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New diazo coupling of metoclopramide with 2,6-dimethyl phenol after using cloud point extraction method

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ABSTRACT

An environmentally safe spectroscopic technique has been developed for the determination of metoclopramide (MCP) in pharmaceutical samples. This method is rapid, practical, and suitable for the analysis of MCP both in its pure form and within pharmaceutical preparations, with or without the application of point cloud extraction technology. The procedure involves the nitration of metoclopramide at 5°C using sodium nitrite, followed by its reaction with 4-nitrophenol in an alkaline medium in order to yield a purple-coloured product. All experimental variables were optimized *a priori* so as to achieve robust and reproducible results. After stabilization of the chromophore, absorbance measurements were performed at 440 nm. Within the concentration range of 1–12 μg×mL^{-1}, the method adhered to Beer's law.

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1. Introduction

Metoclopramide (MCP), a benzamide alternative, is widely regarded as an antiemetic agent that supports gastrointestinal function and alleviates certain forms of nausea and vomiting. Its therapeutic action is attributed to the strengthening of the lower oesophageal sphincter and the acceleration of gastric emptying – both for liquids and solids – into the small intestine. MCP also reduces gastroesophageal reflux and mitigates regurgitation. Notably, it is prescribed in order to manage chemotherapy-induced emesis. To date, diverse analytical approaches for MCP estimation have been documented, including voltage calibration techniques and UV–visible spectrophotometry[1,2].

2. Methodology

2.1. Instrumentation

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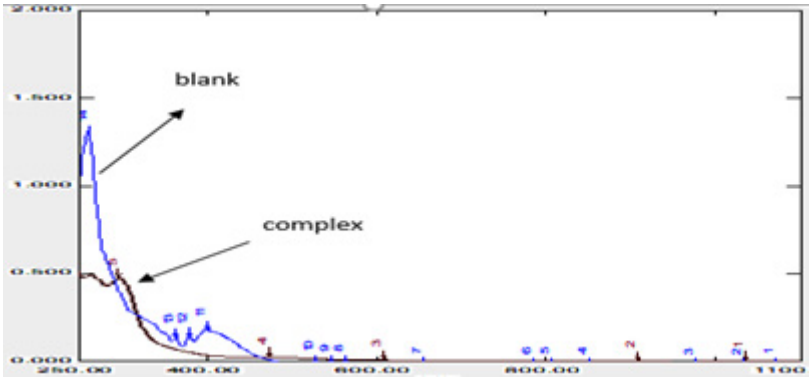

Figure 1. *Spectra of metoclopramide (MCP) and 2,6-dimethylphenol. Notes: the y axis represents absorption, while the x axis indicates wavelength (in nm).*

Key laboratory equipment included a pH meter, a Korean-made centrifuge, a German-manufactured electronic balance, a German-made water bath, and a SHIMADZU UV–visible spectrophotometer.

2.2. Preparation of standard solutions

High-purity reagents and drug samples were dissolved in distilled water. Sodium nitrite and sulfamic acid solutions (1,000 ppm) were prepared by dissolving 1 g of each substance in a 100-mL volumetric flask. Other acidic and basic solutions were prepared *via* standard dilution protocols. Surfactants were concentrated to 10% by adding 10 mL of surfactant to a 100-mL volumetric flask.

2.3. General Procedure for Azo Coupling

Diazonium salt formation was performed in a 10-mL volumetric flask maintained in an ice bath. The sequential additions were: 1 mL MCP, 1 mL hydrochloric acid, 1 mL sodium nitrite (while chilled), 1 mL sulfamic acid, 1 mL of the coupling reagent, 1 mL sodium hydroxide, and 1 mL distilled water. The optimal wavelength for the absorbance measurement of the resulting complex was determined from its spectral profile (see Figure 1).

3. Results and Discussion

3.1. First method (azo complex formation)

Absorbance was measured at 420 nm, and the influence of various parameters was examined. Using fixed additions and varying HCl volumes (0.1–1 mL), maximum absorbance was achieved at 0.4 mL. Among the different bases used, KOH yielded optimal absorbance at a volume of 0.5 mL. Absorbance increased with a $NaNO_2$ volume up to 1 mL, beyond which impurity effects (including diazonium instability due to excess nitrate) led to diminished absorbance[3]. After varying the 2,6-dimethylphenol reagent volume (0.2–0.6 mL), it was observed that 1 mL provided the highest absorbance[4]. Finally, a calibration curve for the MCP–4-nitrophenol complex was constructed by measuring the absorbance for MCP concentrations ranging from 1–12 $\mu g \times mL^{-1}$, thereby demonstrating compliance with Beer's law[5].

3.2. Second method (cloud point extraction)

The surfactant Triton X-114 was selected based on prior findings[6], with micelle-mediated separation enhanced by ethanol addition in order to improve both efficiency and absorbance. Extraction efficiency increased with the surfactant volume, peaking at 1.2 mL after a 20-min incubation at 60°C. Finally, solutions of MCP (1–12 $\mu g \times mL^{-1}$) were incubated at 50°C for 20 min. After cloud point formation and ethanol-mediated separation, absorbance was measured[7].

4. Conclusion

The combined cloud point extraction – spectrophotometric method proved effective for the MCP esti-

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mation, offering high sensitivity, excellent extraction efficiency, and environmental compatibility. The technique is simple, requires minimal volumes, and facilitates reliable preconcentration. MCP's affordability and reagent-grade availability allow its repurposing as a coupling agent in other reactions. Additionally, the method yields a strong relative standard deviation and a commendable detection limit, making it well-suited for broader analytical applications.

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Conflicts of interest

None exist.

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