

Comparison of UV- Spectrophotometry and High- Performance Liquid Chromatography for Determination of Chlorpheniramine Maleate in Tablet in The Presence of Tartrazine

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2 Comparison of UV-spectrophotometry and high-performance liquid chromatography for determination of chlorpheniramine maleate in tablet in the presence of tartrazine

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ABSTRACT: The presence of tartrazine, yellow coloring agent, suspected to interfere with the CPM determination in CPM tablets using direct spectrophotometry or high performance liquid chromatography. Overlap spectra of tartrazine and CPM at an analytical wavelength and peak tailing were the main problem occurs in CPM tablets analysis. The aim of this study was to develop a derivative UV spectrophotometry and a modified HPLC to overcome the problem in CPM tablet analysis. Both validated methods were applied for the determination of CPM content in three registered CPM tablets. As a result, the first derivative spectrophotometry method obtained the $\delta A/\delta \lambda$ of tartrazine in matrix tablet was nearly zero at the wavelength of 232 nm and did not interfere with the $\delta A/\delta \lambda$ of CPM. The selective mobile phase for separation of CPM from tartrazine using HPLC method was a mixture of phosphate buffer pH 4 and methanol (60:40 v/v) with a flow rate of 1 ml/min. The CPM separated from tartrazine and other peaks in sample(s) with Rs of >1.5. The linearity, accuracy, and precision of these two methods fulfilled the reference requirement. No significant difference observed between the CPM content in artificial tablets when analyzed using first-derivative spectrophotometry and HPLC method. The concentration of CPM in one registered tablet that had been assayed using spectrophotometry, HPLC and the standard method was not significantly different. As a conclusion first-derivative spectrophotometry and HPLC method were valid for the determination of CPM in a tablet containing tartrazine. However, the first-derivative spectrophotometry method was more efficient than HPLC.

KEYWORDS: Chlorpheniramine maleate; tartrazine; UV-spectrophotometry; HPLC; method validation.

1. INTRODUCTION

Most of chlorpheniramine maleate (CPM) tablets use tartrazine (FD&C yellow no. 5) as a yellow coloring agent. CPM tablet is one of over-the-counter (OTC) medicines that rarely marketed with a color other than yellow. CPM is the first generation of antihistamine (AH1) that relieves most symptoms associated with allergic rhinitis or hay fever. CPM has mild sedative action and slight anticholinergic activity [1].

CPM is a basic substance that forms a salt with an equimolar portion of maleic acid (Figure 1A) [2], whereas tartrazine is a trisodium salt of dye anion (pKa 4.5) (Figure 1B) [3]. Tartrazine and CPM are polar substances that have similar solubility in water, methanol, 0.1 N NaOH and 0.1 N HCl, which are the solvent use to extract CPM from the tablet. The presence of tartrazine in CPM tablet solution suspected to interfere with the CPM determination. The tartrazine interference in the CPM determination in tablet dosage form not reported yet.

The official procedure for CPM determination in the tablet dosage form is UV-spectrophotometry after tedious extended extraction process using hexane [2,4,5]. In addition, CTM determination in extended-release capsule dosage form [2] or in the mixture with other compounds in common cold relieving drugs such as pseudoephedrine [2], paracetamol, caffeine [6] and dexamethasone [7] is using high performance liquid chromatography (HPLC).

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The overlapping of UV-spectra between CPM and tartrazine makes the CPM determination using direct UV-spectrophotometry without preceded by tartrazine separation is implausible. In the previous study, the combination the UV-spectrophotometry with multivariate analysis has been done for CPM determination in a mixture with dexamethasone and propylparaben [7,8,9]. While CPM determination using HPLC methods [2][9] need a relatively long retention time (t_R) and caused the peak tailing of tartrazine.

The aim of this study was to obtain a simple, efficient and valid method for the determination of CPM in a CPM tablet containing tartrazine. The valid proposed methods would be compared with the compendial method for the determination of CPM in three registered CPM tablets coded A[®], B[®], and C[®].

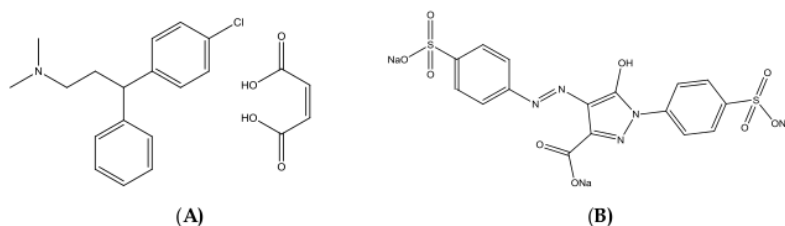


Figure 1. Structure molecules of chlorpheniramine maleate (A) and tartrazine (B).

