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Research Article

Stability Indicating UV Spectrophotometric Method for Estimation of Omeprazole and Its Application to Content Uniformity Testing

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ABSTRACT

Omeprazole is a most commonly used antiulcer agent in clinical practices. A least time consuming efficient and simple ultraviolet spectrophotometric method for the assay of omeprazole has been developed. The assay was based on the ultraviolet absorbance maxima at about 217.80 nm wavelength of omeprazole using sodium hydroxide as the solvent. In the present study comprehensive stress degradation was carried out according to ICH Q1 (R2) guidelines. The drug was subjected to acidic (0.1N HCl), basic (0.1N NaOH), oxidative (1% H2O2), photolytic and thermal degradation conditions. The developed UV spectrophotometric method showed high degradation under acidic condition, moderate degradation under basic, photolytic and thermal conditions. But it was relatively stable under oxidative conditions. The pathway for degradation has been proposed. The method was validated for Linearity, Accuracy, Precision, Specificity, Ruggedness and Robustness. The method shows good linearity in the range of 2-20µg/ml. The LOD and LOQ were found to be 0.1 µg/ml and 1.1 µg/ml. The %RSD was found to be with in limit i.e. <2%.The mean recovery of placebo was 100.68%. It can be concluded that the developed procedure is valid and can be applicable for determination of content uniformity for available brands of omeprazole. This method is applicable for the daily routine quality control quantitative analysis of omeprazole.

Keywords: Validation, UV Spectrophotometry, Omeprazole brands (Omez FF, Ometab, Oskar, TackoM).

INTRODUCTION

Stress studies of an Active Pharmaceutical Ingredient (API) help in identifying the degradation pathways and degradation products which in turn paves the way to study stability of molecules and validate stability indicating analytical methods. Food and Drug administration (FDA) and International Conference on Harmonisation (ICH) provide guidelines to evaluate stability data that helps to understand quality, efficacy and safety of drug product. The forced degradation studies are carried out under several conditions like acidic, basic, oxidative, photolytic and thermal that gives idea on stability studies of drug products. The long term and short term stability studies are used to determine the expiration date of drugs. Forced degradation studies facilitate pharmaceutical development in the areas of formulation development, manufacturing and packaging, regulatory affairs[1]. Omeprazole (Fig.1) is chemically5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-pyridinyl) methyl]Sulfinyl]-1*H*-benzimidazole, a substituted benzimidazole that inhibits gastric secretion by altering the activity of H^+/K^+ ATPase, which is the final common step of acid secretion in parietal cells[2]. It is employed in treatment of peptic ulcers, reflux esophagitis and Zollinzers Ellison syndrome[3-5]. It is officially documented in USP 24 and BP 98[6,7]. All potential drugs being organic molecules has great tendency to absorb UV Visible radiation which proves the importance and role of UV Spectrophotometry for determination of drugs in their bulk and pharmaceutical dosage forms. Even though the selectivity merely depends on chromophore of drug the method have several applications in series like quantification of drugs in formulations where no interference of excipients is seen, drug release profile in dissolution studies, drug degradation kinetics and identification of drug moiety using UV spectrum Literature survey reveals different analytical techniques for omeprazole determination where a Flow injection analysis method was adapted for assay of omeprazole[8], different HPLC, HPTLC, TLC densitometry methods[9,10,11] indirect argentometric titration[12] and capillary electrophoresis method[13] were also being used. An adsorption isotherm determination of omeprazole on self-made chiral column for enantiomer study was performed[14]. Liquid chromatography method was established using micellar mobile phases[15]. A Spectrofluorimetric method using 1, 10 –Phenanthroline complex is also being used[16]. Bio-Equivalence study on omeprazole capsule formulations was carried out on healthy volunteers[17]. A Solid phase extraction procedure with capillary electrophoresis method has been reported[18]. Simulated moving bed chromatography was a new analytical method that is being used for omeprazole estimation[19]. Validation of omeprazole and pantoprazole sodium by using spectrophotometry via metal chelates has been summarised well[20]. Simultaneous determination of omeprazole and Domeperidone by using UV spectrophotometry is explained[21]. Different electro chemical methods involving HPLC with colorimetric

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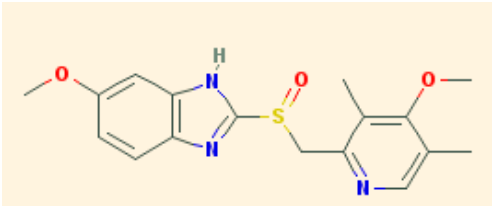

Figure 1: Chemical Structure of Omeprazole.

