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DEVELOPMENT AND EVALUATION OF GRANISETRON TRANSDERMAL PATCHES FOR SUPPORTIVE THERAPY OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

The study was designed to fabricate transdermal patches of Granisetron hydrochloride for curbing the chemotherapy induced nausea and vomiting and also evaluated the physicochemical properties and performance of transdermal patches of Granisetron hydrochloride. The formulations were assessed for thickness, folding endurance, content uniformity, weight, surface pH, percentage flatness, percentage elongation, moisture content, moisture uptake, and swelling index. Thickness ranged from 0.231 ± 0.004 mm to 0.393 ± 0.011 mm, affecting drug-loading capacity and flexibility. Folding endurance varied significantly, with TPF4 showing the highest flexibility and durability. All formulations demonstrated high content uniformity, ensuring consistent drug delivery. The surface pH values were close to the skin's natural pH, indicating good tolerance. High flatness values suggested that the patches maintained their shape well. TPF6 exhibited the highest elongation,

providing superior flexibility. Moisture content and uptake influenced stability and drug release, with TPF4 showing the highest values. Swelling studies revealed varying fluid absorption rates, impacting drug release and patch performance. Overall, TPF4 and TPF6 were identified as promising formulations, balancing drug delivery efficacy, flexibility, and stability. Further in vivo studies are recommended to confirm these findings and optimize the formulations for clinical use.

Keywords: Granisetron hydrochloride, Chemotherapy induced nausea and vomiting, Transdermal patch, Polyvinyl alcohol

INTRODUCTION

Transdermal patches are an innovative drug delivery system designed to administer medications through the skin, directly into the bloodstream. This method offers several advantages over traditional oral or injectable routes. One of the primary benefits is the ability to provide a controlled release of the drug over an extended period, which helps maintain consistent therapeutic levels in the body (Dhiman et al., 2011; Pastore et al., 2015). This can enhance the efficacy of the treatment and improve patient compliance, as patches are often more convenient and less invasive than frequent oral doses or injections. Transdermal patches are particularly valuable for medications that require steady plasma levels to be effective or for drugs that have a narrow therapeutic window. They bypass the gastrointestinal tract, avoiding issues related to oral administration such as gastrointestinal irritation, first-pass metabolism in the liver, and variable absorption rates. This can lead to improved bioavailability and a reduction in side effects (Dhiman et al., 2011). The need for transdermal patches is growing, driven by the demand for more patient-friendly drug delivery systems and advancements in patch technology. They are used in various therapeutic areas, including pain management, hormone replacement therapy, nicotine addiction, and chronic conditions like hypertension and heart disease. By providing a non-invasive, efficient, and patient-centric method of drug administration, transdermal patches address many of the limitations associated with conventional drug delivery methods and represent a significant advancement in pharmaceutical technology (Al Hanbali et al., 2019).

The fabrication of a Granisetron transdermal patch is driven by the need for a more efficient and patient-friendly method of delivering this antiemetic medication. Granisetron is primarily used to prevent nausea and vomiting associated with chemotherapy, radiation therapy, and surgery. Traditional oral or intravenous administration of Granisetron poses several challenges, including the need for frequent dosing, first-pass metabolism, and variable absorption rates, which can affect its efficacy and patient compliance (Kalia et al., 2016; Nagendrakumar et al., 2010; Rathore et al., 2019).

A transdermal patch offers a solution by providing a controlled and sustained release of Granisetron, maintaining steady plasma levels over an extended period. This continuous drug delivery is crucial for managing symptoms consistently, especially in patients undergoing chemotherapy, where nausea and vomiting can be severe and persistent (Ahmed et al., 2014). By bypassing the gastrointestinal tract, the transdermal route avoids the issues of gastric irritation and first-pass metabolism, enhancing the drug's bioavailability and reducing side effects (Nagendrakumar et al., 2010). Moreover, a transdermal patch is non-invasive and

convenient, improving patient adherence to the treatment regimen. It eliminates the discomfort and inconvenience associated with repeated injections or the need to take multiple daily oral doses. This method can significantly enhance the quality of life for patients, providing a reliable and effective means of controlling nausea and vomiting. Thus, the development of a Granisetron transdermal patch represents a significant advancement in supportive care for cancer patients and others suffering from severe nausea and vomiting (Ahmed et al., 2014; Nagendrakumar et al., 2010). Therefore, this present study aimed to design and fabricate the transdermal patches of Granisetron hydrochloride for sustained delivery to support the cancer patients suffering from nausea and vomiting.

MATERIALS AND METHODS

Materials

Granisetron was received from Tesmed Lab Pvt. Ltd. in Baddi, Himachal Pradesh, India, as a gift sample. We bought sodium hydroxide, potassium dihydrogen phosphate, and PVA from Loba Chemie Pvt Ltd, Mumbai, India. The supplier of the HPMC E5 was Sigma Aldrich in Mumbai. We bought PVP, Methanol, Dibutyl Phthalate, Chloroform, and DMSO from Research-Lab Fine Chem Industries in Mumbai. The supplier of Eudragit L100 was from Himedia, India. The analytical grades comprised all other reagents.

Setting up the backing membrane

In order to create the backing membrane, 4% w/v polyvinyl alcohol (PVA) was dissolved in water. A homogeneous solution was created by continuously stirring and briefly heating the mixture to 60 °C for a few seconds after adding 4 grammes of PVA to 100 millilitres of warm, distilled water. After that, 15 millilitres of the uniform solution were transferred into 63.5 cm2 glass Petri dishes, and they were left to dry for six hours at 60 degrees Celsius in a hot air oven (Mehdizadeh et al., 2004; Mukherjee et al., 2006).

Preparation of placebo films

Using a hit-and-trial approach, different hydrophilic and hydrophobic polymer combinations were used to create the varied placebo films (Chandrashekar & Rani, 2008). The polymeric blends that demonstrated flexible and smooth films were chosen to create the drug-incorporated matrix systems. The solvent evaporation method was used to prepare each film. Different ratios of Hydroxy Propyl Methyl Cellulose (HPMC E5) with Polyvinyl pyrrolidone (PVP), Ethyl cellulose, Eudragit L 100, and Eudragit S100 were used to make the matrix-type transdermal patches containing Granisetron hydrochloride.

Formulation of transdermal patches

Granisetron hydrochloride-containing transdermal films were created using two distinct polymers—HPMC E5: Eudragit L 100 and HPMC E5:PVP K30—and applied to a petri dish by a solvent evaporation technique (Singh & Bali, 2016). The ratios of polymer to polymer and drug were set at 1:1, 1:2, and 2:1, respectively. All six formulations employed three distinct concentrations of HPMC E5, and each of the other two polymers, PVP K30 and Eudragit L100, was used in each of the three formulations at a different concentration (table 1). Propylene glycol and N-dibutyl phthalate were employed as plasticisers. In each formulation, 1% DMSO was utilised as a permeation enhancer (Prabhakara et al., 2010).