2. RESULTS AND DISCUSSION

2.1. Validation method

2.1.1. Selectivity of the first derivative spectrophotometry

The overlapping UV spectra profile of standard CPM and tartrazine was depicted in Figure 2. A higher absorbance value of CPM will be obtained if the same concentration of CPM is in the mixture with tartrazine. This is a determined error in CPM analysis. Therefore, the first-derivative spectrophotometry method was studied as a solution method. By first derivative program, the $\delta A/\delta \lambda$ of tartrazine (also a tablet matrix containing tartrazine) was almost zero at the λ of 232 nm. While the $\delta A/\delta \lambda$ of CPM in a mixture with tartrazine was relatively the same as $\delta A/\delta \lambda$ of CPM without tartrazine. This means that tartrazine does not interfere with the value of $\delta A/\delta \lambda$ CPM at 232 nm anymore. The first derivative ($\delta A/\delta \lambda$) spectra profile of standard CPM and tartrazine was shown in Figure 3. The $\delta A/\delta \lambda$ value at 232 nm was selective for CPM in a mixture with tartrazine.

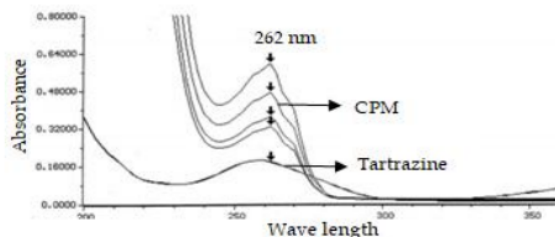


Figure 2. The UV spectra of (20.0- 40.0) ppm CPM and 5.0 ppm tartrazine in methanol:water (1:1).

2.1.2. Selectivity of the HPLC method

An optimum condition HPLC for the determination of CPM in the presence of tartrazine listed in Table 1. The proposed HPLC method completely separated chlorpheniramine (CP) from other substances in the CPM tablet with resolution (R_s) >1.5 as shown in Figure 4. The standard CPM as maleate salt split into maleic acid (MA, t_R of 3.3 minutes) and chlorpheniramine (CP, t_R of 16.89 minutes) (Figure 4A). The pH of the mobile phase and organic solvent composition influenced the CPM ionization. The buffer pH 4 causes the MA ($pK_{a1} = 1.94$) to be in the ionic form and eluted immediately. Whereas CP as the basic amine ($pK_a = 9.47$) was protonated and eluted later. The spectra of MA and CP were inserted in Figure 4A.

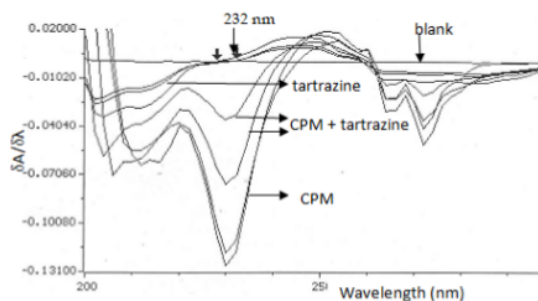


Figure 3. First derivative spectra of standard tartrazine (5.0 ppm, 8.0 ppm, and 10.0 ppm), a mixture of CPM (9.0 ppm, 18 ppm) and tartrazine (5 ppm, 8 ppm) and standard CPM (30 ppm).

Table 1. Optimum HPLC condition for determination of CPM in the tablet.

| Condition | Result |
|-----------------------|--|
| Mobile phase | buffer phosphate solution pH 4 and methanol of (60:40) |
| Flow-rate | 1 mL/minute |
| Injection volume | 20 μ L |
| Detector | DAD, wavelength of 262 nm |
| Retention time of CPM | 17.78 \pm 0.27 minutes |
| Peak purity of CPM | 0.9999 |
| Tailing factor | 1.06 \pm 0.03 |
| Theoretical plate | 2304 \pm 53 |

The tablet matrix containing tartrazine showed two peaks (Figure 4B). At the same time, the chromatogram of the tablet matrix without tartrazine (blank) showed no peak (the picture is not presented). The two peaks in the tablet matrix suspected to come from tartrazine and its impurity (Tar I and Tar II). The UV spectra of Tar II looks like tartrazine spectra with a maximum wavelength of 425 nm [3,11], whereas the first peak of tartrazine (Tar I) was overlapped with maleic acid peaks of CPM. All substance in tablet matrix eluted before CP and completely separate.

