Research Article

Quality by Design Approach for Development of Simple, Rapid and Stability Indicating Method for Simultaneous Estimation of Diphenhydramine and 8-Chlorotheophylline in Complex Pharmaceutical Formulation

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Accepted on: 26-04-2016; **Finalized on:** 31-07-2016.

ABSTRACT

The focus of this paper was on implementation of QbD (quality by design) principles for the analytical method development for estimation of Diphenhydramine (DPH) and 8-Chlorotheophylline (CT) in Dimenhydrinate ODT (Orally disintegrating tablets) formulation. The method was developed by UPLC (Ultra performance liquid chromatography) with predefined analytical target profile, method understanding and control based on sound science and risk management using Xbridge BEH C18 (100, 2.1mm and 2.5µm) with mobile phase composition of Phosphate buffer pH 2.8: Methanol (50:50). The injection volume was 2µl and column temperature is 30°C with flow rate of 0.4ml/minute. The working wavelength was 225nm. The selectivity changes with regard to the organic modifier (Methanol and Acetonitrile) in mobile phase were evaluated. With focus on quality risk management; pH, percentage organic modifier and concentration of TEA (Triethylamine) were optimized using DOE (Design of experimentation). Main effects of pH of buffer, percentage organic and concentration of TEA and their interaction effects on critical quality attributes (CQA) were established. The CQA's with different stationary phases were evaluated. The working point of method was established using central composite design. The QbD compliant method was successfully developed and validated as per International conference on harmonization (ICH) guidelines.

Keywords: Quality by design, Diphenhydramine, 8-Chlorotheophylline, Design of experiments.

INTRODUCTION

For an analytical method used in product development or pharmaceutical quality control, it is essential that there should be a thorough understanding on the method. The drawbacks for an analytical method development with OFAT (One factor at a time) approach have been discussed in detail[1]. In 1980's, the set of procedures that assure the measurement integrity were derived and these rules were complimentary to the good manufacturing practices (GMPs) discussed in regulatory law[2]. Quality of product can be best measured by following a set of instructions (compliance) that are shown to repeatedly give the same product and is supported by analytical testing[3]. The use of ''Quality by Design'' (QbD) as a basis for product development has been well practiced in engineering for several years, and has been already described in guidance by the FDA for development of Medical Devices[4]. The QbD is a novel concept outlined in ICH Q8 (R2), Q9 and Q10 for the development of pharmaceutical formulations[5-7]. Even though these guidelines does not discuss more specific towards the analytical method developments, it is very essential to explore the possibility of using these concepts equally to analytical method development for the following reasons.

- Difficulty in out of specification (OOS) investigations because of lack of understanding on the method.
- Frequent out of trend (OOT) and OOS observations.
- Improper and lack of timely support for product development and improvement because of poor quality of methods.
- Repeating OOS observations for different products across the industry and a very less understanding on cause of variability.
- Any change in the existing methods call for post approval change, causing delay in regulatory approvals and in availability of the product in market.

QbD requires a systematic evaluation on proposed purpose of the method development and routine use built upon a detailed understanding of science supporting the analytical methodology selected. The concept of QbD for analytical methods can be categorized in to two parts[3]. The first one is the analytical target profile (ATP) which defines the objective of measurement and forms the basis for development of initial method. The second concept addresses on how QbD steps and approaches can be applied to design, development and lifecycle management of an analytical method that can be used for execution in a manner equivalent to those described for pharmaceutical formulations. Also, the measurement integrity can best be achieved by following a set of instructions that are shown to repeatedly give the same result[8]. This paper describes QbD as a system for analytical method development for a pharmaceutical drug product and describes the application of enhanced scientific understanding, the use of quality management systems (QMS) and structured risk assessments to