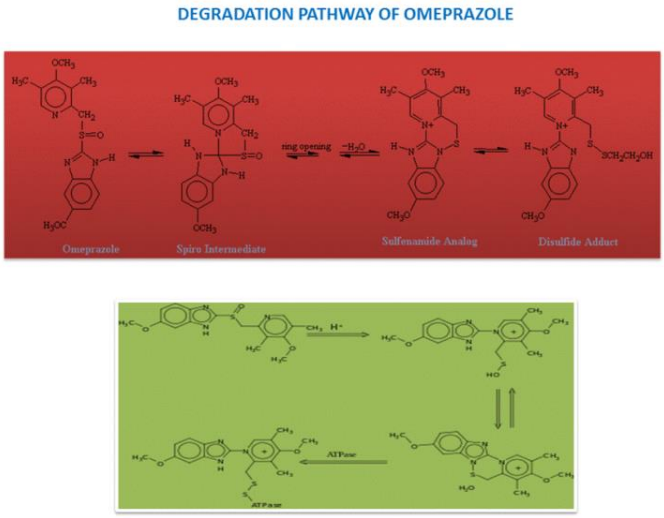

Figure 2: Proposed Degradation Pathway of Omeprazole.

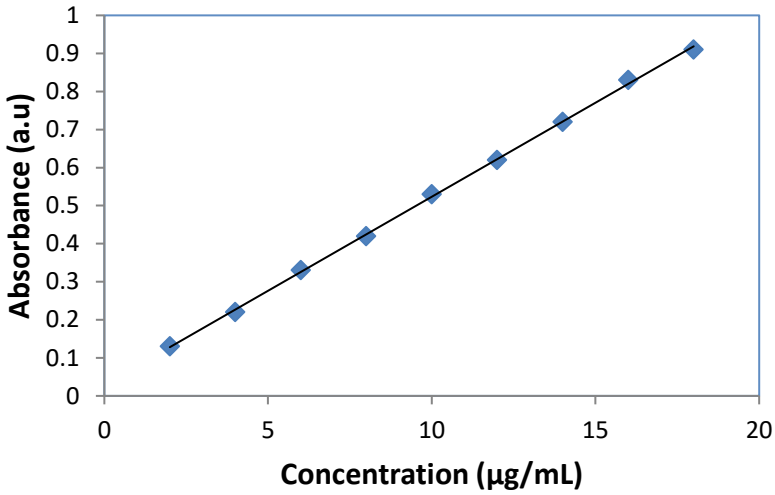

Figure 3: Linearity graph of Omeprazole (2-18µg/ml).

Table 1: Linearity study of developed method.

Parameters	Results
Linearity range (µg/ml)	2-18
Intercept (c)	0.0292
Slope (m)	0.0494
Correlation co-efficient (r)	0.9997
S.D of residuals ($S_{y/x}$)	0.0067
S.D of Intercept	0.0049
S.D of Slope	0.004
Limit of detection, LOD (µg/ml)	0.33
Limit of quantitation LOQ (µg/ml)	0.99

determination[22], and voltammetric behaviour of omeprazole[23] were also studied based on oxidation on imidazole moiety in omeprazole. Derivative spectrophotometric technique was employed to study stability studies of omeprazole[24]. Many of the Extractive Spectrophotometric methods using Folin ciocelteau reagent, Celestine blue, chloramine-B, $FeCl_3$ and N-Bromo Succinamide (NBS) were employed[25-27]. The aim of present study is to determine a simple, reliable, accurate, precise, and cost effective stability indicating method for determination of omeprazole in its in standard and pharmaceutical formulations which proves to be highly advantageous than other analytical techniques that are cumbersome, tedious, expensive. Although many UV Spectrophotometric methods were reported for the study of omeprazole in its bulk and combination; all the method employs time consuming extractive procedures and costly reagents. As a matter of fact determination of omeprazole always involved in combination with other formulations, hence a simple attempt was made to study complete degradation profile of omeprazole using UV Spectrophotometry as an alternative analytical technique and a simple pathway (Fig.2.) has been proposed. The method was completely validated as per ICH guidelines[28] and further extended to content uniformity testing according to USP guidelines.

MATERIALS AND METHODS

Table 2: Accuracy study of developed method.

