CHAPTER –II

Literature of selected drugs and objectives of the present investigation
Survey of literature of selected drugs

The literature survey was done with the intention of developing simple, accurate, and reproducible analytical methods for the estimation of selected from bulk and pharmaceutical dosages forms. As by Literature survey it was found that only few methods are available for the estimation of these drugs. But there were no body reported proposed spectrophotometeric methods for the analysis of these selected drugs in bulk and pharmaceutical dosage forms in the literature.

(a) Rabeprazole

Literature survey revealed that, Various methods were reported in literature for determination of rabeprazole individually and in combination with other drugs which includes Spectrophotometric method\textsuperscript{1-15}, Spectrophotometric and chromatographic determination\textsuperscript{16} Capillary electrophoresis method\textsuperscript{17}, liquid chromatography- tandem mass spectrometry\textsuperscript{18}, RP-HPLC method\textsuperscript{19,20}, HPLC method\textsuperscript{21-26}, HPTLC method\textsuperscript{27-29}, Column reversed-phase high-performance liquid chromatographic method\textsuperscript{30} and Voltammetric determination\textsuperscript{31}

Amol M etal\textsuperscript{1}, reported an important and simple kinetic spectrophotometric method for the determination of rabeprazole in pharmaceutical formulations. Alkaline potassium permanganate is used in this
method for oxidation of rabeprazole at room temperature. The increase in the absorbance at 610nm owing to the formation of MnO$_4^{2-}$ was measured spectrophotometrically. Calibration curve procedure was adopted for the assay of the drug.

Syed AA and Ayesha Syeda$^2$ reported spectrophotometric method for the determination of certain proton pump inhibitors belonging to the benzimidazole class of compounds. The method is based on the reaction of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole with iron (III) and subsequent reaction with ferricyanide under neutral condition which yields Prussian blue product with maximum absorption at 720–730 nm. The commonly encountered excipients and additives that often accompany pharmaceutical preparations did not interfere with the determination. The method was applied for the determination of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole in pharmaceutical preparations and no difference was found statistically. Thus, the spectrophotometric method can be applied as inexpensive, rapid, easy, accurate and precise method for the routine analysis of the five proton pump inhibitors in pharmaceutical preparations.

Garcia CV et al$^3$, reported the aim of this work is to develop and validate the derivative spectrophotometric method for determination of the proton pump inhibitor rabeprazole sodium in pharmaceutical formulations. The technique is
applied using water (pH 10.0) as diluent. The first-order derivative spectra were
obtained 6.0 to 18.0 µg/mL. Accuracy was also evaluated and results were
satisfactory (mean recovery of 99.15%). The detection and quantification limits
were 0.055 and 0.17 µg/mL\(^{-1}\), respectively. The method was demonstrated to be
adequate for routine analysis in quality control.

Dinesh Sahu et al\(^4\) described a simple, precise and highly selective
analytical method for simultaneous estimation of aceclofenac and rabeprazole
Sodium in solid dosage form. Estimation was carried out by multi-component
mode of analysis at selected wavelength of 277 nm and 283 nm for aceclofenac
and rabeprazole Sodium respectively in methanol. The method was found to be
linear in the range of 1-40 µg/ml for aceclofenac and 1-30 µg/ml accuracy of
the method was confirmed by recovery studies of solid dosages forms and was
found to be for batch-A 98.33% and 98.44% for batch-B 99.24% and 98.77%
for aceclofenac and rabeprazole Sodium respectively. Initially lab samples were
utilized to validate developed method according to ICH guidelines\(^1\) followed by
determination of % concentration of aceclofenac and rabeprazole Sodium in
marketed formulation that was found to be for batch-A 98.07 ± 0.51 and 96.81±
0.51 for batch-B 98.23 ± 0.65 and 97.98± 0.65 respectively. The values of
precision and robustness lie within acceptable limit. Thus the proposed method
can be successfully applied for simultaneous determination of aceclofenac and
rabeprazole sodium respectively in routine analytical work.
Shweta S. Sabnis et al\textsuperscript{5} reported a new simple, economical, rapid, precise and accurate method for simultaneous determination of rabeprazole sodium and itopride hydrochloride in capsule dosage form. The method is based on ratio spectra derivative spectrophotometry. The amplitudes in the first derivative of the corresponding ratio spectra at 231 nm (minima) and 260 nm were selected to determine rabeprazole sodium and itopride hydrochloride, respectively. The method was validated with respect to linearity, precision and accuracy.

Ramesh L et al\textsuperscript{6}, described the present work aimed to develop and validate spectrophotometric methods for simultaneous estimation of rabeprazole sodium and aceclofenac in a pure and capsule dosage form. Materials and Methods: Method 1 is based on solving a simultaneous equation. Absorbances of rabeprazole sodium and aceclofenac were measured at their respective absorbance maxima ($\lambda_{\text{max}}$) of 283 and 276 nm. Method 2 is the Q-analysis or absorption ratio method. Absorbances were measured at 256 nm (isosbestic point) and 276 nm ($\lambda_{\text{max}}$ of aceclofenac). Methods are validated according to ICH guidelines. Results: A linearity range for rabeprazole sodium and aceclofenac is 10-60 $\mu$g/ml at respective selected wavelengths. The coefficient of correlation for rabeprazole at 283 nm and for aceclofenac at 276 nm is 0.9981 and 0.9997, respectively. A percentage estimation of rabeprazole sodium and aceclofenac from the capsule dosage form by method 1 is 100.22 and 99.96 and by method 2 is 99.99 and 100.05, respectively, with a standard deviation less than
2. Conclusion: The proposed methods are simple, rapid, and validated and can be used successfully for routine simultaneous estimation of rabeprazole sodium and aceclofenac in a pure and capsule dosage form.

Mandhanya Mayank et al\textsuperscript{7}, reported Paracetamol \{N- (4-hydroxyphenyl) acetamide\} and Aceclofenac \{2-[(2, 6-dichlorophenyl) amino] phenyl acetoxy acetic acid\} are NSAIDs which acts by inhibiting the synthesis of prostaglandins. Rabeprazole \{2-[(4-(3-methoxypropoxy)-3-methyl-pyridine-2-yl) Methylsulfinyl- 1H benzoimidazole\} is an anti ulcer drug which is a proton pump inhibitor. Nospectroscopic method has been reported for the simultaneous estimation of paracetamol, aceclofenac and rabeprazole in combined tablet dosage formulation. Hence simple, sensitive, reliable and rapid spectroscopic methods have been developed for the determination of paracetamol, aceclofenac and rabeprazole in combined tablet dosage form. Determinations were performed on Shimadzu UV-Visible double beam recording spectrophotometer (Model UV-1700). The linearity of paracetamol, aceclofenac and rabeprazole was found to be 3-30µg/ml, 2-20 µg/ml, and 2-20µg/ml respectively. The stability of the solution was found to be 72 hrs. The method was validated for accuracy, precision, repeatability as per ICH Guidelines. This method can be used commercially for routine estimation of various compounds in pharmaceutical dosage forms.
Pillai S and Singhvi\textsuperscript{1}, reported two simple, accurate, economical and reproducible UV spectrophotometric methods and one HPLC method for simultaneous estimation of two component drug mixture of itopride hydrochloride and rabeprazole sodium from combined capsule dosage form. First developed method involves formation and solving of simultaneous equations using 265.2 nm and 290.8 nm as two wavelengths. Second method is based on two wavelength calculation, wavelengths selected for estimation of itopride hydrochloride was 278.0 nm and 298.8 nm and for rabeprazole sodium 253.6 nm and 275.2 nm. Developed HPLC method is a reverse phase chromatographic method using phenomenex C\textsubscript{18} column and acetonitrile: phosphate buffer (35:65 v/v) pH 7.0 as mobile phase. All developed methods obey Beer's law in concentration range employed for respective methods. Results of analysis were validated statistically and by recovery studies.

Sabnis SS\textsuperscript{9}, reported three methods viz. absorbance ratio method (I), dual wavelength method (II) and first order derivative spectroscopic method (III) for simultaneous estimation of rabeprazole sodium and itopride hydrochloride. The drugs obey Beer's law in the concentration range 2-20 µg/mL for RAB and 5-75 µg/mL for ITO. The results of analysis of drugs have been validated statistically and by recovery studies.