The chromatogram of the artificial CPM tablet (a mixture of tablet matrix and standard CPM) showed in Figure 4C1. This chromatogram profile was identical to the chromatogram of registered CPM tablet sample coded A® and C®. While the registered CPM sample tablet coded B® showed four peaks (Figure 4C2). However, the CP peak of all samples separated from other nearest compound peaks with R_s of >1.5. The intraday instrument precision of CP area was 0.82 %. The selectivity of HPLC was fulfilling the reference recommendation [12,13].

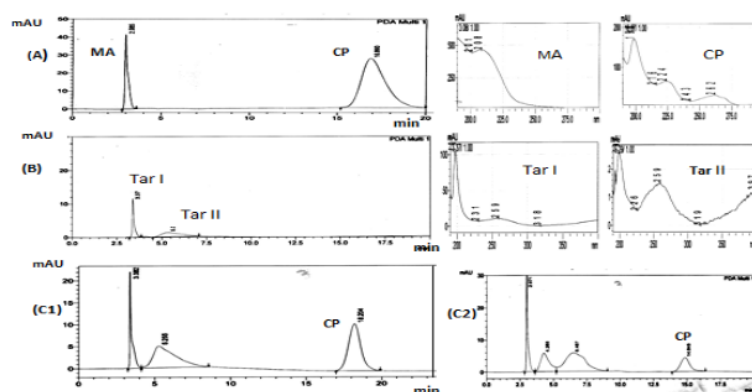


Figure 4. Chromatogram profile of CPM standard, inserted with MA and CP spectra (A), tartrazine and the impurities (B), artificial CPM tablet (C1) and CPM tablet sample coded B® (C2).

2.2. Linearity

The first derivative spectrophotometry obtained linearity parameter (R^2) of CPM was 0.999 in the CPM concentration range of (10-40) ppm. The linear equation was $Y = (-3,331 \times 10^{-3}) X - 2,487 \times 10^{-3}$ and function's standard deviation (V_{xo}) was 1.33%.

The HPLC method obtained the linearity parameter (R^2) of CPM in concentration range of (10-80) ppm was 0.999. The linear equation was $Y = 12526 X + 19662$ and function standard deviation (V_{xo}) was 2.45%. It can be concluded that the two method fulfilled the reference requirement [12,13] for linearity test.

2.3. Accuracy and precision

A comparison of the accuracy and precision between the first derivative spectrophotometry and HPLC for CPM determination in an artificial tablet presented in Table 2.

The independent t-test using SPSS obtained no significance differences between the mean value of both methods ($p = 0.492 > 0.05$). To sum up, the first derivative spectrophotometry and HPLC method were accurate and precise for CPM determination in tablet within the presence of tartrazine. As reference requirement for the accuracy and precision were 98-102% and 2%, respectively [12,13].

Table 2. The accuracy and precision of the first derivative UV spectrophotometry and the HPLC method for CPM determination in the artificial tablets.

| CPM relative concentration in each artificial tablet | CPM recovery (%) | |
|--|------------------------------------|--------------|
| | First derivative Spectrophotometry | HPLC |
| 80% | 99.81 | 98.20 |
| | 99.01 | 99.47 |
| | 99.82 | 98.08 |
| 100% | 98.24 | 99.69 |
| | 98.68 | 99.35 |
| | 98.11 | 100.67 |
| 120% | 99.47 | 99.39 |
| | 100.41 | 101.28 |
| | 100.21 | 100.50 |
| Average | 99.31 ± 0.01 | 99.62 ± 0.93 |
| CV | 0.84% | 0.93% |

2.4. Determination of CPM in tablet containing tartrazine

Three registered CPM tablets were analyzed using thin layer chromatography (TLC) prior to CPM determination for tartrazine identification. The TLC results showed that all samples contained tartrazine (data not shown). A comparison of the result of CPM determination in registered tablet A®, B® and C® using official procedure [2], first derivative spectrophotometry and HPLC was listed in Table 3. The official procedure for CPM determination in the tablet was direct UV-spectrophotometry where the CPM absorbance was measured after CPM has been previously separated from tartrazine by liquid-liquid extraction.

The results of CPM determination in sample A® using derivative UV-spectrophotometry was significantly different from the obtained result using reference methods ($P = 0.007 < 0.05$). This difference may be caused by the zero point selection of $\delta A / \delta \lambda$ tablet matrix being less accurate. The different composition of the tablet matrix could shift the zero point as the basis for analytical wavelength selection. Therefore, the analytical wavelength must be re-confirmed to obtain the derivative absorbance of the matrix relative zero to the CPM.

