A new stability-indicating RP-HPLC method for the determination of dicyclomine hydrochloride and dimethicone combination in tablet dosage forms

J. Saroja 1,2, Anantha Lakshmi P.V. 1*, Y. Rammohan 2 and D. Divya Reddy 2

Abstract

Background: We describe a "stability-indicating liquid chromatography" technique for the estimation of dimethicone (DEC) and dicyclomine hydrochloride (DEH) in the established tablet formulations. Individual quantification of DEH and DEC was reported. But simultaneous quantification of DEH and DEC was lacking. DEH and DEC were analyzed on an "XTerra C18 column (250 mm × 4.6 mm, 5 μm)" with the mobile phase solvent run isocratically with 0.1M K2HPO4-acetonitrile (55:45, v/v) on a flow speed of 1.0 mL/min.

Results: The chromatographic run period for the DEC and DEH assay was 6.0 min with retention times of 2.134 and 2.865 min, respectively. The method was validated for accuracy (99.453 to 100.417% and 99.703 to 100.303% recovery values for DEH and DEC, respectively), precision (RSV value 0.135% for DEC and 0.171% for DEH), linearity (5–15 μg/mL for DEH and 20–60 μg/mL for DEC), selectivity (no hinderance from excipients) and specificity (no hinderance from degradants) recovery.

Conclusion: The developed stability-indicating liquid chromatography process was well applied to established tablet formulations.

Keywords: Dicyclomine hydrochloride, Dimethicone, Stability indicating, Fixed formulation, Analysis

Background

Dicyclomine hydrochloride (DEH) is an artificial analogue of acetylcholine with anticholinergic and antimuscarinic activities [1]. Gastrointestinal disorders including irritable bowel syndrome and acidic peptic disorder have been managed with DEH [2, 3]. Dimethicone (DEC) is a polyorganosiloxane and an anti-flatulence/anti-flatulence medication which collapses gas bubbles and facilitates free passing of gas [4]. The DEH and DEC fixed-dose formulation was available as oral drops [5], capsule [6], suspension [7] and tablet [8]. Structures of DEH and DEC are provided in Fig. 1.

Pharmaceutical analysis was often performed out to verify that the drug substance or medication satisfies the two most critical attributes of quality: safety and effectiveness [9]. Manufacturing corporations need both qualitative including quantitative studies to guarantee that its raw materials fulfill the requisites and that the finished material is of high quality. DEH quantification in tablet formulation (by UV spectrophotometry, colorimetry and voltammetry) [10–12] and in milk, serum and urine (by potentiometry and voltammetry) [12, 13] was described. DEC quantification in capsule and tablet formulations (by HPLC and infrared spectroscopy) [14, 15] was published. Quantification of DEH in blend with other drugs using UV spectroscopy [16], HPTLC [17] and

* Correspondence: pvanantha.ou@gmail.com; ananthaprasad2003@osmania.ac.in
1Department of Chemistry, University College of Science, Osmania University, Hyderabad 500007, India
Full list of author information is available at the end of the article

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HPLC [18–24] was also reported. HPLC quantification of DEC in blend with other drugs was also described [25]. Analytical method for DEH and DEC simultaneous quantification was lacking. The main goal of this study was to concurrently analyse the content of DEH and DEC in tablet formulations employing the developed and authenticated “stability-indicating liquid chromatography” (SILC) method. There seems to be no published analytic method for evaluating the content of DEH and DEC in the tablet formulations, to the fullest of our awareness. The uniqueness of the proposed SILC method is that this is the first analysis tool reported for the simple, accurate, sensitive and precise measurement of the DEH and DEC content in tablet formulations.

**Methods**

**Instruments**

Chromatographic analysis of DEH and DEC was performed employing “Waters HPLC system” furnished with quaternary pump, autosampler, column oven and degasser. UV spectrometric detection operated at 265 nm was used for DEH and DEC detection and quantitation. Hardware regulation, data acquisition and management were done using “Waters Empower 2” software.

**Pure samples**

Reference standards of DEH (99.8% purity) and DEC (98.4% purity) were gifted by “Rainbow Pharma Training Labs”, Hyderabad.

**Formulations**

Colicare Tablets (“Omega Pharmaceuticals Pvt Ltd”, Chennai) with labelled content of DEH 10 mg and DEC 40 mg were analysed employing the developed and authenticated SILC method.

