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Will The Detection of Granisetron inits Pharmaceutical Products Prove Significance in Chemotherapy Supportive Care Plan?

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ABSTRACT

Background: Granisetron is an antiemetic drug that is highly selective to the 5-HT3 receptor, and used in the management of chemotherapy-induced nausea and vomiting, and included in the supportive care plan.

Aim: This work aimed to develop a sensitive, precise, accurate, and specific analytical method for quantitative estimation of granisetron in pharmaceutical products to use it as a quality control tool for testing granisetron products pre-market and post-market distribution to ensure the presence of labeled drug amount in the dosage form.

Methods: Determination of granisetron in commercial pharmaceutical formulations, which are dispensed in hospitals and community pharmacies and administered by patients, by developing an in-house High-Performance Liquid Chromatographic (HPLC) method to add for literature methods a validated selective and sensitive method.

Results: The method is sensitive, specific, selective and linear R2>0.999 within concentration range of 0.2 to 3 µg/ml for dissolution medium USP (pH6.5), and 0.1 to 1.6 µg/ml for dissolution medium pH1.2, 4.5, and 6.8. Moreover, the results were accurate within the range of 98 - 102% and the precision CV% was less than 2%. The assayed tablet's mean recovery was98.398%. Also, the dissolution results were fulfilling the required limit of 75% percent dissolution within 30 minutes.

Conclusion: The in-house developed analytical method is sensitive and fully validated for use in the quantification of granisetron in pharmaceutical products.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) one of the debilitating side effects of chemotherapy and radiation therapy. These symptoms limit the patient's desire to eat and drink, and causes a remarkable reduction in quality of life, threaten therapy success, and result in high morbidity, and mortality rates, besides elevated health care costs [1, 2]. The occurrence of chemotherapy-induced nausea and vomiting (CINV) depends on to how extent the chemotherapeutic agent is emetogenic, besides patients' risk factors like young age, female gender, history of emesis during pregnancy, history of low alcohol intake, impaired quality of life, and previous chemotherapy [3, 4]. Total prevention of chemotherapy-induced nausea and vomiting (CINV) is achieved in 70 to 84 % of patients despite new antiemetic agents' discovery [5, 6].

Granisetron is an antiemetic agent that is highly selective to the 5-HT3 receptor and exerts a minimal effect on other receptors [7]. Granisetron hydrochloride is an indazole with the formula C18H24N4O. HCl and Mwt 348.87. It is a white to off-white solid substance, and soluble in water and normal saline solution. Granisetron is lipophilic and basic. Its protein binding is moderate(65%) [8].

A clinical study suggested that Granisetron is more effective in preventing Postoperative nausea and vomiting during 6 hours after the surgery in comparison with Ondansetron which makes it a favourable alternative for preventing Postoperative nausea and vomiting [9].

Current guidelines suggest that granisetron is an optional treatment for nausea and vomiting in pregnancy (NVP) despite a lack of evidence to support fetal safety. A clinical study showed that Granisetron exposure was not associated with increased risk for minor or major fetal anomalies. This study provides preliminary reassurance regarding the safety of in-utero exposure to granisetron [10].

Different formulas are available like, an intravenous, tablet, oral solution and transdermal, and an extended-release injection that is recently approved by the FDA [11].

A high performance liquid chromatographic method is reported in British Pharmacopeia for granisetron determination [12]. Literature review revealed a few methods for granisetron determination in pharmaceutical dosage forms and dissolution medium that may lack adequate sensitivity in some in-vitro applications. Previously reported methods were mainly focused on HPLC methods with fluorescence detection [13-15] and LC-MS/MS methods [16, 17] for the determination of granisetron in human biological fluids.

In this work, the proposed validated in-house developed method is a sensitive, precise, accurate, and specific analytical method for granisetron determination in pharmaceutical dosage form, and in dissolution testing. Validation items are performed as per ICH and FDA guidelines. [18, 19] . Assay testing, in-vitro dissolution procedures, and criteria are performed as per FDA Biowaiver/Biopharmaceutics classification system Guidelines [20], and United States Pharmacopeia (USP) [21].