Even though the chromatogram profile of tablet sample B® (Figure 4C2) presented an unknown peak after tartrazine, the result of CPM determination in sample B® was not significantly different among the three methods used (oneway anava, $P = 0.421 > 0.05$). It can be concluded that the derivative spectra of the unknown analyte in sample B® was not affected the CPM derivative absorbance at the zero point.

The results of CPM determination in sample C® using HPLC was significantly different compared with the result of the official methods ($P = 0.004 < 0.05$). Nevertheless, the CPM content in all registered tablets using all methods fulfilled the reference requirement [2].

Comparison of derivative spectrophotometry and proposed HPLC method indicated that spectrophotometry was more efficient, rapid and reproducible. It was suggested that the derivative

spectrophotometry could be used for in process control of CPM tablet production or in development of CPM tablet formula in the research development laboratory.

Table 3. Result of CPM determination in registered tablet.

| Sample | Replicate | The CPM content in each registered tablet using the method: | | | | | |
|-------------------|-----------|---|--------|------|--------|----------|-------|
| | | First derivative Spectrophotometry | | HPLC | | Official | |
| | | mg | % | mg | % | mg | % |
| A® | 1 | 3.66 | 91.50 | 3.92 | 98.00 | 3.93 | 98.23 |
| | 2 | 3.64 | 91.00 | 3.88 | 97.00 | 3.75 | 93.78 |
| | 3 | 3.66 | 91.50 | 3.98 | 99.50 | 3.89 | 97.29 |
| Average A® | | | 91.33 | | 98.17 | | 96.43 |
| B® | 1 | 4.02 | 100.5 | 4.07 | 101.7 | 3.93 | 98.23 |
| | 2 | 4.04 | 101.0 | 4.16 | 104.0 | 4.17 | 104.4 |
| | 3 | 4.02 | 100.5 | 4.06 | 101.5 | 3.61 | 90.25 |
| Average B® | | | 100.67 | | 102.4 | | 97.63 |
| C® | 1 | 3.90 | 97.50 | 4.14 | 103.5 | 3.64 | 91.19 |
| | 2 | 3.88 | 97.00 | 4.17 | 104.25 | 3.67 | 91.74 |
| | 3 | 3.88 | 97.00 | 3.88 | 97.00 | 3.75 | 93.92 |
| Average C® | | | 97.17 | | 101.58 | | 92.28 |

3. CONCLUSION

Based on this study, it could be concluded that the derivative spectrophotometry and modified HPLC methods were valid for determination of CPM in a tablet containing tartrazine. The derivative spectrophotometry was more efficient than HPLC provided the matrix tablet composition is known.

4. MATERIALS AND METHODS

4.1. Materials

Chlorpheniramine Maleate p.g. (a gift from Interbat Pharmaceutical Industry), tartrazine (a gift from Aditama Raya Pharmaceutical Industry), methanol p.a (Sigma), KH_2PO_4 p.a (Sigma), H_3PO_4 p.a (Sigma). Placebo tablet containing starch 1500, micro-crystalline cellulose, magnesium stearate of pharm. Grade purity and three commercially registered CPM tablets coded A®, B® and C®.

4.2. Instrument

UV-Vis Spectrophotometer Hewlett Packard 8452A, HPLC Shimadzu L20-AD with Diode Array Detector (DAD), μ bondapak C-18 (10 μ m, 300 x 3.9 mm) column, Soccorex micropipette (d=1.0 μ L), Vortex (Genius 3), centrifuge apparatus (EBA20 Hectic), ultrasonic bath (Branson 43510), analytical balance Toledo (d=0.001 mg), pH meter Ohaus-starter 3000.

4.3. 0.05 M Phosphate buffer pH 4

6.804 gram KH_2PO_4 dissolved in sufficient 2940ml of water and adjusted with 85% H_3PO_4 to a pH4 before added the water until 1000 mL in a volumetric flask. The solution was filtered using membrane filter with a pore of 0.45 μ m.

4.4. Preparation of standard CPM and tartrazine solutions

12.5 mg CPM dissolved in a mixture of methanol: water (1:1) as a solvent. The solution transferred into a 50.0 ml volumetric flask and added the solvent until the marked line. The CPM solution diluted using the same solvent to obtain CPM working solution with a concentration range of (20-40) ppm. The tartrazine standard solutions were prepared by the same manner and diluted to obtain tartrazine working solution in the concentration range of 4-6 ppm.