Table 1: Formulation Details of Granisetron hydrochloride Transdermal Films

	Formulations					
Ingredients	**TPF1**	**TPF2**	**TPF3**	**TPF4**	**TPF5**	**TPF6**
Granisetron hydrochloride (mg)	21.7	21.7	21.7	21.7	21.7	21.7
HPMC (E5) (mg)	250	150	350	250	150	350
PVP K 30 (mg)	250	400	200	-	-	-
Eudragit L 100 (mg)	-	-	-	250	350	150
Ethanol (ml)	9	9	9	9	9	9
Chloroform: Methanol (1:1) (ml)	-	-	-	6	6	6
n-Dibutyl Phthalate (ml)	9	9	9	9	9	9
Propylene glycol (ml)	0.6	0.6	0.6	0.6	0.6	0.6
DMSO (ml)	0.1	0.1	0.1	0.1	0.1	0.1

(All quantities are in mg/ml)

In order to create a transparent solution, the polymers were precisely weighed, dissolved in 10 millilitres of ethanol, and, in the case of Eudragit L 100, a chloroform:methanol (1:1) solution was also utilised. The medication Granisetron hydrochloride was dissolved in the aforementioned mixture and stirred until a clear solution formed. Next, the formulation was gradually supplemented with the plasticiser and permeation enhancers, mixing them thoroughly. After a 24-hour room temperature drying period and glycerin lubrication, the homogeneous solution was transferred to a petri plate. The petri dish was covered with an inverted funnel to stop the solvent from evaporating too quickly. The dried patches were removed after 24 hours and kept in a desiccator for additional research (Shivaraj et al., 2010).

Evaluation of transdermal patches

Folding endurance

Folding endurance is a critical measure of the mechanical strength and flexibility of transdermal films, which reflects their ability to withstand repeated folding without breaking. This parameter is essential for evaluating the durability and usability of transdermal patches, as these patches must maintain their integrity and functionality throughout their application period. To determine folding endurance, a specific section of the transdermal film, consistently measuring 2 cm by 2 cm, is carefully cut from the larger patch. This ensures uniformity in testing and allows for accurate comparisons between different formulations or batches. The cut strip is then subjected to repeated folding at the same spot, involving folding the film back and forth along the same line while applying consistent pressure each time. The folding is performed manually or using a machine designed to replicate the folding motion, ensuring that each fold is uniform in terms of angle and pressure applied. The number of folds is carefully counted until the film either breaks or develops noticeable cracks, which are considered signs of mechanical failure indicating that the film has reached its limit of flexibility. The folding endurance value is determined by the total number of folds the film can withstand before breaking or showing significant cracks, serving as an important indicator of the film's

durability.

Folding endurance provides valuable insights into the mechanical robustness of the transdermal patch. A higher folding endurance value indicates that the film can withstand repeated mechanical stress, making it more durable and reliable during application. This parameter also reflects the flexibility of the film, as flexible films are less likely to crack or break when subjected to movements and handling by the user, ensuring consistent drug delivery throughout the intended period of use. As a critical quality control measure in the manufacturing of transdermal patches, folding endurance helps identify potential issues related to film formulation, such as the choice of polymers and plasticizers, which directly impact the mechanical properties of the film. Films with high folding endurance are less likely to cause discomfort or fail during use, enhancing patient compliance and satisfaction (Bangale et al., 2010; Keleb et al., 2010).

Tensile strength

Tensile strength is a vital parameter that indicates the mechanical robustness of transdermal patches. It measures the maximum stress the film can withstand while being stretched before breaking. To determine the tensile strength of the patch, a tensiometer (Erection and Instrumentation, Ahmedabad) was utilized. This device consists of two load cell grips: the upper grip is movable, while the lower one is fixed. A film strip measuring 2 cm by 2 cm was carefully positioned between the cell grips. Once securely in place, force was gradually applied through the movable upper grip. This force was steadily increased until the film snapped. The tensile strength was then calculated using the dial reading from the tensiometer, which is recorded in kilogrammes. This method provides a precise measurement of the film's ability to resist breaking under tension. The results are crucial for ensuring that the patches can endure the mechanical stresses they might encounter during storage, handling, and application by patients. High tensile strength indicates that the patch material is strong and durable, which is essential for maintaining the integrity and efficacy of the transdermal delivery system (Shivaraj et al., 2010).

Percentage elongation break test

The percentage elongation break test is a crucial method for determining the flexibility and ductility of transdermal patch materials. This test measures the extent to which a film strip can stretch before breaking, providing valuable insights into the patch's mechanical properties. To conduct the test, a strip of the transdermal patch, typically measuring 2 cm by 2 cm, is prepared and positioned between the grips of a tensiometer. The upper grip of the tensiometer is movable, while the lower grip is fixed. Force is gradually applied through the movable grip, stretching the film until it breaks. The length of the film strip immediately before breaking, referred to as the final length, is noted. This measurement is compared to the initial length of the strip before any force was applied. The percentage elongation break is then calculated using the formula (Patel & Kavitha, 2011; Venkateswari et al., 1995):

Percentage Elongation=Final length of strip−Intial length of strip/Intial length of stripx100

Thickness

The thickness of the transdermal patches was determined using a digital micrometer screw

gauge, ensuring precision in measurement. To obtain accurate and representative data, the thickness was measured at three different locations on each patch. This approach helps to account for any variations in thickness across the patch surface. The readings from these three measurements were then averaged to calculate the mean thickness. Additionally, the standard deviation (SD) was computed to provide an indication of the variability or consistency of the thickness measurements. This combined approach of using the mean and standard deviation offers a comprehensive understanding of the patch's thickness uniformity, which is crucial for ensuring consistent drug delivery and overall patch performance (Keleb et al., 2010; Pandit et al., 2009).

Drug content

To determine the drug content in the transdermal patches, a 2 cm by 2 cm patch was dissolved in 100 ml of methanol. The solution was shaken continuously for 24 hours to ensure complete dissolution of the drug. Following this, the entire solution was ultrasonicated for 15 minutes to further aid in the dissolution process and to ensure uniform dispersion of the drug within the solvent. After the ultrasonication step, the solution was filtered to remove any undissolved particles or debris. The filtrate was then analyzed using spectrophotometry. The absorbance of the solution was measured at a wavelength of 263 nm, which is specific to the drug being tested. This absorbance value was used to calculate the drug content in the transdermal patch, ensuring accurate quantification of the active ingredient within the patch. This method provides a reliable and precise measurement of the drug content, which is essential for quality control and to ensure consistent therapeutic efficacy of the transdermal patches (Garala et al., 2009).