Performing invitro testing like assay, uniformity of dosage units and dissolution is an important step in determining the validity of dosage form for the intended use. Moreover, predicting dosage form behaviour before conducting bioequivalence studies if required. Some research institutes are working on in-vivo in-vitro correlation to predict pharmacokinetic behaviour and bioequivalence of generic drug products from in-vitro dissolution results. Drug assay should be within the limit of 92 to 108% of the labelled claim, and dissolution limit should be not less than 75% of the drug dissolute within 30 minutes to ensure valid and safe for the administration of granisetron tablets, to obtain an effective therapeutic outcome.

Routine random drug samples should be selected from community and hospital pharmacies and subjected to quality control testing to ensure that the dosage form is keeping its integrity and the labelled claim of the active ingredient complies with the required specification after they are exposed to market transportation conditions and shelf-storage in pharmacies. Also, the absence of any drug degradative or toxic product is important and should be checked.

Finally, accurate investigations of granisetron in pharmaceutical products could not be relied upon unless a valid analytical method is well developed for drug determination. The aim of this routine check is to ensure that the patients are administering a valid and safe therapeutic product to obtain the desired therapeutic outcomes and avoid the incidence of drug toxicity or adverse events.

MATERIALS AND METHOD

Routine random drug samples are selected from community pharmacies and hospital pharmacies. Quality control testing like assay testing and dissolution testing is performed on those samples to ensure that the dosage form preserving its integrity and no degradative product formation, and the labelled claim of the active ingredient complies with the required specification after they are exposed to market transportation conditions and shelf-storage in pharmacies. The aim is to ensure that the patients are administering a safe and valid drug product to attain the required therapeutic efficacy and avoid any potential drug toxicity or side effects.

1.1.Materials:Granisetron HydrochlorideUSP reference standard. All solvents were of the HPLC grade and were purchased from Merck (Germany). The rest of the chemical agents used were of AR grade and were purchased from Scharlau (Spain).

ANALYTICAL METHODS

1.2.1.Instrumentation: The analysis was performed by using the analytical balance sartorius, pH meter portable BOECO, the HPLC used is thermo spectra system 4000 HPLC system, equipped with spectra system P4000 gradient pump, spectra system auto sampler fitted with a 100 µl loop and spectra systemP1000 ultra-violet detector was used. The output signal was monitored and processed using chromo quest 4.2 Software. The chromatographic column used was a 150 mm x 4.6 mm, phenomenexC18 with 5µm particles. Before using, the mobile phase was vacuum-filtered through a 0.45 µm membrane filter and degassed with sonication. The water was distilled and then purified by an ELGAPURE water purification system (England).

1.2.2.Chromatography conditions: The mobile phase consisted of 0.5% phosphoric acid: acetonitrile 80:20 (V/V), mobile phase flow rate was1.2 mL/min. Peaks were monitored at 300 nm, and analysis performed at room temperature; the volume of solution injected onto the column was 40µL.

1.2.3.Preparation of stock and standard solutions: A master solution of granisetron (100µg/ml) was prepared by accurately weighing an equivalent amount to 10 mg of granisetron into 100 ml volumetric flask and dissolved in 70 ml of methanol and volume completed with methanol. Four ml aliquot from the standard master solution of granisetron were transferred using A-grade pipettes into 100 ml volumetric flask, and solution were made up to volume with methanol to obtain a solution containing 4ug/ml. From this solution, aliquots

were transferred using A-grade pipettes into a 10ml volumetric flask, and solutions were made up to volume with mobile phase to obtain final concentrations of 0.2 to 3 µg/ml.

METHOD VALIDATION

The in-house developed HPLC method validation was performed as per ICH guidelines.

1.2.4.1.Specificity: It is the capability of the analytical method to determine the target analyte in the presence of all potential impurities. Stress study was performed at a concentration of a 3 µg/ml granisetron active pharmaceutical ingredient (API) and formulated tablet samples to indicate stability and specificity of the developed analytical method. Intentional drug degradation was performed under stress conditions of heat (Exposed at 85°C for 1 h), acid (1N HCl for 1 h at 85°C), and base (1N NaOH for 1 h at 85°C).

