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Spectrophotometric Determination of Antiulcer drugs using 2,2'-bipyridine as Complexing agent

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Abstract:
Simple, sensitive and rapid spectrophotometric method for the determination of certain proton pump inhibitors belonging to the benzimidazole class of compounds has been developed. The method is based on the reaction of these antiulcer drugs namely omeprazole (OMZ), lansoprazole (LNZ), pantoprazole (PNZ), rabeprazole (RBZ) and esomeprazole (EMZ) with iron (III) and subsequent complexation with 2,2' -bipyridine which forms a pink coloured product with maximum absorption at 530 nm. The commonly encountered excipients and additives along with the drug did not interfere with the determination. Antiulcer drugs in the range of 200 - 4000 ng mL^{-1} for LNZ, PNZ and RBZ, 80 - 2800 ng mL^{-1} for OMZ and 200 - 3800 ng mL^{-1} for EMZ can be determined by this method. Results of the analysis of commercial capsules/tablets (omelac capsule, lanpro capsule, pan tablet, rabeloc tablet and raciper tablet for OMZ, LNZ, PNZ, RBZ and EMZ, respectively) by this procedure agree well with those of the reported method.

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Introduction:

Ulcer is considered as a very common and conventional disease all over the world and the statistical data indicates that more than 10% of the adult population are affected within their life time. In developing countries like India because of the high cost of the prescribed antiulcer drugs (proton pump inhibitors) new antiulcer substances are very much essential. Peptic and duodenal ulcer is a peptic ulcer disease which arises due to the defect in the mucosal surface of the stomach or duodenum. Peptic ulcer occurs more often in individuals from 20 to 60 years of age with males. The symptoms of peptic ulcer include abdominal pain, nausea, epigastric gnawing, heartburn, acid eructations, haemorrhage, anaemia, weight loss, and vomiting [1,2].

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Gastric ulcers occur due to the imbalance in the equilibrium between mucosal damaging (acid and pepsin) and protecting mechanism of the gastric mucosa. Acid secretion is a physiologically important function of the stomach, as gastric acid (HCl) induces pepsinogen activator that helps to initiate digestive process [3]. Gastric ulcers are caused by several factors like the over consumption of the nonsteroidal anti-inflammatory drugs such as aclofenac and nimesulide, steroidal drugs such as prednisolone, tobacco smoking, psychological stress, alternative lifestyle, and alcohol abuse [4]. Helicobacter pylori is the main cause of inflammation which causes damage to the gastric mucosa through excessive acid secretion from parietal cells by increasing the parietal cell mass due to its inflammatory effects on parietal cells of gastric mucosa [5]. Although H. pylori is the major cause for the development of ulcer, a number of investigations through the mechanism via H. pylori was established in the gastric environment and is also responsible for the pathogensis of gastric ulcer. Even though half of the population of the world is affected by H. pylori only about 5-10 % of the population develop ulcer [6,7].

Some of the molecules with antiulcer activities are natural single molecule such as: curcumin which is a polyphenol isolated from the rhizome of curcuma longa. It is used as ayurvedic medicine against peptic ulcer and duodenal ulcer [8], cinnamic acid is an active ingredient in cinnamon, obtained from the inner bark of several tree species from the genus cinnamomum, and has shown anti-ulcer activity. In a recent study, protection against ulcer and gastritis by cinnamomi ramulus bark extract and cinnamic acid was shown in acid neutralizing capacity against H. pylori [9], thymol is a monocyclic monoterpene compound isolated from Thymus vulgaris L. The water extract of this herb protected gastric mucosa with the oral doses of 0.08 mg/kg when evaluated in Rainsford's cold stress ulcer model [10], menthol is a cyclic monoterpene alcohol, isolated from Mentha piperita L, which is commonly known as peppermint [11].

The plant products with exhibit antiulcer activities are: aloe has been used for millennium which is more like a cactus plant, growing in dry climates, containing compounds such as amino acids, saponins, enzymes, anthraquinones, flavonoids, gallic acid, and vitamins [12], carica papaya belongs to the family Caricaceae. The fruit of this plant contains papain which is responsible for anti-ulcer activity [13]. Hydroalcoholic extract of unripe fruit of carica papaya was evaluated in pylorus ligation induced ulcer model and the result showed reduction in the ulcer index [14], Zingiber officinale chemically contains resin. In recent studies, the aqueous extract of these plants (200 and 400 mg/kg) was applied in indomethacin-induced gastric damage in rats, and a significant percentage inhibition of gastric ulcer was observed [15], Mimosa pudica belongs to the family of Fabaceae, commonly known as "touch me not" and known as Lajjalu in Ayurveda. Different solvent extracts of M. pudica were used orally to exhibit anti-ulcer activity in albino rats, where ulcer was induced with alcohol and aspirin. The study showed that the plant has good anti-ulcer activity when compared with ranitidine. The ethanolic leave extract of this plant may be useful as a natural antioxidant in the treatment of ulcer. Alkaloid mimosine is active compound of this plant which was considered for anti-ulcer activity [16,17].