Percentage moisture content

The prepared transdermal films were individually weighed and stored in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and the percentage moisture content was determined from the following formula (Keleb et al., 2010). Percentage Moisture Content =Inital weight −Final weight/Final weightx100

Percentage moisture uptake

The prepared transdermal films were individually weighed and stored in a desiccator containing a fused saturated solution of potassium chloride to maintain 84% RH for 24 h at room temperature. After 24 h, the films were reweighed and the percentage moisture uptake was calculated using the following formula (Keleb et al., 2010).

Percentage Moisture Uptake=Final weight−Inital weight/Inital weight x100

Swelling study

The formulated transdermal patches were weighed (W1) individually and incubated at 37±0.5 ° C separately in agar gel (2%) plate. The patches were removed from the petri dish at regular time intervals of every 15 min up to 1 h and the excess water on the surface was removed carefully with filter paper. The swollen patches were reweighed (W2) and the swelling index was calculated by using the formula (Nishad et al., 2018; Pandey et al., 2016).

Swelling index=W2−W1/W1 x 100

***In vitro* drug release studies**

A Franz diffusion cell with a receptor compartment capacity of 60 ml was used for the *in vitro* drug release tests (Suksaeree et al., 2012). The drug was determined using a cellulose acetate

membrane from the prepared transdermal matrix-type patches. The diffusion cell's donor and receptor compartments were separated by a 0.45 μ pore size cellulose acetate membrane. The prepared transdermal patch was and mounted on the cellulose acetate membrane, which was then sealed with aluminum foil. The diffusion cell's receptor compartment was filled with phosphate buffer pH 7.4.

The entire assembly was mounted on a hot plate magnetic stirrer, and the solution was constantly and continuously stirred at 50 rpm during the experiments using magnetic beads, as described by Simon et al., 2016 (Simon et al., 2016) in the receptor compartment, while the temperature was maintained at 37±0.5 °C, which corresponds to normal human body temperature. The samples were taken at various intervals and spectrophotometrically analyzed for drug content. During the experiment, the manual sampling requires constant careful attention since air bubbles are easily entered in the receiver compartment when the samples are taken. At each sample removal, the receptor step was replenished with an equal volume of phosphate buffer.

***In vitro* permeation study**

An in vitro permeation study was carried out by using Franz diffusion cell using full-thickness abdominal skin of male Wistar rat weighing 200 to 250 g (Singh et al., 1993). Hair was carefully removed from the region of the abdominals with an electrical clipper; the dermal side of the skin was thoroughly cleansed with distilled water to remove any adhesion of tissues or blood vessels. It was equilibrated for an hour in Phosphate buffer saline, pH 7, before beginning the experiment. A thermostatically controlled heater maintained the cell temperature at 37±0.5 °C (Hwang et al., 1997; Pongjanyakul et al., 2000). The piece of rat skin was mounted between the diffusion cell compartments, and the epidermis faced up into the donor compartment (Hardainiyan et al., 2017). At regular intervals, the 1 ml sample volume was removed from the receptor compartment at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h, and an equal volume of fresh medium was replaced. The samples have been filtered through the Whatman filter and analyzed in Shimadzu UV 1800 double-beam sodium (Shimadzu, KYOTO/Japan) at 263 nm for Granisetron hydrochloride.

Drug release kinetics

To understand the drug release kinetics from the transdermal patches, the in vitro drug release data were analyzed using various kinetic models. These models help elucidate the mechanism and order of drug release, which are essential for optimizing the formulation and ensuring consistent therapeutic outcomes. The first model used was the zero-order kinetics model, where the cumulative amount of drug released was plotted against time. This model describes a release process where the drug is released at a constant rate, independent of its concentration. A straight line in this plot would indicate zero-order kinetics, suggesting a constant release rate. The second model applied was the first-order kinetics model, which describes a release rate proportional to the remaining drug concentration in the patch. The data were plotted as the logarithm of the cumulative percentage of drug remaining versus time. A linear relationship in this plot would indicate first-order kinetics, where the release rate decreases over time as the drug concentration diminishes.

The third model used was Higuchi's model, which describes drug release from a matrix system based on Fickian diffusion. In this model, the cumulative percentage of drug released was plotted against the square root of time. A straight line in this plot would suggest that the release

mechanism follows Higuchi's model, indicating diffusion-controlled drug release.

By fitting the in vitro release data to these kinetic models, the best-fit model was determined, providing valuable insights into the release mechanism of the drug from the transdermal patches. This analysis is crucial for optimizing the formulation, ensuring predictable drug release profiles, and ultimately enhancing the therapeutic efficacy of the transdermal delivery system (Hadjiioannou et al., 1993; Higuchi, 1963; Shivalingam et al., 2021).

Mechanism of drug release

The mechanism of drug release from the prepared transdermal patches of Granisetron was investigated using the Korsmeyer-Peppas equation. This model is instrumental in identifying the release mechanism by analyzing the relationship between the cumulative percentage of drug released and time on a logarithmic scale. The data were plotted as the log cumulative percentage of drug released versus log time, and from this plot, the exponent 'n' was determined through the slope of the resulting straight line. The value of the exponent 'n' indicates the specific mechanism of drug release. For a thin film like a transdermal patch, if $n \leq 0.5$, the release mechanism is Fickian diffusion, meaning the drug release is controlled primarily by diffusion. If $0.5 < n < 1.0$, the release follows anomalous (non-Fickian) transport, indicating a combination of diffusion and polymer relaxation (swelling) controls the release. If $n=1$, it implies case-II transport, suggesting that polymer relaxation or erosion controls the drug release. Values of $n>1$ indicate super case-II transport, suggesting a more complex release mechanism involving significant swelling and erosion of the polymer matrix. By calculating the exponent 'n' through the slope of the log cumulative percentage of drug released versus log time plot, the specific mechanism of drug release from the Granisetron transdermal patches was accurately characterized, providing critical insights for optimizing the patch formulation for effective drug delivery (Korsmeyer et al., 1983).

Statistical analysis

To ensure the reliability and validity of the results, each experiment was repeated at least three times, and the outcomes are expressed as mean ± standard deviation (SD). Statistical analysis was conducted to determine the significance of differences among the groups. A one-way analysis of variance (ANOVA) was employed to test the statistical significance of differences among multiple groups. This method is particularly useful for comparing the means of three or more groups to see if at least one group is significantly different from the others. Additionally, the statistical significance of the differences between the means of two specific groups was determined using Student's t-test. This test helps to ascertain whether the observed differences between two groups are statistically significant or if they occurred by chance. By applying these statistical methods, the study ensured rigorous analysis and validation of the experimental data, providing robust conclusions regarding the performance and characteristics of the transdermal patches.