1.2.4.2.Linearity: Linearity was studied by preparing standard solution at eight concentration levels from 80 to 120% of the target analyte concentrations i.e. Concentrations ranging from 0.2 to 3 µg/ml. These analyses were performed in triplicate [16, 17].

1.2.4.3.Precision: It is an assessment of intra-day variability in results obtained at three concentrations, with nine determinations in one laboratory, on the same day. Calculated %RSD is used to express precision [16, 17].

1.2.4.4.Lower limit of detection (LLOD) / Lower limit of quantitation (LLOQ): Can be defined as the concentration of analyte that would yield signal-to-noise ratios of 3 for LLOD and 10 for LLOQ respectively. LLOD and LLOQ were determined by the standard deviation of y-intercepts of regression lines and slope of calibration [16, 17].

1.2.5.Estimation of granisetronin pharmaceutical dosage form: To determine the assay of granisetron in tablets (labeled claim: 1 mg granisetron), not less than five tablets were weighed and transferred to a 50ml volumetric flask.25ml of diluent (sodium phosphate dihydrate buffer pH 2) was added. Sonication with intermittent shaking was performed for 20 minutes till the tablets disintegrate completely then the flask was left to cool at room temperature. The volume was completed with diluent. And 0.45 µm nylon filter was used to filter solutions. The sample solution was injected into HPLC with an injection volume40µl, three times, under the predetermined validated chromatographic conditions. Drug chromatographic responses were determined at 300 nm and concentrations in the samples were determined by comparing sample chromatographic response with that of the standard.

1.2.6.Estimation of granisetron content uniformity in pharmaceutical dosage form: To determine the content uniformity of granisetron in tablets (labeled claim: 1 mg granisetron) ten tablets were weighed, and transferred, each one individually to a 10ml volumetric flask. 5ml of diluent (sodium phosphate dihydrate buffer pH 2) was added. Sonication with intermittent shaking was performed for 20 minutes till the tablet disintegrate completely, then the flask was left to cool at room temperature. The volume was completed with diluent. And 0.45 µm nylon filter was used to filter solutions. The sample solution was injected into HPLC with an injection volume 40µl, three times, under the predetermined validated chromatographic conditions. Drug chromatographic responses were determined at 300 nm, and concentrations in the samples were determined by comparing sample chromatographic response with that of the standard.

1.2.7.Estimation of granisetronin in-vitro dissolution testing of pharmaceutical dosage form: Dissolution testing procedures were applied on twelve dosage units (Tablets) under USP dissolution medium Phosphate Buffer pH6.5, and media pH1.2, pH4.5, pH6.8 using UPS Type II device at 50 rpm for Phosphate Buffer pH6.5USP medium, and 75 rpm for pH1.2, 4.5, and 6.8 media as follows:

1- The above-mentioned dissolution conditions were applied and performed by placing six tablets in six vessels (one Tablet in each vessel). Five ml of each sample was withdrawn after 10, 15, 20, 30, 45, and 60 minutes of dissolution where, 5ml of blank (dissolution media) was added to replace this withdrawn volume and achieve a constant volume of Dissolution media (500ml) for USP medium and (900ml) for pH1.2, pH4.5, pH6.8.

2- The withdrawn 5ml at each sampling interval was added in a coded labelled test tube and then filtered through a syringe membrane filter (PTFE 0.45µm).

3- The previously mentioned procedures were repeated on another six film-coated Tablets.

4- The filtered withdrawn samples were then injected in the HPLC-UV apparatus for drug detection and quantification at 300 nm.

RESULTS

Determination of granisetron was carried out by RP-HPLC using mobile phase having a composition of 0.5% phosphoric acid: acetonitrile 80:20 (V/V). Then finally filtered using 0.45µ nylon membrane filter and degassed in a sonicator for 10 minutes. The column used was C18 phenomenex150X4.6 mm p.s. 5um. The flow rate of the mobile phase was 1.2 ml/min, system suitability parameters such as theoretical plates were above 2500, and the tailing factor less than1.3.

1.3.Method Validation:

After the development of the analytical method, it was subjected to method validation according to ICH and FDA guidelines [16, 17]. The aim of validation is to demonstrate whether the method is acceptable for its required application or not. A standard procedure is followed to evaluate required validation items (specificity, linearity, accuracy, precision, the Lower limit of detection, and the lower limit of quantitation, and system suitability).

