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Analytical study on determination of some drugs in pure form and in dosage form

The Thesis Submitted
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

}} رِبِّ أَوْزَعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ عَلَيَّ وَعَلَيَّ وَالِدَيَّ
وَأَنْ أَعْمَلَ عَالِمًا تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ
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Analytical study on determination of some drugs in pure form and in dosage form

ABSTRACT

Several methods were developed for determination of omeprazole, lansoprazole, mesalazine in pure forms and in pharmaceutical preparations. The first proposed method was spectrophotometric method, involves the oxidation of these drugs with potassium iodate in acidic medium with the liberation of iodine and subsequent extraction with cyclohexane followed by measuring the absorbance at $\lambda = 520$ nm under the optimized experimental conditions. Beer's law is obeyed in the concentration range of 5-200 and 15-200 $\mu\text{g mL}^{-1}$ with apparent molar absorptivities of 2.42×10^{-4} and 2.01×10^{-4} $\text{L mol}^{-1} \text{cm}^{-1}$ for omeprazole and lansoprazole, respectively. The second method was the potentiometric method involved the direct titration of the drugs with N-bromosuccinimide in acid medium and the end point is subsequently potentiometrically determined using platinum indicator electrode under the obtained optimum conditions. Omeprazole and lansoprazole could quantitatively be determined in the concentration range 25-100 and 15-100 mg mL^{-1} with standard deviation of 0.007-0.042 and 0.005-0.034, and with relative standard deviation of 0.79-2.4 and 1.4-2.9. The third method TLC-densitometric method for drugs omeprazole using silica gel plates in simultaneous determination of omeprazole, tinidazole and doxycycline in bulk powder; laboratory prepared mixture and combined dosage form. The technique adapted for quantification is coupled TLC-densitometry. The mobile phase used a mixture of methylene chloride : butanol : acetonitrile : Amonia (11:12:5:0.5 v/v/v/v). The detection of spots was carried out densitometrically using a UV detector 380 nm in absorbance mode. This system was (R_f found to give compact spots for omeprazole (R_f 0.49), tinidazole (R_f 0.66) and doxycycline (R_f 0.92). The fourth method depended on preparation of ZnMn_2O_4 nanomaterial which investigated and used for the determination of omeprazole and lansoprazole using nanotechnology. The fifth method was investigated mesalazine using thermal analysis (TA) measurements and electron impact mass spectral fragmentation at 70 and 15 eV of electron energy. The optimum molecular geometry and the total energy of the neutral and the positively charged Mesalazine molecules were calculated by density functional theory method with 6-311++G(d,p) basis sets. The results of this method were in good agreement with those given using a reference method. The pharmaceutical additives other than active ingredients did not interfere.

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Synthesis and characterization of a ZnMn_2O_4 nanostructure as a chemical nanosensor: a facile and new approach for colorimetric determination of omeprazole and lansoprazole drugs

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We have developed a facile method for preparation of ZnMn_2O_4 nanostructures *via* an auto-combustion method using various fuels: urea, glycine and L-alanine. The type of fuel and pH of the combustion media have a significant effect on the combustion products. Glycine fuel generated spinel ZnMn_2O_4 on combustion, and calcination of the sample produced pure spinel ZnMn_2O_4 nanoparticles with an average crystallite size of 19 nm. Whereas, other fuels generated multiphase compounds on combustion. The products were elucidated by means of XRD, FE-SEM, EDS, TEM, FT-IR, and UV-Vis diffuse reflectance spectra. The as-fabricated product was applied to construct a novel chemical nanosensor for the determination of omeprazole and lansoprazole drugs. Different factors influencing the colorimetric determination of the drugs were examined such as contact time, temperature, initial drug concentration, and ZnMn_2O_4 dose. The proposed chemical nanosensor revealed high sensitivity, low detection limit, and a relatively wide linear range (0.80–8.0 and 0.80–8.8 $\mu\text{g mL}^{-1}$ at λ_{max} 454 nm for omeprazole and lansoprazole, respectively).