Nesrin K et al\textsuperscript{10} reported three simple and sensitive methods were developed for the determination of a mixture of rabeprazole sodium RB and
domperidone DP without prior separation. The first method A, isoabsorptive point comprised of measurement the total content of the mixture at their isoabsorptive point, while the content of RB was determined by measuring the first order derivative of its spectra at 231 nm, and the content of DP could be calculated by subtraction. The second method, B was based on the mean centering of ratio spectra, the concentration of RB was determined by measuring the amplitude at 256.4 nm and the concentration of DP was determined by measuring the amplitude at 311.8 nm. The third method C, dual wavelength method, the wavelengths selected for determination of rabeprazole were 270 nm & 301 nm, whereas, the wavelengths selected for determination of domperidone were 260 and 297.2 nm. The percentages mean accuracy for RB were 99.74 ± 0.498 % for method (A), 100.52 ± 0.478 % for (B) and 100.43 ± 0.502 % for (C) respectively. And that of DP were 100.28 ± 0.488 % for method (A), 99.24 ± 0.551 % for (B) and 99.95 ± 0.516 % for (C) respectively. The obtained results were statistically compared with those obtained by the official methods, showing no significant difference with respect to accuracy and precision.

Raj Prasad K\textsuperscript{11}, reported six simple, rapid, accurate, precise and cost-effective methods, I; formation and solving of simultaneous equation method, II; absorbance ratio method, III; dual wave length method, IV; area under curve method, V; first order derivative spectrophotometry method and VI;
multicomponent method have been developed for simultaneous estimation of rabeprazole sodium and diclofenac sodium in capsule dosage form. Rabeprazole sodium showed absorbance maxima at 292 nm and diclofenac sodium showed at 276 nm in 0.01N NaOH solution. Beer’s law was obeyed in concentration range 5-30 µg/ml for rabeprazole sodium and 5-35 µg/ml for diclofenac sodium respectively for all proposed six methods. The sampling wavelengths for method VI, selected for both the drugs were 260nm, 276nm, 286nm, 292nm and 295 nm on trial and error basis using 0.01 N NaOH solutions as solvent. All the six methods allowed rapid analysis of binary pharmaceutical formulation with accuracy. Results of analysis for six methods were tested and validated for various parameters according to ICH guidelines.

Patel AH et al\textsuperscript{12} described the use of first order derivative spectroscophtometry allowed simultaneous determination of domperidone and rabeprazole sodium, in fixed dose combination products. The absorbance values at 253.2 nm and 266.4 nm of first derivative spectrum was used for the estimation of domperidone and rabeprazole sodium, respectively without mutual interference. This method obeyed beer’s law in the concentration range of 9-45 µg/ml and 6-30 µg/ml for both domperidone and rabeprazole sodium, respectively. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method.
Revathi Gunji et al\textsuperscript{13} reported a novel, simple, safe, sensitive, and economical method of spectrophotometric estimation in UV region has been developed using 5M urea solution as hydrotropic solubilizing agent for the quantitative determination of rabeprazole sodium and diclofenac sodium. Two methods are described for the simultaneous determination of rabeprazole sodium and diclofenac sodium in combined pharmaceutical tablets. Urea did not show any absorbance above 225nm, there was no interference during estimation of diclofenac and rabeprazole. The first method is simultaneous estimation using vierodt’s equation where absorption maxima found at 285nm and 276nm for rabeprazole and diclofenac, respectively. The second method is based on Q-Absorption ratio method using two wavelengths, at 281nm (Isobestic point) and 276nm ($\lambda_{\text{max}}$ for diclofenac). Two methods follow Beer’s linearity in the range of 4-28µg/ml and 5-25µg/ml with correlation coefficient $r^2$ of 0.999 and 0.998 for rabeprazole and diclofenac, respectively. According to ICH norms the parameters linearity, precision, accuracy, limit of detection, and limit of quantification were studied, the results of analysis were validated statistically and by recovery studies. The proposed methods were simple, cost effective and were successfully applied to the determination of these drugs in quality control of combined pharmaceutical dosage.

Baldha R G et al\textsuperscript{14}, described rapid, precise, accurate and specific ratio spectra derivative spectrophotometry and a simple UV spectrophotometry using
simultaneous equation method were developed for the simultaneous determination of rabeprazole sodium and domperidone in combined pharmaceutical dosage forms. For ratiospectra derivativespectrophotometry, the amplitudes were measured at 249 nm for rabeprazole sodium and at 271.5 nm for domperidone. In the simultaneous equation method, the signals were measured at 258 nm and 287 nm corresponding to the absorbancemaxima of rabeprazole sodium and domperidone respectively in 0.05 M methanolic HCl. Concentration of each drug was obtained by using the absorptivity values calculated for both the drugs at two wavelengths, 258 and 287 nm. Commercial tablet formulations were successfully analyzed using the developed methods.

Pattanayak P et al\textsuperscript{15} described two simple, rapid, accurate, and economical analytical methods for the simultaneous estimation of rabeprazole Sodium and itopride Hydrochloride in combined capsule dosage form. First method is based on the determination Q-values and second method is based on simultaneous equation method. Rabeprazole Sodium has absorbance maxima at 284 nm and Itopride Hydrochloride has absorbance maxima at 258 nm in methanol AR. Both the drugs obey Beer's law in the concentration ranges employed for these methods. Both the methods were found to be simple, rapid, accurate, and can be adopted in routine analysis of drugs in formulations. The accuracy and reproducibility of the proposed method was statistically validated by recovery studies.
El-Gindy A et al\textsuperscript{16}, described three methods for the determination of rabeprazole (RA) in presence of its degradation products. The first method was based on high performance liquid chromatographic (HPLC) separation of RA from its degradation products on a reversed phase, ODS column using a mobile phase of methanol–water (70:30, v/v) and UV detection at 284 nm. The second method was based on HPTLC separation followed by densitometric measurement of the spots at 284 nm. The separation was carried out on Merck HPTLC sheets of silica gel 60 F 254, using acetone–toluene–methanol (9:9:0.6 v/v) as mobile phase. The third method depends on first derivative of the ratio spectra (\textsuperscript{1}DD) by measurement of the amplitudes at 310.2 nm. Moreover, the proposed HPLC method was utilized to investigate the kinetics of the oxidative and photo degradation
(b) omeprazole

Literature survey revealed that HPTLC and TLC method\textsuperscript{32}, TLC densitometric determination\textsuperscript{33}, Electrochemical method\textsuperscript{34}, polarographic techniques\textsuperscript{35-37}. HPLC method\textsuperscript{38-42}, voltammetric method\textsuperscript{43}, RP-HPLC\textsuperscript{44,45}, liquid chromatography tandem mass spectrometry\textsuperscript{46} spectrofluorimetric method\textsuperscript{47} Spectrophotometric and liquid chromatographic methods for the determination\textsuperscript{48,49} and spectrophotometric methods\textsuperscript{50-55}, were reported for determination of omeprazole in tablet dosage forms.

Various methods were reported in literature for determination of omeprazole in combination with other drugs which includes, Spectrophotometric method\textsuperscript{56-59}, LC-MS Method\textsuperscript{60} RP-HPLC and Densitometric HPTLC\textsuperscript{61}, Reversed-Phase High Performance Liquid Chromatographic Method\textsuperscript{62}.

Gallardo V et al\textsuperscript{48}, reported to determine the stability of the pH sensitive drug, omeprazole, within different solid oral pharmaceutical formulations and to determine whether the addition of antacid and surfactant agents, at varying concentrations, influenced drug stability and release. Spectrophotometric and chromatographic techniques were used for evaluation purposes, giving good results concerning linearity, precision and specificity within the range of concentrations used in this study. However, the results show that the degradation products of omeprazole interfere with spectrophotometric
evaluation, making this technique insufficiently selective for omeprazole. On the other hand, liquid chromatography proved to be more sensitive, accurate and precise. Additionally, in an attempt to improve the administration form of the drug, an extemporaneous suspension was designed, which after evaluation proved to be a satisfactory administration vehicle. The best formulation of omeprazole studied is: omeprazole: 0.5%; corn starch 34.2%; aluminum hydroxide 26%; magnesium hydroxide 13%; simple syrup 24.8%; SDS 1%.

