ejpmr, 2023,10(9), 306-309

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF IRINOTECAN HYDROCHLORIDE TRIHYDRATE USP IN BULK AND PHARMACEUTICAL DOSAGE FORM BY USING HPLC AND RP-HPLC METHOD

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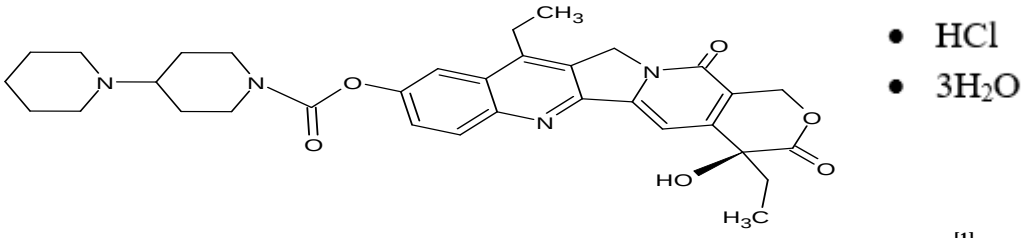
Article Received on 11/07/2023 **Article Revised on 01/08/2023** **Article Accepted on 22/08/2023**

ABSTRACT

Analytical method development and validation represent ongoing and autonomous tasks intertwined with research and development, quality control and quality assurance departments. The pivotal role of an analytical procedures in equivalence risk assessment underscores their contribution to establishing tailored acceptance criteria and result stability. The validation process confirms the appropriateness of analytical procedures for their designated purpose. The study explores HPLC and RP-HPLC methods for analyzing irinotecan hydrochloride trihydrate USP in bulk and pharmaceutical formulations, Parameters were defined and validated according to ICH guidelines, encompassing aspects such as solvent selection, linearity, range, precision, accuracy, robustness, specificity, LOD, LOQ and stability indicating analytical validation. The resulting methods are characterized by reproducibility, rendering them suitable for analyzing irinotecan hydrochloride trihydrate USP in both bulk and pharmaceutical forms.

KEYWORDS: Irinotecan hydrochloride trihydrate USP, HPLC, Validation, ICH-guidlince.

INTRODUCTION



IRINOTECAN HYDROCHLORIDE TRIHYDRATE USP (IHT) or (IRN)[1]

(S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo- 1H-pyrano [3',4':6,7]-indolizino [1,2-b] quinoline-9-yl-[1,4'bipiperdine]-1'-carboxylate, monohydrochloride, trihdrate.[2]

Synonym: Camptosar.[1]

Molecular formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$.[1]

Molecular weight: 677.1.[6]

Chemical class: Chemotherapeutic agent[3], anti-neoplastic agent.[2,9]

Category: Used for the treatment of colon -rectal cancer.[6]

Used for salvage therapy of breast cancer in Europe.[6]

It was approved for use in breast cancer treatment in Japan.[6]

Irinotecan is a semisynthetic natural alkaloid obtained from the Chinese plant Camptothecin acuminta.[1,2] IRN under the brand name Camptosar[1] and also it is a derivative of Camptothecin (CPT).[2,3] IHT is a pale yellow colour to crystalline solid compound.[6] It is soluble in solvents such as Methanol, water.[6] It is a chemotherapeutic agent[3], which has the potency to inhibit the action of topoisomerase -I. IRN prevents relegation of the DNA -strand by binding to topoisomerase I-DNA complex and mainly used for the first line drug choice for colon-rectal cancer.[3] The most significant adverse effects of IRN are severe diarrhea and extreme suppression of the immune system and also the immune system is adversely impacted which is reflected in dramatically lowered WBC count in blood.[3] IRN essentially a prodrug and hydrolyzed by

carboxylesterases to form the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38).[7] IRN HCl if officially listed in the IP-2007.[3]

METHOD

IRN HCl officially listed in the IP-2007, which describes the HPLC method for the estimation IRN HCl injection formulation. Several HPLC methods, LS-MS methods, HPTLC Method, visible spectrophotometric method, and a cyclic volumetric method has been reported for the determination of IRN HCl.[3]

A literature survey revealed that estimation of Irinotecan HCl was done by various analytical methods such as Visible Spectrophotometric method (Balaram et al., 2011), RP-UPLC method (Saini et al., 2009) and HPLC method (Shende et al., 2009; Satyanarayana et al., 2009; Venkateswara Rao et al., 2007; B. Mohammed Ishaq et al., 2010; Gogineni Ratna Prasad et al., 2011). Estimation of related substance in Irinotecan HCl was done mostly in human plasma (Iman Barilero et al., 1995; Iman Barilero et al., 1992; wei Zhang et al., 2009 and Owens et al., 2008). Sushama Talegaonkar et al., 2011, developed the stability indicating studies of Irinotecan HCl by HPTLC. Ali mohammad et al., 2010, developed a simultaneous estimation of Irinotecan HCl and SN-38 by RP-HPLC. No studies had reported on the estimation of related substance and forced degradation studies of Irinotecan HCl by RP-HPLC. Hence the present study was under taken to develop and validate a method for determination of related substance in Irinotecan HCl formulation and its stability indicating studies by RP-HPLC.[3]

