropisetron SR tablets ($TSR_{10}$ to $TSR_{12}$)**

***In vitro* drug release profile**

The dissolution studies for all Tropisetron SR matrix tablets were conducted for the initial two hours in HCl buffer at pH 1.2, followed by a replacement with phosphate buffer at pH 6.8 for the subsequent ten hours, as the formulations were intended to remain in the gastric environment for the first two hours and in the intestinal environment for the next ten hours. To optimize the in vitro drug release profile of Tropisetron SR matrix tablets, HPMC K4M, HPMC K15M, Eudragit RSPO, and Eudragit RLPO hydrophobic matrix polymers were employed to create twelve distinct formulations. Formulations $TSR_1$ to $TSR_{12}$ contain various grades of HPMC and Eudragit as polymers. HPMC K15M exhibits a higher viscosity grade than HPMC K4M, resulting in a more controlled release profile when comparing the two HPMC grades utilized. The drug's greatest release occurred over 8–9 hours due to its hydrophilic nature, with the HPMC polymer solely responsible for the first burst release. An additional hydrophobic polymer, Eudragit, was incorporated into the formulations to mitigate the initial burst release. Eudragit RSPO had a more pronounced sustained release effect compared to Eudragit RLPO. The formulation $TSR_{12}$, including 20% HPMC K15M and 10% Eudragit RSPO, was selected as the optimal formulation due to its initial release of 15.42% and its capacity to release up to 99.50% of the medication within 12 hours. The concentration of Eudragit grew despite the initial release rate being far slower than anticipated. It was considered that 10% of Eudragit was optimal. The drug release characteristics of several Tropisetron SR tablet formulations are illustrated in plots showing the proportion of controlled drug release over time, as presented in figures 9 to 12.

