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Development of Green High Performance Liquid Chromatography Method for Determination for Ranitidine Hydrochloride in Solid Dosage Form by Applying Lean Sigma principles.

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ABSTRACT

This study was applied in developing new reverse phase liquid chromatographic method to reduce the organic solvent from the analytical method by applying the Lean Six Sigma (LSS) methodology and waste management. LLS is considered one of the successful approaches in the field of quality improvement and cost reduction. A simple, specific and accurate reverse phase liquid chromatographic method has been developed for the estimation of Ranitidine HCl from tablet formulation. The drug is official with Indian Pharmacopeia, United States Pharmacopeia British Pharmacopoeia, however these Compendial procedures does not involve aqueous solvent as diluents. Define, Measure, Analysis, Improve and Control (DMAIC) principles were used for problem solving, root cause investigation, risk management to improve method performance. The process capability evaluation of the method before and after modification revealed that proposed method has better process capability. We subjected a high performance liquid chromatographic (HPLC) analytical procedure used for quantification of Ranitidine HCl to a Failure Mode and Effects Analysis (FMEA), including technical risks as well as risks related to human failure. An FMEA tool broke down the HPLC analytical method into process steps and identified possible failure modes for each step. Each failure mode was ranked on estimated frequency of occurrence (O), probability that the failure would remain undetected later in the process (D) and severity (S), each on a scale of 1–10. Failure risks were calculated by Risk Priority Numbers (RPNs) =O×D×S. Failure modes with the highest RPN scores were subjected to corrective actions and the FMEA was repeated, showing reductions in RPN scores and resulting in improvement indices up to 5.0. The separation was carried out using 25 cm x 4.0 mm packed with octadecylsilane bonded to porous silica (10 µm) column and the mobile phase consisted of (methanol: ammonium Acetate- 85:15) in isocratic mode. The flow rate was 1.00 ml/min and effluent was monitored at 322 nm. The method was successfully used for quantitative determination of Ranitidine HCl from tablet dosage form. The capabilities of IP and new assay methods were determined and compared. It was studied which factors had the largest effects on the capability of chromatographic HPLC methods in order to reduce the organic solvent and improve their precision and accuracy. This was done using DMAIC principles. The investigations showed that it was feasible to define an alternative HPLC method with a better capability as the IP method. Aqueous solution of Ranitidine HCl tablet formulation was found with enhanced the method capability with solution stability up to 72h.

Keywords: Ranitidine HCl; HPLC method; Lean Six Sigma; DMAIC; FMEA; Indian Pharmacopeia.

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INTRODUCTION

Green chemistry is the design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment. Green chemistry is a fundamentally different approach that protects human and environmental health by replacing hazardous chemicals, processes, and products with safer alternatives. The practice of chemistry in a manner that maximizes its benefits while eliminating or at least greatly reducing its adverse impacts has come to be known as green chemistry. ''Green Chemistry is the use of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, by-products, solvents, reagents, etc. that are hazardous to human health or the environment''. In short, it is the use of chemistry for pollution prevention. One of the Parameters determining 'Green Nature' of analytical chemistry is eliminating (or at least reducing the consumption) chemical reagents particularly organic solvents, which is also one of the highlighting aims of industries in cost reduction and reducing carbon footprint. One way to reduce company's carbon footprint is by reducing or eliminating organic solvents and replace with aqueous one in the process. Organic solvent reduction helps the environment because it reduces carbon output, also helps a business since the less organic solvent that use, the lesser is the process cost. Plus, the elimination of excess energy output also improves the overall efficiency of the organization, which is one of the main goals of Green Six Sigma.

Green Six Sigma as a process has been around for years as a way to reduce errors and improve processes. It has only been recently, however, that the concept of green Six Sigma has started really catching on. Green Six Sigma helps companies not only deal with the traditional issues within manufacturing and non-manufacturing process, but it also helps companies reduce their environmental impact. Green Six Sigma is a very new concept so the details are still being hammered out. Generally, however, the goal of green six sigma is to help companies in planning for sustainability and energy reduction while increasing the profits. The Six Sigma approach has been increasingly adopted worldwide in the manufacturing sector in order to enhance productivity and quality performance and to make the process robust to quality variations [1]. Quality is defined as the fitness for use or purpose at the most economical level [2]. It is an integral part of the process of design, manufacture and assembly. It can be assured by having effective procedures and controls at various stages. In manufacturing industries, to overcome the competition problem and to retain the share of the market, it is necessary to constantly improve the quality of the product without the increase in the price. The price is influenced by the cost of production, which in turn is influenced by waste, rework, rejection and downgrading rates. Attention to quality assurance can reduce the process waste, which results in a quality production and company's growth and profitability. Six sigma methodology was introduced for quality improvement [3]. Six Sigma has two key methodologies: DMAIC and DMADV. DMAIC is used to improve an existing business process. DMADV is used to create new product designs or process designs in such a way that it results in a more predictable, mature and defect free performance. DMAIC is a closed-loop process that eliminates unproductive steps, often focuses on new measurements, and applies technology for continuous improvement.