1.3.1.Specificity: Bank samples containing solvent were injected and showed no drug detected figure (a). The drug was unstable under acidic stress conditions figure (b), and the drug was degraded approximately to 51%. But it was more stable in neutral and basic conditions when the drug was refluxed with water for 1 h, and was degraded approximately to 9%(figure 3)& (figure 4). The stability of stock solution under conditions of (2to8oC) was determined by quantitation of granisetron and comparison to freshly prepared standard (figure 2). No remarkable change occurred in the stock solution response in comparison to freshly prepared standard.

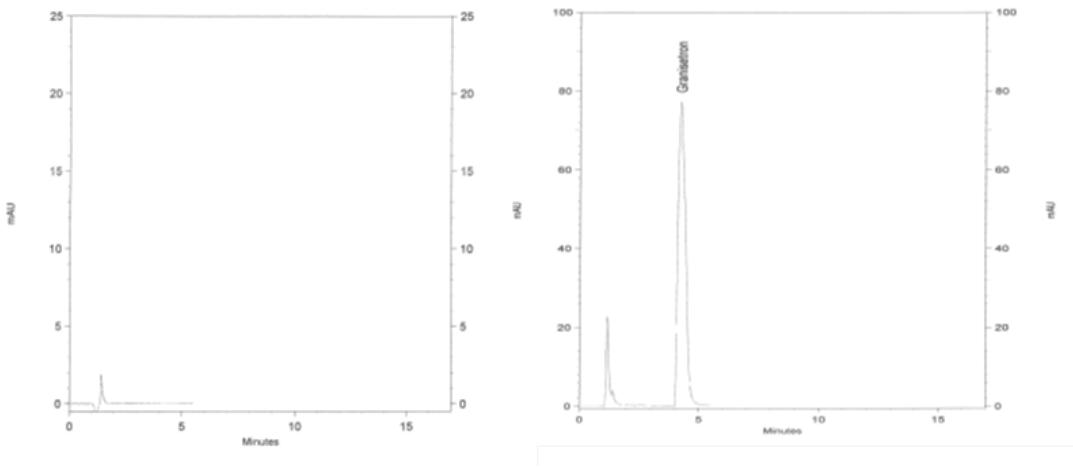

Figure (a): Chromatogram of Blank solventFigure (b): Chromatogram of Granisetron Stress HCL

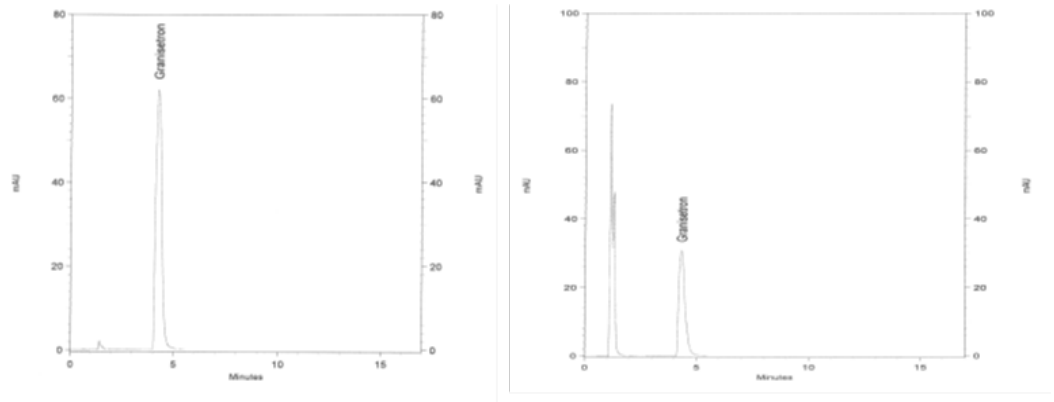

Figure (c): Chromatogram of GranisetronStress HeatFigure (d): Chromatogram of GranisetronStress NaOH

