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Smart manipulation of ratio spectra for resolving a pharmaceutical mixture of Methocarbamol and Paracetamol

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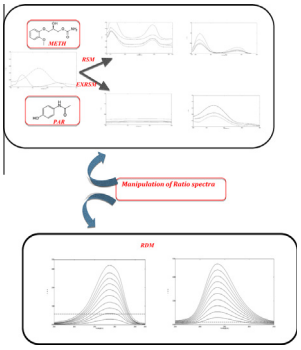
HIGHLIGHTS

- Application of smart and simple recently developed spectrophotometric methods manipulating the ratio spectra.
- The described methods are outstanding key for analysis of complex binary mixtures.
- Rapid methods without the need for sophisticated instruments or preliminary separation steps.
- Green, safe, economic, highly accurate and reproducible methods.
- The recently developed RDSM revealed higher selectivity and minimum data manipulation.

GRAPHICAL ABSTRACT



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ABSTRACT

Two smart, specific, accurate and precise spectrophotometric methods manipulating ratio spectra are developed for simultaneous determination of Methocarbamol (METH) and Paracetamol (PAR) in their combined pharmaceutical formulation without preliminary separation. Method A, is an extended ratio subtraction one (EXRSM) coupled with ratio subtraction method (RSM), which depends on subtraction of the plateau values from the ratio spectrum. Method B is a ratio difference spectrophotometric one (RDM) which measures the difference in amplitudes of ratio spectra between 278 and 286 nm for METH and 247 and 260 nm for PAR. The calibration curves are linear over the concentration range of 10–100 μg mL^{-1} and 2–20 μg mL^{-1} for METH and PAR, respectively. The specificity of the developed methods was investigated by analyzing different laboratory prepared mixtures of the two drugs. Both methods were applied successfully for the determination of the selected drugs in their combined dosage form. Furthermore, validation was performed according to ICH guidelines; accuracy, precision and repeatability are found to be within the acceptable limits. Statistical studies showed that both methods can be competitively applied in quality control laboratories.

Introduction

Methocarbamol is 3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate (METH), with molecular formula of $C_{11}H_{15}NO_5$ [1,2], Fig. 1a. It is a centrally acting skeletal muscle relaxant, it relaxes skeletal muscles through depression of reflex impulse conduction within the spinal cord. Methocarbamol is prescribed to outpatients for acute muscle spasm as well as for the treatment of chronic spasitcity [3].

Paracetamol is N-acetyl-p-aminophenol (PAR) Fig. 1b [1]. It is classified as a mild analgesic. It is commonly used for the relief

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of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies [3].

Literature survey reveals that there are few analytical reports for the determination of the selected drugs in their pharmaceutical preparation by derivative and mathematical spectrophotometry [4–6], gas liquid chromatography [7] and high-performance liquid chromatography [8,9]. Even though the determination and validation of each drug either individually or in combination with other drugs is reported [10–13], the PAR–MET mixture is not yet official in any pharmacopoeia.

This study demonstrates the resolution power of newly introduced experimental spectrophotometric methods, namely; extended ratio subtraction method coupled with ratio subtraction method and ratio difference method for accurate determination of METH and PAR in bulk material and in combination tablet.

Theory of the proposed methods

Extended ratio subtraction method (EXRSM) coupled with ratio subtraction method (RSM)

Extended ratio subtraction method (EXRSM) starts with the ratio subtraction method (RSM) [14] which depends on that, if you have a mixture of two drugs *X* and *Y* having overlapped spectra and one of them is extended (*Y*), one can determine *X* by dividing the spectrum of the mixture by a known concentration of *Y* as a divisor *Y*′. The division will give a new curve that represents *X*/*Y*′ + constant. If we measure this constant which is parallel to the wavelength axis in the region where *Y* is extended, then a new curve is obtained after subtraction of the constant. Then the zero order spectrum of component *X* could be obtained by multiplying the obtained ratio spectrum by the divisor *Y*′. This can be summarized as the following:

$$(X + Y)/Y' = X/Y' + Y/Y' = X/Y' + \text{constant}$$

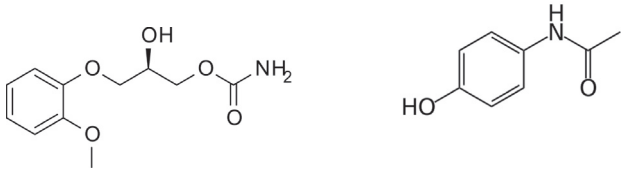
$$X/Y' + \text{constant} - \text{constant} = X/Y'$$