Ranitidine hydrochloride is a histamine H2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro oesophageal reflux disease (GERD).Ranitidine hydrochloride is subject to degradation upon aging and that such degradation is accelerated by moisture and light. For dealing with such stability problem of Ranitidine, tablets are film coated with suitable polymers. Ranitidine hydrochloride tablets are film coated as ranitidine hydrochloride is hygroscopic in nature. Generally these tablets are formulated as immediate release tablets and the coating material used is non enteric coating material. The materials used for film coating are HPMC, Methyl HEC, EC, HPC, Povidone, Na CMC, PEG, Acrylate polymers, Opadryl etc. Some of these materials are soluble in water but not organic solvents and some are soluble in organic solvents but not in water. As methanol: ammonium acetate (85:15) can extract ranitidine from triturated coated tablets, even coating material or other excipients are not soluble in it, water can also have same property as ranitidine hydrochloride is freely soluble in water as it is in methanol. In IP method for analysis of Ranitidine hydrochloride tablet, the mobile phase and diluent is Methanol: 0.1 M Ammonium acetate (85:15). The diluent required for one sample preparation is 525 mL excluding standard preparation and the retention time of Ranitidine is about 3 to 4 min. The requirement of methanol as diluent is more than its requirement as a mobile phase. 'Assuming production of 1 batch/formulation/day', there are 9490 batches of Ranitidine HCl are produced per year in India. Hence, in a year at least 5694 L of methanol consumed only for assay of Ranitidine hydrochloride tablets by IP method [4].

In order to optimize any analytical method for solvent reduction, it is necessary to select a suitable diluent or to replace it by safe solvent compared to existing solvent.

Thus to optimize Ranitidine hydrochloride tablet IP method for solvent reduction, in the present paper it is proposed that water can be preferred as diluent considering its properties and its advantages over organic solvents from the point of view of green chemistry, carbon foot prints and cost. It is expected that the developed analytical method will bring about reduction in the usage of organic solvent leading to green initiative for safer environment. The objective of this research work was to initiate green initiative in method development which will lead to safer environment using operational excellence tools such as Supplier, Input, Process, Output, and Customer*(*SIPOC), 5 why's, Cause and Effect, and FMEA etc. The assay of a drug substance (DS) in solid dosage form is one of the tests required to confirm the Active Pharmaceutical Ingredient (API) quality at release.

EXPERIMENTAL

Reagents

Methanol, Ammonium Acetate, Acetic Acid, Hydrochloric Acid, Sodium Hydroxide and Hydrogen Peroxide were used of Analytical grade reagent. Purified water was used from Millipore's Milli-Q.

Reference standards

Ranitidine Hydrochloride reference standards and bulk sample was obtained from GlaxoSmithKline Pharmaceuticals Ltd.

Instrumentation

Mettler Toledo XP 105 Delta Range analytical balance was used to weigh the required materials, Mettler Toledo Seven Multi pH meter was used to adjust the pH of solutions. Waters Alliance chromatographic system with 2690 separation module, and 2487 dual wavelength detector was used. Agilent 1100 series chromatographic system was used to assess the robustness of the method.

Reference solution and Resolution solution preparation

56 mg of Ranitidine hydrochloride RS weighed in 100 mL volumetric flask, dissolved in water, sonicated for 5 min, make up volume by water this solution was labelled as solution A.

5mL of solution A was further diluted to 25 mL by water. This solution was labelled as solution B.20 mg of Ranitidine s oxide solution was weighed in 100 mL volumetric flask, dissolved in water, sonicated for 5 min, make up volume by water. This solution was labelled as solution C.2 mL of solution A and 5 mL of solution C was diluted to 100 mL with water.

Solution B was used as Reference solution and solution C was resolution solution. Before injecting, each solution was filtered through 0.45 µ filter by discarding first 5mL.

Preparation of Test solution

Weighed and finely powdered 20 tablets using mortar and pestle. Weighed 1.5 g of the powder in 500 mL volumetric flask, added 400 mL of the Water, sonicated this solution for 20 minutes and made up to volume with Water, centrifuged 5 to 10 mL of this stock solution for 10 minutes at 2500 RPM, diluted the supernatant of centrifuged solution with the Water to obtain a solution containing the equivalent of 0.012 percent (w/v) of Ranitidine. Before injecting the working solution was filtered through 0.45 µm nylon membrane filter to avoid column deterioration.

Blank preparation

Water was filtered through 0.45 µm nylon membrane filter and injected to HPLC system.

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HPLC technique

Waters HPLC with 2690 separation module and 2487 dual wavelength detector. Ranitidine HCl and Ranitidine S-Oxide impurity peaks were resolved on stainless steel column with 25 cm length, 4.0 mm internal diameter, packed with octadecylsilane bonded to porous silica with 10 µm particle size. The chromatographic conditions are listed under **Table 1**.

Table 1: Chromatographic Conditions.

Sr.No	Parameter	Condition
1	Mobile phase	A mixture of 85 volumes of methanol and 15 volumes of 0.1 M ammonium acetate
2	Column Temperature	Ambient
3	Flow rate	2 ml per minute
4	Detection Wavelength	322 nm
5	Injection volume	20 µL

RESULTS AND DISCUSSION

Define phase is the first and foremost phase of the project where the quantified objectives, project scope, deliverables and constraints were clearly defined. This step acts as road map for the project and has wide implications on success of the project.During Define phase preliminary data was collected, problem statement was defined, variables related to Supplier, Input, Process, Output, and Customer (SIPOC) were identified,and analysis process was mapped.Ranitidine HCl assay determination process in the tablet dosage formas per IP 2010 monograph is composed mainly of the following steps. Tablets are ground to fine powder from which sufficient amount of fine powder is weighed then the diluent is added to dissolve and extract the drug from the sample matrix. Weighed 1.5 g of the powder in 500 mL volumetric flask, added 400 mL of the Water, sonicated this solution for 20 minutes and made up to volume with Water, centrifuged 5 to 10 mL of this stock solution for 10 minutes at 2500 RPM, diluted the supernatant of centrifuged solution with the Water to obtain a solution containing the equivalent of 0.012 percent (w/v) of Ranitidine. Before injecting the working solution was filtered through 0.45 µm nylon membrane filter to avoid column deterioration.SIPOC is an acronym standing for supplier, input, process, output, and customer. It refers to the technique of analyzing a process relative to these parameters to fully understand their impacts. A SIPOC diagram for the Ranitidine HCl assay determination process is given in **Figure 1**.