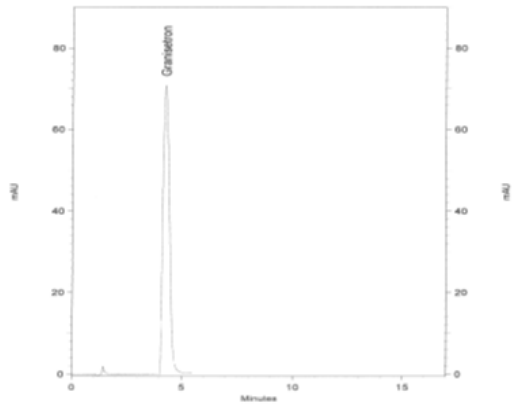

Figure (e): Chromatogram of Standard Granisetron.

1.3.2.Linearity: Granisetron showed linearity from 0.2 to 3µg/ml in USP medium and from 0.1 to 1.6 µg/ml in dissolution medium pH1.2, 4.5, and 6.8 with (r2 = 0.999) for HPLC. Linearity was evaluated by determining eight standard working solutions in the range of 0.2-3 µg/ml in triplicate using USP medium, buffer pH 6.5, and in the range of 0.1 to 1.6 µg/ml using media pH 1.2, pH 4.5, and pH 6.8 as a solvent. Peak areas of Granisetron were plotted versus Granisetron concentration (µg/ml) and linear regression analysis performed on the resultant (table 1).High-value Correlation Coefficient (r2) and low value intercept CV% (less than 5%)indicate validation of analytical method linearity adherence of the system to Beer's law. The resulted chromatogram showed a sharp, symmetrical, and well-separated peak at a retention time of 4.1 min figure (e).

Analyte	Granisetron
Range	0.2 to 3µg/mL
Linearity correlation equation	
At Dissolution medium (pH6.5)	Y= 167651.663827X +284.813742
Range	0.1 to 1.6 µg/mL
Linearity correlation equation	
At Dissolution medium (pH1.2)	Y= 84629.972543X + 287.263591
At Dissolution medium (pH4.5)	Y= 100074.12685X – 513.215541
At Dissolution medium (pH6.8)	Y= 83383.679297X – 887.678748
Linearity correlation coefficient R^2	
At Dissolution medium (pH6.5)	0.999828
At Dissolution medium (pH1.2)	0.999651
At Dissolution medium (pH4.5)	0.999986
At Dissolution medium (pH6.8)	0.999895
Mean Slope ±SD	
At Dissolution medium (pH6.5)	167651.664±649.161
At Dissolution medium (pH1.2)	84629.973±346.585
At Dissolution medium (pH4.5)	100074.127±141.051
At Dissolution medium (pH6.8)	83383.679±359.222
Mean Intercept ± SD	
At Dissolution medium (pH6.5)	284.814±571.860
At Dissolution medium (pH1.2)	287.264±62.769
At Dissolution medium (pH4.5)	513.216±140.228
At Dissolution medium (pH6.8)	887.679±286.996
Standard error of slope	
At Dissolution medium (pH6.5)	374.793
At Dissolution medium (pH1.2)	200.101
At Dissolution medium (pH4.5)	81.436
At Dissolution medium (pH6.8)	207.397
Standard error of intercept	
At Dissolution medium (pH6.5)	330.164
At Dissolution medium (pH1.2)	36.240
At Dissolution medium (pH4.5)	80.961
At Dissolution medium (pH6.8)	165.697

All forced degradation samples were analyzed with the aforementioned HPLC conditions using a UV detector to monitor the homogeneity and purity of the Granisetron peak. Individual related substances, placebo, and Granisetron showed no interference, thus providing a specific analytical method.

Where, n=3, average of three determinations, SD (±): standard deviation.

1.3.3.Precision: The intra-day variations can be demonstrated in terms of % RSD values. The %RSD values in dissolution medium USP (buffer pH6.5), pH1.2, pH4.5, and pH6.8 showed to be less than or equal to 2 %, indicating good precision. It is acceptable according to the acceptance limit of these parameters. The mean RSD% in medium USP (pH6.5), pH1.2, pH4.5, and pH6.8 were 0.437, 0.230, 0.232%, and 0.751%.