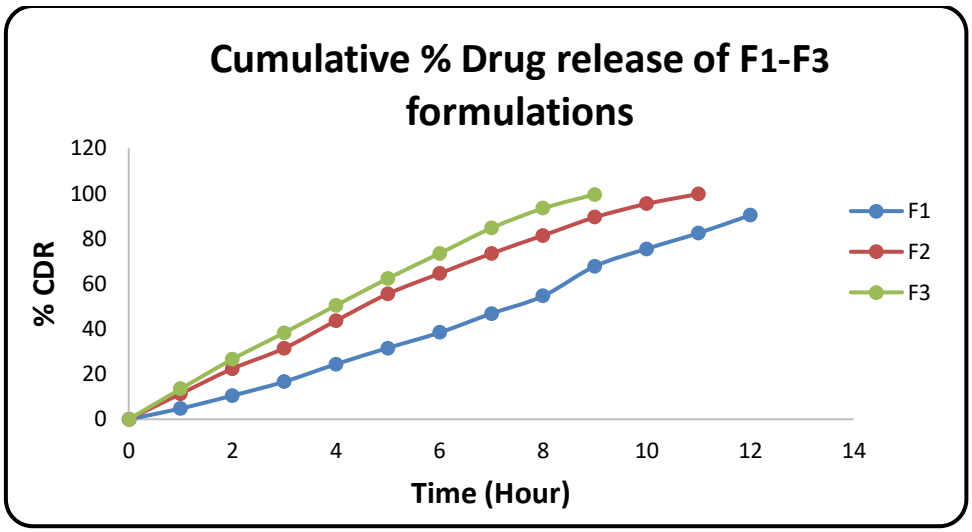


**Fig. 9: Study of the Tropisetron SR formulations' *in vitro* release $TSR_1$ to $TSR_3$**

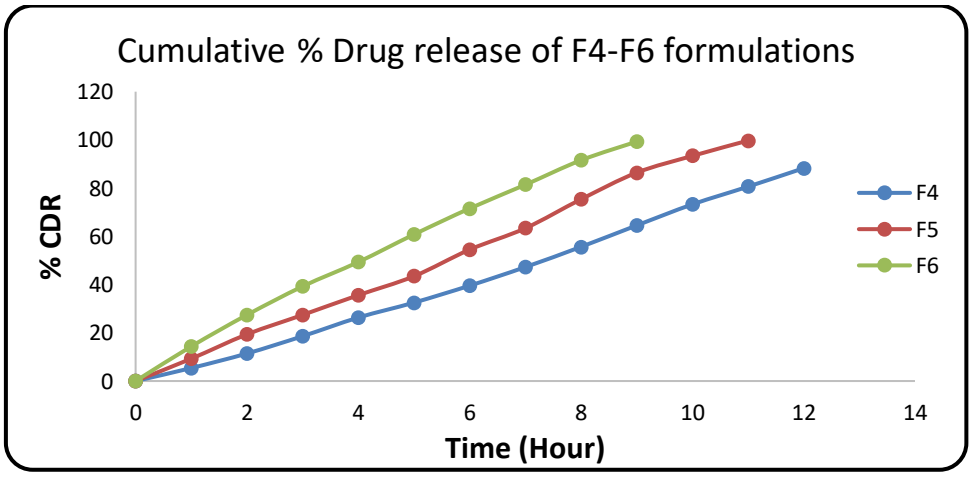


**Fig. 10: Study of the Tropisetron SR formulations' *in vitro* release $TSR_4$ to $TSR_6$**

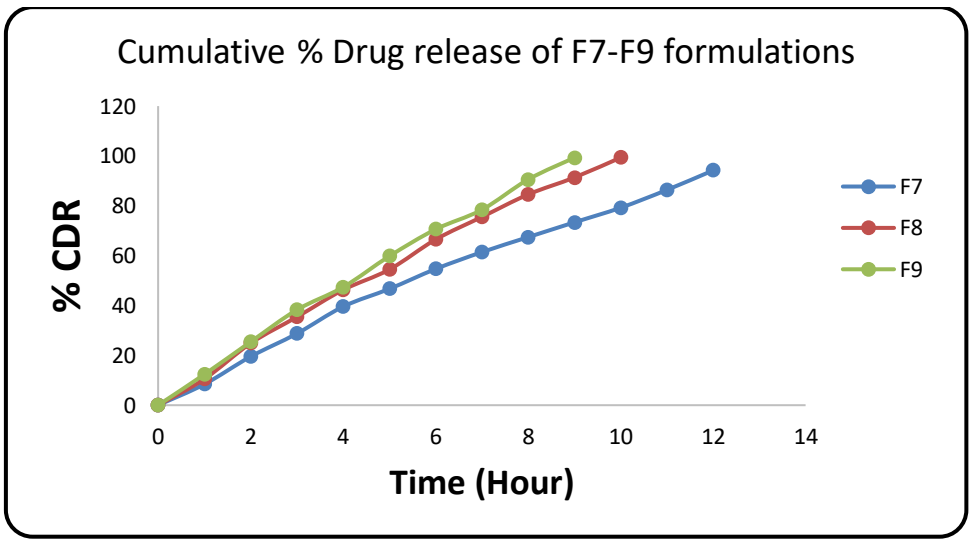


**Fig. 11: Tropisetron SR formulations TSR7 to TSR9 *in vitro* release studies**

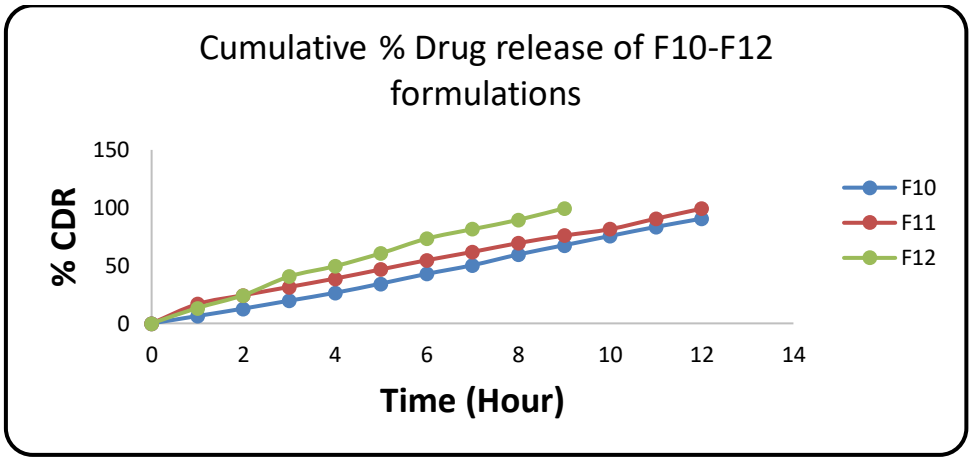


**Fig. 12: Tropisetron SR formulations $TSR_{10}$ to $TSR_{12}$ *in vitro* release studies**

***In vitro* dissolution kinetic studies**

The in vitro dissolving data of the optimized formulation $TSR_{12}$ were analyzed using several kinetic models, including the graphical representations and equations for Peppa's zero-order, first-order, Higuchi, Hixon-Crowell, and Korsmeyer models (Figures 13 to 17). The greatest regression score of 0.9934 in the zero-order release plot indicates a relatively linear relationship. In the optimized formulation $TSR_{12}$, the release exponent 'n' was determined to be 0.7320 ($0.5 < n < 1$), suggesting an anomalous diffusion linked to erosion. Consequently, zero-order release kinetic models were employed in this study's in vitro drug release kinetics of the optimized formulation of Tropisetron SR matrix tablets ($TSR_{12}$), indicating that the drug release mechanism involves anomalous diffusion along with erosion.