Data Collection

Preliminary data was collected wherein Ranitidine HCl assay determined as per IPmonograph. The average percentage assay was found about 98.5 against the input of 100% of Ranitidine HCl. With 97.5 as minimum and 99.5 as maximum assay values. Then a powerful methodical technique such as lean six sigma was needed to be implemented to replace organic solvent completely from the diluent and improve the Ranitidine HCl assay against the input.

Problem Statement

To investigate and identify the green solvent for quantitative determination of Ranitidine HClfrom tablet formulation.

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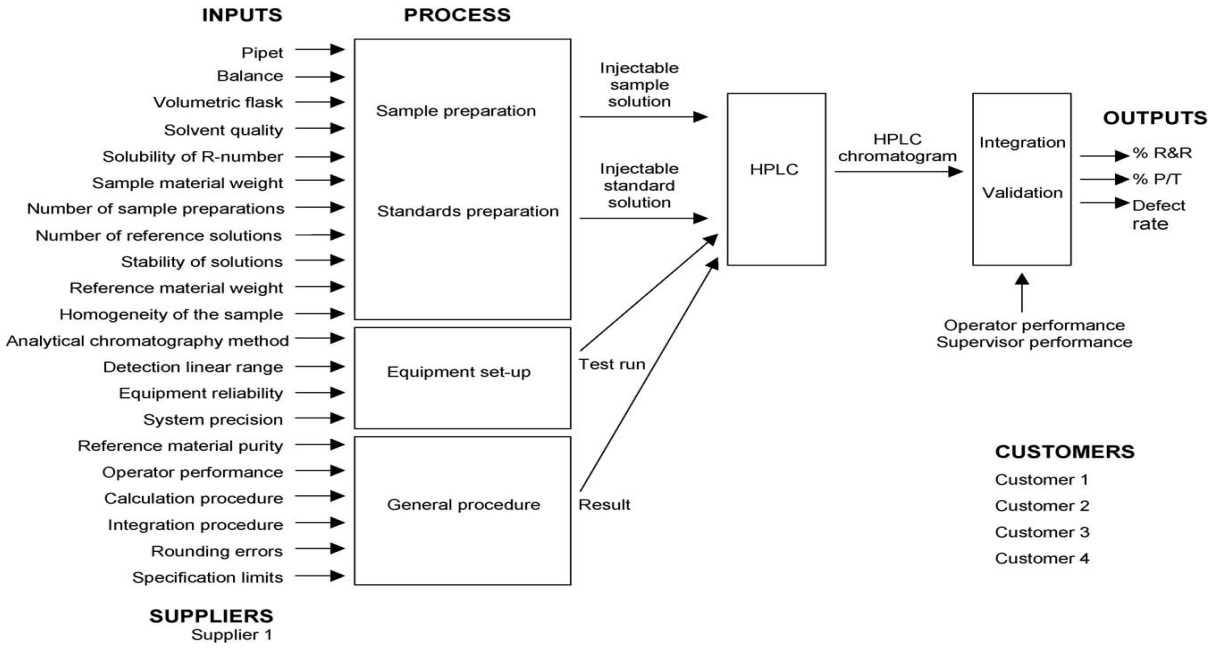

Figure 1: SIPOC diagram for Ranitidine HCl assay determination process.

Process Mapping

In order to have a detailed understanding of the sample preparation processes in the assay method of analysis as per the methodology official in IP Ranitidine HCl tablets and their relationships, the process map **(Figure 2)** as one of the tools of LSS was used. The process map highlights the different areas where the reduction in organic solvent is possible. Studying the process elements revealed that the significant amount of organic solvent is used for the sample preparation wherein 525 mLMethanol is consumed for one sample preparation.

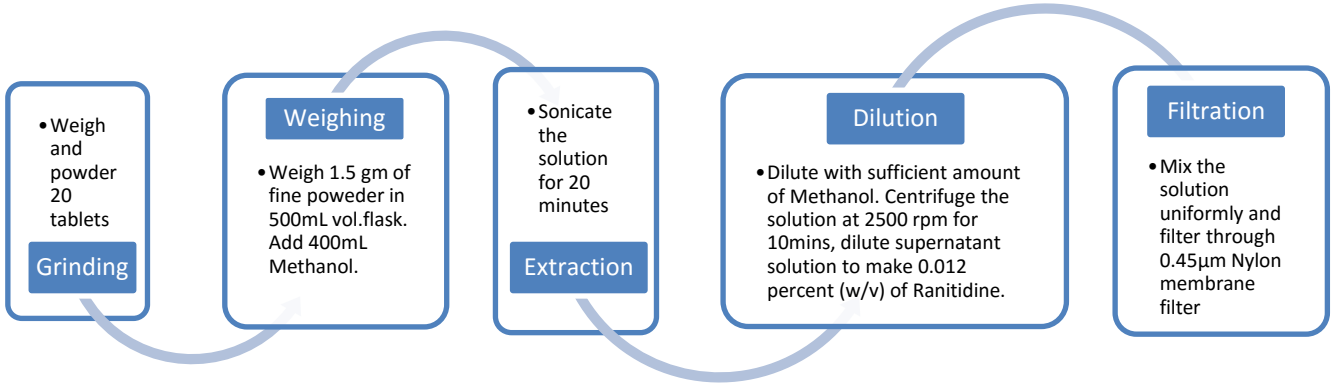

Figure 2: Process Map - Sample preparation as per IP 2010 Thyroxin sodium tablets assay method.