RESULTS AND DISCUSSION

Thickness and Folding Endurance

The thickness of the transdermal patches varied among the different formulations, with values ranging from 0.231 ± 0.004 mm for TPF1 to 0.393 ± 0.011 mm for TPF5. The relatively small standard deviations indicate consistent measurements across the samples. Thicker patches, such as TPF5 and TPF6, may have a higher drug-loading capacity but could potentially affect

the flexibility and comfort of the patch. Folding endurance, which measures the mechanical strength and flexibility of the patches, showed considerable variation among the formulations. TPF4 exhibited the highest folding endurance at 170.2 ± 8.59, indicating superior flexibility and durability. In contrast, TPF3 had the lowest folding endurance at 132.8 ± 14.48, suggesting it is less flexible and more prone to mechanical failure under repeated folding. This variability in folding endurance could be attributed to differences in the polymer composition and thickness of the patches.

Content Uniformity and Weight

Content uniformity is a critical parameter ensuring that each patch delivers a consistent amount of the drug. All formulations demonstrated high content uniformity, with values close to 100%, indicating that the drug is evenly distributed throughout the patches. TPF6 showed the highest content uniformity at 101.31 ± 3.72, while TPF5 had the lowest at 98.93 ± 3.19. The low standard deviations further suggest that the drug content is consistently uniform across the samples. The weight of the patches also varied, with TPF1 being the lightest at 86.5 ± 3.01 mg and TPF6 being the heaviest at 95.5 ± 3.09 mg. The weight differences could be due to variations in thickness and polymer composition. Heavier patches like TPF5 and TPF6 may indicate higher drug content or the use of denser materials.

The physicochemical evaluation of the Granisetron hydrochloride transdermal patches reveals significant insights into their potential performance. Thicker patches, such as TPF5 and TPF6, might offer higher drug-loading capacities but could compromise flexibility and patient comfort, as reflected in their moderate folding endurance values. In contrast, thinner patches like TPF1 and TPF2 exhibit better flexibility but may have limitations in drug loading. Folding endurance is crucial for ensuring that the patches can withstand the mechanical stresses of application and wear without breaking. TPF4, with the highest folding endurance, stands out as the most durable and flexible, potentially offering the best balance between mechanical strength and drug delivery efficacy. Content uniformity across all formulations is excellent, indicating reliable and consistent drug release, which is essential for therapeutic effectiveness. This consistency ensures that each patch delivers the intended dose, minimizing the risk of underdosing or overdosing. The weight of the patches correlates with their thickness and potentially their drug content. While heavier patches may indicate higher drug content, they must be balanced against the need for flexibility and patient comfort. In conclusion, TPF4 appears to offer the best combination of flexibility, durability, and consistent drug delivery. However, the choice of the optimal formulation may depend on the specific therapeutic requirements and patient preferences. Further studies, including in vivo evaluations, would be necessary to confirm these findings and determine the most effective formulation for clinical use.

Table 2: Physicochemical Evaluation of Transdermal Patches of Granisetron hydrochloride

Formulation	Thickness (mm)	Folding Endurance	Content Uniformity (%)	Weight (mg)
TPF1	0.231±0.004	166.7±10.76	99.98±3.41	86.5±3.01
TPF2	0.272±0.002	148.4±15.78	99.52±2.88	90.1±3.02

TPF3	0.373±0.010	132.8±14.48	100.11±3.89	87.5±3.02
TPF4	0.350±0.004	170.2±8.59	99.96±3.49	92.4±3.02
TPF5	0.393±0.011	152.1±14.17	98.93±3.19	94.5±3.01
TPF6	0.388±0.009	153.3±13.86	101.31±3.72	95.5±3.09

(All values are mean±SD; Thickness n=3; Folding Endurance, Content Uniformity, and Weight n=10)