REVIEW OF LITERATURE

1. **Ch. Kameshwara Rao[1] *et al.,*** A validated HPLC technique for the determining Irinotecan hydrochloride (IRN) in pharmaceutical dosage form was developed. For this chromatographic investigation, isocratic elution at a flow rate of 1.0ml/min was utilized on zorbax C18, 150mm 4.6mm, 5µ or similar. The mobile phase is made up of 45 volumes of the methanol and 55 volumes of the buffer Solution. The UV detection wavelength was 220nm, and a sample of 10.0µl was injected. The run time for sample, unmarked, placebo, system suitability and sensitivity solutions Approximately 12 minutes, and 60 minutes for diluted regular. The approximate retension time for IRN was determined to be 3.8 minutes. The %RSD IRN was determined. Irinotecan means % recovery was found to be within the specified limit. The approach was validated in accordance with ICH guidlince. The suggested HPLC method may .be successfully used for the routine formulation quality control examination.
2. **A. Sowndarya[2] *et al.,*** This work concerned with the simple and economic method for the estimation of Gemcitabine, IRN in bulk and pharmaceutical dosage form by RP- HPLC method stationary phase and mobile phase prepared with a mixture of ACN: Methanol (90: 10), the rate of flow is 1.0ml / min. Injection volume is 20µl, at detection wavelength 247 nm and run time at 10.0 mins. The analytical method is valid for estimation of Gemcitabine, IRN over a range of 12µg/ml -28µl/ml. The results of system suitability test, linearity, precision and accuracy, robustness, specificity, LOD and LOQ and stabilities presented in this report are with in the acceptance range. A specific, sensitive, economic method estimation of gemcitabine, IRN has been developed based on the ICH guidelines with bulk and dosage form.
3. **Rajasekaran Aiyalu[3] *et al.,*** A simple and reliable isocratic RP- HPLC stability indicating method has been developed and subsequently validated for the determination of IRN HCl and its related substance (SN-38) in pharmaceutical dosage forms as per ICH guidlinces. The separation achieved on the reversed phase Phenomenex Luna C18 column (5µ, 250 × 4.60 mm) as a stationary phase and 0.5% tricloro acetic acid: Acetonitrile: Methanol (60: 20: 20 v/v/v) as mobile phase at a flow rate of 1.0 ml /min. The UV detection was performed at 372 nm. The retension time for IRN HCl and SN-38 was found to be 8.65 and 7.30 min respectively. The detector response was linear in the concentration range of 30-150µg/ml. the respective linear regression equation being Y = 5233.x + 13299 with $R^2_{=\ 0.999}$. The percentage of IRN HCl in pharmaceutical dosage form was found to be 100.5% and the percentage of related substance (SN- 38) in formulation was found to be 0.19%. The limit of detection and the limit of quantification were found to be 0.014µg / ml and 0.045µg/ml respectively. The results of the study showed that, the proposed RP-HPLC method was simple, rapid, precise, accurate and stability indicating, which can be used for the routine determination of IRN HCl and its related substance (SN-38) in pharmaceutical dosage form.
4. **P. Praveen Srikumar[4] *et al.,*** A stability indicating RP-HPLC method has been developed and subsequently validated for the determination of irinotecan hydrochloride trihydrate (IHT) in bulk and injection formulation. The separation was achieved with a C_{18} water symmetry (250 × 4.6mm, 5µm) consist of a UV detector. Potassium dihydrogen phosphate buffer (P^H 3.5): Acetonitrile: Methanol (60:20 :20 v/v/v/) as a mobile phase, the flow rate was found to be 1ml/min. The UV detection was performed at a wavelength of 220nm. The described method linear range from 40-120µg/ml. The accuracy of the method was demonstrated at 5 levels in the range of 50 -150% of the specified limits and recovery of IHT was found to be in the range of 101-102.5%. This analytical research work is simple, rapid, selective, accurate, and more precise so this method is useful in the quality control of bulk manufacturing. In this research paper we have mainly observed that the

IHT sample solution in mobile phase was found to be stable for at least 24hrs at 25 ˚C (Room temp).