**Chemicals and reagents**

K₂HPO₄, H₂O₂, HCl and NaOH of analytical grade were from “Finar Chemicals Limited”, Ahmedabad; acetonitrile and Millipore water of chromatography grade were purchased from “Merck India limited”, Mumbai, and “Loba chemicals limited”, Mumbai, respectively.

**SILC method conditions**

“XTerra C18 column (250 × 4.6 mm, 5 μm)” was applied for chromatographic separation of DEH and DEC using 0.1 N K₂HPO₄ (55% vol. ratio; pH 4.5) and acetonitrile (45% vol. ratio) in an isocratic elution mode. Separation of DEH and DEC was done at a stream rate of 1.0 mL/min with an injection volume of 10 μL with column warmth of 27°C.

**Stock DEH and DEC solution**

Quantities equal to 40 mg DEC and 10 mg DEH reference standards were appropriately measured and properly transferred to the 100-mL flask, and 40 mL mobile phase was introduced to the same flask. The solution was well shaken and flask volume was completed with the same mobile phase to achieve 400 μg/mL DEC and 100 μg/mL DEH.

**Working DEH and DEC solution**

The working DEH and DEC solutions were prepared by appropriate dilution of their formerly prepared stock DEH and DEC solution (400 μg/mL DEC and 100 μg/mL DEH) with the mobile phase solvent to obtain a 10-mL working solution of 40 μg/mL DEC and 10 μg/mL DEH.

**Calibration curve**

Quantity ranges covering 5 to 15 μg/mL for DEH and 20 to 60 μg/mL for DEC were made from stock DEH and DEC solution (400 μg/mL DEC and 100 μg/mL DEH) using the mobile phase solvent. The solutions were evaluated using the SILC technique proposed. Calibration curves were prepared with a regression line equation to map each analyte’s peak area against its concentrations.

**DEH and DEC content evaluation in tablets**

Ten Colicare tablets containing a specific of DEH (10 mg/tablet) and DEC (40 mg/tablet) were taken and were crushed to a finer powder with the pestle and mortar. A
weighed quantity of the tablet formulation crushed powder, corresponding to 10 mg of DEH and 40 mg of DEC, was transferred properly to a 100-mL flask. Forty milliliters of mobile phase was introduced to the same flask and was sonicated for nearly 20 min and then filtrated using Whatman no. 1 paper. The flask volume was completed with the same mobile phase to achieve 40 μg/mL DEC and 10 μg/mL DEH. The sample for analysing Colicare tablets was made ready by diluting an aliquot (1 mL) of tablet formulation sample to 10 mL with the mobile phase. The tablet formulation test solution was evaluated using the SILC technique proposed.

Forced degradation study
Forced degradation tests were made on tablet formulation samples of 400 μg/mL DEC and 100 μg/mL DEH concentrations under "ICH Q1A (R2)" given conditions [26].

Sonicating tablet formulation samples (10 mL) at 27 °C in 0.1 N HCl (10 mL) for 30 min and in 0.1 N NaOH (10 mL) for 30 min were used for degradation tests in acid and base stresses, respectively. Peroxide facilitated oxidation was studied by exposing the tablet formulation sample (10 ml) to 30% H2O2 (10 mL) for 30 min at 27 °C in the dark. Photolytic degradation was executed by exposing the tablet formulation crushed powder, corresponding to 10 mg of DEH and 40 mg of DEC, to the sunlight directly for 24 h. Similarly, for thermal stress, the tablet formulation crushed powder was exposed at 105°C for 30 min in the oven.

Each sample was properly diluted by the mobile phase at the end of exposures to acid, H2O2 and base, to achieve an ultimate amount of 40 μg/mL DEC and 10 μg/mL DEH. The solutions from the tablet formulation crushed powder exposed to sunlight and dry heat were made as portrayed in the section “DEH and DEC content evaluation in tablets”. All the sample solutions were evaluated using the SILC technique proposed.