Nutraceuticals which contain antiulcer components are: garlic is a very common food material used, especially in India and China, obtained from Allium sativum belonging to the

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family Liliaceae. According to Ayurveda, the mustard or coconut oil in which garlic has been fried was a proper nutrient to avoid maggots infesting ulcer, ulcerated surface, and wounds, etc [18], banana whose benefits to human health have been promulgated for centuries. Banana belongs the family Musaceae is cultivated all over the world. It composed of a significant number of monomeric flavonoids, especially leucocyanidin, which is the active component possessing anti-ulcer action in indomethacin-induced ulcer model [19], honey is a natural non-plant food. Honey significantly reduced gastric acid when it was administered orally in combination with fenugreek seeds in rats against ethanol-induced ulcer model. It was observed that honey in combination with turmeric showed anti-ulcer activity in rats via antisecretory, antioxidant, and cellular protective mechanisms [20], cucumber belongs to the family Cucurbitaceae and contains Vitamin C, Vitamin K, linoleic acid, oleic acid, stearic acid, etc. It is cultivated in all over the world. The hydroalcoholic fruit extract of cucumber was given orally against pylorus ligation, indomethacin-, and ethanol-induced ulcer models in rats, which reduced total acidity and ulcer index via prostaglandin synthesis or blockade of back diffusion of H^+ ions [21,22].

Omeprazole (OMZ), lansoprazole (LNZ), pantoprazole (PNZ), rabeprazole (RBZ) and esomeprazole (EMZ) belong to a class of antiulcer drugs. Various methods have been proposed for the determination of antiulcer drugs include: indirect argentometry [23], capillary electrophoresis [24], polarography [25-27], voltammetry [28,29], flow injection analysis [30,31] and high-performance liquid chromatography [32-37]. Simple methods based on UV-visible spectrophotometry have now a days become an accepted analytical tool for the assay and evaluation of drugs.

Electroanalytical techniques have been used for the determination of a wide range of pharmaceutical preparations with advantages and in most instances, there is no need for derivatization and these methods are less sensitive to matrix effects compared to other analytical techniques [38]. However, these techniques have proved costly and cumbersome due to their high selectivity with regard to the solvent and the choice of the electrode material. Chromatographic methods are valuable for identification of impurities in preformulations or metabolites in biological matrices rather than routine quantitative analysis. Further, these methods need special equipment and their maintenance cost is high. Automated methods are economical only in case of large number of samples. But for routine analysis, spectrophotometric methods seem to be the most appropriate analytical approach. It is convenient and simple and can be relatively inexpensive.

Visible spectrophotometric methods are convenient, simple, sensitive and are relatively inexpensive. The spectrophotometric methods for the determination of antiulcer drugs employ different routes in the determination of chromogen produced and these are of four types. Type I method involves the oxidative coupling of the drug with an electrophilic reagent in the presence of an oxidant and measurement of the resulting chromophore [39]: method of type II involves the use of electron acceptor and the antiulcer drug as electron donar in which the resultant product is coloured molecular complex [40]. Type III method consists in the formation of a charge transfer complex between the drug and the reagent [40]. Finally, Type IV method is based on the use of a suitable oxidant to produce colour for the spectrophotometric measurement [41]. Methods of Type I, II, and III are lengthy; however, the method of Type IV

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although is simple and straight forward, but lacks selectivity as the coloured product is presumed to be the radical cation of the drug. Also, the above methods have not utilized a co-ordinated complex as a chromogen for the determination of antiulcer drugs. These deficiencies have encouraged the author to develop a simple, sensitive, rapid and reliable method for the determination of antiulcer drugs.

The work describes a new method for the determination of antiulcer drugs like OMZ, LNZ, PNZ, RBZ and EMZ which is based on the reduction of iron (III) to iron (II) by the drugs and subsequent complexation with 2,2' -bipyridine which produces a pink coloured product having a maximum absorption at 530 nm.

Experimental

Apparatus: UV-VIS spectrophotometer UVIDEC-610 type with 1.0-cm matched cell was employed for measuring the absorbance values.

Reagents:

Omeprazole (OMZ), lansoprazole (LNZ), pantoprazole (PNZ), rabeprazole (RBZ) and esomeprazole (EMZ), ammonium iron (III) sulphate and 2,2' -bipyridine were used. All the other chemicals and solvents were of analytical grade. Double distilled water was used throughout. Weighed (100 mg) samples of the drugs were dissolved in about 10.0 mL of alcohol and the solution was diluted with distilled water in 100-mL volumetric flask. The solutions were stored in a refrigerator and diluted daily to get the required concentrations. Aqueous solution of 0.001N ammonium iron (III) sulphate containing a few drops of dilute sulphuric acid and 0.2% (*w/v*) of 2,2' -bipyridine solution were prepared in doble distilled water and alcohol, respectively.