Level of spiking	Concentration taken (µg/ml)	Concentration Found (µg/ml)	%Recovery	%RSD
80	8	7.978±0.117	99.73±1.460	1.46
100	10	10.205±0.117	102.05±1.169	1.14
120	12	12.161±0.202	101.35±1.687	1.66

Data represented as mean ± SD (n=3)

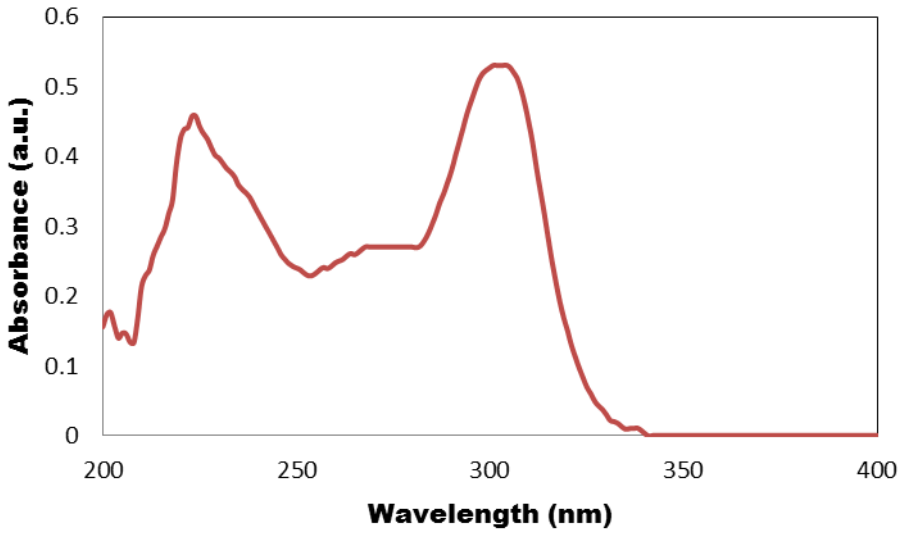

Figure 4: UV Spectrum of Omeprazole (10µg/ml).

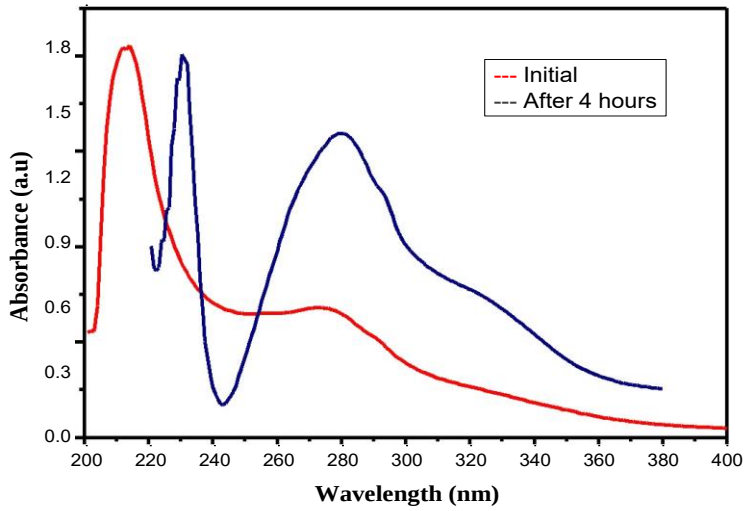

Figure 5: Acidic Degradation of Omeprazole.

Chemicals and Reagents

Omeprazole (purity 99%) standard was procured from Alfa Aesar, England, United Kingdom. All the solvents used were of analytical grade with 99% purity. Sodium Hydroxide, Hydrochloric acid, 30 % Hydrogen peroxide, Dimethyl Formamide were obtained from MERCK, New Jersy, United States. Spectroscopy grade Ethanol and Methanol was purchased from FINAR, Ahmedabad, India. Different brands of omeprazole were brought from local pharmacy.

Instrumentation

The entire spectrophotometric analysis was carried out using SHIMADZU™ UV-2600 (model) double beam UV-Vis Spectrophotometer (shimadzu, Japan) with 10 mm quartz cuvettes. This equipment was loaded with UV Probe software version 2.2. Robustness of the method was evaluated using shimadzu™ UV-Vis mini 1240 model spectrophotometer (Kyoto, Japan). For weighing Shimadzu analytical balance and for sonication of sample solutions ultra sonicator was being used. Standard

Table 3: Precision study (Intra-day and Inter-day) of developed method.