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1. Introduction

A growing interest in spinel metal oxide nanostructures; AB_2O_4 (A and B = metal), has been observed in the past few years.^{1–4} This intensive interest is due to the unique physical and chemical properties that these oxides possess, which make them suitable for various applications.^{5–9} Among these spinel nanostructures, nano-sized zinc manganite (ZnMn_2O_4) has received a considerable attention due to its various applications such as in sensors, electrodes, lithium rechargeable batteries, specific memory devices, thermistors, and catalysis.^{10–14} Therefore, many research groups have devoted their efforts to synthesizing spinel ZnMn_2O_4 nanostructures. In this light, ZnMn_2O_4 nanostructures with different morphologies and particle sizes have been prepared using various routes such as pyrolysis, solvothermal, electrospinning, hydrothermal, sol-gel, and the solid state method.^{15–18} However, some of these techniques are time-consuming, relatively complicated and expensive, as well as they include sophisticated instruments. Searching for a facile, inexpensive, and less time-consuming process for the production of ZnMn_2O_4 nanostructures is still

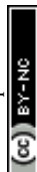
a challenge. Besides, combustion process can fulfill these requirements since it is an inexpensive, simple, short time-consuming, and scalable procedure.^{19–21} In addition, this method produces porous materials with high surface areas owing to the evolution of gasses during the combustion process.^{19–21} In this respect, reports on the synthesis of ZnMn_2O_4 nanostructures using combustion methods are still limited.^{22,23} However, the combustion processes were not extensively investigated in those reports. And the reported preparations applied higher temperatures, during the calcination steps, and produced nanoparticles with larger crystallite sizes in comparison to our current investigation, as will be explained later in the Results and discussion section.

On the other hand, lansoprazole; $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2\text{S}$, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphonyl]-1H-benzimidazole, is a proton pump inhibitor, and it is effectively used for treatment of gastric ulcers and duodenal.²⁴ This drug is a chemosensitizing cytotoxic, and it can treat various human tumor cells.²⁵ In addition, omeprazole; $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$, 6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]methyl]sulphonyl]-1H-benzimidazole, is a proton pump inhibitor which can be used for treatment of symptomatic gastro-esophageal reflux, gastroduodenal ulcers, and Zollinger-Ellison syndrome.^{26,27} This drug can enhance the oral digoxin bioavailability by decreasing the acid production in the stomach and increasing the gastric permeability to digoxin.²⁶ Some methods have been developed for quantitative determination of

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Optimization and Validation of Spectrophotometric and Potentiometric Methods for Determination of Lansoprazole and Omeprazole in Pure and Capsules

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Nassar, *et al.*: Optimization and Validation of Spectrophotometric and Potentiometric Methods

Two fairly sensitive, simple and accurate methods have been developed and validated for the assay of omeprazole and lansoprazole in pure and dosage forms. The proposed spectrophotometric method was based on the oxidation of the title drugs with acidic potassium iodate solution resulted in liberation of iodine, which was then extracted and measured at λ 520 nm under the optimized experimental conditions. The method was proved to be accurate and precise and the linearity was found to be in the concentration range of 5-200 and 15-200 $\mu\text{g/ml}$, for omeprazole and lansoprazole, respectively, with apparent molar absorptivities of 2.42×10^{-4} and $2.01 \times 10^{-4} \text{ l mol}^{-1} \text{ cm}^{-1}$, and with the corresponding Sandell sensitivity value of 0.0281 and 0.0473 mg cm^{-2} for the afore mentioned drugs, respectively. Moreover, the kinetics of these reactions was investigated. On the other hand, the potentiometric method was based on the direct titration of the drugs with acidic N-bromosuccinimide solution with determination of the end point potentiometrically using a platinum indicator electrode under the optimum conditions. The concentration ranges were found to be 25-100 and 15-100 $\mu\text{g/ml}$ with standard deviation of 0.007-0.042 and 0.005-0.034, and with relative standard deviation of 0.79-2.4 and 1.4-2.9 for omeprazole and lansoprazole, respectively. Additionally, the proposed methods could successfully be applied for the determination of the cited drugs in pharmaceutical dosage forms. The relative standard deviations for the results did not exceed 1%, confirming the high precision of the method and reproducibility of the results

Key words: Omeprazole, lansoprazole, potassium iodate, N-bromosuccinimide, spectrophotometry, potentiometry and kinetics

Omeprazole (Prilosec), 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphonyl]-1H-benzimidazole^[1] (fig. 1a), is the first-in-class of the proton pump inhibitors (PPIs) that is widely used for the prophylaxis and treatment of both gastroduodenal ulcers and symptomatic gastro-esophageal reflux^[2]. Consequently, this drug can increase the bioavailability of oral digoxin by suppressing acid production in the stomach and raising gastric permeability to digoxin^[3,4]. Also, it is highly effective in the treatment of Zollinger-Ellison syndrome^[5]. Its empirical formula is $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$, with a molecular weight of 345.42.