Procedure:

Assay with iron (III) and 2,2' -bipyridine: aliquots of standard solutions of OMZ, LNZ, PNZ, RBZ and EMZ were transferred into 25-mL calibrated flasks. To each of the flask was added ammonium iron (III) sulphate (2.0 mL) and 2,2' -bipyridine (2.0 mL). The flasks were kept in a boiling water bath (80^0C) for 10 mins and then cooled to room temperature (27^0C). After cooling the solutions were made up to the volume with distilled water. The absorbance of the pink colour was measured at 530 nm against the corresponding reagent blank and calibration graphs were constructed. The optical characteristics are presented in Table 1.

Pharmaceutical preparations

Twenty capsules each of omeprazole and lansoprazole were carefully emptied and the mass of the collected contents was determined. The capsule contents were finely powdered in a mortar. In case of pantoprazole, rabeprazole and esomeprazole twenty tablets each were finely powdered. An accurately weighed 50 mg of the powdered drug was dissolved in about 10.0 mL of alcohol and filtered through a Whatman No. 42 filter paper. The filtrate was made up to 100 mL wit distilled water in a volumetric flask. A suitable volume of the filtrate was accurately diluted with water so as to obtain a sample concentration of 10 µg mL^{-1}. An aliquot of this solution was treated as per the procedure described earlier for the determination of antiulcer drugs.

Results and discussion:

Omeprazole (OMZ), lansoprazole (LNZ), pantoprazole (PNZ), rabeprazole (RBZ) and esomeprazole (EMZ) belong to a class of antisecretory compounds. These compounds are acid

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labile and reversibly transformed in acidic medium to a sulphonamide [42]. They are referred to as proton pump inhibitors (PPI) being introduced for the management of duodenal ulcer, gastric ulcer or pathogenic hypersecretory condition [43]. Gastric PPI is a prodrug that requires an acid induced activation. It is a weak base that is converted to its active form by gastric acid before acting on the proton pump. It inhibits gastric acid secretion by covalently binding to the proton pump (H^+/K^+ AT Pase)[44].

2,2'-bipyridine is a derivative of 1,10-phenantroline and it is used as a bacteriostatic, fungistatic, ant fibrillating agent, virus inactivator, paint and oil drier, enzyme inhibitor and activator, anthelmintic and bactericidal agent, polymerization agent, catalyst and electroplating agent. [45].

The method for the determination of antiulcer drugs involves the reaction of these drugs with iron (III) salts, in the presence of 2,2'-bipyridine to produce a pink colour with maximum absorption at 530 nm. The reaction involves the reduction of iron (III) to iron (II) by OMZ, LNZ, PNZ, RBZ and EMZ which subsequently reacts with 2,2'-bipyridine to give a pink colour product in neutral medium. Beer 'law limits, molar absorptivity, Sandel's sensitivity, regression equation and correlation coefficients obtained by least square treatment of these results are given in Table 1.

Table 1: Optical characteristics of the antiulcer drugs as determined using 2,2'-bipyridine

Parameters	**OMZ**	**LNZ**	**PNZ**	**RBZ**	**EMZ**
Beer's law (ng mL^{-1})	80-2800	200-4000	200-4000	200-4000	200-3800
Recommended drug concentration (ng mL^{-1})	1400	2000	2200	2000	2000
Molar absorptivity (L mol^{-1} cm^{-1})	$8.03x10^4$	$6.32x10^4$	$6.05x10^4$	$5.80x10^4$	$6.73x10^4$
Sandell's sensitivity (µg cm^{-2})	0.004	0.006	0.006	0.006	0.005
Regression equation*					
Slope (a)	0.2444	0.1219	0.1175	0.1291	0.2301
Intercept (b)	-0.0061	0.0484	0.0410	0.0022	-0.0410
Correlation coefficient	0.9988	0.9827	0.9790	0.9980	0.9865
R.S.D**	±0.79	±1.01	±0.63	±1.11	±1.05

*y=ax+b where x is the concentration of OMZ, LNZ, PNZ, RBZ or EMZ in ng mL^{-1}

** relative standard deviation(n=5)

The pink colour developed in the method showed a maximum absorption (λmax) at 530 nm and it was found to stable for 24 hours.

Spectral Characteristics:

A pink coloured product with maximum absorbance at 530 nm was formed when OMZ reacts with ammonium iron (III) sulphate, in the presence of 2,2'-bipyridine in neutral medium.