Concentration (µg/ml)	Repeatability (Intra-day) Absorbance±SD	%RSD	Intermediate (Inter-day) Absorbance±SD	% RSD
10	0.53±0.004	1.16	0.52±0.006	1.19

Data represented as mean ± SD (n=3)

Table 4: Robustness and Ruggedness study of developed method.

Concentration taken (µg/ml)	Method Robustness Wavelength (nm)* %RSD	Method Ruggedness Inter-analyst %RSD	Inter-cuvettes %RSD
10	0.18	1.46	0.88
10	0.18	1.48	0.87
10	0.53	1.46	0.88

* Wavelengths used were 302,303,304 nm

glassware supplied by Royal scientific suppliers, Trichy, Tamil Nadu, India has been used.

Preparation of Standard Stock Solution

Standard stock solution of omeprazole was prepared by dissolving 10mg of omeprazole standard in 50 ml of Ethanol, sonicated for five minutes and then made upto mark with100ml of solvent to get concentration of 100µg/ml.

Preparation of calibration curve

Calibration solutions were prepared in the range of 2-18 µg/ml using standard solution in 10 ml calibrated flasks and made upto mark using the diluent ethanol and the absorbances were recorded for the prepared aliquots at wavelength of maximum absorbance. Fig.3. represents the calibration curve.

Pharmaceutical Preparations

From different public medical stores four different brands of omeprazole were purchased. Each brand labelled to contain 20mg of omeprazole per tablet.20 tablets of each brands of omeprazole were weighed individually and uniformly crushed by the help of mortar and pestle. In the 25ml volumetric flask average weight of each brand sample powder equivalent to 20mg of omeprazole was transferred, about 60 ml of Ethanol was added and flasks were sonicated for nearly 30 min. Then dilutions were made covering entire calibration range i.e. 2-18 µg/ml and analysis was carried out after filtration with Whatmann filter paper. The content was determined from calibration curve.

Forced Degradation Studies

Standard Solution

A 50 µg/ml of standard stock solution was prepared by addition of 2.5 mg of the standard drug weighed accurately; transferred into 50ml volumetric flask and made up to the mark with ethanol. The stock solution was diluted to achieve a concentration of 10µg/ml for UV analysis. Fig.4.

Dry heat studies

10 mg sample of omeprazole was taken in petridish and exposed to a temperature of 150°C for 14 hours in an oven. After 14 hours 2.5mg of sample was diluted with ethanol in order to make up the volume to 10ml and it is subjected to UV analysis.

Acidic Degradation

2 ml of standard stock solution of omeprazole was transferred to a flask containing a mixture of 0.1N HCl and ethanol (5 ml each); the contents of flask were refluxed for nearly 24 h at 50 °C. Then the resulting solution was placed aside to reach ambient temperature and then neutralised using 0.1 N NaOH. Finally ethanol was added upto the mark to achieve a concentration of 10µg/ml and subjected to absorbance measurement.

Alkali Degradation

2 ml of standard stock solution of omeprazole was transferred to flask containing a mixture of 0.1 N NaOH and 5 ml of ethanol; the contents of flask were refluxed for nearly 24 h at 50 °C. Then the resulting solution was placed aside to reach ambient temperature and then neutralised using 0.1 N HCl. Finally ethanol was added upto the mark to get concentration of 10µg/ml and subjected to absorbance measurement.

Oxidative Degradation

2 ml of standard stock solution of omeprazole and 4ml of 1% H_2O_2 was added in 10ml volumetric flask and refluxed for nearly 24 h at 50 °C. After reaching to ambient temperature the contents of flask were diluted using ethanol and made upto the mark to achieve a concentration of 10µg/ml and subjected to absorbance measurement.

Photo Degradation

Directly expose the solid drug to sunlight for 2 days. Transfer it to 50ml volumetric flask made up to the volume with ethanol. Prepare dilution of 10µg/ml and record the UV spectrum in the wavelength range of 200-400nm for every 2 hour.

Content uniformity testing of a drug

Four different brands of omeprazole were selected to determine their individual contents. By application of official USP guidelines[29] content of each tablet unit for all available pharmaceutical formulations were estimated. The contents of tablets were calculated from corresponding regression equation or previous calibration curve.