Results
SILC method development
Until an optimal response and peak shape for DEC and DEH were obtained, the column and mobile phase solvents were optimised. Columns examined include YMC C18, Thermo C18, Waters C18 and XTerra C18. Solvent combinations investigated include 0.1% phosphoric acid-methanol and 0.1M K2HPO4-acetonitrile. Optimal response and symmetrical peak shapes for DEC and DEH were achieved with an “XTerra C18 column (250 mm × 4.6 mm, 5 μm)” having column slot temperature of 25°C using 0.1M K2HPO4, pH 4.5-acetonitrile (55:45, v/v) as mobile phase with isocratic flow type run of 1.0 mL/min. UV detection with 265 nm setting was found as the best fit for an optimal peak response and to quantity DEH and DEC. The chromatographic run period for the DEC and DEH assay was 6.0 min with retention times of 2.134 and 2.865 min observed for DEH and DEC, respectively (Fig. 2).

Validation
The proposed SILC method was validated under “ICH Q2 (R1)” given conditions [27].

System suitability
For this assessment, DEC (40 μg/mL) and DEH (10 μg/mL) working solutions were infused six times to report the specifications of system suitability. Table 1 outlines the reports of system suitability for the assessment of DEC and DEH combination.

Selectivity
Mobile phase blank, working DEC (40 μg/mL) and DEH (10 μg/mL) solution and tablet DEC (40 μg/mL) and DEH (10 μg/mL) solution were analysed with the SILC technique proposed to ascertain the selectivity of the established SILC method. In order to track interference

Fig. 2 DEH and DEC chromatogram with the optimized SILC method
from mobile phase solvents and tablet excipients at the retention times of DEC and DEH, the chromatograms of the related solutions were evaluated (Fig. 3).

**Linearity**

The detector responses for DEH and DEC have been computed to be linear over the 5- to 15-μg/mL and 20- to 60-μg/mL ranges, respectively. The linearity of the SILC technique proposed was assessed by its calculated coefficient of determination value, slope value and intercept value. The linearity regression equation portrayed them as:

$$y = 217520.92x - 18853.6$$ and $$R^2$$-value = 0.99998 for DEH

$$y = 166284.84x - 19926.8$$ and $$R^2$$-value = 0.9995 for DEC

**Sensitivity**

Based on the standard deviation value of DEC and DEH responses and the slope of DEC and DEH linearity curves, LOD and LOQ were assessed. The assessed values were 0.017 μg/mL (LOD) and 0.056 μg/mL (LOQ) for DEC and 0.006 μg/mL (LOD) and 0.022 μg/mL (LOQ) for DEH.

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**Table 1** DEC and DEH system suitability

| Values        | ReT  | ReA  | ReS  | PCS   | TF    | K'   | HETP | α’   |
|---------------|------|------|------|-------|-------|------|------|------|
| **Dicloclomine hydrochloride** |      |      |      |       |       |      |      |      |
| Avg$^a$       | 2.127| 2173795 | –    | 4477  | 1.436 | 1.127 | 0.056 | Avg$^a$ 1.648 |
| SV            | 0.0081| 5667.4136 | –    | 39.8535 | 0.0089 | 0.0079 | 0.0005 |
| RSV           | 0.381 | 0.261 | –    | 0.890 | 0.623 | 0.701 | 0.887 | SV 0.0039 |
| **Dimethicone** |     |      |      |       |       |      |      |      |
| Avg$^a$       | 2.858 | 4249950 | 4.920 | 4954  | 1.294 | 1.858 | 0.050 | RSV 0.237 |
| SV            | 0.0088 | 7331.8554 | 0.0141 | 30.4844 | 0.0055 | 0.0093 | 0.0003 |
| RSV           | 0.309 | 0.173 | 0.287 | 0.615 | 0.423 | 0.499 | 0.636 |     |

$^a$Average of five estimates

SV standard variation, RSV relative standard variation, ReT retention time, ReA response area, ReS resolution, PCS plate counts, TF tailing factor, K’ capacity factor, HETP height equivalent to theoretical plates, α’ selectivity factor

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**Fig. 3** Selectivity evaluating chromatograms
Precision
The precision of the SILC technique proposed was verified by injecting six DEC (40 μg/mL) and DEH (10 μg/mL) replicates of the working sample. The values achieved for the six replicates yield a DEC peak area RSV of 0.135% and a DEH peak area RSV of 0.171%.

Accuracy
The accuracy of the SILC technique proposed was tested by injecting three spiked tablet sample solutions with DEC and DEH reference standards and analysed in three replicates at three separate concentration scales. The spiked values were 19.80 μg/mL DEC and 4.95 μg/mL DEH at 50% level, 39.60 μg/mL DEC and 9.90 μg/mL DEH at 100% level and 59.40 μg/mL DEC and 14.85 μg/mL DEH at 150% level. In Table 3, the recoveries of DEC and DEH are provided.

