2. REVIEW OF LITERATURE

A detailed review of literature was carried out on oral extended release on the selected drugs namely Valsartan and Ranolazine. The literature review was carried for the year 1973 to 2012.

2.1. Valsartan

Soumya and coworkers\(^5^7\) developed bilayered sustained release matrix tablets of valsartan. Sustained release tablets were prepared by using Eudragit RSPO and Eudragit RLPO polymers. The tablets contained an immediate releasing layer with the loading dose of the drug and a sustaining layer with maintenance dose of drug prepared by wet granulation method. The release of valsartan from the bilayered tablet was studied in 900 ml of phosphate buffer pH 6.8. The bilayered tablets showed an initial burst effect to provide a loading dose of the drug, followed by sustained release for 12 h, indicating a promising potential of the Valsartan bilayered tablet as an alternative to the conventional dosage form.

Mahajan and coworkers\(^5^8\) developed sustained release matrix tablets of valsartan, using hydroxypropylmethylcellulose alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method. The granules were evaluated for angle of repose, bulk density and compressibility index. The tablets were subjected to weight variation test, drug content, hardness, friability, and \textit{in vitro} release studies. The granules showed satisfactory flow properties, compressibility, and all the tablet formulations showed acceptable pharmacotechnical properties. The formulated tablets were also compared with a marketed product. \textit{In vitro} dissolution studies indicate that EC significantly reduced the rate of drug release compared to HPMC. But no significant difference was observed in the release profile of matrix tablets made by higher percentage of EC. The result of dissolution study indicated that the formulation prepared by low viscosity grade HPMC showed maximum drug release up to 8 h and high viscosity grade HPMC and EC formulation showed up to 12 h. In case of formulation containing combination of HPMC and EC prepared using factorial design, showed drug release up to 24 h, whereas the marketed product released drug up to only 3 h. Mathematical treatment of the \textit{in vitro drug release} data suggest that, optimized formulation F3 fitted in to Korsmeyer and Peppas release kinetic showed a \(r^2\) value
Drug release from the matrix occurred by combination of two mechanism, diffusion and erosion of tablet.

Anjankumar\textsuperscript{59} designed and evaluated mucoadhesive bi-layered buccal devices of valsartan containing mucoadhesive layer and a drug free backing membrane. The bilaminated films were composed of a mixture of valsartan and chitosan, with HPMC and backing layer. The films were fabricated by solvent casting technique and were evaluated for thickness, drug content uniformity, bio-adhesion strength, percent, swelling index, folding endurance and in vitro drug release. The combination of chitosan and HPMC (1:1) using propylene glycol (50\% by weight of polymer) as plasticizer gave promising results. The optimized film exhibited an \textit{in vitro} drug release of approximately 90\% in 5 h along with satisfactory bio-adhesive strength.

Adhvait and coworkers\textsuperscript{60} developed a self-micro emulsifying drug delivery system (SMEDDS) to enhance diffusion the rate and oral bioavailability of valsartan. The valsartan SMEDDS was prepared using Capmul MCM (oil), Tween 80 (surfactant), and polyethylene glycol 400 (co surfactant). The particle size distribution, zeta potential, and polydispersity index were determined. The \textit{in vitro} drug release was carried out in pH 6.8 buffer and analyzed by a HPLC. Bioavailability studies of valsartan SMEDDS was also carried out in rabbits. Results of diffusion rate and oral bioavailability of valsartan SMEDDS were compared with those of pure drug solution and of marketed formulation. Diffusion of valsartan SMEDDS showed maximum drug release when compared to pure drug solution and marketed formulation.