4.5. Preparation of CPM tablet matrix

All the matrix components were mixed homogenously for 100 artificial tablets and stored the matrix powder in a dry container until to be used. Each artificial tablet containing matrix composition as follow: Avicel 102 (110 mg), micro-crystalline cellulose (89 mg), magnesium stearate (0.37 mg) and tartrazine (0.50 mg). This model composition was adopted from a tablet standard formula [13].

4.6. Sample preparation for CPM determination by derivative UV spectrophotometry and HPLC

Twenty CPM tablets were weighted and finely grinded. The average weight of the tablets was determined. The tablet powder was weighted accurately equivalent to 4 mg of CPM to be transferred into a 100 mL volumetric flask, added with 50 mL methanol and shaking in an ultrasonic bath for 15 minutes. Finally, distilled water was added up to the marked line, and shake homogenously. The supernatant was filtered using membrane filter with pore of 0.2 μm . This solution contains CPM of 40 ppm and ready to analyze with spectrophotometer or HPLC.

4.7. Validation of the method

4.7.1. Selectivity of the first derivative spectrophotometry method

The first derivative spectra of standard solutions of CPM, tartrazine and tablet matrix were overlaid at the wavelength range of 200-400 nm. As a blank solution was a mixture of methanol: water (1:1). The wavelength where $\delta A/\delta \lambda$ of tartrazine almost zero was determined. When $\delta A/\delta \lambda$ of tartrazine was zero, the measured $\delta A/\delta \lambda$ was CPM. At that selected wavelength the increase or decrease $\delta A/\delta \lambda$ CPM will be linear with the increasing CPM concentration.

4.7.2. Selectivity of the HPLC method

Operational conditions were selected based on the requirements of the selectivity parameter as follows: resolution (R_s) between CP and tartrazine was ≥ 1.5 , theoretical plate (N) >2000 and CPM tailing factor ≤ 2 . To meet the requirements of the selectivity, variation in operational conditions such as mobile phase composition and the flow rate were carried out. The ratio of phosphate buffer solution and methanol as mobile phase modified in the range of (75:25)-(60:40), the pH variation of phosphate buffer (pH 3 to 4) and the mobile phase flow rate range of (0.8-1.5) mL/minutes.

The instrument precision acquired by 6 times injection the CPM solution at the same operational condition. The relative standard deviation of the t_R and area of CPM should be not more than 2.0 % [2].

4.7.3. Linearity test

The five CPM working solutions in the range concentration of (10-80) ppm were measured their signal using UV spectrophotometer and HPLC to obtain the linear relationship equation ($Y = bx+a$). The AOAC requirement [12] for linearity are the coefficient of correlation (r) more than 0.99 and standard deviation of function (V_{so}) not more than 5%.

4.7.4. Accuracy and precision

Each standard CPM of 3.2 mg, 4.0 mg and 4.8 mg in a different 100 mL volumetric flask was added with 200 mg matrix powder. A mixture of standard CPM and matrix powder was processed according to step 4.6. The signal of the solution was measured using UV spectrophotometer and HPLC. Each mixture was processed in 3 times replication.

4.8. Assay of CPM in tablet using official procedure [2,4]

Not less than 20 tablets were weighed and finely powdered. A portion of powdered tablets equivalent to 4 mg of CPM was weighed accurately and transferred to a 125 mL separator. Twenty mL of dilute HCl (1=100) was added to the separator and shaken vigorously for 5 minutes, and then added with 20 mL hexane, shaken carefully, and the acid phase was filtered into a second 125 mL separator. The hexane phase was shaken with two 10 mL portions of dilute HCl (1=100). Each portion of acid was filtered into the second separator, and the hexane phase discarded. The acid extract was added with 10 mL of 1 M NaOH and 50 mL hexane, shaken carefully. The aqueous phase transferred into the third 125 mL separator containing 50 mL hexane. The third separator was shaken carefully, and the aqueous phase discarded. The two hexane solutions washed, in succession, with a single 20 mL portion of water, and the water discarded. Each of the two hexane solutions extracted with the 20, 20 and 5 mL portion of dilute HCl (1=100). The acid extracts were combined in a 50 mL

volumetric flask, diluted to volume, and mixed. The CPM absorbance was measured at the wavelength of 264 nm using 12 spectrophotometer.

The standard solution was prepared by accurately weighing 40 mg of CPM standard to dissolve in 200.0 mL of dilute HCl (1:100) and treated 20.0 ml of this solution in the same manner as the solution of the portion tablet taken.

This procedure involves a long extraction process before CPM absorbance measured by direct UV spectrophotometry. The result of CPM determination using the official procedure used as a reference in compares with the results of CPM determination using derivative UV spectrophotometry and HPLC.

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