1.3.4.Lower limit of detection (LLOD) and lower limit of quantification (LLOQ): The LLOD and LLOQ of the developed method were

determined by injecting progressively low concentrations of the standard solutions using the developed RP-HPLC method. The LLOD is the smallest concentration of the analyte that gives a measurable response. The LLOD for granisetron was found to be 0.011, 0.002, 0.005, and 0.011µg/mL for dissolution media pH 6.5, pH 1.2, pH 4.5, and pH 6.8 respectively. The LLOQ is the smallest concentration of the analyte, which gives a response that can be accurately quantified. The LLOQ was 0.034, 0.007, 0.014, and 0.034µg/ml for dissolution media pH6.5, pH 1.2, pH 4.5, and pH 6.8 respectively.

1.4.Assay (potency)of granisetron: The developed and validated method was applied for the assay of granisetron in the tablet dosage form. Results were found out as mean % recovery 98.398% for granisetron reference tablets. The results indicating that the method is selective for the assay of granisetron with no interference from the inactive ingredients.

1.5.Content uniformity of granisetron: The developed and validated method was applied for content uniformity of granisetron in the tablet dosage form. Results were found out as a mean recovery of 99.257%. The acceptance value was0.512 for granisetron reference tablets.

1.6.Dissolution of granisetron: The developed and validated method was applied for dissolution testing of granisetron Tablets. Results were found out as a dissolution profile for mean percentage drug dissoluted of granisetron in Reference tablets. The results showed that the reference product complies with FDA Biowaiver /Biopharmaceutics classification system Guidelines [20], and United States Pharmacopeia (USP) [21].

The results of dissolution percent of granisetron 1mg tablet upon dissolution in buffer pH6.5 (USP medium) after 10, 15, 20, 30, 45, and 60 minutes was 63.175, 69.192, 74.017, 76.492, 79.271, 83.225% respectively.

The results of dissolution percent of granisetron 1mg tablet upon dissolution in medium pH1.2 after 10, 15, 20, 30, 45, and 60 minutes was 86.603, 88.830, 91.883, 94.500, 97.073, 99.158% respectively.

The results of dissolution percent of granisetron 1mg tablet upon dissolution in medium pH4.5 after 10, 15, 20, 30, 45, and 60 minutes was 83.370, 87.045, 89.693, 92.468, 94.973, 98.708% respectively.

The results of dissolution percent of granisetron 1mg tablet upon dissolution in medium pH6.8 after 10, 15, 20, 30, 45, and 60 minutes was 81.788, 87.803, 90.750, 93.660, 96.923, 99.683% respectively.

The previous results of analytical method validation, Assay testing, and dissolution testing indicate that the method validation and pharmaceutical drug product is in compliance with the required specifications, and thereby will provide the required therapeutic effect in the management of chemotherapy-induced nausea and vomiting (CINV).

DISCUSSION

It is worthy of mentioning that the estimation and assaying of granisetron in pharmaceutical products including tablets, and evaluation of its in-vitro behavior, including dissolution with a validated analytical method are important to ensure the clinical efficacy of granisetron.

As shown previously, the clinical importance of granisetron as an antiemetic drug in the management of chemotherapy-induced nausea and vomiting (CINV) in those patients on cytotoxic chemotherapy[1-2]. and so contribute to the improvement of patients' quality of life and reducing incidence of morbidities and mortalities. Moreover, granisetron showed to be a 5-HT3 receptor antagonist with a minimal effect on other receptors [7].

Investigations showed that subcutaneous injection of granisetron could afford similar analgesic patterns on mechanical sensory and pain thresholds as well as thermal sensory thresholds over the facial skin as lidocaine. Also, the absence of paraesthesia, and reduced pain intensity and pressure pain sensitivity shown in previous studies indicate that granisetron might be a novel candidate as a local anaesthetic [22].

Few analytical methods were developed for granisetron determination in pharmaceutical dosage forms. An HPLC method has been developed for to estimate both granisetron and dexamethasone simultaneously using CN column 250×4.6 mm and a mobile phase acetonitrile: 100 mM Triethylaminebuffer pH 3 (25:75 V/V) at a flow rate 2 ml/min. UV detection was set at 242 nm. The method showed linearity in the range of 25 to 400ug/ml, LOD of 1.69ug/ml, and LOQ of 5.125 ug/ml [23].