Castro D et al\textsuperscript{49}, described first derivative spectrophotometric method for the determination of omeprazole in aqueous solutions during stability studies. The derivative procedure was based on the linear relationship between the omeprazole concentration and the first derivative amplitude at 313 nm. The first derivative spectra was developed between 200 and 400 nm ($\Delta \lambda=8$). This method was validated and compared with the official high-performance liquid chromatography (HPLC) method of the USP. It showed good linearity in the range of concentrations studied (10–30 $\mu$g ml$^{-1}$), precision (repeatability and inter-day reproducibility), recovery and specificity in stability studies. It also seemed to be 2.59 times more sensitive than the HPLC method. These results allowed considering this procedure as useful for the rapid analysis of omeprazole in stability studies since there was no interference with its decomposition products.
Amol Bhandage et al\textsuperscript{50}, reported a simple, rapid and selective method for the extractive spectrophotometric determination of omeprazole using acidic dyes. Extractive spectrophotometric determination of omeprazole was developed using acidic dyes- bromophenol blue and orange G - as ion-pairing agents in aqueous medium (pH7.0 and 6.0, respectively). The ion pair chromogen formed, which was extracted with chloroform, was measured quantitatively at 408 nm and 508 nm, respectively. The developed method was used to analyse commercial omeprazole tablets.

Sastry CS et al\textsuperscript{51}, reported four simple and sensitive methods for the assay of omeprazole (OMZ). These methods are based on the formation of colored species by treating OMZ with 3-methyl-2-benzothiazolinone hydrazone (MBTH) following oxidation with ferric chloride (method A) or m-aminophenol following oxidation with chloramine-T (CAT) (method B) or Folin-Ciocalteau reagent (FC) (method D), or by oxidizing OMZ with excess N-bromosuccinimide (NBS) and determining the consumed NBS with a decrease in color intensity of Celestine blue (CB) (method C). All variables have been optimized. Regression analysis of Beer's plots showed good correlation in the concentration range of 1.0-10, 2.0-32, 0.4-2.4 and 0.8-10 µg ml\(^{-1}\) for methods A, B, C and D, respectively. No interference was observed for formulation additives and the validity of each method was tested by analysing capsules containing OMZ. Recoveries were 98.7-100.1\%. 

42
Syed AA et al\textsuperscript{52}, described spectrophotometric method for the determination of certain proton pump inhibitors belonging to the benzimidazole class of compounds. The method is based on the reaction of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole with iron (III) and subsequent reaction with ferricyanide under neutral condition which yields Prussian blue product with maximum absorption at 720-730 nm. The commonly encountered excipients and additives that often accompany pharmaceutical preparations did not interfere with the determination. The method was applied for the determination of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole in pharmaceutical preparations and no difference was found statistically. Thus, the spectrophotometric method can be applied as inexpensive, rapid, easy, accurate and precise method for the routine analysis of the five proton pump inhibitors in pharmaceutical preparations.

Abdel-Aziz M Wahbi et al\textsuperscript{53} reported the compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) applied to the direct determination of omeprazole, lansoprazole and pantoprazole in their pharmaceutical preparations. The methods have been validated; the limits of detection were found to be 3.3×10\textsuperscript{−2}, 3.0×10\textsuperscript{−2} and 3.5×10\textsuperscript{−2} µg ml\textsuperscript{−1} for the three drugs, respectively. The repeatability of the methods was found to be 0.3–0.5%. The linearity ranges were found to be 0.5–3.5 µg ml\textsuperscript{−1}. The proposed methods have been applied to
the determination of the three drugs in their gastro-resistant formulations. The difference spectrophotometric method is unaffected by the presence of acid induced degradation products; hence can be used as a stability indicating assay.

Karljikovic-Rajic K et al\textsuperscript{54}, reported the first-order UV-derivative spectrophotometry, applying zero-crossing method for the determination of omeprazole (OM), omeprazole sulphone (OMS), pantoprazole sodium salt (PANa), and $N$-methylpantoprazole (NPA) in methanol–ammonia 4.0% v/v, where the sufficient spectra resolutions of drug and corresponding impurity were obtained, using the amplitudes $^{1}D_{304}$, $^{1}D_{307}$, $^{1}D_{291.5}$ and $^{1}D_{296.5}$, respectively. Method showed good linearity in the ranges ($\mu$g ml$^{-1}$): 1.61–17.2 for OM; 2.15–21.50 for OMS; 2.13–21.30 for PANa and 2.0–20.0 for NPA, accuracy and precision (repeatability and reproducibility). The experimentally determined values of LOD ($\mu$g ml$^{-1}$) were 1.126; 0.76; 0.691 and 0.716 for OM, OMS, PANa and NPA, respectively. The obtained values of 2.91% w/w for OMS and 3.58% w/w for NPA in the presence of their parent drug, by applying the method of standard additions, point out the usage of the proposed method in stability studies. Zero-crossing method in the first-order derivative spectrophotometry showed the impurity–drug intermolecular interactions, due to the possible intermolecular hydrogen bonds, confirmed by divergences of experimentally obtained amplitudes for impurities OMS and NPA in
comparison to expected values according to regression equations of calibration graphs.

Gehad Mohamed G et al\textsuperscript{55}, described two spectrophotometric procedures for the determination of three irreversible proton pump inhibitors, rabeprazole (RAB), omeprazole (OMP) and pantoprazole (PAN) in pure form and in different pharmaceutical formulations. The first method is based on the oxidation of RAB and PAN with potassium iodate in an acidic medium followed by extracting the liberated iodine with cyclohexane and measurement at $\lambda = 520$ nm. Beer's law is valid in the concentration ranges from 10–400 and 5–400 $\mu$g ml$^{-1}$ for RAB and PAN, respectively. The apparent molar absorptivities of the resulting coloured product were found to be $1.34 \times 10^3$ and $1.64 \times 10^3$ l.mol$^{-1}$. cm$^{-1}$ for RAB and PAN, respectively. The second method is based on the interaction of the basic drugs, OMP, RAB and PAN, in 1,2-dichloroethane with bromophenol blue (BPB), bromocresol green (BCG) and bromocresol purple (BCP) in the same solvent to produce stable coloured ion pairs with maximum absorbance at 385–405 nm. Regression analysis of Beer's plots showed good correlation in the concentration ranges 10–60, 10–60 and 5–40 $\mu$g ml$^{-1}$ for OMP, 10–150, 10–150 and 10–60 $\mu$g ml$^{-1}$ for RAB and 10–250, 10–150 and 10–100 $\mu$g ml$^{-1}$ for PAN with BPB, BCG and BCP reagents, respectively. The limits of detection are 0.46–7.69 $\mu$g ml$^{-1}$ and limits of quantification range between 1.52–8.53 $\mu$g ml$^{-1}$. The optimum assay conditions
were investigated and the recovery of the drugs from their dosage forms ranged from 99.33% to 100.5%. Intraday relative standard deviations (RSD) were 0.029–1.397% and the correlation coefficients ranged from 0.9992 to 1. The two methods can be applied successfully for the determination of these drugs in tablets. The results of analysis were validated statistically through recovery studies. Copyright © 2009 John Wiley & Sons, Ltd.

Lobhe GA et al\textsuperscript{56}, described two simple, rapid, accurate and precise UV-spectrophotometric methods for simultaneous estimation of ondansetron hydrochloride and omeprazole in bulk and tablet dosage form. Method 1 involves, formation of simultaneous equation using Cramer’s rule and Method 2, multi component mode of analysis. In ethanol, ondansetron hydrochloride and omeprazole showed \(\lambda_{\text{max}}\) at 246.2 nm and 301 nm, respectively. Linearity was observed in the concentration range of 4 - 24 \(\mu\)g/ml for ondansetron hydrochloride and 5-30 \(\mu\)g/ml for omeprazole. The methods were successively applied to tablet formulation; no interferences from the tablet excipients were found. The methods have been validated statistically and by recovery studies.

Lakshmi S et al\textsuperscript{57} reported a simple, fast and precise multi-component mode analysis and Q-analysis UV spectrophotometric method for the simultaneous determination of omeprazole and domperidone in combined capsule dosage form. Shimadzu UV-1601 instrument was used and the \(\lambda_{\text{max}}\) of omeprazole and domperidone was found to be 272nm and 286nm using
methanol as a solvent and linearity lies between 10-60 \( \mu g/mL \) for omeprazole and 5-30 \( \mu g/mL \) for domperidone at their respective wavelengths.