Measure phase

During this stage, one measures the existing system and establish valid and reliable metrics to help monitor progress towards the project goals. Initially Identification, classification and description of the potential critical defects is carried out. Based upon historical data, collected data, brainstorming sessions and various tools like statistical process control the key potential problems are identified. The central idea of SPC is to control variation so as to avoid product defects. There are two kinds of variation in any process: common causes and special causes. Common causes refer to occurrences that contribute to the natural variation in any process. Special causes are unusual occurrences that are not normally (or intentionally) part of the process. While some degree of common cause variation will naturally occur in any process, it's important to identify and attempt to eliminate special causes of variation. During measure phase percentage assay values were

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subjected for statistical evaluation wherein control chart was utilised to evaluate whether IP2010 test method within statistical process control.

Statistical Process Control and Process Capability

The individual control chart shows no trend of the data with variability. Themoving range chart shows no point is outside the control limits exhibiting a random pattern, suggesting no presence of special causes shown in **Figure 3**. Analysis process as per IP Ranitidine HCl tablets monograph is observed to be non-variable with no special cause.The control chart is under statistical control and can be used for monitoring andcontrolling the future production batches.

The probability plot indicates that the assumption of population normality is reasonable. The R chart and a Cp index greater than the reference value of 1.33 suggest stability of subgroup variation and indicate that the within-subgroup variation process is acceptable. However, the Pp index greater than the reference value of 1.33, so the overall capability of this process is adequate due to similarity between subgroups. The Xbar Chart and plot of the last 9 subgroups also depict this similarity. This process doesn't need improvement.

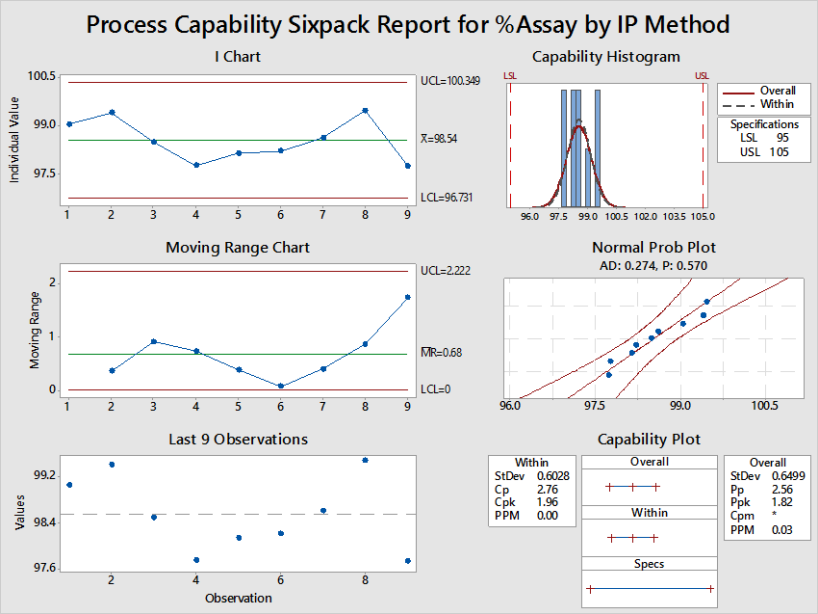

Figure 3: Process capability–Ranitidine HCl % assay as per IP.

Analyse phase

Statistical analysis is used to examine potential variables influencing the CTQs and seek to identify the most significant root causes and develop a prioritized list of factors influencing the desired outcome. Here one isolates and verify the critical processes. The potential list of the problems is narrowed to the vital few and the input/output relationship which directly affects specific problems is identified and potential causes of process variability were verified. Cause and Effect, Process flow cause and effect and Failure mode effect analysis was performed during this phase.

A cause and effect illustrating the main parameters controlling the results of analysis is presented in **Figure 4** wherein factors affecting recovering of assay value were identified.

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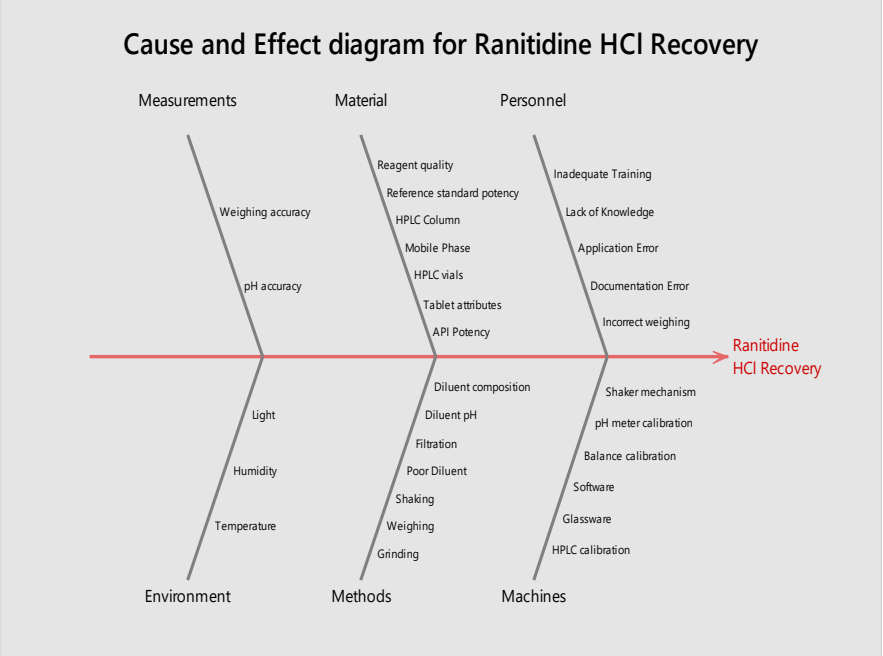

Figure 4: Cause and effect diagram of factors affecting Ranitidine HCl recovery.