Another high performance liquid chromatographic method has been developed for estimation of granisetron in tablet formulation. Luna C18 column was used to achieve separation, and phosphoric acid buffer pH 7.5: acetonitrile (70: 30v/v) was used as mobile phase. The flow rate was set at 1.2 ml/min. Detection was carried out using a UV detector at 305 nm. The method has been validated as per requirements. The method showed to be linear within 40 to 60 µg/ml. LOD and LOQ showed to be 1.8266 ug/ml, and 5.5352ug/ml respectively [24].

A more sensitive analytical method using HPLC has been developed and validated for the determination of granisetron in pharmaceutical dosage forms. Chromatography performed using Gemini NX C18 250mm × 4.6mm, 5µm column, and mobile phase 0.01M sodium phosphate buffer of pH 7.5 :acetonitrile (80 : 20 V/V),and the flow rate was set at 1.5ml/min. UV wavelength was set at 305nm. All validation requirements were fulfilled. The method showed linearity in the range of 2 to 10µg/ml. LOD and LOQ were found to be 0.1502µg/ml, and 0.4553µg/ml respectively [25].

The developed HPLC – UV method applied in this study was simple, and of excellent sensitivity, specificity, precision, and accuracy. Materials and reagents used in the analysis are common, convenient, and available, like C18 column 250mm X 4.6mm, phosphoric acid, and Acetonitrile. Mobile phase pumped in an isocratic mood, and total run time was 5.1 minutes, which permits analysis of up to 250 samples per 24 hours. The method showed an advantage over the reported methods regarding the lower limit of quantitation [23 - 25].

The calibration curve using buffer pH 6.5 as a solvent was linear over the range of 0.2 to 3µg/ml and LOQ of 0.034µg/ml. And when using pH 1.2, pH 4.5, and pH 6.8 media as a solvent was linear over the range of 0.1 to 1.6 µg/ml, and LOQ was 0.007µg/ml, 0.014µg/ml, and 0.034µg/ml respectively.r2 was equal to 0.999, the accuracy of the results was

in the limit of 98% - 102%, and RSD% were less than 2% which is as per ICH and FDA guidelines [18, 19]. The standard deviation for intercept value was less than 5%, system suitability parameters as theoretical plates were above 2500, tailing factor less than 1.3,and so it could be used for determination of granisetron in bulk and pharmaceutical products.

The method is appropriate for use in preliminary and routine quality control check on distributed granisetron products in the market to ensure compliance of marketed distributed products under different storage conditions in pharmacies and hospitals with specifications, absence of probable degradative product formation, and reduction of active ingredient quantity in the dosage form, and safe administration of granisetron products with no side effects, and avoiding lack of clinical efficacy.