Salama F et al\textsuperscript{58}, reported spectrophotometric procedures for the determination of two irreversible proton pump inhibitors, omeprazole (OMZ) and pantoprazole (PNZ) sodium. The procedures are based on the formation of 2:1 chelates of both drugs with different metal ions. Pantoprazole sodium is quantified by a stability-indicating procedure through chelation with iron (III) in aqueous-ethanol medium to form an orange chelate picked at 455 nm. The procedure retains its accuracy in presence of up to 70\% of its degradate, sulfenic acid prepared by degrading the pure drug in borate buffer of pH 8 at 37 °C for 5 days. The colored chelates of OMZ in ethanol are determined spectrophotometrically at 411, 339 and 523 nm using iron (III), chromium (III) and cobalt (II), respectively. Regression analysis of beer's plots showed good correlation in the concentration range of 15–95, 10–60 and 15–150 \( \mu g ml^{-1} \) of pure OMZ using iron (III), chromium (III) and cobalt (II), respectively, and in the range of 30–300 \( \mu g ml^{-1} \) of PNZ sodium using iron (III). The limits of detection are 0.22–3.65 \( \mu g ml^{-1} \) while limits of quantitation range between 0.74 and 12.17 \( \mu g ml^{-1} \). The optimum assay conditions are investigated and the recovery of the cited drugs from their dosage forms ranges from 97.2 to 100.3\%. Good values of precision are obtained, intraday R.S.D. are 0.93–1.75\% and the inter day R.S.D. are 0.51–3.29\%
Sabrina Flor et al.\textsuperscript{59}, reported a simple, fast, and sensitive HPLC method with UV detection for the quantitation of omeprazole (OMZ) and major related substances in raw material and pharmaceutical formulation (paste) using a column of reduced length (50 mm) and diameter (2.1 mm) packed with hybrid particles. Chromatographic conditions were: 25°C, 1 µl injection volume, and UV detection at WV of 280 nm. The flow rate was 0.3 mL/min using methanol-phosphate buffer (pH 7.6) (40:60) as the mobile phase. Chromatographic purity was also determined with the same chromatographic conditions. The method was validated according to international guidelines (ICH guidelines) for specificity, linearity, LOD, LOQ, precision, accuracy, and robustness. The HPLC-UV method was found to be suitable for the quality control and stability studies of OMZ in a pharmaceutical formulation.
(c) Pantoprazole

The literature survey reveals that only few methods are available for the
determination of pantoprazole in dosage forms includes voltammetry\textsuperscript{63-66},
Reversed-phase high performance liquid chromatographic method(RP-HPLC)\textsuperscript{67-72},
High-Performance Liquid Chromatography and High-Performance Thin-
Layer Chromatography Method\textsuperscript{73}, high performance liquid chromatography
(HPLC)\textsuperscript{74,76} and capillary electrophoresis\textsuperscript{77,78}; spectrophotometric
determination\textsuperscript{79-85}.

Few methods were reported in literature for the estimation of
pantoprazole and other combination drugs which includes spectrophotometric
methods\textsuperscript{86-88}, HPLC method\textsuperscript{89} and RP-HPLC method\textsuperscript{90}.

Urdigere Rangachar et al\textsuperscript{79} reported two simple, sensitive and rapid
methods for the determination of pantoprazole sodium sesquihydrate in bulk
drug and in formulations using N- bromosuccinimide as the oxidimetric reagent.
The methods involved the addition of a known excess of NBS to PNT in HCl
medium followed by estimation of the unreacted oxidant by two reaction
schemes involving the use of iron(II) and thiocynate (method A) or
iron(method(B) In both methods the absorbance is found to decrease linearly
with PNT concentration. Beer’s law is obeyed over the range 0.25-3.5 and 1-
15μg/ml for method A and Method B respectively.
Basavaiah K et al\textsuperscript{80}, described two sensitive spectrophotometric methods for the determination of pantoprazole sodium sesquihydrate (PNT) in bulk drug and in formulations. The methods are based on the oxidation of PNT by in situ generated bromine, followed by determination of unreacted bromine by two different reaction schemes. In one procedure (method A), the residual bromine is reduced by an excess of iron(II) and the resulting iron(III) is complexed with thiocyanate and measured at 470 nm. The second approach (method B) involves reducing the unreacted bromine with a measured excess of iron(II) and the remaining iron(II) is complexed with ortho-phenanthroline at a raised pH, and measured at 510 nm. In both methods, the amount of reacted bromine corresponds to the amount of PNT. The experimental conditions were optimized. In method A, the absorbance is found to decrease linearly with the concentration of PNT \((r = -0.9959)\), whereas in the method B a linear increase in absorbance occurs \((r = 0.9984)\). The systems obey Beer's law at concentrations 0.12-1.25 and 0.25-2.5 \(\mu\text{g}\cdot\text{ml}^{-1}\) for method A and method B, respectively. The calculated molar absorptivity values are 2.2x10\(^5\) and 1.2x10\(^5\) \(\text{l}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}\) for method A and method B, respectively, and the corresponding Sandell sensitivity values are 0.0019 and 0.0035 \(\mu\text{g}\cdot\text{cm}^{-2}\). The limits of detection (LOD) and quantification (LOQ) are also reported for both methods. Intra-day and inter-day precision, and accuracy of the methods were established as recommended by the current ICH guidelines. The methods were successfully
applied to the determination of PNT in formulations and the results tallied well with the label claim. The results were statistically compared with those of a literature method by applying the Student's t-test and F-test. No interference was observed by the concomitant substances normally added to tablets. The accuracy and validity of the methods were further ascertained by performing recovery experiments via the standard-addition method.

Rahman N, Kashif M, reported a simple and selective kinetic spectrophotometric method for the determination of pantoprazole in pharmaceutical preparations. The procedure is based upon a kinetic investigation of the reaction of the drug with 1-fluoro-2,4-dinitrobenzene in DMSO at room temperature. The absorbance of the coloured product was measured at 420 nm. The plot of the logarithm of the initial rate of the reaction vs. the logarithm of molar concentration of pantoprazole is linear over the range 10-20 µg/mL. The procedure retains its accuracy in the presence of a large excess of its degradate, sulfenic acid, which is prepared by degrading the pure drug in borate buffer of pH 8 at room temperature for seven days. The results are validated statistically and through recovery studies. The method has been successfully applied to the determination of pantoprazole in commercial tablets. Statistical comparison of the results with the reference method shows excellent agreement and indicates no significant difference in accuracy and precision.
Nafisur Rahman et al\textsuperscript{82}, reported a kinetic spectrophotometric method which is based on the oxidation of pantoprazole with Fe(III) in sulfuric acid medium. Fe(III) subsequently reduces to Fe(II), which is coupled with potassium ferricyanide to form Prussian blue. The reaction is followed spectrophotometrically by measuring the increase in absorbance with time (1 - 8 min) at 725 nm. The initial rate method is adopted for constructing the calibration graph, which is linear in the concentration range of 5 - 90 µg ml\textsuperscript{-1}. The regression analysis yields the calibration equation, $v = 3.467 \times 10^{-6} + 4.356 \times 10^{-5}C$. The limits of detection and quantification are 1.46 and 4.43 µg ml\textsuperscript{-1}, respectively. The proposed method was optimized and validated both statistically and through recovery studies. The experimental true bias of all samples is $< \pm 2.0\%$. The method has been successfully applied to the determination of pantoprazole in pharmaceutical preparations.

Kalaichelvi R et al\textsuperscript{83} proposed a simple and sensitive extractive spectrophotometric method for the assay of pantoprazole sodium either in pure form or in pharmaceutical solid dosage form. The developed method involves formation of colored chloroform extractable ion-association complex of pantoprazole sodium with bromo thymol blue in aqueous acidic medium. The extracted complexes showed absorbance maxima at 428 nm. Beer’s law is obeyed in the concentration range of 10-50 µg mL\textsuperscript{-1}. Correlation coefficient was found to be 0.9997. The proposed method is useful for the routine estimation of
pantoprazole sodium in bulk and tablet dosage form. Results of analysis were validated statistically. The excipients present in the formulations do not interfere with the assay procedure.

Okram Zenita Devi, Kanakapura Basavaiah, reported two simple, sensitive and selective spectrophotometric methods for the determination of pantoprazole sodium sesquihydrate (PSS) and validated. The methods are based on the reduction of ferric chloride by PSS in neutral medium and subsequent chelation of iron (II) with 1, 10-phenanthroline (phen) (method A) or 2′, 2′-bipyridyl (bipy) (method B). The resulting red colored chromogens are measured at 510 and 520 nm, for method A and method B, respectively. Under the optimum conditions, Beer’s law is obeyed in the concentration ranges of 0.25-4.0 and 2.5-50 µg/mL with molar absorptivity values of 5.35x10^4 and 0.789x10^4 mol-1cm^-1 and Sandell sensitivities 0.008 and 0.055 µg cm^-2 for method A and method B, respectively. The limits of detection (LOD) and quantification (LOQ) are also reported. The proposed methods were applied successfully to the determination of PSS in pure form and in its tablets and no interference was observed from common excipients present in pharmaceutical formulations. Statistical comparison of the results of the proposed procedures with those obtained by the reference method showed excellent agreement and indicated that no significant difference in accuracy and precision. The validity
of the method was established by recovery studies via standard-addition technique with satisfactory results.