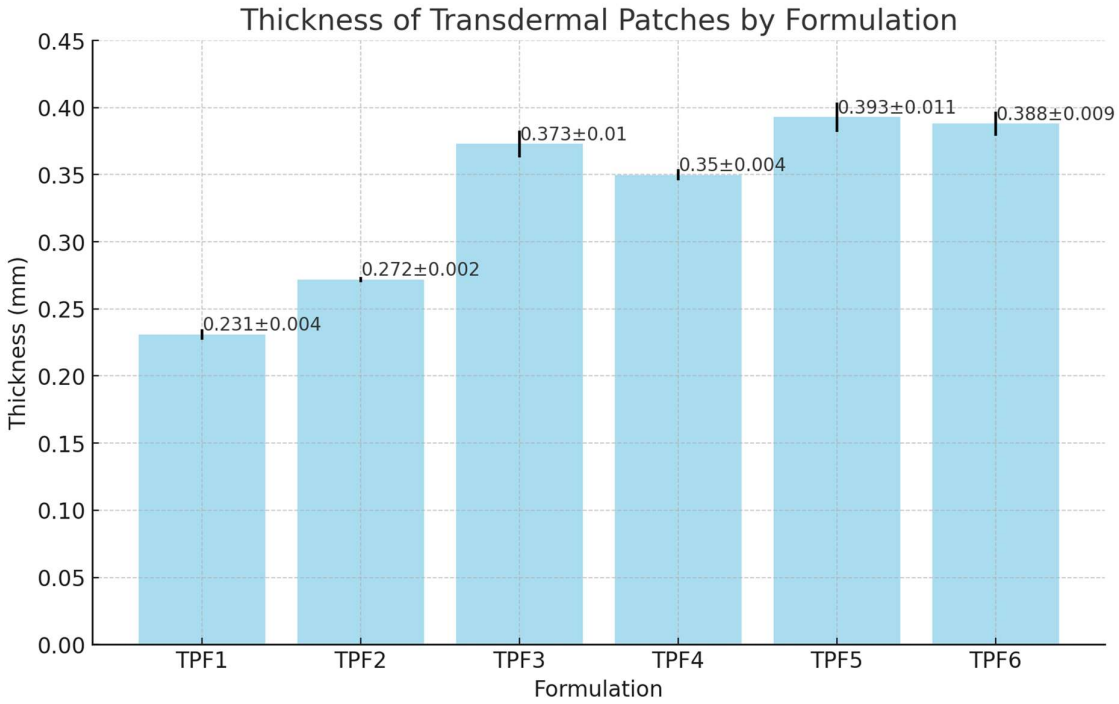

Figure 1. Thickness of the transdermal patch formulations

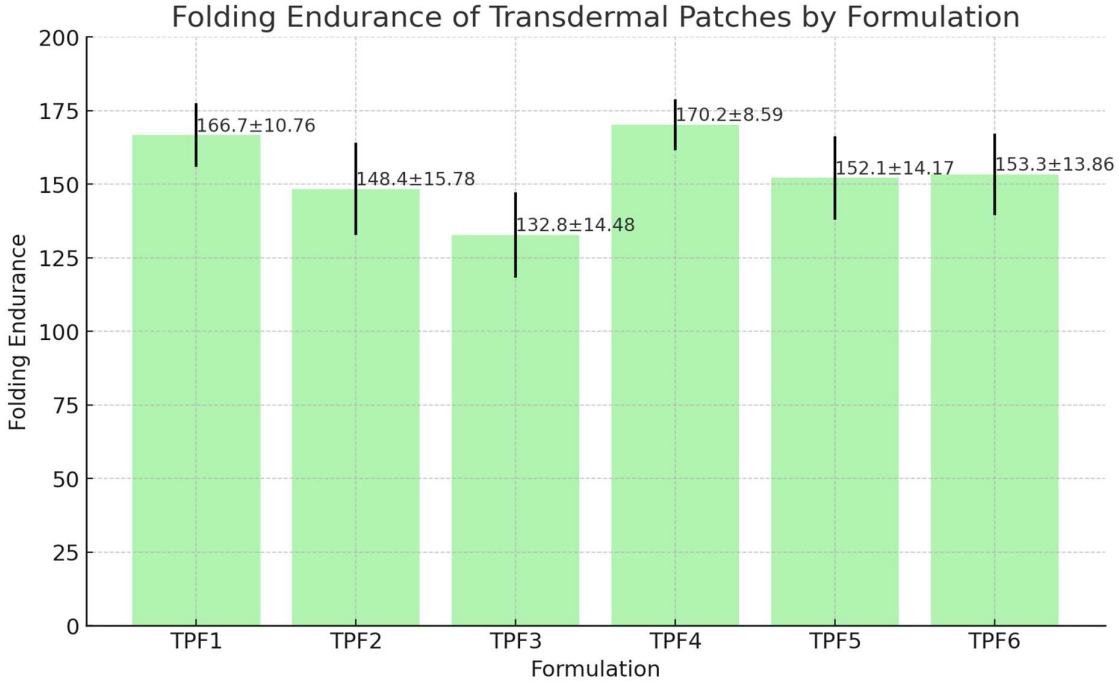

Figure 2. Folding Endurance of the transdermal patch formulations

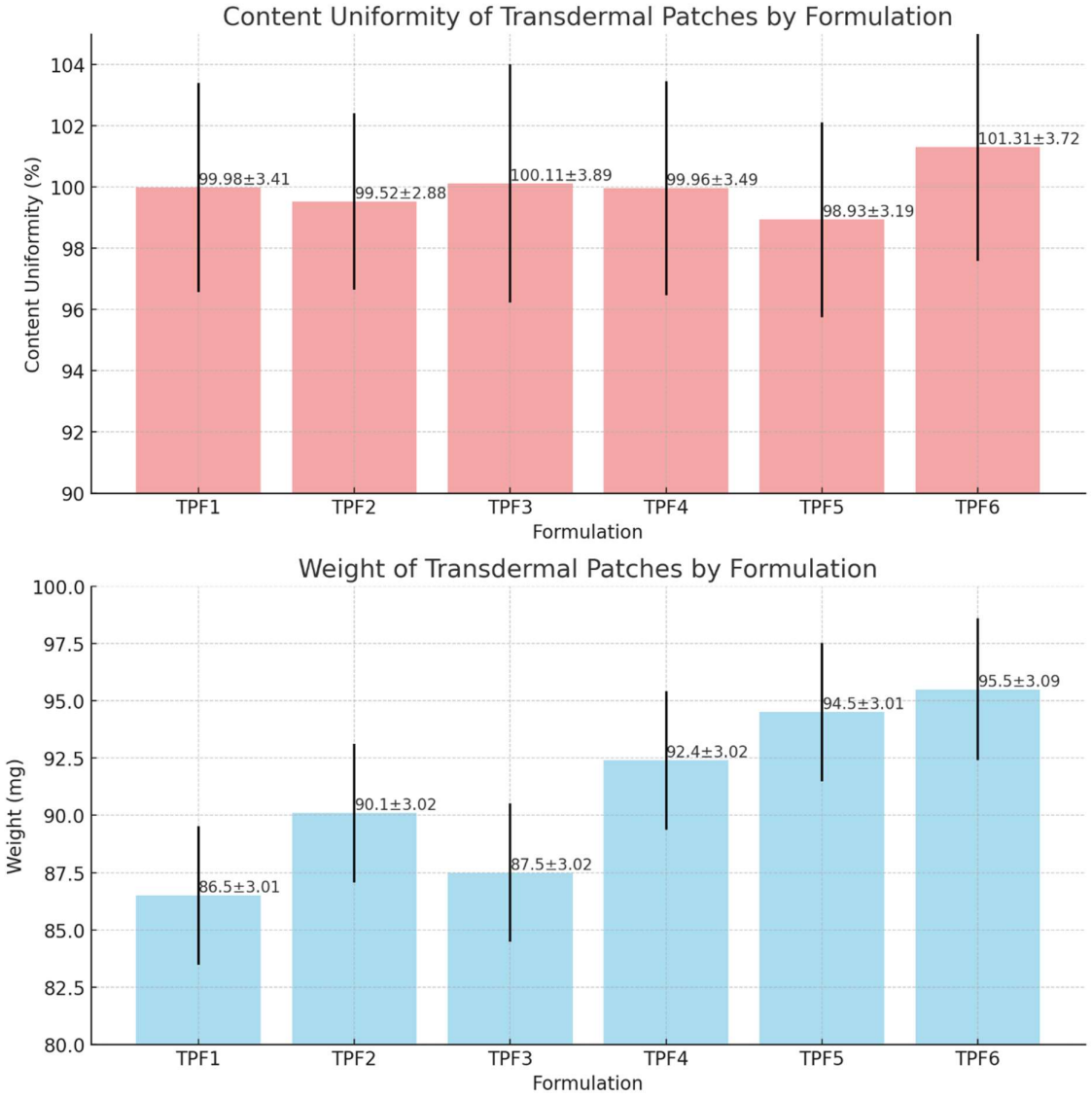

Figure 3. Content Uniformity (%) and Weight (mg) of the transdermal patch formulations

Surface pH and Percentage Flatness

The surface pH values of all formulations ranged from 6.15 ± 0.07 to 6.29 ± 0.07, indicating that the patches have a slightly acidic to neutral pH, which is close to the skin's natural pH. This is crucial to avoid skin irritation and ensure patient comfort. The small standard deviations suggest that the surface pH is consistent across different batches of the same formulation. Percentage flatness values for the patches were all close to 100%, ranging from 97.69 ± 2.90 for TPF5 to 100.69 ± 0.59 for TPF6. High flatness values indicate that the patches maintain their shape and do not show significant deformation, which is essential for uniform drug distribution and adherence to the skin. TPF6 showed the highest flatness, suggesting excellent structural integrity.