analytical methods. In this sense, an extensive literature search activity was undertaken to comprehend the use of QbD concept for analytical method development. There are few publications which focus on analytical method development using QbD Concept[9-23]. These papers lack in the detailed discussion about interaction effects of method factors which is the main focus area and advantage of DOE. Also there are few publications which discuss about the separation of Diphenhydramine (DPH) and 8-Chlorotheophylline (CT) in the pharmaceutical formulations[24-28]. However, for simultaneous estimation of DPH and CT from the pharmaceutical formulation, none of the available analytical methods so far can be considered to be reliable enough to provide complete understanding of the method performance. Also, these papers have not evaluated the QTPP (quality target product profile) and CQA (critical quality attribute) of the product from method development point of view. Barbas C[28] have worked on the separation of Caffeine, CT and DPH using an isocratic HPLC method. But the run time of the method is 30 minutes, high retention range for the peaks and hence is not good for usage in regular quality control applications with more consumption of instrument hours, chemicals and other lab resources. Moreover, the method have not been developed based on QbD concept where in the QTPP of the product, interaction effects of the method variables on the overall separation and design space for the method has not been established. Hence the method is not flexible enough to meet the day to day laboratory variations. Thus, it was thought worthwhile to develop a method based on QbD principles and validate the same as per ICH guidelines.

Dimenhydrinate (DMH) is an over-the-counter antihistamine drug used for treatment of nausea, vomiting, and dizziness caused by motion sickness. Dimenhydrinate is a combination of two drugs: DPH and CT.DPH is the primary constituent of Dimenhydrinate and is responsible for causing the primary effect. By weight, DMH is between 53.0% to 55.5% of DPH and 44.0% to 47.0% CT[26], a chlorinated derivative of theophylline, which counteracts the drowsiness.

MATERIALS AND METHODS

Standards and Reagents

High purity standards of DMH, DPH and CT were provided by SPI Pharma Inc, India. The purity of these standards was determined by HPLC and was found to be 99.4%, 98.9% and 98.3% respectively. Sodium hydroxide, Hydrochloric acid, Hydrogen Peroxide, Ammonium acetate, Orthophosphoric acid Triethylamine (TEA) and monobasic potassium phosphate of AR grade and Acetonitrile & Methanol (HPLC grade) were purchased from Rankem, India. The impurity standards (Benzhydrol, Benzophenone and Theophylline) were provided by SPI Pharma Inc, India. Impurity A of Diphenhydramine was purchased from European pharmacopoeia (EP). Dimenhydrinate ODT 50 mg (Test product) with batch number 078/E026A, 078/E026B and placebo were manufactured at SPI Pharma Inc., India branch.

Instrumentation

The Chromatographic columns; Xbridge BEH C18 (100*2.1mm, 2.5µm), Xbridge BEH C8 (100*2.1mm, 2.5µm), Xbridge BEH Phenyl (100*2.1mm, 2.5µm) and XSelect HSS T3 columns (100*2.1mm, 1.8 µm) were purchased from Waters Corporation (Milford, MA, USA). Analytical method development and Quantitative analysis was performed on Waters Acquity UPLC (Binary) system equipped with PDA Detector and Waters Acquity UPLC H-Class (Quaternary) with an injection cycle time of <30 seconds also with flow through needle technology, column heater with column switching valve and a UV-PDA detector.

The UPLC instruments were operated through Waters Empower 3 Software. The pH measurements were done using pH meter SevenEasy Model (Mettler Toledo, Columbus, OH, USA).The statistical treatment of the data was done using Design expert software version 8.0.7.1 (Stat ease, USA).

Methods

ICH Q8 (R2) defines QbD as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"[5].

The method development was initiated with a predefined ATP based on the chemistry of the molecules, quantitative composition details of the drug product, QTPP (Quality target product profile) requirements for the product development and CQA's(Critical quality attribute) of the drug product.

The analytical target profile aims at; the method must be able to quantify both CT and DPH simultaneously, in a complex pharmaceutical formulation consisting of functional excipients, sweetener, flavor and color. The method should be specific and stability indicating for the quantification of CT and DPH.

The precision of the method must be such that the % RSD (Relative standard deviation) for the assay of 6 independent sample preparations must be ≤ 2.0%.

The accuracy of the method must be such that the recovery values for the method are within the range of 100 ±3.0% of the true values and must be with the linearity correlation coefficient and regression coefficient of (Not less than) NLT 0.99.

With these predefined analytical target profile, the separations were recorded ranging from 210 nm to 400nm.

Optimization of Chromatographic Conditions

Selection of column stationary phase for the separation is an important step in the method development. Various

stationary phases were evaluated (Xbridge BEH C18, Xbridge BEH C8, Xbridge BEH Phenyl and XSelect HSS T3). The selectivity and retention range of peaks were used in screening the stationary phase for the column. Acetonitrile and Methanol were evaluated for the usage as organic modifier in mobile phase along with aqueous buffer.