5. **Milind B. Ubale[5] *et al.,*** In this research work an isocratic reversed phase stability- indicating high Performance liquid chromatographic assay method was developed and validated for quantitative determination of Irinotecan hydrochloride in bulk drugs. An isocratic, reverse phase HPLC method was developed to separate the drug from the degradation products, using an Inertsil ODS C_{18} (250 × 4.6) mm, 5u column and mobile phase containing sodium dihydrogen phosphate buffer: Methanol: Acetonitrile in the ratio of 55: 28: 17 v/v/v. The detection was carried out at wavelength 254nm. The developed method was validated with respect to linearity, accuracy(recovery), precision, system suitability, selectivity, robustness proves the stability indicating ability of the method.
6. **A.K. Srivastava[6] *et al.,*** A HPLC method with UV detection to understand degradation path Path and quantification of Irinotecan in injection as pharmaceutical dosage form has been developed and validated as per guidelines from ICH, USP and other regulatory agencies. A linear isocratic elution was employed starting with 72% A and 28% B upto30min. In this review paper used two mobile phases, mobile phase A consist 0.005M Heptane sulphonic acid and 0.05M Dibasic phosphate buffer of p^H 3.0. Mobile phase B consist only acetonitrile. The UV detection was performed at 254nm. The chromatographic column was hypersil $C_{18,}$ hyper bond (300nm × 3.9mm) 10.0 µ kept at room temperature. All impurities were separated and it was possible to quantify the Irinotecan in formulation with reasonable accuracy and precision. The method was validated for its specificity, Accuracy, linearity, ruggedness and robustness. The correlation coefficient for Irinotecan peak Area was found to be 1.000 for linearity ranging between 32.49 µg/ml to 48.74 µg/ml and limit of detection was found to be 0.50 µg/ml. this method is employed in the routine and stability analysis.
7. **Ali Mohammadi[7] *et al.,*** A new simple, precise and accurate high performance liquid Chromatography (HPLC) method was developed and validated for the simultaneous Determination of Irinotecan (CPT-11) and two related compounds in pharmaceutical dosage form. Chromatography was accomplished using a reversed-phase C_{18} column and ultraviolet (UV) detection and an isocratic mobile phase consisting of 3% v/v triethylammonium acetate buffer (P^H 3) and acetonitrile (70: 30 v/v). The linear range of quantitation for all the compounds was 0.1-10 µg/ml. The limit of quantitation for all the compounds ranged between 0.01-0.05 µg/ml. This method has the requisite accuracy, selectivity, sensitivity and precision to assay of CPT -11 and related compounds in pharmaceutical dosage forms and bulk API.
8. **P. Shende[8] *et al.,*** an isocratic reversed-phase high performance liquid chromatographic (RP-HPLC) method for analysis of irinotecan HCl has been developed and validated. Separation was achieved on a C_{18} column with potassium dihydrogen phosphate buffer (adjusted to 3.5 with orthophosphoric acid)- acetonitrile-methanol 55: 25: 20 (v/v) as mobile phase at a flow rate of 1.0 ml min^{-1}. UV detection was performed at 254nm. The method is simple, sensitive, rapid and selective, and linear over the range 30-70µg ml^{-1} for assay of irinotecan HCl. The precision of the assay method was below 1.0% RSD. Mean recovery was in the range 98.0-102.0%. Recovery of the API from the dosage forms Ranged from 99.0 to 101.0%. This method is useful for the quality control in bulk Manufacture and of the pharmaceutical formulation.
9. **Venkateshwara Rao J.[9] *et al.,*** A simple and rapid reverse phase high performance liquid Chromatography (RP-HPLC) method was developed and validated for the quantitative Determination of Irinotecan in bulk drug samples and formulations. Irinotecan was analyzed by using reverse phase cyano column (4.6mm × 25 cm, 5µ), with mobile phase consisting of Phosphate buffer: acetonitrile (75: 25 v/v), p^H adjusted to 2.5 with phosphoric acid. The flow rate was set 0.8 ml/min and the analysis was performed at wavelength 225nm photo Diode Array (PDA) detector at ambient temperature. The method was validated and stability studies were conducted under different conditions. The retention time for Irinotecan was around 5.82minutes. The calibration curves were linear ($r \geq 0.9998$) over a concentration range from 20.0 to 80.0 µg/ml. The LOD and LOQ were found to be 8µg/ml and 24µg/ml respectively. The developed method was successfully applied to estimate the amount of Irinotecan in injection formulations.

CONCLUSION

The comprehensive literature survey, a multitude of analytical techniques includes HPLC, RP-HPLC and sum simultaneous methods have been developed and documented. These methods were meticulously validated in accordance with ICH guidelines, demonstrating their reproducibility and selectivity. The collective evidence underscores that these established approaches are viable and effective for development of new analytical method for estimation and validation of novel anti-cancer drug Irinotecan hydrochloride trihydrate USP in both its bulk and pharmaceutical dosage form.