Method Validation

The developed UV Spectrophotometric method was validated according to ICH guidelines for Linearity, Accuracy, Precision, Robustness and ruggedness. The accuracy was assessed by using standard addition technique and the study was performed in triplicate. The percentage recovery was calculated. The repeatability (Intraday) and reproducibility (Interday) was studied by analysing 100% test concentration standard solution at different time intervals on the same day and also on successive days by different analysts and their percentage RSD was calculated. Robustness and ruggedness study of developed method was performed by analysing

Table 5: Pharmaceutical Assay of available brands of Omeprazole.

Omeprazole Brands	Amount taken (µg/ml)	Amount Found (µg/ml)	%Assay	% RSD
Omez ff	10	9.58±0.096	95.79±0.956	1.0
Tacko m	10	10.16±0.044	101.60±0.438	0.43
Ometab	10	9.97±0.042	99.71±0.417	0.42
Oskar	10	10.16±0.042	101.67±0.417	0.41

Data represented as mean ± SD (n=3)

Table: 6 Forced degradation studies of Omeprazole by developed method.

Degradation condition	Time (hours)	(%) Drug degraded	(%) Drug remaining	Result
Acidic(0.1NHcl)	10	75.63	24.37	High degradation
Basic(0.1N NaOH)	10	49.47	50.53	Moderate degradation
0xidative (1 %H_2O_2)	10	1.764	98.235	Negligible degradation
Photolytic (day 1)	8	14.39	85.61	Moderate degradation
Photolytic (day 2)	8	1.976	98.024	Very low degradation
Thermal	8	10.148	89.852	Low degradation

Table 7: Content Uniformity Testing of available brands of Omeprazole.

Tablet No	Omez ff	Tacko m	Ometab	Oskar
1	98.36	102.08	98.77	101.35
2	103.22	98.87	96.63	103.61
3	101.55	100.53	97.13	100.31
4	100.11	100.01	98.70	101.52
5	98.95	100.63	96.63	104.03
6	99.80	101.46	98.27	102.22
7	102.00	102.81	9.06	101.56
8	100.14	100.63	101.48	100.79
9	99.80	102.60	97.42	102.15
10	100.08	102.39	97.92	101.32
Mean	100.40	101.20	98.10	101.89
SD	1.46	1.28	1.41	1.17
Accepted Value (AV)[29]	3.50	3.07	2.58	2.80
L1[29]	15	15	15	15

omeprazole under different conditions like by changing wavelength, different analysts and different cuvettes. The Limit of detection (LOD) and Limit of quantitation (LOQ) were calculated from regression analysis.

RESULTS

Linearity

Aliquots of different solutions were prepared from standard solution ranging in the concentration of 2-18 µg/ml and their absorbance was recorded at the wavelength of maximum absorbance of 302 nm using ethanol as solvent. Then a plot of absorbance vs. concentration was plotted and the regression analysis was performed to analyse the results. The plot was linear and obeyed Beers law with good co-relation co-efficient value. Figure 3 shows the Linearity curve of omeprazole. Table 1 represents the Linearity parameters of the developed method.

Accuracy

Accuracy of the method was assessed by using standard addition technique. The standard addition procedure was done by addition of 80%, 100%, and 120% of omeprazole standard in the sample. The percentage recovery was within the range of 100-102 % which shows the reliability of developed method. The results are tabulated in Table 2.

Precision

Intraday (Repeatability) and Interday (Intermediate) precision was evaluated by using 100% test concentration solution of omeprazole prepared from standard stock solution. The readings were recorded for six times with in the same day at different time intervals on the same day and three successive days by different analysts. The % RSD was calculated and was found to be in good terms with < 2 %. Results are tabulated in Table 3.

Robustness and Ruggedness

Robustness of the method was assessed by small and deliberate changes in wavelength and the ruggedness of the developed method was evaluated by using different analysts and different cuvettes by single analyst and the % RSD was calculated which was found to be within the specified limit. Results are tabulated in Table 4.

Assay of pharmaceutical preparation

The assay of omeprazole proposed by developed method for four different brands of omeprazole was found to be within the limit of label claim with their percentage Assay values in the range of 95-102 %. Results are tabulated in Table 5.

