Summary

In this study, four different spectrophotometric methods were applied for determination of cimetidine and erythromycin ethylsuccinate drugs in pure form and in their pharmaceutical preparations. The suggested methods are simple, sensitive, accurate, not time consuming and inexpensive. The results showed the following:

The first method: Based on the formation of ion pair complex of each drug with bromothymol blue (BTB) as a chromogenic reagent. The formed complexes were extracted with chloroform and their absorbance values were measured at 427.5 nm for cimetidine and 416.5nm for erythromycin ethylsuccinate; against their reagents blanks.

Two different methods, univariate method and multivariate method, were used to obtain the optimum conditions for the spectrophotometric determination of the cited drugs via ion pair formation. The Multivariate method involves the simplex optimization in addition to design of experiment (DOE)for the case of cimetidine.

The study shows that the optimum conditions for the instantaneous formation of the ion-pair complexes, in aqueous medium, were: solution pH is 5.5 and 4.0 for cimetidine and erythromycin ethylsuccinate respectively, when 0.5 ml of phthalate buffer is used followed by the addition of 1 ml of 0.038% (for cimetidine) and 0.020% (for erythromycin ethylsuccinate)of BTB reagent. Moreover, the influence of different factors affecting the chloroformic extraction of the formed complexes was studied in each case. It was found that 6 min (for the case cimetidine complex) and 3 min (for the case erythromycin ethylsuccinate) shaking with one portion of 5 mL of chloroform was enough for quantitative extraction of the mentioned complexes.

The calibration graphs are linear in the ranges of (0.5-15.0) $\mu g.mL^{-1}$ with detection limit 0.222 $\mu g.mL^{-1}$ for cimetidine and (0.5-50.0) $\mu g.mL^{-1}$ with detection limit 0.286 $\mu g.mL^{-1}$ for erythromycin ethylsuccinate. The molar absorptivities were 13172 and 18103 $L.mol^{-1}.cm^{-1}$for the two complexes respectively.

The results showed that 1:1 complexes were formed with BTB through the electrostatic attraction between the positive protonated cimetidine and erythromycin ethylsuccinate with the anion of BTB.

Finally no interferences from the studied excipients on the determination of these drugs were found. The proposed methods have been successfully applied for the determination of cimetidine and erythromycin ethylsuccinate (with two of its derivatives) in some pharmaceutical compounds.

The second method: Based on the formation of charge transfer complexes between the studied drugs, as n-donors, and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), as π acceptors.

The colored products were measured spectrophotometrically and exhibit absorption maxima at 587nm for cimetidine complex and 585.5nm for erythromycin ethylsuccinate complex in acetonitrile against the reagent blanks.

The optimum conditions found by following the univariate i.e. one - factor – a time method and the simplex multivariate method. It was found that, at room temperature, 0.3 ml of 0.1% DDQ solution was sufficient for the quantitative formation of cimetidine-DDQ complex while, 0.2mL of the reagent is sufficient to form the erythromycin complex; using acetonitrile as organic solvent.

Beer's law is obeyed in a concentration range of; (5.0-70.0) µg.mL^{-1} for cimetidine with a detection limit of 0.268µg.mL^{-1} and (10.0-110.0) µg.mL^{-1} with detection limit of 0.351 µg.mL^{-1} for erythromycin ethylsuccinate. The molar absorptivities were found to be (4794.4 L.mol^{-1}.cm^{-1}) for cimetidine and (4568.9 L.mol^{-1}.cm^{-1}) for erythromycin ethylsuccinate. The results showed that both complexes were formed with a ratio of 1:1 drug:DDQ. No interferences from the studied excipients on the determination of these drugs were found therefore, the proposed methods were applied successfully for the determination of the cimetidine and erythromycin ethylsuccinatein dosage form.

The third method: H-point standard addition method (HPSAM) has been applied for simultaneous spectrophotometric determination of cimetidine and erythromycin ethylsuccinate in their mixture.