Design of Experimentation

Design of Experimentation (DOE) is an integral part of the QbD concept to screen for vital few factors from trivial many factors causing influence on the separation and to decide on acceptable levels of the factors. It was also used to study the effect of individual factors and their interaction effects. The screening DOE's were constructed considering pH of aqueous buffers, percentage of methanol and for concentration of TEA (v/v) each at two levels. The responses were the retention time (RT) of Diphenhydramine (in minutes) peak and resolution (R_s) between CT and DPH peaks. Based on findings from the screening DOE, full factorial two level design was constructed using Design expert software for the factors and levels as given in Table 1.

Table 1: Two Level Factorial Design for the Method Variables

Factor	Lower Level	Higher Level
Concentration of TEA (%) (%v/v)	0.3	1.5
pH of the Buffer	2.8	3.2
Methanol (%v/v)	48	52

CCD for the Establishment for the Design Space

Factor	Higher	Central	Lower
Methanol (%)	53	50	47
Flow Rate (ml/min)	0.5	0.4	0.3

To establish the design space for method, a central composite design (CCD) model was constructed considering Methanol (v/v) and flow rate (ml/min) of the mobile phase as factors. The flow rate was introduced as a factor at the later point of the DOE as it has direct impact on the RT of peaks in chromatogram without change in the selectivity. The central composite design was run at 3 levels in two blocks as given in Table 1.

Totally 14 runs were recorded and data was subjected for statistical treatment. The working point and design space were constructed using data obtained by CCD.

The newly developed, QbD compliant method was validated as per ICH Q2 (R1) guideline.

Specificity

The specificity of the method was demonstrated by checking the interference of sample matrix, blank and degradation impurities with DPH and CT peaks. The stability indicating nature of the method was demonstrated by forced degradation studies. The acid degradation studies were performed in 0.1N HCl at room temperature for 1 hour. Alkali degradation was performed with 2ml of 2N NaOH for 2 hours at room temperature. For oxidation degradation, the sample was treated with 3% Hydrogen peroxide solution and kept at 60°C for 1 hour. For thermal degradation, the sample was kept at 80°C for 2 hours in an oven. At the end of exposure time, samples were taken out and cooled to room temperature. The sample solutions were prepared as per the procedure. Samples were injected and peak purity for both DPH and CT peaks were checked in each of the stress conditions. The known impurity solutions were prepared at 0.4 µg/ml and injected to establish the RT for each of them.

Accuracy

The accuracy of the method was demonstrated by spiking known quantity of DMH in to placebo matrix and checked for the amount recovered for DPH and CT. The accuracy was performed in three levels at 22.0 µg/ml, 42.8 µg/ml and 51.0 µg/ml of DPH and 18.5 µg/ml, 36.4 µg/ml and 43.5 µg/ml of CT, triplicate preparations in each level.

Filter Compatibility

0.2 micron PVDF syringe filter (make Merck millipore) was selected for the filter compatibility evaluation as PVDF filter is more hydrophobic compared to other types of filters used for pharmaceutical analysis purposes. The evalution was performed by injecting unfiltered sample, 2 ml and 4 ml filtrate discard volumes.

Solution Stability Data

The stability of the analytes in the diluent was determined periodically at 25°C by injecting replicate preparations of standard and sample solutions at different intervals of time duration stored in a sample tray. The initial peak areas of DPH and CT were used as reference to determine the relative stability of analytes at subsequent time points.

Linearity

The linearity of method was performed in 6 levels at 22, 27, 35, 44, 48, 55 µg/ml and 19, 23, 30, 37, 41, 47 µg/ml for DPH and CT respectively by preparing solutions at six different concentration levels.

Precision

The precision study for method was performed by separately determining the assay content of CT and DPH in a batch of Dimenhydrinate ODT 50mg. 6 independent sample preparations were done using mobile phase as diluent. The individual assay values for DPH and CT were calculated. The Mean assay value and % RSD were determined.

Range

Range of the method was determined by data obtained from the linearity, accuracy and precision studies.