A process flow cause- effect analysis is drawn for the total process to identify exact location of occurrence in complete process. Sample preparation of Ranitidine HCl as per IP **[4]**, the process is started from the grinding and completed after filtration. The intermediate stages are weighing, extraction and dissolving. The process flow cause- effect diagram is developed to identify the causes, sub causes and exact location of causes for the defects in lowering of assay values. As defects in product may occur anywhere in the total process, so it is very necessary to identify and eliminate the causes which are responsible for defects in the process. The process flow cause- effect diagram is shown in **Figure 5.**

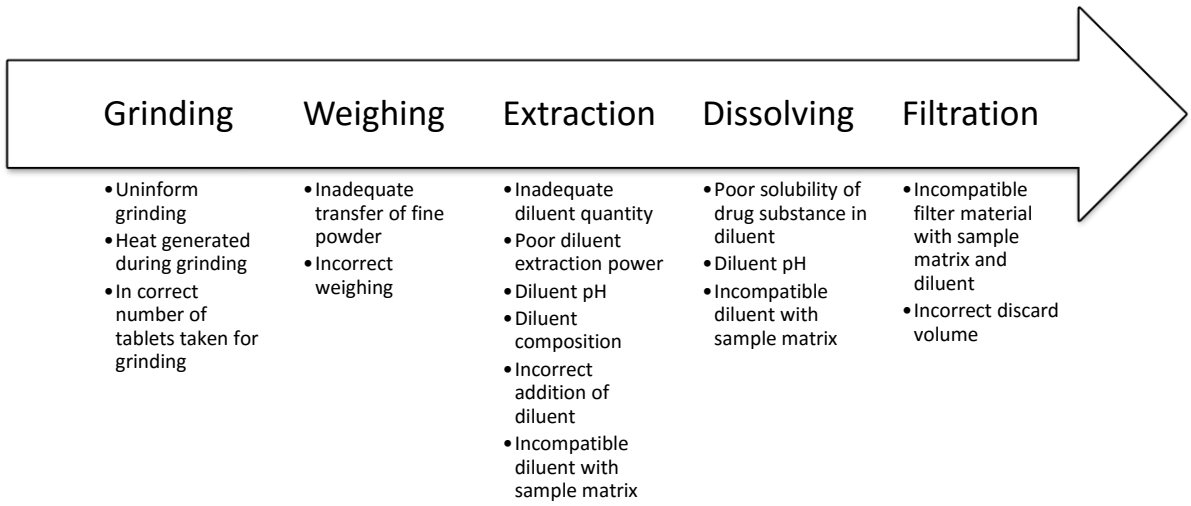

Figure 5: Process flow cause-effect diagram for sample preparation as per IP 2010.

Ranitidine HCl sample preparation method as per IP **[4]** method was broken down to single process steps these steps are listed under **(Table 2)**. Subsequently, failure modes were identified for each of theirmeaning steps. Each failure mode was then ranked by its estimatedfrequency of occurrence (O), its probability that the failurewould remain undetected (D) and its severity (S), each on a scale of 1–10. A high number represents a high risk. Ranking was performedby a consensus decision of the team.

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Table 2: Ranitidine HCl sample preparationsingle process steps IP 2010.

Step No.	Process
1	Grinding of tablets to fine powder
2	Weighing of fine powder accurately 1.5 gm
3	Extracting drug substance from sample matrix to Methanol
4	Dissolving drug substance in diluent
5	Filtering diluted solution using 0.45µm nylon membrane filter and subjecting to HPLC system

For each identified failure mode, the RPN was calculated bymultiplying the rankings for O, D and S. Consequently, the highestRPN that was theoretically possible became 1000 (10×10×10) and the lowest theoretically possible RPN became 1. FMEA results were reviewed with respect to the four failure modes with the highest RPN scores. The calculated RPN score and corrective actions are listed under **(Table 3)**. It was revealed that the inadequate diluent and extraction were scored high with RPN 400. The investigation was targeted to the factors affecting inadequate diluent and extraction.

Table 3: Ranitidine HCl sample preparation FMEA IP method.

Step	Failure mode	Possible effect	Possible cause	Estimated frequency of occurrence	Estimated frequency of detection	Estimated severity	RPN	Corrective action
1	Inadequate grinding	Incorrect assay value	Human error	3	10	5	150	Training
2	Inadequate weighing	Incorrect assay value	Human error	3	10	5	150	Training
3	Inadequate Diluent	Incorrect, aberrant assay values. Poor solution stability	Diluent pH, composition, extraction capacity	8	10	5	400	Change in diluent
4	Inadequate extraction	Lowering of Assay values	Diluent pH, composition, extraction capacity	8	10	5	400	Change in sample preparation method and diluent
5	Inadequate filtration	Incorrect assay value	Incompatible filter material, incorrect discard volume	4	10	5	200	Change in filter type with accurate discard volume

The literature survey revealed that Ranitidine HCl is soluble in water, Acetic Acid, Methanol andsparingly soluble in Ethanol, Insoluble in Chloroform [4-7].This suggests that Methanol can be replaced with Water completely as the drug is soluble in water as well.These causes were considered in the improve phase of the lean six sigma process to be addressed for possible improvement according to the available resources.