Depending on the results obtained from the first method (i.e. ion-pair formation), it was observed that a substantial convergence between the absorption maxima of cimetidine-BTB complex (nm 427.5) and erythromycin ethylsuccinate-BTB complex (416.5nm). Therefore, attempts were carried out to adopt the HPSAM in estimating cimetidine in the presence of erythromycin ethylsuccinate (as interferent) and to estimate erythromycin ethylsuccinate in the presence of cimetidine (as interferent), with the possibility of simultaneous estimation of the interferent at each time.

It was found that the method is able to accurately determine cimetidine in the presence of erythromycin at 370nm and 460 nm in different ratios of analyte to interference (with best ratio of 1:4) in mixed samples containing (1–5 µg.ml^{-1}) of cimetidine. On the other hand, the determination of erythromycin ethylsuccinate in the presence of

cimetidine was carried at 400 and 460 nm in different ratios of analyte to interference (with best ratio of 4:1) in mixed samples containing (2-10 μg.ml^{-1}) of erythromycin.

The results show the absence of interferences from the studied excipients on the determination these drugs, limits of detection were calculated in each case and were found to be (0.282μg.ml^{-1}) and (0.431μg.ml^{-1}) for cimetidine and erythromycin ethylsuccinate respectively. The proposed method has ben successfully applied for the simultaneous determination of cimetidine and erythromycin ethylsuccinate in pharmaceutical compounds.

The fourth method: Derivative spectrophotometry**,** this method based on the first and second derivative spectra of absorption for simultaneous determination of cimetidine and erythromycin ethylsuccinate in their mixtures in the ultraviolet region. The method offers an advantage of getting rid of the resulting error in the values of absorption because of the presence of each drug with other or the presence of interferences from the excipients recognized during the determination of these drugs in pharmaceutical compounds.

It was possible to estimate cimetidine in the range of (2-10) μg.mL^{-1}; in mixtures containing different concentrations of erythromycin ethylsuccinate (0, 10, 20, 30) μg.mL-^{1}, as (interferent), by using the first derivative of the spectrum at 188.7 nm, 191.1 nm and 230.9 nm (peak to base line & zero cross measurements), and at 191.1-192.5 nm and 193.5-194.9 nm (peak to peak measurements), and at 183.7-206.6 nm and 218.3-255.7 nm (peak area measurements), while the adopted wavelengths at 187.1 nm 189.1 nm, 191.3 nm, 192.4 nm, 193.5 nm and 194.7 nm (peak to base line & zero cross measurements) and wavelengths at 191.1 -192.4 nm, 192.4-193.5 nm and 193.5-194.7 nm (peak to peak

measurements) and wavelengths at 188.0-190.0 nm, 190.0-192.3 nm, 191.2-193.5 nm, 192.3-194.6 nm and 193.5-195.8 nm (peak area measurements) were used for determination of cemitidine depended on second derivative spectrum.

Erythromycin ethylsuccinate was determined for the range of (10-50) $\mu g.mL^{-1}$; in a mixture containing different concentrations of cimetidine (0, 2, 4, 8) $\mu g.mL^{-1}$ as (interferent). It was found that the wavelengths at 189.1 nm, 191.2 nm and 195.1 nm (peak to base line & zero cross) and wavelengths at 184.1-191.8 nm and 192.1- 247.3 nm (peak area), were useful for determination of erythromycin ethylsuccinate depending on its first derivative spectrum. On the other hand, the wavelengths at 184.2 nm, 186.9 nm, 188.6 nm, 189.8 nm, 191.9 nm and 194.5 nm were found useful for peak to base line & zero cross determinations and wavelengths at 188.6 nm - 189.8 nm were used for peak to peak measurements and wavelength at 184.0–189.0 nm, 189.0–191.0 nm and 189.0-192.5 nm are used for measuring the area under the peak for the determination of erythromycin ethylsuccinate depending on its second derivative spectrum.

The results obtained, by applying this method using the mentioned measurements, show the absence of interferences from the excipients on the determination of these drugs, therefore; it was possible to be applied them for the determination of the cited drugs in dosage form.