Rajnish Kumar et al\textsuperscript{85}, reported a simple and sensitive spectrophotometric method for the assay of pantoprazole either in pure form or in pharmaceutical solid dosage form. Absorption maxima of pantoprazole in water were found to be at 292 nm. Beer’s law is obeyed in the range 5-70\(\mu\)g/mL. Result of percentage recovery and placebo interference shows that the method was not affected by the presence of common excipients. The percentages assay of pantoprazole in tablet was more than 99%. The method was validated by determining its sensitivity, accuracy and precision which proves suitability of the developed method for the routine estimation of pantoprazole in bulk and solid dosage form.

Azza Moustafa AM\textsuperscript{86}, reported spectrophotometric procedures for determination of two irreversible proton pump inhibitors, lansoprazole (I) and pantoprazole sodium sesquihydrate (II). Two methods were based on charge transfer complexation reaction of these drugs, where they act as \(n\)-donors, with either \(\pi\) acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and with \(\sigma\) acceptor as iodine. A third method was also investigated depending on ternary complex formation with eosin and copper (II). The colored products were quantified spectrophotometrically using absorption bands at 457 nm for DDQ (method A) at 293 and 359 nm for iodine (method B) and at 549 nm using
ternary complex formation (method C), for both drugs. The molar combining ratio and the optimum assay conditions were studied. These methods determined the lansoprazole in concentration ranges from 10 to 90, 1.48 to 6.65 and 3.69 to 16.61 µg ml$^{-1}$ with mean percentage recovery 99.63% for DDQ, 99.71%, 99.18% for iodine and 99.76% for ternary complex and with relative standard deviation 0.11, 0.24, 0.13 and 0.36%, respectively. For pantoprazole, the concentration ranges were 10–60, 17.7–141.6 and 4.3–25.9 µg ml$^{-1}$ with mean percentage recovery 99.51, 98.97, 99.84 and 99.46% and relative standard deviation 0.53, 1.21, 0.65, 0.81% for the three mentioned methods, respectively. Investigation of the formed complexes was made with respect to its composition, molar ratio of the reaction, association constant $K_{c}^{AD}$, molar absorptivity $\varepsilon_{\lambda}^{AD}$ and free energy change $\Delta G$ for methods (A) and (B). The proposed methods have been applied successfully to the analysis of the cited drugs either in pure form or in pharmaceutical formulations, with good accuracy and precision, compared statistically with those given by the reported methods. They are recommended for quality control and routine analysis.

Ravi Kumar et al$^{87}$ reported simple, precise, rapid and selective simultaneous equation and Q- analysis UVspectrophotometric methods for the simultaneous determination of domperidone and pantoprazole from combined tablet dosage forms. The methods involve solving of simultaneous equations and Q-value analysis based on measurement absorptivity at 216, 287 and 290
nm respectively. Linearity lies between 1-15 μg/mL for domperidone and 0-50 μg/mL for pantoprazol.

Kakde RB et al. described three-wavelength spectrophotometric methods for the simultaneous estimation of pantoprazole (PAN) and domperidone (DOM) in pharmaceutical preparations. The absorbance value at 331nm was used for the estimation of PAN where DOM showed zero absorbance. The absorbance value for DOM was estimated by taking difference of absorbance at two wavelengths 284 nm and 364.5 nm. These method obeyed Beer’s law in the concentration range of 10-50 μg/ml for PAN, DOM and their mixture. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method. The method was found to be simple, rapid and accurate. Hence it can be used for routine simultaneous estimation of these drugs in formulations.
(d) Lansoprazole

The literature survey reveals that few methods are available for the determination of lansoprazole in dosage forms includes spectrophotometric method\textsuperscript{91-100}, capillary electrophoresis\textsuperscript{101}, RP-HPLC method\textsuperscript{102}, HPLC method\textsuperscript{105}, Voltammetry method\textsuperscript{106}.

Sherje, AP et al\textsuperscript{91}, described two simple, accurate and precise spectrophotometric methods for simultaneous determination of lansoprazole and domperidone in pharmaceutical dosage form. Method A involves formation of Q-absorbance equation at 256.0 nm (isoabsorptive point) and at 294.2 nm while method B is two wavelength method where 277.6 nm, 302.1 nm were selected as $\lambda_1$ and $\lambda_2$ for determination of lansoprazole and 231.3 nm, 292.0 nm were selected as $\lambda_1$ and $\lambda_2$ for determination of domperidone. Both the methods were validated statistically and recovery studies were carried out. The Beer's law limits for each drug individually and in mixture was within the concentration range of 5-50 $\mu$g/ml. Linearity of lansoprazole and domperidone were in the range of 24-36 $\mu$g/ml and 8-12 $\mu$g/ml, respectively. The proposed methods have been applied successfully to the analysis of the cited drugs either in pure form or in pharmaceutical formulations with good accuracy and precision. The method herein described can be employed for quality control and routine analysis of drugs in pharmaceutical formulations.
Rahman Nafisur et al\textsuperscript{92}, reported a simple kinetic spectrophotometric method for the determination of lansoprazole in pharmaceutical formulations. The method is based on the oxidation of the drug with alkaline potassium permanganate at room temperature. The reaction was followed spectrophotometrically by measuring the increase in the absorbance owing to the formation of MnO$_4^{2-}$ at 610 nm (Method A) and the decrease in the absorbance at 530 nm due to the disappearance of MnO$_4^{-}$ (Method B). Calibration procedures were adopted for the assay of the drug. The calibration curves were linear over the concentration ranges of 5-150 and 5-70\(\mu\)g ml$^{-1}$, with the corresponding calibration Equations: rate $= -3.915\times10^{-6} + 5.271\times10^{-5}c$ and $\Delta A = 1.04\times10^{-3}+1.78\times10^{-3}c$ for methods A, and B, respectively. A statistical comparison of the results of the proposed procedures with those of the reference spectrophotometric method show excellent agreement and indicated no significant difference between the compared methods in terms of accuracy and precision. Interval hypothesis tests were also performed, which indicated that the true bias of all samples was less than $\pm 2\%$.

Kanakapura Basavaiah et al\textsuperscript{93}, describes two spectrophotometric methods for the assay of lansoprazole (LPZ) in bulk drug and in dosage forms using ceric ammonium sulphate (CAS) and two dyes, methyl orange and indigo carmine, as reagents. The methods involve addition of a known excess of CAS to LPZ in acid medium, followed by determination of residual CAS by reacting with a
fixed amount of either methyl orange, measuring the absorbance at 520 nm (method A), or indigo carmine, measuring the absorbance at 610 nm (method B). In both methods, the amount of CAS reacted corresponds to the amount of LPZ and the measured absorbance was found to increase linearly with the concentration of LPZ, which is corroborated by the correlation coefficients of 0.9979 and 0.9954 for methods A and B, respectively. The systems obey Beer's law for 0.5-7.0 µg mL\(^{-1}\) and 0.25-3.0 µg mL\(^{-1}\) for methods A and B, respectively. The apparent molar absorptivities were calculated to be 3.0 \(\times\) \(10^4\) and 4.4 \(\times\) \(10^4\) L mol\(^{-1}\) cm\(^{-1}\) for methods A and B, respectively. The limits of detection (LOD) and quantification (LOQ) were calculated to be 0.08 and 0.25 µg/mL for method A, and 0.09 and 0.27 µg/mL for method B, respectively. The intra-day and inter-day precision and accuracy of the methods were evaluated according to the current ICH guidelines. Both methods were of comparable accuracy (\(e_t \leq 2\%\)). Also, both methods are equally precise as shown by the relative standard deviation values < 1.5%. No interference was observed from common pharmaceutical adjuvant. The accuracy of the methods was further ascertained by performing recovery studies using the standard addition method. The methods were successfully applied to the assay of LPZ in capsule preparations and the results were statistically compared with those of the literature UV-spectrophotometric method by applying Student's \(t\)-test and \(F\)-test.
Wahbi AA et al\textsuperscript{94}, reported the compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) have been applied to the direct determination of omeprazole, lansoprazole and pantoprazole in their pharmaceutical preparations. The methods have been validated; the limits of detection were found to be $3.3 \times 10^{-2}$, $3.0 \times 10^{-2}$ and $3.5 \times 10^{-2}$ microgram ml$^{-1}$ for the three drugs, respectively. The repeatability of the methods was found to be 0.3-0.5\%. The linearity ranges were found to be 0.5-3.5 $\mu$g/mL. The proposed methods have been applied to the determination of the three drugs in their gastro-resistant formulations. The difference spectrophotometric (DeltaA) method is unaffected by the presence of acid induced degradation products; hence can be used as a stability indicating assay.