Improve phase

This Phase of the project comprises the optimisation of significant parameters derived from Analyse phase. Simultaneously improvement actions for significant parameter are implemented during this phase so as to reduce risk associated with a particular Failure mode or cause. Various actions taken during the course of this project are enlisted below:

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Based on previous studies and processknowledge, the most important controllable factors are solubility of Ranitidine HCl in thediluent used for sample preparation. IP Ranitidine HCl method was proposed for diluent composition used for standard and sample preparation only with rest method parameters unaltered. Method parameters compared and listed under **Table 4** for method parameters comparison.

Table 4: Ranitidine HCl tablets method comparison IP andproposed IP 2010.

Parameters	I.P. Assay Method	Optimized method
Mobile phase	A mixture of 85 volumes of methanol and 15 volumes of 0.1 M ammonium acetate	A mixture of 85 volumes of methanol and 15 volumes of 0.1 M ammonium acetate.
Diluent*	Mobile phase	Water
Reference solution*	A 0.0112 per cent w/v solution of ranitidine hydrochloride RS in the mobile phase.	Reference solution-A 0.0112 per cent w/v solution of ranitidine hydrochloride RS in theWater. 2. Resolution solution-A 0.00112 per cent w/v solution of ranitidine hydrochloride RS and 0.001 per cent w/v solution of ranitidine -s -oxide in theWater.
Test solution/Sample preparation*	Weigh and powder 20 tablets. Shake 1.5 g of the powder with 400 ml of the mobile phase, dilute to 500.0 ml with the mobile phase, filter and dilute the filtrate with the mobile phase to obtain a solution containing the equivalent of 0.01 per cent w/v of ranitidine.	-Weigh and powder 20 tablets. -Weigh 1.5 g of the powder in 500 ml volumetric flask, add 400 ml of the water, Sonicate for 20 min. make up volume with the water, centrifuge 5 to 10 ml of this stock solution for 10 min. at 2500 RPM, dilute the supernatant with the water to obtain a solution containing the equivalent of 0.012 percent w/v of ranitidine. Before injecting filter through 0.45 µ membrane filter to maintain column efficiency.
Column*	steel column 25 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm)	Stainless steel column 25 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (10 µm)
Column Temp.	Ambient	Ambient
Flow rate	2 ml per minute	2 ml per minute
Detection Wavelength	322 nm	322 nm
loop injector	20 µL	20 µL
Retention Time	3 to 4	3 to 4
System Suitability Criteria: The test is not valid unless*	Relative standard deviation for replicate injections of Reference solution is not more than 2.0 Percent	RSD for replicate 5 injections of Reference solution is NMT 2.0 Percent Resolution between peaks due to Ranitidine and Ranitidine s oxide is not less than 1.5

***** indicates change in parameter / criteria in optimized method than IP method

Samples were analyzed as per IP and proposed IP 2010 method using parameters indicated in **Table 4**. Assay results obtained from IP and proposed method were compared using interval plot at 95% confidence interval refer **Figure 6**. The comparison revealed that the mean assay value obtained from proposed method was higher compared to IPmethod. The interval plots shows; for IP method, the means and confidence intervals appear to drift downward and for proposed method, the means and confidence interval appear to drift upward compared to IP method.Interval plots concludes that the variance is related to the mean. Percentage assay values by both the methods were subjected to One-way ANOVA, which revealed that the mean Percentage assay values by IP and proposed methods are significantly different as both the intervals has zero as an endpoint refer **Figure 7**.

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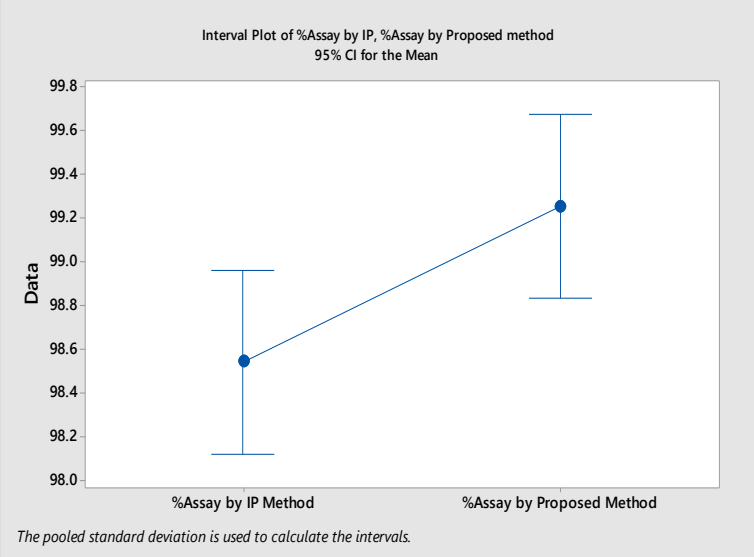

Figure 6: Interval plot percentage assay values by IP and proposed method.