RESULTS AND DISCUSSION

Different types of buffer like Ammonium acetate buffer (0.025 M, pH 4.0), dibasic potassium phosphate buffer (0.025 M, pH 4.5) were prepared and were evaluated for theoretical plates, resolution between DPH and CT and for RT of DPH.

Acetate buffer did not yield satisfactory peak properties for DPH.

Different concentrations of Orthophosphoric acid (OPA) and TEA mixture buffers were explored at pH values from 1.2 to 6.8 at 4 levels in the mobile phase using screening DOE. It was determined that pH 2.8 was the best pH to work for the method. The selectivity changes with change in organic modifier portion of mobile phase were evaluated with methanol and acetonitrile separately at different concentrations (v/v).

Main Effects and Interaction Effects

Significant Factor for RT

The main effect and interaction effect plots for the concentration of TEA (% v/v), methanol (% v/v) and pH for RT of DPH is as presented in Figure 1.

The data was further subjected to Analysis of Variance (ANOVA) and is given in Table 2.

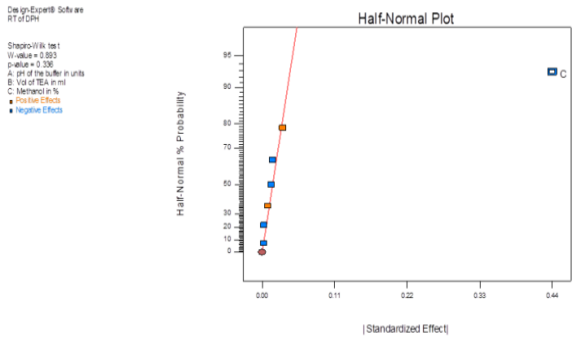

Figure 1: Half-normal plot for effect of concentration of methanol on RT of DPH

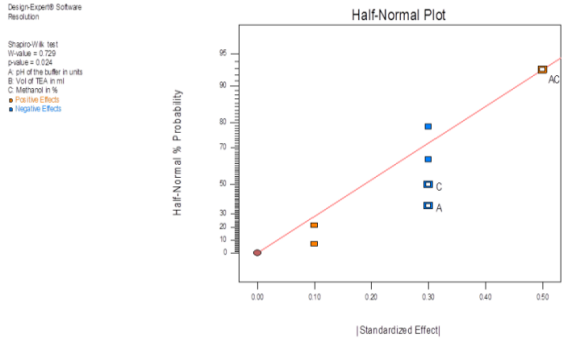

Figure 2: The half-normal plot for the response Resolution (R_s)

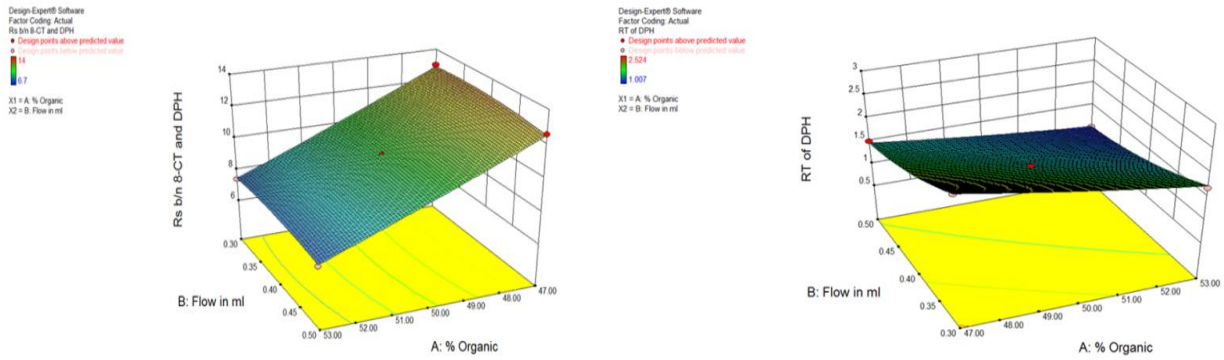

Figure 3: The 3D plot for Resolution (R_s) and RT of DPH in CCD

The percentage of methanol in mobile phase has very high impact on the RT of the DPH peak. With the increase in methanol concentration in the mobile phase, RT of the DPH decreases. Also, there is no interaction effect between the factors at the concentration ranges considered.