Moustafa AA\textsuperscript{95}, describes spectrophotometric procedures for determination of two irreversible proton pump inhibitors, lansoprazole (I) and pantoprazole sodium sesquihydrate (II). Two methods were based on charge transfer complexation reaction of these drugs, where they act as n-donors, with either pi acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and with sigma acceptor as iodine. A third method was also investigated depending on ternary complex formation with eosin and copper (II). The colored products were quantified spectrophotometrically using absorption bands at 457 nm for DDQ (method A) at 293 and 359 nm for iodine (method B) and at 549 nm using
ternary complex formation (method C), for both drugs. The molar combining ratio and the optimum assay conditions were studied. These methods determined the lansoprazole in concentration ranges from 10 to 90, 1.48 to 6.65 and 3.69 to 16.61 µg/mL with mean percentage recovery 99.63% for DDQ, 99.71%, 99.18% for iodine and 99.76% for ternary complex and with relative standard deviation 0.11, 0.24, 0.13 and 0.36%, respectively. For pantoprazole, the concentration ranges were 10-60, 17.7-141.6 and 4.3-25.9 µg/mL with mean percentage recovery 99.51, 98.97, 99.84 and 99.46% and relative standard deviation 0.53, 1.21, 0.65, 0.81% for the three mentioned methods, respectively. Investigation of the formed complexes was made with respect to its composition, molar ratio of the reaction, association constant K(C)AD, molar absorptivity epsilon(λ)AD and free energy change delta G for methods (A) and (B). The proposed methods have been applied successfully to the analysis of the cited drugs either in pure form or in pharmaceutical formulations, with good accuracy and precision, compared statistically with those given by the reported methods. They are recommended for quality control and routine analysis.

Anil Kumar A et al.96, reported a simple, sensitive, accurate and economical spectroscopic method for the estimation of lansoprazole in Bulk and its pharmaceutical dosage forms. An absorption maximum was found to be at 298 nm with the solvent system 0.01 M Phosphate Buffer of pH 6.8. The drug
follows Beer law in the range of 5-30 µg/ml with correlation coefficient of 0.9996. The percentage recovery of lansoprazole ranged from 99.8 to 100.2 % in pharmaceutical dosage form. Results of the analysis were validated for accuracy, precision, LOD, LOQ and were found to be satisfactory. The proposed method is simple, rapid and suitable for the routine quality control analysis.

Ozaltín N\textsuperscript{97}, have developed two different ultraviolet (UV) spectroscopic methods for determination of Lansoprazole in pharmaceutical dosage forms. The solutions of the standard and the sample were prepared in 0.1 M NaOH and phosphate buffer pH 6.6. Both UV spectrophotometric and derivative spectroscopic techniques were applied. Second-order derivative spectra were generated between 200 and 400 nm at N = 9, delta lambda = 31.5. The linear range for the UV spectrophotometric method was 3.0-25.0 µg/mL and that for the derivative spectroscopic method was 0.5-25.0 µg/mL. The developed methods were applied to three different pharmaceutical preparations. The percentage recovery was 100.2%.

K. Basavaiah et al\textsuperscript{98}, developed two sensitive spectrophotometric methods are described for the determination of lansoprazole (LPZ) in bulk drug and in capsule formulation. The methods are based on the oxidation of lansoprazole by generated bromine followed by determination of unreacted bromine by two different reaction schemes. In one procedure (method A), the residual bromine
is treated with excess of iron (II), and the resulting iron (III) is complexed with thiocyanate and measured at 470 nm. The second approach (method B) involves treating the unreacted bromine with a measured excess of iron (II) and remaining iron (II) is complexed with orthophenanthroline at a raised pH, and measured at 510 nm. In both methods, the amount of bromine reacted corresponds to the amount of LPZ. The experimental conditions were optimized. In method A, the absorbance is found to decrease linearly with the concentration of LPZ \((r=-0.9986)\) where as in the method B a linear increase in absorbance occurs \((r = 0.9986)\). The systems obey Beer's law for 0.5-4.0 and 0.5-6.0 \(\mu\)g mL\(^{-1}\) for method A and method B, respectively. The calculated molar absorptivity values are \(3.97\times10^4\) and \(3.07\times10^4\) L mol\(^{-1}\)cm\(^{-1}\) for method A and method B, respectively, and the corresponding Sandell sensitivity values are 0.0039 and 0.0013 \(\mu\)g cm\(^{-2}\). The limit of detection (LOD) and quantification (LOQ) are also reported for both methods. Intra-day and inter-day precision, and accuracy of the methods were established as per the current ICH guidelines. The methods were successfully applied to the determination of LPZ in capsules and the results tallied well with the label claim and the results were statistically compared with those of a reference method by applying the Student's t-test and F-test. No interference was observed from the concomitant substances normally added to capsules. The accuracy and validity of the methods were further ascertained by performing recovery experiments \textit{via} standard-addition method.
Duygu Yeniceli et al\(^{99}\), The direct determination of lansoprazole by using a flow injection analysis (FIA) with UV-detection and its application to the pharmaceutical capsules. The best carrier solvent was found to be 0.01 M NaOH and it was determined at optimum conditions such as flow rate of 1 ml min\(^{-1}\) and wavelength of 292 nm. Examining the repeatability of the method that was found to be 1.72% for intra-day and 2.13% for inter-day precision using the 8.01×10\(^{-6}\) M lansoprazole concentration has validated the method. The linear range of the method was 5.4×10\(^{-6}\) to 5.4×10\(^{-5}\) M. The limit of detection and quantification was found to be 5.8×10\(^{-7}\) and 1.7×10\(^{-6}\) M, respectively. The proposed method was applied to the pharmaceutical capsules and very good results obtained. Thus, the FIA method for the quantification of lansoprazole can be proposed as a cheap, rapid, easy, accurate, and precise method for the routine determination in pharmaceutical preparations.

Parimi Uma Devi et al\(^{100}\), reported four simple, accurate and highly sensitive spectrophotometric methods for the determination of lansoprazole in both pure and in pharmaceutical preparations. The method A and B are based on the ion association complex formation between lansoprazole and supracen Violet 3B (method A) or Tropaeolin OOO (method B) the third and fourth are indirect methods where the drug is oxidised by a known excess of chloramine T and determining the consumed chloramine T with decrease in colour intensity of the dye galloycyanine (method C) or oxidation with excess of N-Bromosuccuminide
in acid medium, followed by the determination of unreacted N-bromosuccinimide with the dye Celestine Blue-(method D). Regression analysis of Beer’s law plots showed good correlation in the concentration range of 5.0 - 40 µg ml\(^{-1}\), 5.0 - 25 µg ml\(^{-1}\), 2.5–12.5 µg ml\(^{-1}\), 1.0–6.0µg ml\(^{-1}\) for methods A,B,C and D respectively, and the corresponding molar absorptivity values are \(0.9232 \times 10^4\), \(1.0857 \times 10^4\), \(7.0997 \times 10^4\) and \(2.3265 \times 10^4\) 1mol\(^{-1}\)cm\(^{-1}\). All variables have been optimized and the results were statistically compared with those of literature methods by employing the student’s \(t\)-test and \(F\)-test. No interference was observed from excipients normally added to the tablets.
(e) Abacavir Sulphate

Literature survey reveals few analytical techniques have been reported for the determination of abacavir sulphate in bulk and dosage forms which includes spectrophotometric method\textsuperscript{107-122} RP-HPLC\textsuperscript{123-126}, HPLC\textsuperscript{127-134}. HPTLC Method\textsuperscript{135}.

Srinivas Rao M et al\textsuperscript{107}, proposed a simple, accurate and economical spectrophotometric method in visible region for the determination of Abacavir sulphate in bulk and dosage forms. This method is based on the oxidation of MBTH with Fe (III) followed by coupling with mentioned drug forming a highly stable violet colored chromogen measured at 620 nm. Common excipients used as additives in pharmaceutical preparations do not interfere in the proposed methods. The results of analysis have been validated statistically and recovery studies confirmed the accuracy of the proposed method. The results were favorably compared with those obtained by reference UV spectrophotometric method. No interference was observed from common pharmaceutical adjuvant. These two methods were successfully applied to the pharmaceutical formulations.