Robustness
For this assessment, DEC (40 μg/mL) and DEH (10 μg/mL) working solutions were evaluated after implementing the variables to the optimised SILC process. For robustness, the variables deemed include:

- Influence of pH in the mobile phase (±0.2)
- Influence of acetonitrile in the mobile phase (±5%)
- Influence of wave length (±2 nm)
- Influence of flow rate (±10%)
- Influence of column temperature (±2 °C)

Table 2 DEC and DEH precision

| Values | DEC        | DEH        |
|--------|------------|------------|
| Avg    | 4228366    | 2155217    |
| SV     | 5691.0040  | 3680.2056  |
| RSV    | 0.135      | 0.171      |

SV standard variation, RSV relative standard variation

*Average of six peak area estimates
The data obtained (RSD for peak areas) is shown in Table 4.

### Specificity

Forced degradation tests were made on tablet formulation samples of 400 $\mu$g/mL DEC and 100 $\mu$g/mL DEH concentrations under stress conditions of acid, thermal, base, photo and peroxide. In all stress conditions put in, the DEC and DEH have been noticed to degrade. As an indicator of degradation, detection of supplementary peaks and/or declines in the response area of peaks of DEC and DEH was considered. Table 5 outlines the degradation nature of DEC and DEH under various conditions of stress and displays the related chromatograms in Fig. 4.

The specificity of the SILC technique proposed was investigated by performing a photodiode-array study to examine the integrity of the DEC and DEH peaks and to confirm the purity of DEC and DEH peaks. The peak purity angle measures of DEC and DEH (Table 5) were observed as lesser than their peak purity threshold measures, which means that the DEC and DEH peaks were pure and that stress degradants did not intervene.

### Discussion

The purpose was to establish a method capable of separating and evaluating DEC and DEH efficiently in the shortest feasible run time with reasonable accuracy and reliability. The system was considered to be significantly acceptable for analysing DEC and DEH using the recommended SILC methodology from the data collected (Table 1) [28]. Co-elution of mobile phase solvents and tablet excipients with the main DEC and DEH peak was not observed (Fig. 3). This outcome indicates the SILC method’s appropriate selectivity [29]. The outcomes like the coefficient of determination values for DEC and DEH indicate the SILC method’s appropriate linearity [30]. The low findings of LOD and LOQ conveyed the sufficient sensitivity of the SILC technique for the assessment of DEC and DEH [29]. The RSV outcomes less than 2% (Table 2) indicate the SILC method’s appropriate precision [31]. From recovery measures of DEC and DEH (Table 3), it was shown that the SILC approach was accurate [31]. The data obtained (RSD for peak areas) after implementing the variables to the optimised SILC process had appreciably revealed that the SILC technique proposed is robust (Table 4) [32].

### Table 3 Recovery estimates for DEH and DEC

| Drug | Spike level (%) | Concentration | Recovered (%) |
|------|----------------|---------------|---------------|
|      | Spiked drug ($\mu$g/mL) | Analysed drug ($\mu$g/mL) |               |
| DEH  | 50             | 4.950         | 4.923         | 99.453        |
|      | 100            | 9.900         | 9.905         | 100.053       |
|      | 150            | 14.850        | 14.912        | 100.417       |
| DEC  | 50             | 19.800        | 19.742        | 99.703        |
|      | 100            | 39.600        | 39.629        | 100.073       |
|      | 150            | 59.400        | 59.581        | 100.303       |

SV standard variation, RSV relative standard variation
*Average of three estimates

The data obtained (RSD for peak areas) is shown in Table 4.