CONCLUSION

The HPLC analytical method developed for the determination of granisetronin bulk and marketing products and dissolution samples as revealed by the validation data enables specific, accurate, and precise analysis of the drug. The developed analytical method showed enough sensitivity for granisetron quantification in pharmaceutical dosage forms and can be used for routine analysis, quality control, and stability studies of pharmaceutical preparations and consequently assuring to some extend the efficacy and safety of granisetron in the management of chemotherapy-induced nausea and vomiting.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Sussman N. Reactions of patients to the diagnosis and treatment of cancer. Anticancer Drugs. 1995; 6(suppl 1): 4 – 8.
2. Osoba D, Zee B, Warr D, Latreille J, Kaizer L, Pater J. Effect of post chemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. Support Care Cancer. 1997; 5(4): 307 – 313.
3. Navari RM, Aapro M. Antiemetic prophylaxis for chemotherapy induced nausea and vomiting. NEJM. 2016; 374(14): 1356-1367.
4. Jordan K, Gralla R, Jahn F, Molassiotis A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): Content and implementation in daily routine practice. Europ J Pharmacol. 2014; 722: 197-202.
5. Hesketh PJ, Grunberg SM, Gralla RJ, David GW, Fausto R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of Chemotherapy –induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin. The Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003; 21(22): 4112- 4119.
6. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie MaG, Eldrige K, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer. 2003; 97(12): 3090–3098.
7. Blower PR. Granisetron: relating pharmacology to clinical efficacy. Support Care Cancer. 2003; 11(2): 93–100.
8. Allen A, Crome P, Davie CC, Davy M , Jones RW, et al. The pharmacokinetics of granisetron, a 5-HT3 antagonist in healthy young and elderly volunteers. Eur J Clin Pharmacol. 1995; 48(6): 519- 520.
9. Salajegheh S, Kuhestani S, Kermani MS, Taheri O, Bafghi NN. Comparison of Ondansetron and Granisetron Effects for Prevention of Nausea and Vomiting Following Strabismus Surgery. Open Access Maced J Med Sci. 2019; 7(19): 3195-3200.
10. Shapira M, Avrahami I, Mazaki-Tovi S, Shai D, Zemet R, et al. The safety of early pregnancy exposure to granisetron. Eur J Obstet Gynecol Reprod Biol. 2020; 245: 35-38.
11. https://www.drugs.com/newdrugs/heron-therapeutics-announces-fda-approvalsustol-granisetron-extended-release-prevention-4420.html
12. The British Pharmacopeia; British Pharmacopoeial Commission: UK, 2008.
13. Kudoh S, Sato T, Okada H, Kumakura H, Nakamura H. Simultaneous determination of granisetron and 7-hydroxygranisetron in human plasma by high-performance liquid chromatography with fluorescence detection. J Chromatogr B Biomed Appl. 660(1): 205-210.
14. Boppana V K. Simultaneous determination of granisetron and its 7-hydroxy metabolite in human plasma by reversed-phase high-performance liquid chromatography utilizing fluorescence and electrochemical detection. J Chromatogr A.1995; 692 (1-2): 195-202.
15. Pinguet F, Bressolle F, Martel P, Salabert D, Astre C. High-performance liquid chromatographic determination of granisetron in human plasma. J Chromatogr B Biomed Appl.1996; 675(1): 99-105.
16. Jiang Y, Lin M, Fan G, Chen Y, Li Z, et al. Rapid determination of granisetron in human plasma by liquid chromatography coupled to tandem mass spectrometry and its application to bioequivalence study. J Pharm Biomed Anal. 2006; 42(4): 464 - 473.
17. Nirogi RVS, Kandikere VN, Shukla M, Mudigonda K, Maurya S, et al. Quantification of granisetron in human plasma by liquid chromatography coupled to electrospray tandem mass spectrometry.Biomed. Chromatogr. 2006; 20(9): 888-897.
18. ICH HARMONISED TRIPARTITE GUIDELINE, Validation of Analytical Procedures: Text and Methodology Q2(R1).2005.
19. U.S. Department of Health and Human Services Food and Drug Administration, Guidance for Industry, Analytical Procedures and

Methods Validation for Drugs and Biologics. 2015.

20. U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry Waiver of in Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. 2017.
21. USP35, Granisetron Hydrochloride Tablets,
22. https://www.drugfuture.com/Pharmacopoeia/USP35/data/v35300/usp35nf30s0_m35870.html
23. Ernberg M, Wieslander FA, Hajizadeh KM, Arzt W S, Cankalp T, et al. The Effect of Granisetron on Sensory Detection and Pain Thresholds in Facial Skin of Healthy Young Males. Front Neurol. 2020; 11: 237.
24. Heda AA, Kathiriya JM, Gadade DD, Puranik PK. Development and Validation of RP-HPLC Method for Simultaneous Determination of Granisetron and Dexamethasone. Indian J Pharm Sci. 2011; 73(6): 696-699.
25. Angayer KS, Ajithadas A, Niraimathi V, Jerad SA. Estimation of Granisetron by Rp-Hplc in Oral Solid Dosage Form. Int J Chem Sci. 2011; 9(1): 95-98.
26. Rao SV, Ramu GR, Ravi K, Devarakonda, Rambabu, Cheedalla. A new isocratic RP-HPLC method development for the assay of Granisetron HCl in API and dosage forms. Rasayan Journal of Chemistry. 2012; 5: 229-233.