Venkata Mahesh R and Dhachina Moorthy et al\textsuperscript{108}, proposed a simple visible spectrophotometric method for the estimation of abacavir sulphate in bulk and tablet dosage form. This method is based on the diazotization of abacavir sulphate with nitrous acid to form diazotized abacavir sulphate,
followed by its coupling with β-naphthol to form a red coloured chromogen which shows maximum absorption at 574.0 nm and obeys Beer’s law in the concentration range of 5-20 µg/mL. This method was validated for precision, accuracy, ruggedness and robustness. Statistical analysis proves that the method is reproducible and selective for the estimation of said drug.

Amudhavalli V et al\textsuperscript{109}, have developed simple, precise and sensitive UV method for the estimation of abacavir sulphate in bulk drug and pharmaceutical dosage form by difference spectrophotometric method. Abacavir sulphate has exhibited maximum absorbance at about 248.38 nm and 283.79 nm in acidic and basic solution respectively. Beer’s law was obeyed in the concentration range of 2-12 µg/mL in both the cases. The proposed method was successfully applied for the determination of abacavir sulphate in commercial tablet preparation. As per ICH guidelines the results of the analysis were validated statistically and were found to be satisfactory.

Surya Rao Srikakolapu et al\textsuperscript{110}, have developed three simple, precise and economical UV methods for the estimation of abacavir sulphate in tablet dosage form. Abacavir sulphate has the absorbance maxima at 285 nm (Method A), and in the first order derivative spectra, showed sharp peak at 275 nm (Method B). Method C applied was area under curve (AUC) in the wavelength range of 280-290 nm. Linearity for detector response was observed in the concentration range of 5-35 µg/mL for Method A and 5-40 µg/mL for Method B and Method C. The
proposed methods were successfully applied for the simultaneous determination of abacavir sulphate in commercial tablet preparation. The results of the analysis were validated statistically and were found to be satisfactory.

Sudhakar Reddy J et al\textsuperscript{111}, have developed two simple, sensitive and economical spectrophotometric methods for the determination of abacavir in commercial dosage forms. The method A was based on the formation of chloroform extractable complex of abacavir sulphate with wool fast blue. The absorbance of the extractable ion pair complex is measured at the wavelength of maximum absorbance 590 nm against the reagent blank. Method b was based on the charge transfer reactions of abacavir sulphate as \( n \)-electron donor with acceptor, 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone. The absorbance of the highly intensive coloured solution was measured at 450 nm against reagent blank treated similarly. Statistical analysis proves that the proposed methods are reproducible and selective for the estimation of abacavir sulphate in bulk drug and in its tablet dosage form.

Amudhavalli V et al\textsuperscript{112}, developed visible spectrophotometric methods [I and II] for the estimation of Abacavir sulphate in bulk drug and pharmaceutical formulation. Method [I] based on the reaction between FC reagent with the drug in alkaline condition to give a blue colour chromogen with absorption maximum at 754.6 nm and obeyed beers law in the concentration range of 20-120 \( \mu g/mL \). Method [II] based on the reduction of ferric ions to ferrous ions by
abacavir which further in presence of potassium ferricyanide produce green chromogen with absorption maximum at 712.3 nm and obeyed beers law in the concentration range of 2-12 µg/mL.

Ramana Murthy K.V et al\textsuperscript{113}, have developed, two simple and sensitive UV-spectrophotometric methods for the quantitative estimation of abacavir sulphate in bulk drug and pharmaceutical dosage forms. Abacavir sulphate has an absorption maximum at 287.5 nm in water and at 296 nm in 0.1N HCl. Beer's law was obeyed in the concentration range of 2-10µg/mL in both the cases. The results of analysis have been validated statistically and by recovery studies.

Prasada Rao C.H et al\textsuperscript{114}, proposed a simple visible spectrophotometric method for the estimation of abacavir sulphate in bulk and tablet dosage form. This method is based on the diazotization of abacavir sulphate with nitrous acid to form diazotized abacavir sulphate, followed by its coupling with α-naphthol to form a red coloured chromogen which shows maximum absorption at 574.0 nm and obeys Beer’s law in the concentration range of 5-20µg/mL. This method was validated for precision, accuracy, ruggedness and robustness. Statistical analysis proves that the method is reproducible and selective for the estimation of said.
Mirza Shahed S et al\textsuperscript{115}, developed two simple, accurate, precise, spectrophotometric methods for the estimation of abacavir sulfate and lamivudine in Tablet dosage form. Both the drugs are used against the HIV infection as reverse transcriptase inhibitors. Method A is Simultaneous equation method, wavelength selected for Quantitation are 284.0 nm and 270.0 nm for abacavir sulfate (ABAC) and lamivudine (LAM) respectively which are the $\lambda_{\text{max}}$ of both the drugs. Method B is Q–Analysis method, wavelength selected were 284.0 nm ($\lambda_{\text{max}}$ of ABAC) and 265.0 nm (Isobestic point) for the analysis. In both the methods linearity for detector response was observed in the concentration range of 5–30 µg/mL for ABAC and LAM respectively. The proposed methods were successfully applied for the simultaneous determination of both the drugs in commercial tablet preparation. The results of the analysis have been validated statistically and by recovery studies.

Srihari G et al\textsuperscript{116}, developed two simple, sensitive, accurate and economic methods A and B for the quantitative estimation of abacavir sulfate and its formulations. Method A is based on the diazotization of primary amine group of abacavir sulphate with sodium nitrate and hydrochloric acid followed by coupling with resorcinol to form a orange colored chromogen with a characteristic absorption maximum at 450 nm. Method B is based on the reaction of the abacavir sulfate with methanolic solution of para dimethyl amino benzaldehyde(PDAB) in acidic condition producing Schiff’s base having
absorption maximum at 455 nm. Beer’s law is obeyed in concentrations ranging from 50-250 µg/ml for both methods.

Chandrasekaran N et al\textsuperscript{117}, describes a new simple, sensitive, precise and economical Spectrophotometric method of analysis for abacavir sulphate both as a bulk and tablet formulation was developed and validated. The method developed with 15\% phosphoric acid and distilled water as solvent. The drug was then estimated at 283 nm. The linear regression analysis data for the calibration plots showed good linear relationship with \( r^2 = 0.9998 \) in the concentration range 5-30 µg/ml. The mean value of correlation coefficient, slope and intercept were 0.9998, 0.032 and 0.0294 respectively. The method was validated for precision, accuracy and recovery studies. LOD and LOQ for abacavir sulphate were found to be 0.5671 µg/mL and 1.7187 µg/mL respectively. The method has been successfully applied in the analysis of marketed formulations.

Devmurari et al \textsuperscript{118}, developed a novel, simple, rapid and sensitive spectrophotometer method for simultaneous estimation of lamivudine and abacavir. The method employs formation and solving of simultaneous equation using 280 nm and 297 nm as two analytical wavelengths. Both the drugs obey Beer’s Law in the concentration ranges employed for this method. Accuracy and reproducibility of the proposed method was statistically validated by
recovery studies. The method is found to be rapid, precise and accurate and can easily be employed in the laboratory for the routine estimation of drugs.

Appala et al.\textsuperscript{119}, developed two simple, accurate, rapid and sensitive methods (A and B) for the estimation of abacavir sulphate in its pharmaceutical dosage form. The method A and B are based on the formation of chloroform extractable complex of abacavir sulphate with bromophenol blue (method A) and bromocresol green (method B), which shows absorbance maxima at 460 nm and 469 nm respectively. The absorbance-concentration plot is linear over the range of 1-10 mcg/ml for method A and B respectively. Results of analysis for all the methods were validated statistically and by recovery studies. The proposed methods are economical and sensitive for the estimation of abacavir sulphate in bulk drug and in its tablet dosage form.

Alagar M et al.\textsuperscript{120}, developed a simple, selective and well validated spectrophotometric method for estimations abacavir sulphate in pharmaceutical formulations. The developed spectrophotometric method is simple, rapid, precise, accurate, reliable, and economical when compared to other methods. The method was also applied to tablet formulations. It gives better results in terms of accuracy, precision, and linearity over the concentration range 5-25 µg/ml for abacavir sulphate. The limit of detection in tablet dosage forms is 3 µg/ml.
and the limit of quantification for the tablet are 5 µg/ml. The %RSD is 49.23% and recovery is 84-113%.

Nagulwar Vaishali P and P. Bhusari Kishor, developed an accurate, economical and reproducible UV spectrophotometric method for estimation of abacavir, lamivudine, zidovudine in pure bulk rug and in combined tablet dosage form. The stock solution were prepared in acetonitrile followed by further required dilutions with distilled water. The absorbance maxima for abacavir, lamivudine and zidovudine were observed at 295.6, 279.8 and 266.2 nm respectively and linearity was also shown at these wavelengths in the concentrations range of 5-30 µg/mL, 5-25 µg/mL and 5-30 µg/mL for all three drugs.