### Table 4 Robustness for DEC and DEH assay

| Parameter          | Condition applied | DEC | DEH |
|--------------------|-------------------|-----|-----|
|                    |                   | ReA | SV  | RSV | ReA | SV  | RSV |
| Methanol ratio (%) | 45 (opt)          | 4258655 | 71394.7813 | 1.682 | 2184928 | 42212.8782 | 1.936 |
|                    | 40 (varied)       | 4308985 | 2184928 | 1.936 |
|                    | 50 (varied)       | 4168097 | 2184928 | 1.936 |
| Flow stream (mL/min) | 1.0 (opt)    | 4258655 | 77743.4253 | 1.833 | 2184928 | 30052.3910 | 1.381 |
|                    | 0.9 (varied)      | 4165614 | 2184928 | 1.936 |
|                    | 1.1 (varied)      | 4308985 | 2184928 | 1.936 |
| pH value           | 4.5 (opt)         | 4311359 | 48299.1214 | 1.121 | 2204010 | 15598.0466 | 0.708 |
|                    | 4.3 (varied)      | 4355115 | 2204010 | 1.598 |
|                    | 4.7 (varied)      | 4258655 | 2204010 | 1.598 |
| Detection (nm)     | 265 (opt)         | 4258655 | 76387.8855 | 1.794 | 2184928 | 39019.0224 | 1.788 |
|                    | 263 (varied)      | 4333890 | 2184928 | 1.788 |
|                    | 267 (varied)      | 4181120 | 2184928 | 1.788 |
| Temperature (°C)   | 25 (opt)          | 4311359 | 48299.1214 | 1.121 | 2204010 | 15598.0466 | 0.708 |
|                    | 23 (varied)       | 4355115 | 2204010 | 0.708 |
|                    | 27 (varied)       | 4258655 | 2204010 | 0.708 |

Opt optimised condition, ReA response area, SV standard variation, RSV relative standard variation
Conclusion
We described a stability-indicating liquid chromatography technique for the estimation of DEC and DEH in the established tablet formulations. According to ICH criteria, the verification of the recommended approach was carried out and performance evidence for all the criteria evaluated is appropriate. With less processing time, the proposed stability-indicating liquid chromatography approach is simple. This approach could be considered for DEC and DEH quality control testing in the pharmaceutical industry.

Abbreviations
DEC: Dimethicone; DEH: Dicyclomine hydrochloride; HPLC: High-performance liquid chromatography; RSV: Relative standard variation; UV: Ultraviolet; HPTLC: High-performance thin-layer chromatography; SILC: Stability-indicating liquid chromatography; K2HPO4: Dipotassium hydrogen phosphate; H2O2: Hydrogen peroxide; HCl: Hydrochloric acid; NaOH: Sodium hydroxide; vol.: Volume; ICH: International Conference on Harmonisation; SV: Standard variation; Avg: Average; R2: Correlation coefficient; LOD: Limit of detection; LOQ: Limit of quantification; Temp.: Temperature

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Authors’ contributions
JS and VR developed and designed the study. JS has performed all the experiments with the help of DDR. JS was responsible for the data acquisition. PVAL supervised the experiment. JS and VR interpreted the data. JS wrote the manuscript, VR and DDR reviewed the data and supported for writing the manuscript. The authors have read and approved the final manuscript.

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Availability of data and materials
All data and material are available upon request.

Table 5 Degradation and specificity values for DEC and DEH

| Stress conditions put in | Drug  | Peak response | Degradation (%) | Peak purity Angle Threshold |
|-------------------------|-------|---------------|-----------------|-----------------------------|
| Control without degradation | DEH | 2173795 | - | - |
|                          | DEC | 4249950 | - | - |
| 0.1N HCl                | DEH | 1991167 | 8.64 | 0.349 | 0.560 |
|                          | DEC | 3801785 | 10.9 | 0.266 | 0.458 |
| 0.1N NaOH               | DEH | 2038512 | 6.41 | 0.264 | 0.659 |
|                          | DEC | 3951346 | 7.40 | 0.380 | 0.759 |
| 30% peroxide            | DEH | 2064601 | 5.21 | 0.255 | 0.761 |
|                          | DEC | 3972588 | 6.84 | 0.278 | 0.659 |
| 60°C Temp.              | DEH | 1933228 | 11.24 | 0.238 | 0.661 |
|                          | DEC | 3850464 | 9.76 | 0.386 | 0.859 |
| Sunlight                | DEH | 2030208 | 6.79 | 0.354 | 0.763 |
|                          | DEC | 3908982 | 8.39 | 0.293 | 0.660 |

Declarations
Ethics approval and consent to participate
Not applicable
Consent for publication
Not applicable
Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Chemistry, University College of Science, Osmania University, Hyderabad 500007, India. 2Department of Humanities and Sciences, CMR College of Engineering & Technology, Hyderabad 501401, India.

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