Percentage Elongation, Moisture Content and Moisture Uptake

Percentage elongation, which measures the flexibility of the patches, varied significantly among the formulations. TPF6 had the highest elongation at 81.85 ± 2.90%, indicating that it

is the most flexible and capable of stretching without breaking. In contrast, TPF1 had the lowest elongation at 39.35 ± 2.90%, suggesting it is less flexible. High elongation is desirable as it indicates better adaptability to skin movements, reducing the risk of patch failure during use. Moisture content, which affects the patch's stability and drug release properties, ranged from 8.09 ± 2.68% for TPF6 to 10.99 ± 5.09% for TPF4. TPF4 exhibited the highest moisture content, which could potentially enhance the drug release rate but may also affect the patch's mechanical properties. Consistent moisture content with low standard deviation, as seen in most formulations, is crucial for maintaining the patch's efficacy and integrity. Moisture uptake values indicate the ability of the patches to absorb moisture from the environment, which can impact their weight and drug release profile. The values ranged from 8.69 ± 3.06% for TPF6 to 12.34 ± 6.51% for TPF4. TPF4 showed the highest moisture uptake, which might enhance drug release but could also lead to swelling and potential discomfort for the patient. The variations in moisture uptake reflect differences in the hydrophilicity of the formulations.

The evaluation of transdermal patches of Granisetron hydrochloride reveals significant differences in their physicochemical properties, which can influence their performance and patient acceptability. The surface pH values close to the skin's natural pH suggest that all formulations are likely to be well-tolerated without causing irritation. High percentage flatness values across all formulations indicate that the patches retain their shape well, which is essential for effective drug delivery and patient comfort. The flexibility of the patches, as indicated by percentage elongation, varied significantly, with TPF6 being the most flexible. This high flexibility is advantageous as it allows the patch to conform to the skin and withstand movements without breaking. On the other hand, formulations like TPF1 with lower elongation might be more prone to mechanical failure during use. Moisture content and moisture uptake are critical for the stability and drug release characteristics of the patches. TPF4, with the highest moisture content and uptake, may have enhanced drug release rates but could also be more susceptible to mechanical changes and patient discomfort due to swelling. In contrast, TPF6 showed lower moisture content and uptake, indicating potentially better stability but possibly slower drug release. In conclusion, TPF6 appears to offer a balanced combination of desirable properties, including high flexibility, excellent flatness, and stable moisture content and uptake. These characteristics suggest that TPF6 could provide effective and comfortable drug delivery. However, the final choice of formulation should consider the specific therapeutic requirements and patient preferences. Further in vivo studies would be necessary to confirm these findings and optimize the formulations for clinical use.

Table 3: Evaluation of Transdermal Patches

Formulation	Surface pH	% Flatness	% Elongation	Moisture Content (%)	Moisture Uptake (%)
TPF1	6.15±0.07	98.69±2.09	39.35±2.90	8.60±0.67	9.22±0.77
TPF2	6.19±0.07	98.35±2.32	54.35±1.45	8.63±1.10	9.27±1.28
TPF3	6.25±0.07	98.69±2.53	59.35±1.45	8.80±1.12	9.46±1.32
TPF4	6.29±0.07	99.69±1.16	62.69±1.45	10.99±5.09	12.34±6.51
TPF5	6.22±0.11	97.69±2.90	67.69±1.45	8.43±1.55	9.04±1.82
TPF6	6.25±0.07	100.69±0.59	81.85±2.90	8.09±2.68	8.69±3.06

(All values are mean±SD; n=3)