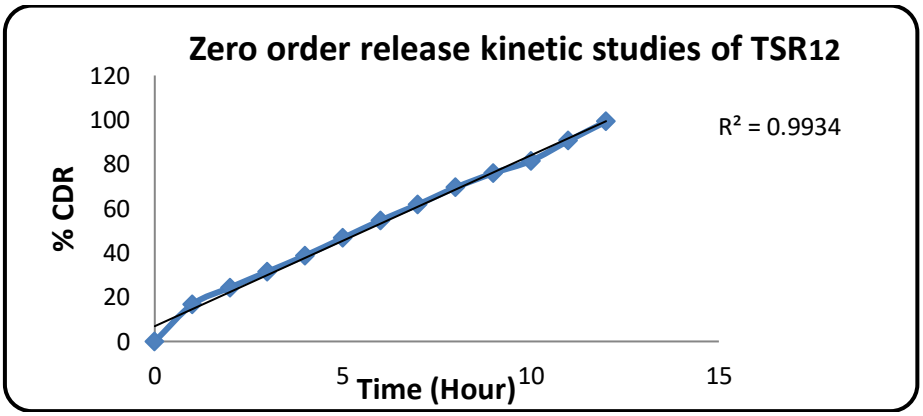


**Fig. 13: Zero-order release kinetic plot of ($TSR_{12}$)**

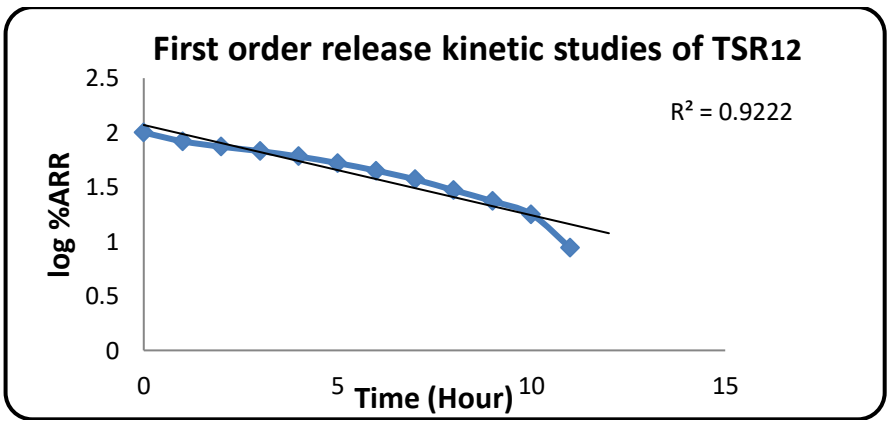


**Fig. 14: First-order release kinetic plot of ($TSR_{12}$)**

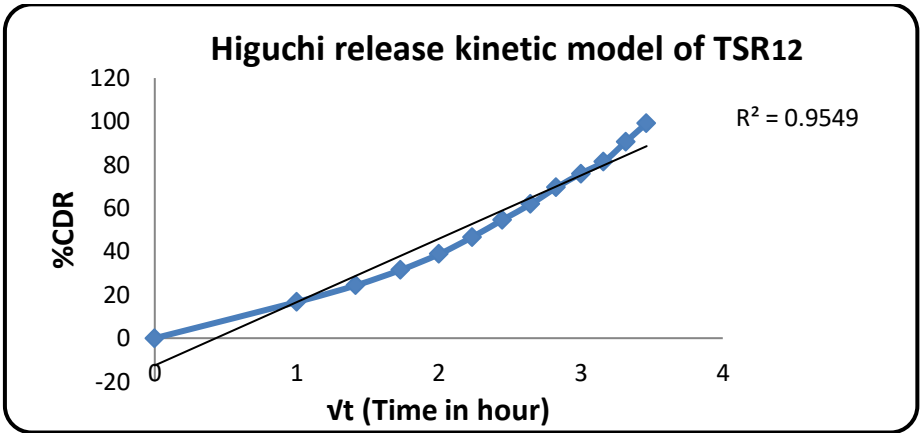


**Fig. 15: Higuchi release kinetic graph of ($TSR_{12}$)**

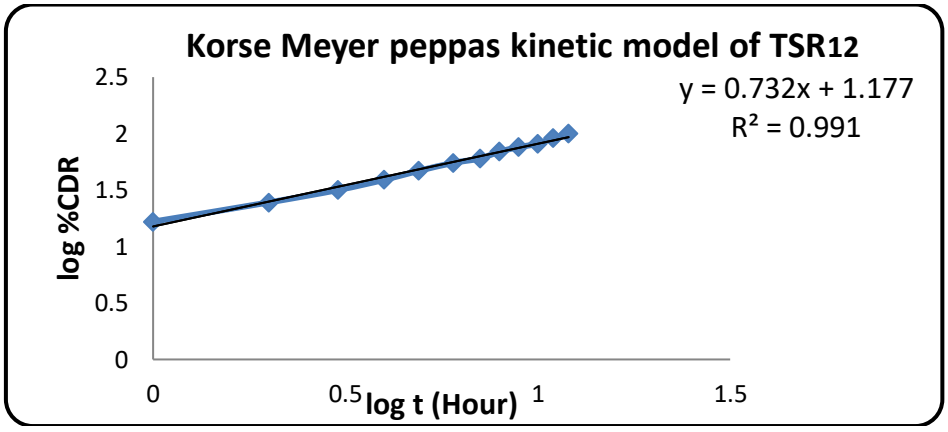


**Table 16: Peppas release kinetic plot of ($TSR_{12}$)**

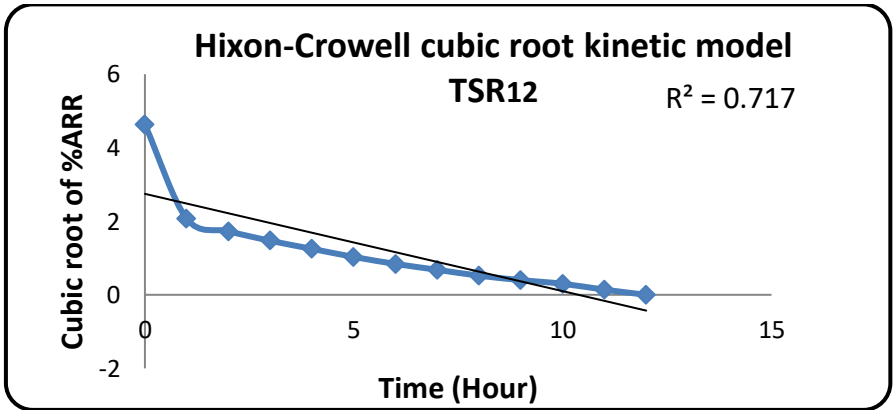


**Table 17: Hixon Crowell release kinetic plot of ($TSR_{12}$)**

**Table 5: Regression values of *in-vitro* release kinetic study of optimized Tropisetron SR matrix tablet ($TSR_{12}$)**

| Formulation | Zero order ($R^2$value) | 1st order ($R^2$value) | Higuchi model ($R^2$value) | Hixon-Crowell model ($R^2$value) | Peppa's model ($R^2$value) | Peppa's model ('n' value) |
|---|---|---|---|---|---|---|
| **$TSR_{12}$** | 0.9931 | 0.9220 | 0.9541 | 0.7170 | 0.9910 | 0.7321 |

**Accelerated stability studies**

Accelerated stability tests are a technique that assesses the stability of a dosage form within a brief timeframe, even under challenging temperature and humidity circumstances. Following the submission of the optimized formulations of Tropisetron SR tablets ($TSR_{12}$) to accelerated stress conditions for ninety days, samples were subsequently extracted and assessed for several physicochemical properties. The metrics encompassed hardness, weight variation, friability, content homogeneity, swelling investigations, and in vitro drug release properties. All tablets produced with optimal formulas exhibited heightened friability, hardness, and weight fluctuation, accompanied by