Table 2: ANOVA for the RT of DPH (Partial sum of squares-Type III)

Source	Sum of Squares	Df (Degrees of Freedom)	Mean Square	F-value	p-value	Model Term
Model	0.39	1	0.39	773.80	<0.0001	significant
Methanol in %	0.39	1	039	773.80	<0.0001	
Residual	3.006 exp. -003	6	5.010 exp.-004	-	-	
Cor. Total	0.39	7	-	-	-	

Table 3: ANOVA table for resolution between DPH and CT (Partial sum of squares-Type III)

Source	Sum of Squares	Df	Mean Square	F-value	p-value	Model Term
Model	0.86	3	0.29	2.87	0.1676	Not significant
pH of the buffer in units(A)	0.18	1	0.18	1.80	0.2508	
Methanol in %(C)	0.18	1	0.18	1.80	0.2508	
Interaction of pH and Methanol	0.50	1	0.50	5.00	0.0890	
Residual	0.40	4	0.100	-		
Cor Total	1.26	7	-			

Table 4: Statistical data of central composite design for RT of DPH and Resolution

For RT of DPH			
Std. Dev.	0.034	R-Squared	0.9968
Mean	1.63	Adj R-Squared	0.9946
C.V. %	2.08	Pred R-Squared	0.9672
PRESS	0.083	Adeq Precision	63.397
F-value	440.58	p-value	<0.0001
For Resolution			
Std. Dev.	0.093	R-Squared	0.9989
Mean	10.11	Adj R-Squared	0.9982
C.V. %	0.92	Pred R-Squared	0.9885
PRESS	0.66	Adeq Precision	114.192
F-value	1317.25	p-value	<0.0001

Table 5: Method validation Data - Accuracy Results for CT

Levels	Actual µg/ml Added	µg/ml Recovered	% Recovery	Mean % Recovery ± SD
Level - 1	19.1894	19.4391	101.3	100.3 ± 0.94
	18.0957	17.9923	99.4	
	18.2384	18.2954	100.3	
Level - 2	36.5609	35.9367	98.3	99.1 ± 0.97
	36.9486	37.0120	100.2	
	35.7489	35.3333	98.8	
Level - 3	43.6646	43.0209	98.5	99.3 ± 0.71
	42.8745	42.6266	99.4	
	43.9170	43.8816	99.9	

Accuracy Results for DPH

Levels	Actual µg/ml Added	µg/ml Recovered	% Recovery	Mean % Recovery ± SD
Level - 1	23.3340	23.2490	99.6	100.0±0.40
	21.2428	21.2214	99.9	
	21.4103	21.5045	100.4	
Level - 2	42.9193	42.2151	98.4	99.6±1.25
	43.3745	43.7622	100.9	
	41.9660	41.7572	99.5	
Level - 3	51.2584	50.6682	98.8	99.6±0.72
	50.3309	50.3619	100.1	
	51.5547	51.5693	100.0	

Solution Stability of Standard and Sample Solution

Solution Stability of Sample				
Duration (hours)	**Area of DPH**	**% Difference**	**Area of CT**	**% Difference**
Initial (0 hour)	400145	-	311109	-
4	400435	+0.1	311631	+0.2
8	398671	-0.4	310138	-0.3
12	397472	-0.7	311267	+0.1
16	394324	-1.5	308411	-0.9
20	392877	-1.8	307877	-1.0
24	390777	-2.3	307736	-1.1
Solution Stability of Standard				
Initial (0 hour)	403029	-	314825	-
4	402991	0.0	314119	-0.2
8	402547	-0.1	314545	-0.1
12	401112	-0.5	313250	-0.5
16	399514	-0.9	312835	-0.6
20	398088	-1.2	312388	-0.8
24	394001	-2.2	311844	-0.9

Linearity of CT

Concentration in µg/ml	Area Response
19	161144
23	194608
30	249849
37	310597
41	343480
47	386904
Regression coefficient	**1.000**
Correlation coefficient	**1.000**
Slope	**4063.55**
Intercept	**6744.03**
Residual sum of squares	**1916.08**

Linearity of DPH

Concentration in µg/ml	Area Response
22	205777
27	250095
35	322263
44	399482
48	440916
55	499083
Regression coefficient	**1.000**
Correlation coefficient	**1.000**
Slope	**5255.09**
Intercept	**6757.51**
Residual sum of squares	**1909.69**