Optimization of analytical variables

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Maximum and constant absorbance values were obtained when the standard flasks were kept in a boiling water bath for 10 min after adding the reagents to the drug solutions which remained stable for 24 hours. It was found that 0.001 N ammonium iron (III) sulphate in the range 1.0-3.0 mL. 0.2%(*w/v*) of 2,2'-bipyridine in the range of 1.0-4.0 mL were necessary to get maximum intensity of colour and stability. Hence, 2.0 mL each of ammonium iron (III) sulphate and 2,2'-bipyridine were found appropriate.

The sequence of addition of ammonium iron (III) sulphate, 2,2'-bipyridine and drug solution was studied *via* the formation of the pink complex. Absorbance or colour of the product did not change appreciably when the order of addition of these reactants was varied.

Table 1 shows the linear calibration ranges and equation parameters for different drugs. Separate determinations at different concentrations of each drug gave a coefficient of variation not exceeding 2%.

Stability

The development of the coloured product was slow at room temperature. The absorbance values were maximum and remained constant in the temperature range 80-100^{0}C.However, after cooling to ambient temperature the products remained stable for 24 hours.

Interference

The effect of common ingredients usually present in pharmaceutical preparations was studied, by taking omeprazole as a representative drug. Commonly encountered pharmaceutical additives and excipients such as glucose, lactose, dextrose, starch, sodium alginate and sodium lauryl sulphate did not interfere, while vitamin C was found to interfere seriously. The results are presented in Table 2.

Table 2: Recovery of omeprazole (OMZ) in presence of excipients and other substances

Material	Amount(mg)	% Recovery of OMZ* ± RSD**
Glucose	50	100.6 ± 1.02
Vitamin B_6	50	98.8 ± 0.78
Dextrose	50	99.6 ± 0.92
Gum acacia	50	101.4 ± 0.60
Starch	50	99.2 ± 1.14
Sodium alginate	50	99.0 ± 0.88
Talc	50	100.4 ± 1.06
Magnesium stearate	50	98.6 ± 0.72
Lactose	50	99.2 ± 1.16
Carboxyl methyl cellulose	50	98.6 ± 0.75
Vitamin C	50	# erratic values

*1000 ng ml^{-1} of OMZ taken

** relative standard deviation(n=5)

Analysis of pharmaceutical formulations

Commercial formulations (capsules/tablets) containing OMZ, LNZ, PNZ and EMZ were subjected to analysis by the proposed method. The values obtained by the proposed and the

reference methods for the pharmaceutical preparations were compared statistically using the F- and t- tests and no difference was found significantly. The results are summarized in Table 3.

Table 3: Determination of certain antiulcer drugs in commercial samples by the proposed method using 2,2'-bipyridine

Drug	Label claim (mg per drug)	*Recovery % ±SD**	Additional analyte added (mg)	*Recovery % ±SD**	Reported method found %
Omelac capsule (Omeprazole)	20	98.2 ± 0.68 F=2.57(6.39) t=1.68(2.77) (n=5)	20	99.2 ± 0.90	97.2 ± 1.09[41] (n=5)
Lanpro capsule (Lansoprazole)	15	99.5 ± 0.19 F=2.98(6.39) t=1.29(2.77) (n=5)	15	100.2 ± 0.62	99.6 ± 0.11[40] (n=5)
Pan tablet (Pantoprazole)	20	99.2 ± 0.90 F=2.18(9.28) t=1.21(3.18) (n=4)	20	99.2 ± 0.90	97.2 ± 1.09[41] (n=4)
Rabeloc tablet (Rabeprazole)	20	99.0 ± 0.88 F=4.00(4.28) t=1.63(2.44) (n=7)	20	98.4 ± 1.08	98.6 ± 1.05[46] (n=7)
Raciper tablet (Esomeprazole)	20	99.3 ± 0.63 F=2.07(4.67) t=1.34(3.14) (n=5)	20	100.8 ± 0.71	96.5 ± 1.11[41] (n=5)

*Proposed method **standard deviation

The figures in the parentheses are the tabulated F- and t-values at 95% confidence level

Conclusion

Today, an extensive array of modern analytical techniques has been employed for pharmaceutical analysis. Nevertheless, spectrophotometry will survive even in the presence of purely instrumental approaches. The proposed spectrophotometric method provides accurate measurement for the determination of OMZ, LNZ, PNZ, RBZ and EMZ in pharmaceutical tablets. We hope that this recommended method using common reagent such as 2,2'-bipyridine and iron (III) salts is simple, sensitive, selective and cost-effective and thus it is well suited for the routine assay and evaluation of drugs in preformulation and dosage forms to assure high standard of quality control. Further, value-addition to this method can be achieved if the procedure is combined with on-line or at-line system and this is currently under investigation.

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