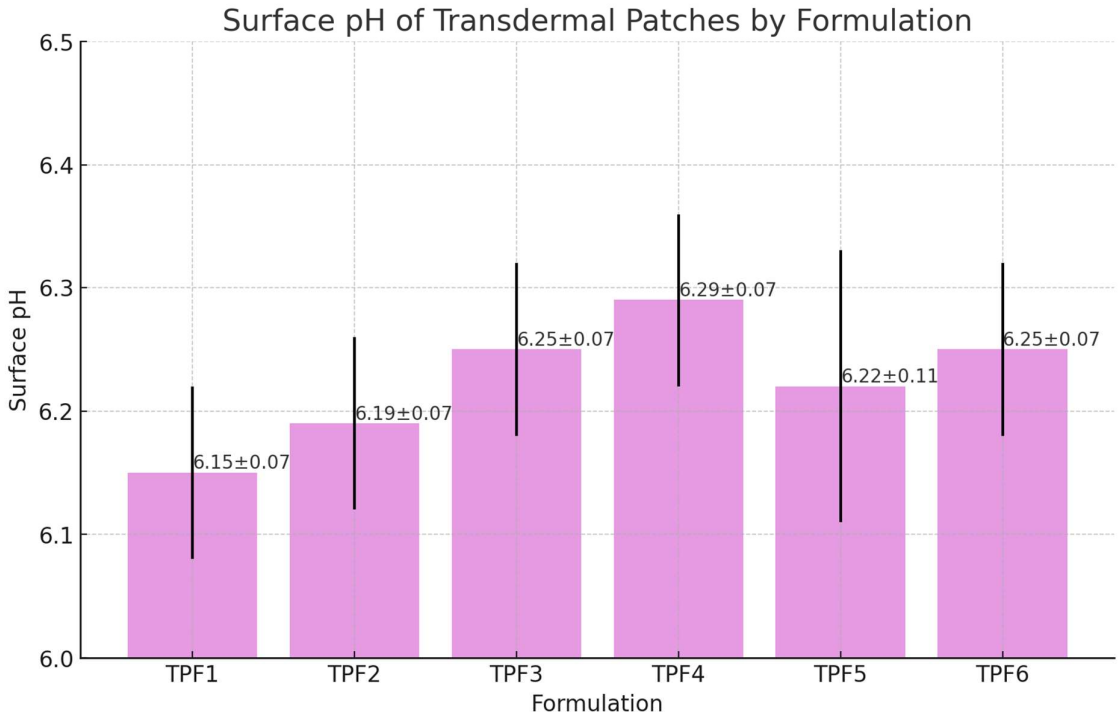

Figure 4. Surface pH of the transdermal patch formulations

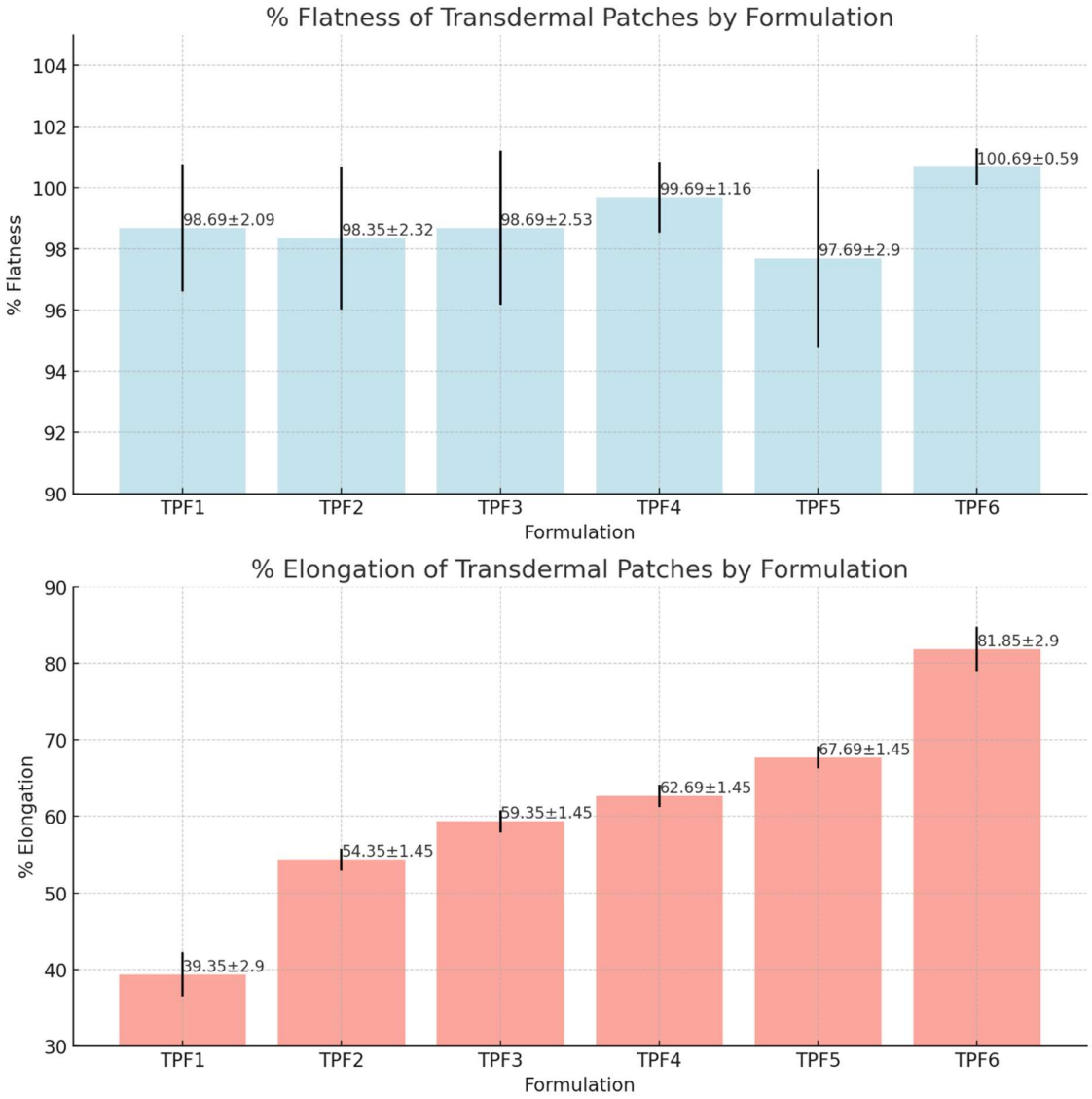

Figure 5. % Flatness and % Elongation of the transdermal patch formulations

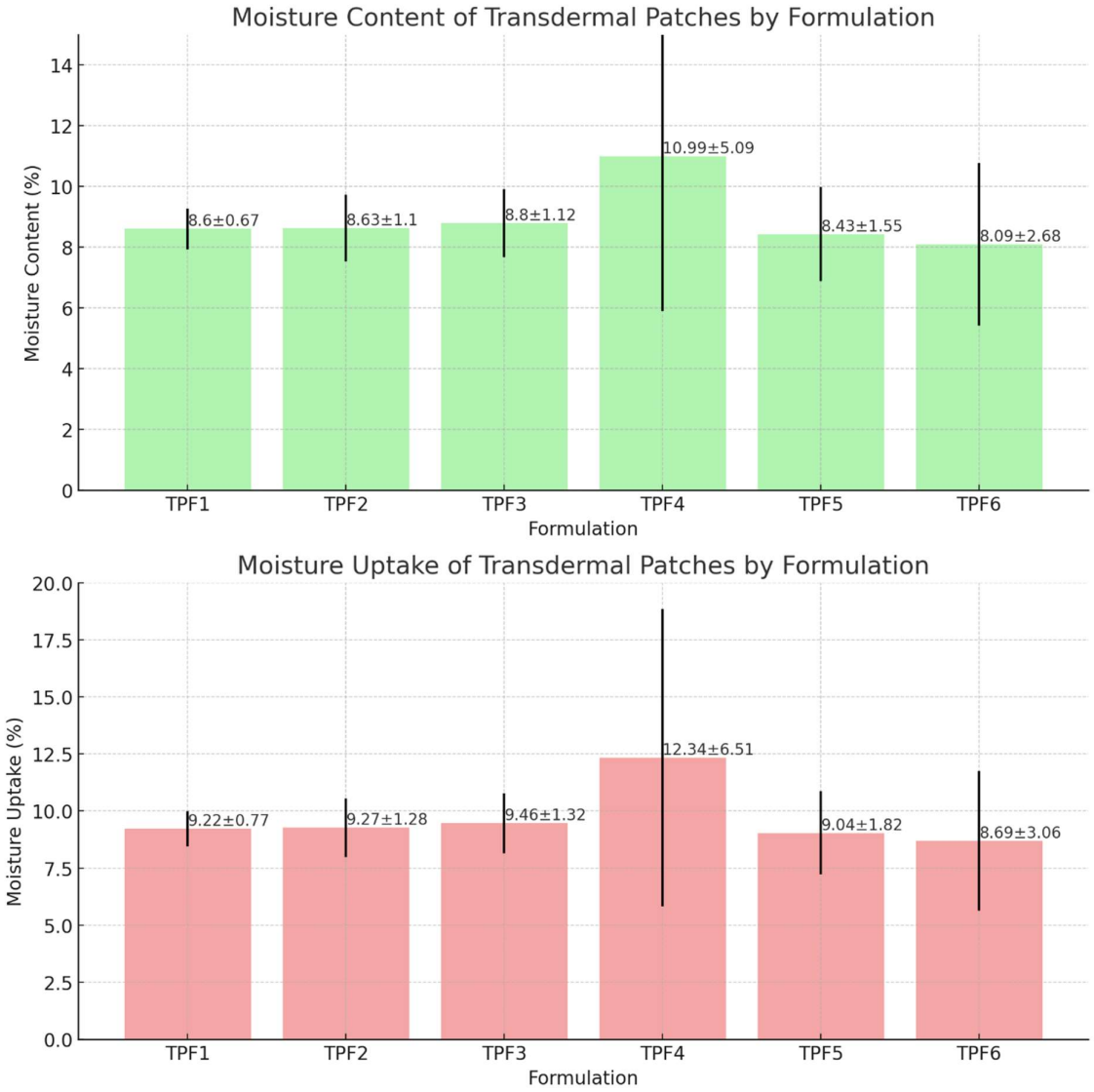

Figure 6. Moisture Content (%) and Moisture Uptake (%) of the transdermal patch formulations