Precision Study of the Method for DPH and CT

Serial Number	DPH (%)	CT (%)
Preparation 1	100.2	98.9
Preparation 2	99.9	100.0
Preparation 3	99.7	100.1
Preparation 4	100.4	99.9
Preparation 5	99.7	100.1
Preparation 6	99.4	100.2
Mean	**99.9**	**100.0**
% RSD	**0.4**	**0.6**

The ANOVA is a statistical method based on the F-test that assesses the significance of experimental results. It involves subdividing the total variation of the data set into component parts. ANOVA values for the effect of % Methanol on the RT of DPH are as given in Table 2. The p-value for the test was conducted using an F-statistic. The F-value in the ANOVA table (Table 2) is the ratio of model mean square (MS) to the appropriate mean square. The larger is their ratio, larger the F-value and more likely that the variance contributed by model is significantly larger than the random error. If the F-ratio lies near the tail of F-distribution, the probability of a larger F is small and the variance ratio is judged to be significant. The F-value was at 773.80 with p-value of < 0.05 indicating that the model is significant. Good retention range for the peaks was obtained with methanol as the organic modifier. Thus, methanol was considered for all further experimentations.

Significant Factor for Resolution

The half-normal plot for resolution between CT and DPH is as given in Figure 2. There are two main effects and two factor interaction effect. To quantitate the main and interaction effects, the data was further subjected to ANOVA and is as given in Table 3.

The data in Figure 2 shows that the pH of buffer and percentage methanol in mobile phase has impact on resolution between CT and DPH. There is an interaction effect between pH of the buffer and percentage of methanol which is greater than the individual effects of these. The p-value in ANOVA table (Table 3) shows that the effect of factors on resolution (R_s) is minimal. The F-value shows that the pH of buffer and methanol concentration does not have significant impact on Rs between DPH and CT. There exist an interaction effect between pH of the buffer and percentage methanol in the mobile phase and is greater than the individual effect of these two. With the model p-value >0.05, the model is statistically not significant.

The design space was constructed using a central composite design using RT of DPH and R_s between DPH and CT as responses. The statistical data for RT of DPH and resolution is as given in Table 4.

The F-value for RT of DPH is 440.58 with p-value falling less than 0.05 indicating that the model is significant. There is only a 0.01% chance that a "Model F-Value" of this large can occur due to noise. The "Pred R-Squared" value of model measures the amount of variation in data examined in the model making use of predicted residual sum of squares (PRESS) is at 0.9672 which is in reasonable agreement with "Adj R-Squared" of 0.9946. "Adeq Precision" measures signal to noise ratio. The ratio of 63.397 indicates adequate signal.

For resolution (R_s), the F-value of the model is 1317.25 with p-value falling less than 0.05 indicating that the model is significant. There is only 0.01% chance that a F-value of this large could occur due to noise. The "Pred R-Squared" of 0.9885 is in reasonable agreement with the "Adj R-Squared" of 0.9982. "Adeq Precision" is at 114.192 indicates an adequate signal. This model can be used to navigate design space.

The 3D plots for the responses was as given in Figure 3.

Each point in the 3D plot (Figure 3) indicates the response value at that particular values of factor. To have reproducible retention time for DPH and resolution between CT and DPH during routine usage of the method, the working point in design space was selected by statistical treatment of the data. The resulting 34 run conditions had the desirability of 1.000. Considering the practicality of the predicted conditions, run 14 was selected for verification. The predicted conditions were verified practically by fresh preparation of the mobile phase and sample solutions. The experimentally obtained values were compared with predicted values and found that there was an excellent correlation between predicted and experimentally obtained values.

Method Validation

Specificity

The DPH and CT peaks were well resolved from blank, sample matrix and degradation impurity peaks. The peak purity was recorded in all degradation conditions using a photodiode array detector.