diminished drug content and swelling index values. It was determined that none of the physicochemical parameters underwent considerable alteration, and any changes that did occur remained within the permissible range. The medicine's composition was examined, and in vitro dissolution experiments were conducted over ninety days; the results indicated that over ninety percent of the drug was preserved. The stability investigations indicate that the tested sustained-release formulations of Tropisetron are stable for a minimum of two years. Table 6 presents the outcomes of diverse physicochemical properties evaluated at different time intervals during stress testing of the optimal Tropisetron sustained-release tablet formulations. Figure 18 illustrates the drug release profile, depicting cumulative drug release (CDR) over time at different intervals under accelerated stress conditions.

**Table 6: Comparative physicochemical characterization of optimized batch at accelerated conditions (40 º C ± 2 º C/ 75% ± 5% RH)**

| Sl. No. | Tablet Properties | Initial | 30 days after | Within 60 days | Within 90 days |
|---|---|---|---|---|---|
| **1** | **Physical Surfacing** | A smooth, concave surface that is pale white and free of fractures | No Change | No Change | No Change |
| **2** | **Weight variation** | 3.67±0.24 | 3.72±0.27 | 3.88±0.52 | 3.95±0.41 |
| **3** | **Hardness** | 5.38±0.2 | 5.16±0.3 | 4.96±0.2 | 4.90±0.4 |
| **4** | **Friability** | 0.62±0.02 | 0.65±0.04 | 0.69±0.03 | 0.74±0.04 |
| **5** | **Swelling index** | 125.6±1.2 | 115±1.3 | 108±1.2 | 101±1.1 |
| **6** | **Drug content** | 101.62±1.1 | 99.05±1.6 | 97.44±1.2 | 94.78±1.1 |