Application to Stability studies

Omeprazole was subjected to different ICH prescribed stress conditions. Degradation was found to occur more in acidic and basic conditions and to some extent in photolytic and thermal conditions while the drug was

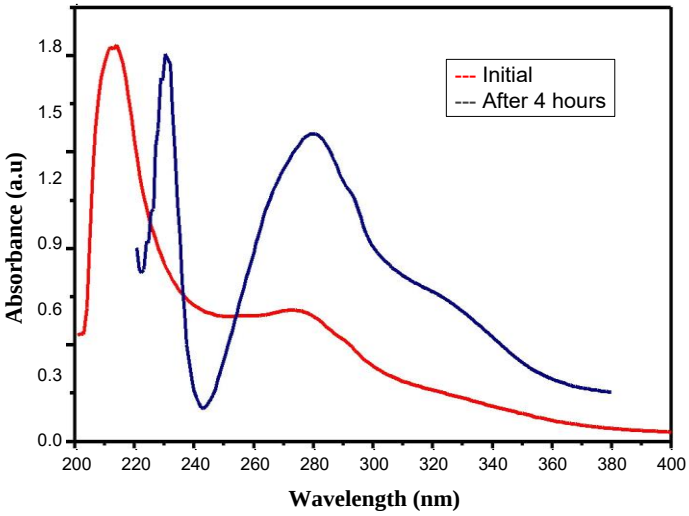

Figure 6: Basic Degradation of Omeprazole.

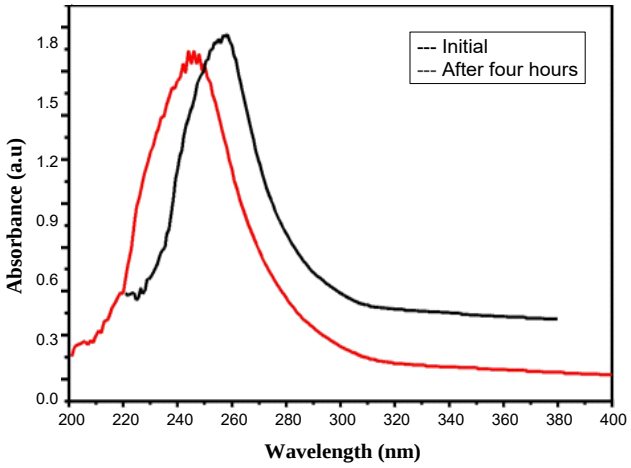

Figure 7: Oxidative Degradation of Omeprazole.

stable to oxidative conditions. Acidic, basic and oxidative degradation shows overlay between the initial absorbance and drug after degradation. Results are tabulated in Table 6. Figures 4, 5 and 6 represents acidic, alkali and oxidative degradation changes.

Application to Content uniformity Testing

The sensitivity of the method could be assessed by performing the content uniformity test. Results obtained by following official USP guidelines were satisfactory with the Accepted Value (AV)[29] to be within the prescribed limit. Results are tabulated in Table 7.

RESULTS AND DISCUSSIONS

The developed method is validated accorded to ICH[28] guidelines for all the validation parameters and the results are also in good terms. The omeprazole ethanolic solution first undergoes a transition state giving a Spiro intermediate followed by ring opening to give a sulphenamide analaog. The cyclic sulfenamide so formed is converted to a disulphide which is highly unstable dimerises to give omeprazole dimer[40]. The sulfenic acid is the active inhibitor to elicit the role of omeprazole in proton pump inhibition. first The stability studies performed under prescribed ICH condition reveals different interesting facts where the electronic spectra of acidic degradation of omeprazole shows two strong peak at 211-214nm and 274nm, which corresponds to n→π* and π→π* transitions of initial spectrum (drug before degradation). After acidic degradation the peak at 211-214nm got shifted to 230nm, the peak at 274nm enhanced to 280nm. In case of basic degradation, two peak at 225nm and 303-308nm which corresponds to n→π* and π→π* transitions shifted to 303nm and got enhanced. The oxidative degradation shows one strong peak at 228-236nm which is shifted to 247nm after drug degradation (Figures 3, 4 and 5). A stability-indicating UV spectrophotometric method was developed for analysis of the drug in the presence of the degradation products.

Content uniformity test proves the sensitivity of the method. Stability studies are very important in ascertaining the drug product safety, efficacy and potency. Hence the developed UV
Spectrophotometric method could be simple, rapid, economical and reliable stability indicating method for quality control application and proves to be beneficial for analysing different pharmaceutical brands of omeprazole.

CONCLUSION

The proposed methodology is useful in terms of accuracy, specificity, selectivity and rapidity. It could definitely be an alternative technique for quantification of omeprazole in its bulk and pharmaceutical formulations. It is very cost effective where the entire analysis was carried out using a simple and advantageous instrument like UV Spectrophotometer which is available in all laboratories and is an added attribute for analysing the pharmaceutical formulations in different quality control laboratories.

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