Swelling study

The swelling studies of the Granisetron hydrochloride transdermal patches provide critical insights into their fluid absorption behaviour and its impact on drug release and patch performance. The swelling index was measured at 15, 30, 45, and 60 minutes for each formulation. TPF1 exhibited a steady increase in swelling from 61.07 ± 4.69 at 15 minutes to 77.60 ± 2.41 at 60 minutes, indicating consistent fluid absorption and likely stable drug release. However, the relatively high swelling might affect the patch's adhesion to the skin over prolonged periods. TPF2 showed the lowest swelling index, starting at 49.61 ± 3.80 and reaching 67.04 ± 3.09 at 60 minutes, suggesting limited fluid absorption and slower drug release, which could be beneficial for controlled and prolonged delivery but might reduce patch flexibility and comfort.

TPF3 and TPF4 had similar swelling profiles, with TPF3 starting at 62.69 ± 3.44 and reaching 73.74 ± 2.20, and TPF4 starting at 62.78 ± 2.85 and reaching 75.90 ± 2.53. Both formulations

exhibited moderate swelling, suggesting good fluid absorption and consistent drug release, providing a balance between drug release and patch integrity. TPF5 showed delayed but moderate swelling, starting at 51.59 ± 5.38 and increasing to 67.05 ± 1.95 at 60 minutes, indicating a slower initial absorption rate that might be useful for delayed drug release but could affect the immediate availability of the drug. TPF6 demonstrated significant initial swelling, starting at 50.30 ± 7.77 and reaching 76.98 ± 3.41 at 60 minutes, indicating robust fluid absorption. This high swelling capacity might enhance the initial drug release rate, making it suitable for conditions requiring rapid drug delivery, but it could impact the patch's structural integrity and adherence to the skin. Overall, the choice of formulation depends on the desired balance between drug release rate and patch stability. TPF3 and TPF4 appear to offer a good balance, with moderate swelling indicating consistent drug release and structural stability. Further in vivo studies are necessary to confirm these findings and optimize the formulations for clinical use, ensuring both efficacy and patient comfort.

Table 4: Swelling Studies of Transdermal Patches of Granisetron hydrochloride

	Swelling Index			
Formulation	**15 min**	**30 min**	**45 min**	**60 min**
TPF1	61.07±4.69	68.65±2.12	72.08±3.31	77.60±2.41
TPF2	49.61±3.80	57.52±3.69	61.64±1.61	67.04±3.09
TPF3	62.69±3.44	65.36±3.27	68.60±2.36	73.74±2.20
TPF4	62.78±2.85	65.72±2.45	69.87±1.69	75.90±2.53
TPF5	51.59±5.38	57.39±1.86	60.87±0.38	67.05±1.95
TPF6	50.30±7.77	67.65±1.87	71.37±2.38	76.98±3.41

(All values are mean±SD; n=3)

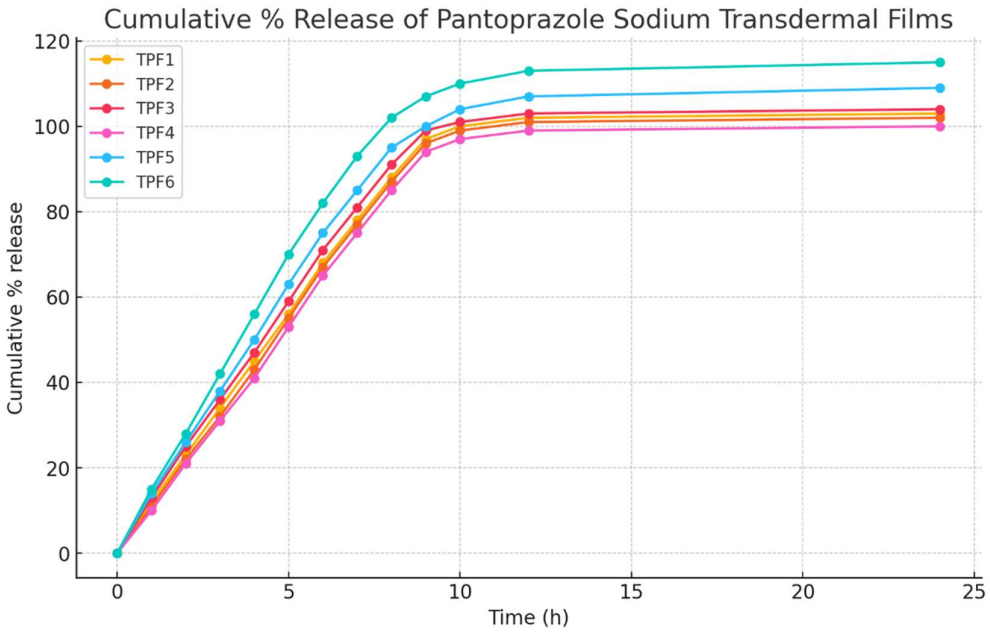

Figure 7. Cumulative (%) release data of the transdermal patch formulations

CONCLUSION

The fabrication and physicochemical evaluation of Granisetron hydrochloride transdermal patches revealed significant insights into their potential performance. Thickness varied across formulations, with thicker patches offering higher drug-loading capacities but potentially compromising flexibility and comfort. TPF4 exhibited the highest folding endurance, indicating superior mechanical strength and flexibility. Content uniformity was excellent across all formulations, ensuring consistent drug release. The weight of the patches correlated with their thickness, influencing drug content and material density. Surface pH values close to the skin's natural pH suggested good tolerance, while high flatness values indicated maintained shape and effective drug distribution. TPF6 demonstrated the highest elongation, providing superior flexibility. Moisture content and uptake varied, with TPF4 showing the highest values, potentially enhancing drug release but affecting mechanical properties. Swelling studies indicated different fluid absorption rates, impacting drug release and patch performance. TPF4 and TPF6 emerged as promising formulations, balancing drug delivery efficacy, flexibility, and stability. Further in vivo studies are necessary to confirm these findings and optimize the formulations for clinical use, ensuring both efficacy and patient comfort.

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