REFERENCE

1. Rao CV, Ramakrishna K, Abbaraju VK, Tadikamalla UR, Rahul D. Development of Method and Validation for Assay in Irinotecan Hydrochloride Injection by applying Stability Indicating HPLC Methodology by HPLC. Rasayan Journal of Chemistry, Oct 1, 2022; 15(4): 2893-900.

2. A Sowndarya, DR. Subhas Sahoo. A Simple Stability Indicating Analytical Method Development and Validation for Simultaneous Estimation of Gemcitabine, Irinotecan in API and Tablet Dosage For by RP-HPLC. International Journal of Advanced Research in Medical and Pharmaceutical Science, Feb. 2, 2020; 5(2): 15-23.
3. Aiyalu R, Cherukuri R, Joghee D. Development and Validation for the Determination of Related Substance in Irinotecan HCl formulation and its Stability Indicating Assay by RP-HPLC method. American Journal of PharmTech Research, 2013; 3(4): 646-56.
4. P. Praveen S, T. Siva Lakshmi, S. Kathirvel, B. Lourbu R AND N. Madhavi. Development and Validation of Stability Indicating RP-HPLC Method for Determination of Irinotecan Injection formulation. International Journal of Pharmacy and Pharmaceutical Sciences, Mar 26, 2013; 5(2).
5. Dhakane VD, Ubale MB. A validated stability-indicating HPLC assay method for Irinotecan Hcl in bulk drug. Int J Res Pharm Bio Sci., 2011; 2(4): 13-18.
6. AK Srivastava, K Pallavi, S Shamshul, SC Khurana. Development of Stability Indicating HPLC Method for the Assay of Irinotecan in the presence of degradents. Analytical Chemistry An Indian Journal, June 31, 2011; 10(10): 665-69.
7. Mohammadi A, Esmaeili F, Dinarvand R, Atyabi F, Walker RB. Simultaneous determination of irinotecan hydrochloride and its related compounds by high performance liquid chromatography using ultraviolet detection. Asian Journal of Chemistry, May 30, 2010; 22(5): 3966-72.
8. Shende P, Gaud R. Validated RP-HPLC analysis of irinotecan HCl in the bulk material and in pharmaceutical formulations. Acta Chromatographica, Mar 1, 2009; 21(1): 71-82.
9. Balaram V M, Rao J VE, Ganesh G RS, Krishna T B. Validated reverse phase HPLC method for the determination of irinotecan in pharmaceutical dosage forms. E-Journal of Chemistry, 2007; 4(1): 128-36.
10. World Health Organization (2019), World Health Organization Model List of Essential Medicines: 21st list 2019, Geneva: World Health Organization.
11. Lindholm J, Development and Validation of HPLC Method for Analytical and Preparative Purpose, Acta Universities Upsaliensis Uppsala, 2004; 13-14.
12. Patel RM, Patel PM, Patel NM, Stability Indicating HPLC Method Development- A Review, Int Res J Pharmacy, 2011; 2(5): 79-87.
13. Kumar VK, Raju NA, Rani N, Rao JVLNS, Satyanarayana T. The estimation of irinotecan HCl in parenterals by RP-HPLC, Asian J. Res Chem., 2009; 2: 54-56.
14. Saini P.K, Jain CL, Mathur SC, Singh GN. Determination and validation of irinotecan hydrochloride by RP-UPLC method. The Indian pharmacist, 2009; 8: 55-58.
15. Abdullah K., Rabba Luqin Si, Kewen Xue, Ming Li, Gao Li. In Situ Intestinal Perfusion of Irinotecan: Application to P-gp Mediated Drug Interaction and Introduction of an Improved HPLC Assay. Journal of Pharmacy and Pharmaceutical Sciences, 2011; 14(2): 138– 147.
16. FDA: Guidance for Industry, Analytical Procedures and Methods Validation, August, 2000.
17. International Conference on the Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Q2B.Validation of Analytical Procedures, Methodology, 1996.
18. System Suitability, Chromatography, Chapter-621, United State Pharmacopiea, Jan-1, 2003; 29.
19. U.S. Pharmacopeia 23, United States Pharmacopeial Convention, Inc., 1994; 1982-84.
20. International Conference on Harmonization, Draft Guideline on Validation of Analytical Procedures: Definitions and Terminology, Federal Register, March 1, 1995; 60: 11260.
21. Reviewer Guidance, Validation of Chromatographic Methods, Center for Drug Evaluation and Research, Food and Drug Administration, 1994.
22. ICH; Stability Testing: Photostability Testing of New Drug Substances and Products (ICH, Geneva, Switzerland, November, 1996.
23. International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human use, Validation of Analytical Procedures: Methodology, Geneva, 1996.
24. ICH Harmonized Tripartite Guideline., ICH Q2A. Text on validation of analytical procedures, 1995.
25. ICH Harmonized Tripartite Guideline., ICH Q2B: Validation of analytical procedures: methodology, 1997.