Nagulwar V.P and Bhusari K.P, developed simple, accurate, precise, economical and reproducible analytical method for the simultaneous estimation of abacavir and lamivudine in pure bulk drug and in combined tablet dosage form by UV spectrophotometric first order derivative method. The stock solutions were prepared in mixture of acetonitrile and methanol followed by the further required dilutions with distilled water. In the first order derivative method, the wavelengths at which abacavir and lamivudine were analyzed were 229.2 nm and 284.8 nm respectively. At 229.2 nm abacavir has absorbance while lamivudine shows zero absorbance. Similarly, at 284.8 nm lamivudine shows absorbance while abacavir has zero absorbance. Thus both the drugs do
not interfere in the quantitation of one another. Calibration graphs were obtained by the concentration ranges of 5-25 μg/ ml of both the drugs. In bulk drugs, abacavir was estimated as 100.05%, lamivudine 100.11% whereas in the marketed tablets abacavir was found as 99.01% lamivudine 99.09% respectively. The results of analysis have been validated as per ICH guidelines and were found to be satisfactory. Hence, present study gives excellent methods for the determination of both the drugs in combined tablet formulation.
(f) Mesalamine

A few spectrophotometric method\textsuperscript{136-139}, HPLC-ESI-MS/MS method\textsuperscript{140}, voltammetry method\textsuperscript{141}, LC method\textsuperscript{142}, HPLC methods\textsuperscript{143-149}, for the estimation of mesalamine have been reported in the literature.

Srinivasa Rao Narala and K. Saraswathi\textsuperscript{136} have developed three simple and sensitive spectrophotometric methods (A, B and C) for the quantitative determination of Mesalamine in bulk and tablet dosage forms. Method–A was based on condensation of Mesalamine with p-dimethyl amino benzaldehyde to form Schiff’s base, which was an yellow colored chromogen showed the absorption maximum at 450 nm.

The Beer’s law range, regression equation and % recovery studies were found to be 10-50µg/mL, $Y=0.00594$, $X=0.0074$ and 99.95±0.045 respectively. Method B and C were based on the oxidation of mesalamine with ferric chloride followed by complex formation with 2,2–bipyridyl or potassium ferri cyanide. The colored complexes formed were measured at 520 nm for method-B and 720 nm for method C respectively. The Beer’s law range, regression equation and % recovery studies were found to 4 –24 µg/mL, $Y = 0.03318 X + 0.105008$, and 99.93 ± 0.101 for method-B, 4–20 µg/ml, $Y = 0.0365 X + 0.1198$ and 99.76 ± 0.075 for method C. All the methods were validated and found to be satisfactory.
Rakesh Kumar Singh et al., proposed a simple UV spectrophotometric method for the determination of mesalazine in pure and its pharmaceutical formulations. Mesalazine exhibits maximum absorbance at 210 nm in methanol and obeyed linearity in the concentration range of 0.2-50 µg/mL. The proposed method was statistically validated.

Sasmita Kumari Acharya et al., have developed five simple, precise and cost effective spectrophotometric methods for the estimation of mesalamine in bulk and its pharmaceutical formulations. Mesalamine shows $\lambda_{\text{max}}$ at 232.0 nm in zero order derivative spectrum (Method A), 241.0 nm in first order derivative spectrum (Method B), 244.5 nm in second order derivative spectrum (Method C) and 240.5 nm in third order derivative spectrum (Method D). Method E is based on calculation of Area under Curve (AUC) for analysis of mesalamine in the wavelength range of 227.0–237.0 nm. The drug follows the Beer-Lambert’s law in the concentration range of 2.0–25.0 µg/mL in all the methods. The methods were validated by following the analytical performance parameters suggested by the International Conference on Harmonization. All validation parameters were within the acceptable range. The developed methods were successfully applied to estimate the amount of mesalamine in bulk and pharmaceutical dosage forms.

Patel, K.M et al., have developed three simple and sensitive visible spectrophotometric methods (A, B, and C) for the quantitative estimation of
mesalamine in bulk drug and pharmaceutical dosage forms. Methods were based on the formation of colored chromogens, which were measured at 552 nm, 440 nm, and 494 nm, respectively. The results obtained with the proposed methods were found to be unsatisfactory with the labeled amounts when the tablet dosage forms were analyzed. Method A is based on Diazotization of mesalamine with nitrous acid, to form diazotized mesalamine followed by its coupling with N-(1-naphthyl) ethylene-diamine dihydrochloride, to form a violet colored chromogen with maximum absorption at 552 nm; it obeyed the Beer's law in the concentration range of 2-30 µg/mL. Method B is based on the condensation of Mesalamine with p-dimethylaminobenzaldehyde to form the Schiff's base that is a yellow colored chromogen and exhibits maximum absorbance at 440 nm; The Beer's law is obeyed in the concentration range of 50-500µg/mL.

In method C, mesalamine has a phenolic group when made to react with Gibb's reagent. In alkaline pH it forms a colored chromogen, exhibiting absorption maximum at 494 nm, and Beer's law is obeyed in the concentration range of 5-60 µg/mL.
(g) Mosapride citrate:

Various methods are reported in literature for the estimation of mosapride citrate which include Colorimetric method\textsuperscript{150}, Spectrophotometric method\textsuperscript{151-152} and HPLC method\textsuperscript{153-156}.

Appala Raju and Shobha M etal\textsuperscript{150} proposed a simple and sensitive UV spectrophotometric method for the estimation of mosapride citrate in bulk drug and its formulations. Mosapride citrate exhibits absorption maximum at 272 nm. Beer’s law obeyed in the concentration range of 2-10 $\mu$g/ml.

Kuchekar BS. etal\textsuperscript{151} proposed a simple colorimetric method for the estimation of mosapride citrate in solid dosage forms. Estimation of mosapride citrate is based on diazotization of mosapride and coupling of the diazonium salt with N-(1-naphthyl) ethylene diamine dihydrochloride to form a stable purple colored chromogen. With absorbance maximum at 540 nm, the chromogen obeyed linearity over 20 -160 $\mu$g/ml.

Revanasiddappa HDand MA. Veena\textsuperscript{152}, have developed two simple described two simple spectrophotometric methods (M1 and M2) for the determination of mosapride in pure and in pharmaceutical preparations. These methods were based on the interaction of diazotized mosapride coupling with chromotropic acid [M1] in alkaline medium and diphenylamine [M2] in acidic medium. The
resulting azo dyes exhibited maximum absorption at 560 nm and at 540 nm for methods M1 and M2, respectively. All variables were studied in order to optimize the reaction conditions. No interference was observed from excipients

Patil Shamkant S et al\textsuperscript{153}, reported three simple, precise and economical UV methods for the estimation of Mosapride in bulk and pharmaceutical formulations. Mosapride has the absorbance maxima at 309 nm (Method A), and in the first order derivative spectra, showed zero crossing at 309 nm, with a sharp peak at 300 nm when n=1 (Method B), Method C applied was Area Under Curve (AUC) for analysis of Mosapride in the wavelength range of 300-320 nm. Drug followed the Beer’s Lamberts range of 5-40 \( \mu \)g/ml for the method A, B, C. Results of analysis were validated statistically and by recovery studies and were found to be satisfactory.
(h) *darunavir*

Few methods are reported in literature for the estimation of darunavir in pharmaceutical formulations which includes Spectrophotometric method\(^{157-158}\) RP-HPLC method\(^{159-161}\) and HPLC method\(^{162}\).

Purushotham Reddy and Rami Reddy N\(^{157}\) reported a simple spectrophotometric method for the determination of darunavir. The method was based on bromination of the darunavir with excess brominating mixture in acidic medium. The yellow colour developed was measured at 350 nm against distilled water blank. Beer’s law was obeyed in the concentration range of 40-200 µg/mL. The proposed methods were simple, rapid, and validated and can be used successfully for routine analysis of darunavir in a pure and tablet dosage form.

Shinde VR et al\(^{158}\), reported a simple accurate and sensitive UV spectrophotometric method for the quantitative estimation of darunavir in bulk and its pharmaceutical formulation. In this method 70% methanol was used as solvent. Darunavir shows maximum absorbance at 262.5 nm and obeys Beer-Lamberts law in the concentration range of 2-25 µg/ml. The linearity was observed in concentration range of 2-25 µg/ml. The method was validated statistically for accuracy, precision and sensitivity.