**All values are expressed as mean± SD; (n=3)**

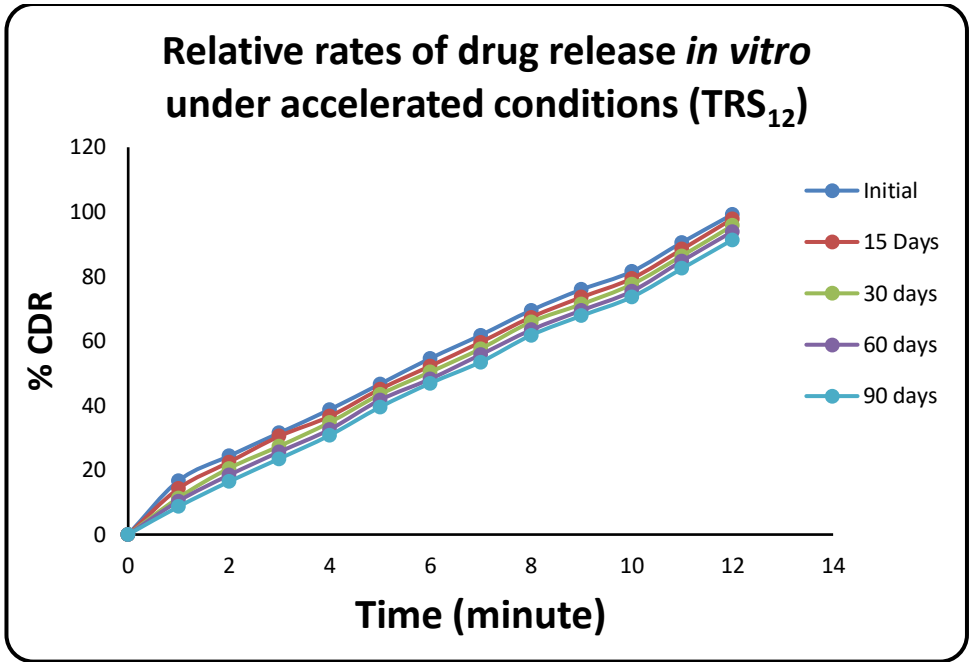


**Fig. 18: The dissolution profile of ($TSR_{12}$) *in vitro* under accelerated circumstances was compared and analyzed (40 ° C ± 2 ° C/ 75% ± 5% RH)**

## 5. CONCLUSION:

Tropisetron is a serotonin 5-HT3 receptor antagonist mostly employed as an antiemetic to alleviate nausea and vomiting post-chemotherapy, while it has been experimentally utilized as an analgesic for fibromyalgia. To reduce once daily dosage and to increase patient compliance, it was decided to formulate once-daily sustained-release tablet of Tropisetron that can be useful for better control of nausea and vomiting post-chemotherapy. Tropisetron is a component of the BCS categorization system's first class and is soluble in water. Because of the rapid diffusion of the dissolved drug via the hydrophilic gel network as well as an initial burst release of medications, the drug release over an extended period employing a hydrophilic matrix system is restricted. This is especially true for highly water-soluble substances. The purpose of this work was to assess and develop sustained released Tropisetron matrix tablets by using hydrophilic synthetic polymers such as hydroxyl propyl methyl cellulose (HPMC K4M & HPMC K15M) and hydrophobic synthetic polymers such as Eudragit RSPO and RLPO. Studies using FTIR and DSC have been carried out to ensure that pharmaceuticals and polymers are chemically, thermally, and physically compatible with one another. The Tropisetron SR tablet was successfully developed in the present study after formulation design and performing pre-compression and post-compression parameters according to specifications. The Tropisetron SR tablet system thus has a promising future as an alternative to the already marketed conventional, as shown by the results of the current study. To evaluate the effectiveness of this formulation useful for better control of nausea and vomiting post-chemotherapy, additional clinical studies are necessary.

**ACKNOWLEDGMENT**

The authors are thankful to Sunshine Laboratories in Mumbai, India and Glenmark Pharma, Nasik, India for providing gift samples of drug and polymer respectively. Authors are also thankful to the chairman & Principal Anwarul Uloom college of Pharmacy, Hyderabad, Telangana, for permitting to carry out research work.

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