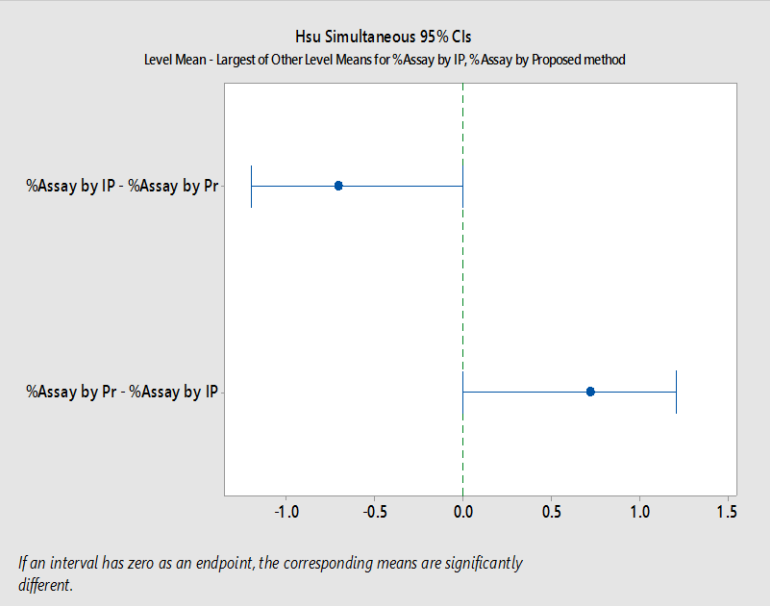

Figure 7: One-way ANOVA of percentage assay values by IP and proposed method.

Statistical equivalency of Ranitidine HCl IP and proposed method was evaluated and found that the compared methods are not statistically equivalent. Null hypothesis was failed hence the equivalency could not be claimed **(Figure 8)**.For the Ranitidine HCl assay values by IP and proposed methods, the confidence interval for the difference is completely outside the equivalence interval. Thus it can conclude that the two methods of Ranitidine HCldoesn't contain equivalent amounts of Ranitidine HCl. The mean percentage assay by proposed method was found comparatively higher than the IP method.

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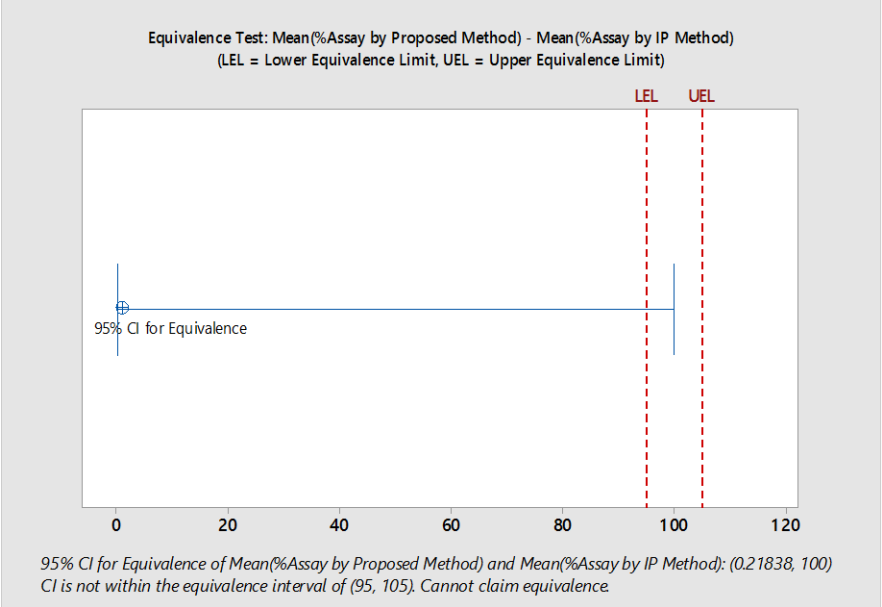

Figure 8: Equivalence test of IP and proposed method.

Solution Stability after improvement

Solution stability is critical parameter to be considered for the change in diluent. During improve phase, Methanol from the sample preparation was completely replaced with Water. pH of sample diluent was checked which was found about 6.8. The solution stability of sample prepared as per proposed method was evaluated. The solution stability study revealed that Ranitidine HCl in sample solution doesn't degrades rapidly in aqueous solution. At T0 the percentage assay value was found to be 98.40 against 97.79% at 72 h which shows that the Ranitidine HCl aqueous solution is stable till 72 h, the regression fitted line plot revealed that all the assay values from T 0 to 72 h are within the 95% confidence interval refer **Figure 9.**

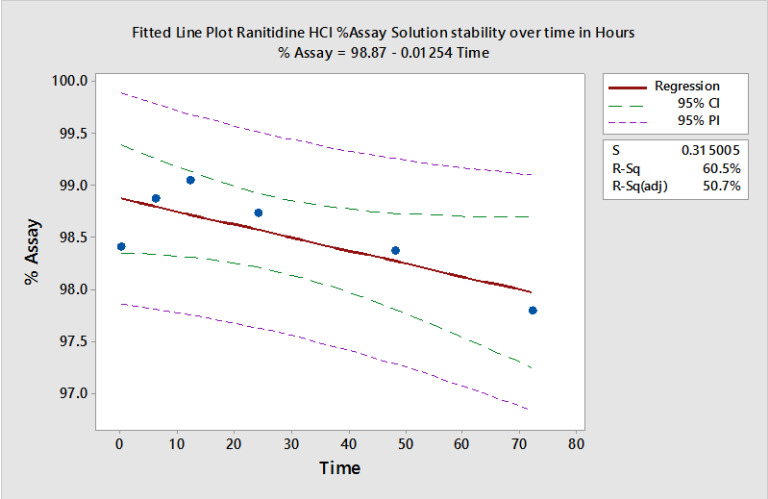

Figure 9: Fitted line plot of Ranitidine HCl solution stability by proposed method.