$$X/Y' \times Y' = X$$

Another extension of the already developed RSM method has been recently established namely extended ratio subtraction [15,16] to get the zero order spectrum of extended component (*Y*). It starts by dividing the obtained D0 spectrum of *X* by a known concentration of *X* as a divisor *X*′ to get the constant *X*/*X*′ for each concentration in the mixtures then follow the same procedure of the ratio subtraction through dividing each mixture by *X*′, then subtracting the corresponding constant *X*/*X*′ and multiplying by (*X*′):

$$Y/X' \times X' = Y$$

The concentration of *X* and *Y* were calculated from the corresponding regression equations (obtained by plotting the absorbance values of the zero order spectra of each drug at its λ_{max} against its corresponding concentrations).



a. Methocarbamol b. Paracetamol

Fig. 1. The chemical structures of Methocarbamol (a) and Paracetamol (b).

Ratio difference spectrophotometric method (RDM)

Ratio difference spectrophotometric method [15–17] was recently developed for analyzing a mixture of two drugs *X* and *Y* having overlapped spectra. It depends on the amplitude difference between two wavelengths λ_1 and λ_2 in the ratio spectra of a mixture is directly proportional to the concentration of the component of interest; independence of the interfering component. if two drugs *X* and *Y* having overlapped spectra, you can determine *X* by dividing the spectrum of the mixture by a known concentration of *Y* as a divisor (Y^0). The division will give a new curve that represents *X* + *Y*/*Y*′ i.e. *X*/*Y*′ + *Y*/*Y*′, where *Y*/*Y*′ is a constant. By selecting 2 wavelengths λ_1 and λ_2 on the obtained ratio spectrum and subtracting the amplitudes at these two points, the constant *Y*/*Y*′ will be canceled along with any other instrumental error or any interference from the sample matrix. This can be summarized as the

$$X + Y/Y' = X/Y' + Y/Y' = X/Y' + \text{constant}$$

Suppose the amplitudes at the two selected wavelength are P_1 and P_2 at λ_1 and λ_2, respectively; by subtracting the two amplitudes the interfering substance *Y* shows no interference; then;

$$P_1 - P_2 = (X/Y')_1 + \text{constant} - [(X/Y')_2 + \text{constant}]$$

$$P_1 - P_2 = (X/Y')_1 - (X/Y')_2$$

where; P_1 is the peak amplitudes of the ratio spectrum at λ_1, P_2 is the peak amplitudes of the ratio spectrum at λ_2.

The concentration of *X* is calculated by using the regression equation representing the linear relationship between the differences of the ratio spectra amplitudes at the two selected wavelengths using *Y* as a divisor (*Y*′) to the corresponding concentrations of drug (*X*). Similarly, *Y* could be determined by the same procedure using a known concentration of *X* as a divisor *X*′.

Experimental

Instruments

Spectrophotometer: Shimadzu UV-1650 PC, dual-beam UV–visible spectrophotometer (Japan), with matched 1-cm quartz cells, connected to an IBM-compatible PC and an HP-600 inkjet printer. Bundled, UV-PC personal spectroscopy software Version 3.7 was used to process the absorption and the derivative spectra. The spectral bandwidth was 2 nm with wavelength-scanning speed of 2800 nm min^{-1}.

Materials and reagents

Pure samples were kindly supplied by Sigma Pharmaceutical Ind. Company, Cairo, Egypt. Their purity was found to be 100.63 ± 0.29 and 99.91 ± 0.56, for METH and PAR, respectively, according to the reported spectrophotometric method [5].

Pharmaceutical formulations, Methorelax® tablets Batch No. 30888, were kindly supplied by Sigma Pharmaceutical Ind. company, Cairo, Egypt and were claimed to contain 400 mg of METH and 325 mg of PAR per tablet. All chemicals and reagents were of analytical grade and the solvents were of spectroscopic grade.

Standard solutions

METH and PAR standard solutions (0.2 and 0.1 mg mL^{-1}, respectively), prepared by dissolving 20 mg of METH and 10 mg of PAR, separately, in a few milliliters of methanol into a 100-mL