The blank, placebo and degradation impurities are well resolved from CT and DPH. The retention time of CT is at 0.910 minutes and DPH at 1.589 minutes. In forced

degradation study samples, CT was found to be relatively stable compared to DPH in all the stress conditions. In acidic medium DPH undergoes fairly rapid degradation (i.e. 23%). The degradation in the acid medium is due to hydrolysis of ether linkage resulting in the formation of Benzyhydrol and 2-(dimethylamino) ethanol as major degradation products. In peroxide condition, DPH degrades by 45% resulting in the formation of toluene, Benzophenone, Benzyl alcohol and other phenolic compounds as probable degradation products. In alkali, DPH is fairly stable and degrade to 25% under slightly harsh degradation conditions. The degradation of CT results in the formation of Theophylline as major degradation product. All the known degradation impurities were identified by the retention time of these peaks in the chromatograms and are well separated from CT and DPH. The attempt for the identification of unknown impurities was not done as the main scope of the work was to quantify DPH and CT in the presence of the known and unknown degradation impurities. Also, the identification of impurities using LC-MS was not taken up as the method uses phosporic acid for the pH modification and will cause quantification issues in the LC-MS detector. Further, for the purpose of LC-MS; any modifications in the method conditions can induce retention time and selectivity changes. In all degradation conditions, the peak purity of DPH and CT were found to be satisfactory, which demonstrates the stability indicating nature of method.

Accuracy

The accuracy of method was assessed by recovery test. Recovery values obtained at each level were characterized by relative standard deviation. The accuracy values are within 100±3.0% at each level with an overall accuracy value of 99.6% and 99.7% with percent RSD of 1.0 and 0.8 for CT and DPH respectively. The method was found to be accurate for the simultaneous estimation of CT and DPH.

Filter Compatibility

The % area count difference for each sample with different discard volumes against unfiltered sample were calculated. It was observed that area difference between unfiltered and different filtrate discard volumes is well within ±2.0% for both CT and DPH indicating that there is no significant filter absorption for CT and DPT. The 0.2µm PVDF syringe filters can be used for the routine filtration of the samples.

Solution Stability

The solutions were considered to be stable if the % area difference for both CT and DPH is within ± 2.0% from the initial area response. The data in Table 5 shows that the area counts for DPH peak is reducing gradually and above 2.0% at 24 hours. CT is relatively stable compared to DPH in solution. This observation was same between standard and sample preparations. Based on the data it was concluded that both standard and sample solutions were stable up to 20 hours at 25°C.

Linearity

The calibration curve was constructed using concentration (µg/ml) on x-axis and area response on y-axis for each of DPH and CT. The calibration curve equation is y=mx+c, where y represents analyte peak area and x represents analytes concentration in µg/ml.

The mean equation of calibration curve (n=6) obtained from 6 points were y=4063.5x+6744 (r^2=1.000) and y=5255.1x+6757.5 (r^2=1.000) for CT and DPH respectively.

From the values, it was concluded that the method was linear for both CT and DPH in the given concentration.

Precision

The % RSD values obtained for assay values of CT and DPH from 6 sample preparations was found to be at 0.6% and 0.4% respectively. The method was considered to be precise.

The results for all the method validation parameters are as given in Table 5.

Range

The range for the method was constructed by the data obtained from linearity, accuracy and precision; range of the method was proved to be between concentrations of 22 µg/ml to 55 µg/ml for DPH and 19 µg/ml to 47 µg/ml CT.

CONCLUSION

In the present work, development of a simple, rapid and QbD compliance method for simultaneous estimation of CT and DPH in Dimenhydrinate ODT was achieved.

The new method is flexible enough to allow routine laboratory variations. The critical factors responsible for separation have been identified and studied in depth and the design space has been established.

The statistical assumptions have been verified and confirmed through experimentations. It was observed that there is a very good correlation between predicted and experimental values. The CQA's of method were identified by scientific judgment.

The vital few factors were screened from trivial many by DOE. The method is ecofriendly with very less consumption of solvents, chemicals, instrument power and waste production.

Also, with a runtime of 2 minutes, it is possible to analyze more than 500 samples per day, reducing the cost of analysis per sample there by reducing the cost of the product.

Furthermore, the newly developed method was validated as per ICH method validation guidelines (Q2 (R1)). It is proved that the method is suitable for the intended purpose.

Acknowledgement: The authors are thankful to SPI Pharma for providing samples, standards and laboratory for performing the experimentation and research work.

Authors are also thankful to Dr. Krishna Venkatesh, Centre for emerging technologies and Dr. Chenraj Roychand, Jain University for their constant support in encouraging this research work.

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Source of Support: Nil, **Conflict of Interest:** None.