On the other hand, lansoprazole is effective in the treatment of various peptic diseases, including gastric and duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome^[1]. The PPIs are unstable at a low pH, and therefore, the oral dosage forms are supplied as

enteric-coated granules encapsulated in a gelatin shell. The PPIs are also considered to be weak base pro-drugs that easily penetrate cell membranes and concentrate in acidic compartments, where they are converted into sulphonamide forms, representing the active inhibitors^[6]. Additionally, PPIs are chemo sensitizing cytotoxic drugs, and active against various human tumor cells^[7-9]. The active ingredient in Prevacid delayed-release capsules and Prevacid delayed-release orally disintegrating tablets is lansoprazole, a substituted

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Structure investigation of mesalazine drug using thermal analyses, mass spectrometry, DFT calculations, and NBO analysis

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Abstract Mesalazine (MZ) drug has been used for several decades as a primary treatment for inflammatory bowel diseases. The drug was investigated using thermal analysis (TA) measurements and electron impact mass spectral fragmentation at 70 and 15 eV of electron energy. The optimum molecular geometry and the total energy of the neutral and the positively charged MZ molecules were calculated by density functional theory method with 6-311++G(d,p) basis sets. Stability of the molecules arising from hyperconjugative interactions, charge delocalization, and the natural atomic charges has been analyzed using natural bond orbital analysis. In electron ionization mass spectrometry, the primary rupture is due to successive loss of H₂O (OH from carboxyl and H from phenolic OH of the ring) and CO of the acetyl group. Thermogravimetric results have revealed two stages of mass loss at 75.3 and 25.3 % in ranges 225–350 and

350–650 °C, respectively. The first one may be due to successive losses of different groups or molecules with fast rate of decomposition. A comparison between MS and TA helped in selection the proper pathway representing the fragmentation mechanism of this drug.

Keywords Mesalazine · Mass spectroscopy · Thermal analysis · DFT calculations · NBO analysis · Structure reactivity relationship

Introduction

Mesalazine (MZ, C₇H₇NO₃, MW = 153) drug known as mesalamine or 5-aminosalicylic acid (5-ASA) is one of the most commonly used drugs for the treatment of active inflammatory bowel diseases (IBD) and for maintenance of remission [1–3]. Mass spectrometry (MS) has become a power tool for drug metabolism studies [4]. The technique is important because it provides a large amount of structural information with little expenditure of sample [5–8]. Despite the importance of this drug in medicine, to the best of our knowledge, the fragmentation mechanisms of the title compound along with thermal studies have not been reported. Thermal analytical techniques can provide important information regarding storage and stability of pharmaceuticals. Thermal analytical methods have thus become important tools for the development of modern medicines [9–13]. Thermogravimetric TG/DTG analysis was used to provide quantitative information on mass losses due to decomposition and/or evaporation of low molecular materials as a function of time and temperature [14–16]. In conjunction with mass spectrometric analysis [17–19], the nature of the released volatilize may be deduced, thus greatly facilitating the interpretation of

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AIM OF THE WORK

The drugs have wide applications in medicine for the treatment of several diseases. The development of selective, accurate and precise method for drugs determination in pure and dosage forms is great importance.

Drugs studied in this thesis were omeprazole, lansoprazole and mesalazine which used in the treatment of dyspepsia, peptic ulcer diseases, respectively.

New methods have been suggested in this thesis. Spectrophotometric method, potentiometry, Thin Layer Chromatography densitometric (TLC-densitometric), Nanotechnology and Natural Bond Orbital (NBO) methods which had become powerful tools for determination drugs in pure form and dosage forms.

The plan of work compares the utilization of the proposed methods for determination of some drugs, in addition, to statistical comparison between the proposed and reference methods.

List of Abbreviations

AUC	Area under the plasma concentration
BCP	Bromocresol purple
BDDE	Boron-doped diamond electrode
BPB	Bromophenol blue
CE	Capillary electrophoresis
CLR	Clarithromycin
CVD	Chemical vapor deposition
DCE	Dichloromethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density function theory
DOX	Doxycycline
EI	Electron ionization
FE-SEM	Field emission scanning electron microscope
HR-TEM	High-resolution transmission electron microscope
LNZO	Lanzoprazole
LOD	Limit of detection
LOQ	Limit of quantitation
MS	Mass spectra
MRT	Mean residence time
MZ	Mesalazine
NBO	Natural bond orbital
NBS	<i>N</i> -Bromosuccinimide
OMP	Omeprazole
PLD	Pulsed laser deposition
PVP	Poly vinyl pyrrolidone
S.D.	Standard deviation
SPE	Solid-phase extraction
TLC	Thin layer chromatography
TND	Tinidazole
XRD	X-ray diffraction analysis
%R.S.D.	% Relative standard deviation

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