Control phase

Confirmation experiments were conducted tocheck the achieved improvement. Individual value, moving range plots, probability plots, capability histogram and capability plotsof proposed method are depicted under **Figure 10**. Process capability six pack analysis revealed no point more than 3.00 standard deviations from centre line was observed hence the test passed.The probability plot indicates that the assumption of population normality is reasonable. The R chart and a Cp index greater than the reference value

of 1.33 suggest stability of subgroup variation and indicate that the within-subgroup variation process is acceptable. However, the Pp index greater than the reference value of 1.33, so the overall capability of this process is adequate due to similarity between subgroups. The Xbar Chart and plot of the last 9 subgroups also depict this similarity. This process doesn't need improvement.The control chart depicted under **Figure 10** shows that the proposed method is instatistical process control and thus can be used for monitoring and controlling the future production batches. Process capability indexes for within and overall process were found improved for the proposed method over the IP method. Within and overall process capabilities for IP and proposed method are compared and listed under **Table 5.**

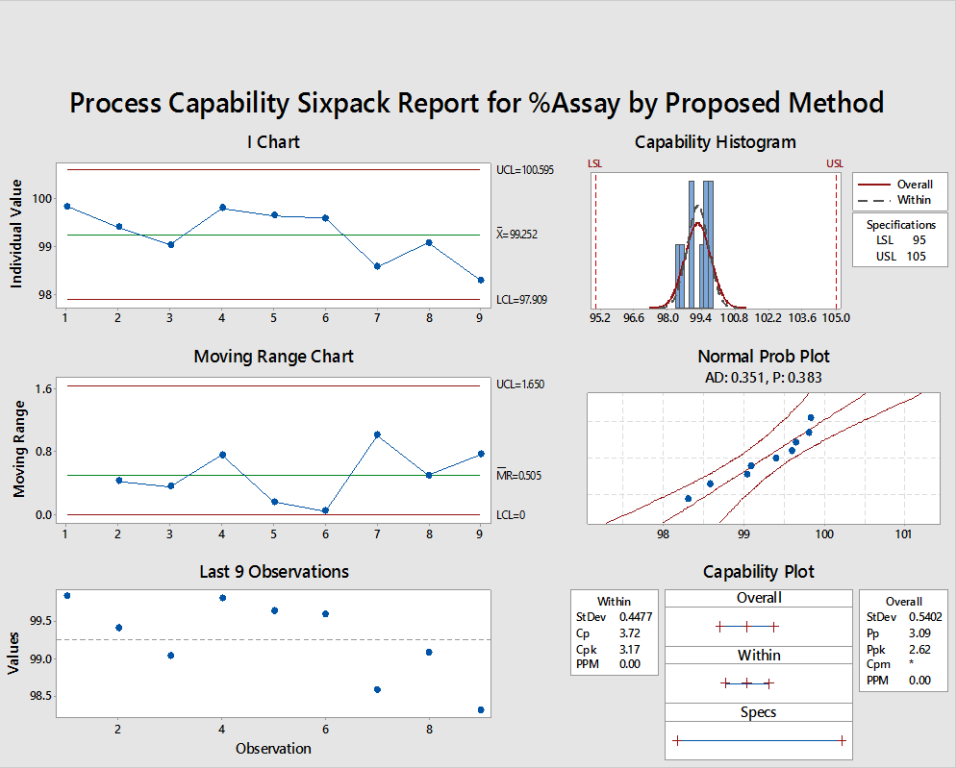

Figure 10: Process capability of percentage assay byproposed method.

Table 5: Ranitidine HCl tablets Process Capability comparison by IP and proposed method.

Method	Within			Overall		
	Std dev	Cp	Cpk	Std dev	Pp	Ppk
IP	0.6028	2.76	1.96	0.6499	2.56	1.82
Proposed	0.4477	3.72	3.17	0.5402	3.09	2.62

CONCLUSION

The present work is a contribution to green analytical chemistry. The new method for the assay of Ranitidine hydrochloride tablet has been developed and appropriately validated for Linearity, accuracy, precision, Robustness, and Specificity. Method is based on modification of Ranitidine Hydrochloride tablet IP assay method for solvent reduction. Solvent reduction is achieved by replacing the diluent (methanol: ammonium Acetate - 85:15) in IP method with water. Critical quality attributes of Ranitidine HClsuch as solubility of in water as well as in methanol, BCS classification, elution strength of water etc. have been considered while selecting the solvent system. Based on the experiments and statistical evaluation the proposed method found to be superior to IP methodwhich has been proved by comparing assay of different batches of same formulation and different marketed formulations by both methods. Advantage of proposed method over IP method is the significant reduction of organic solvent and hence reduction of cost for sample preparations.From the point of view of industries, one of the highlighting aims is cost reduction. In India Ranitidine Hydrochloride is available in 26 formulations (As 75, 150 or 300 mg strength, from 14 different companies). If these formulations would be assayed by the proposed method then the reduction in usage of

organic solvent (Methanol) will be very significant. It contributes to, reduction in cost, reduction in carbon footprints due to organic solvents in environment, improvements in the health and safety of those exposed to chemicals, and enhanced security at facilities with hazardous materials. The proposed method doesn't negatively impact the product quality and hence the proposed method can be considered as alternative quantitative determination of Ranitidine HCl from the tablets dosage form.

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