Sandhyaraj and coworkers\textsuperscript{61} designed sustained release alginate microcapsules of valsartan by orifice-ionic gelation method using HPMC, as mucoadhesive polymer. The microcapsules were discrete spherical and free flowing. The microcapsules were evaluated for drug excipients interactions, % yield, drug content uniformity, particle size distribution, surface morphology, percentage moisture loss, \textit{in vitro} drug release profile, and mucoadhesion study by \textit{in vitro} wash off test, short term stability. The formulation prepared by using alginate – HPMC (K4M) in the ratio of 5:1 along with magnesium stearate, emerged as the overall best formulation based upon their drug release characteristics in phosphate buffer pH 6.8. \textit{In vitro} drug release followed first order
kinetics, Fickian diffusion mechanism \((n<0.5)\) and the results had proven the release of the best formulation had extended up to 13.5 h.

**Howida Kamal Ibrahim and coworkers**\(^{62}\) developed a valsartan orodispersible tablets at 40-mg dose, to improve its poor oral bioavailability. A \(3^3\) full factorial design was adopted for the optimization of the tablets prepared by freeze-drying technique. The effects of the filler type, the binder type, and the binder concentration were studied. The different tablet formulas were characterized for their physical properties, weight variation, disintegration time, surface properties, wetting properties, and *in vitro* dissolution. Amongst the prepared 27 tablet formulas, the tablets consisting of 4:6 valsartan mannitol and 2% pectin had good bioavailability. The two 40 mg valsartan orodispersible tablets were compared with conventional commercial tablets after administration of a single dose to four healthy volunteers. The apparent rate of absorption of valsartan from the prepared tablets was significantly higher than that of the conventional tablets. The results of the *in vivo* study revealed that valsartan orodispersible tablets would be advantageous with regards to improved patient compliance, rapid onset of action, and increase in bioavailability.

**Macek and coworkers**\(^{63}\) developed a high-performance liquid chromatography for the determination of valsartan in human plasma. The assay was based on protein precipitation with methanol and reversed-phase chromatography with fluorimetric detection. The preparation time of a batch of 24 samples were 20 min. The liquid chromatography was performed on an octadecylsilica column \((50\text{mm}\times4\text{mm}, 5\mu\text{ particles})\), the mobile phase consisting of acetonitrile \(-15\text{mM, dihydrogen potassium phosphate, pH 2.0 (45:55, v/v). The run time was 2.8 min. The fluorimetric detector was operated at 234/374 nm (excitation/emission wavelength). The limit of quantitation was 98 ng/ml using 0.2 ml of plasma. Within-day and between-day precision expressed by relative standard deviation was less than 5% and inaccuracy did not exceed 8%. The assay was applied to the analysis of samples from a pharmacokinetic study.

**Hao Li and coworkers**\(^{64}\) developed and validated liquid chromatography/tandem mass spectrometry method for the simultaneous quantification of valsartan and hydrochlorothiazide in human plasma. A simple protein precipitation method was used to separate the analytes. The separation was achieved by Zorbax SB-Aq C18 column, using
acetonitrile –10mM ammonium acetate (60:40, v/v, pH 4.5) as mobile phase at a flow rate of 1.2 ml/min. Valsartan and hydrochlorothiazide were eluted at 2.08 min and 1.50 min, respectively, ionized using ESI source, and then detected by multiple reaction monitoring (MRM) mode. The precursor to product ion transitions of \( m/z \) 434.2–350.2 and \( m/z \) 295.9–268.9 were used to quantify valsartan and hydrochlorothiazide, respectively. The method was linear in the concentration range of 4–3600 ng/ml for valsartan and 1–900 ng/ml for hydrochlorothiazide. The method was successfully employed in a pharmacokinetic study after an oral administration of a dispersible tablet containing 80 mg valsartan and 12.5 mg hydrochlorothiazide.

**María del Rosario Brunetto and coworkers**\(^6^5\) reported determination of losartan, telmisartan, and valsartan by direct injection of human urine into a column-switching liquid chromatographic system with fluorescence detection. Column-switching high-performance liquid chromatographic (HPLC) method was developed and validated for quantification of losartan, telmisartan, and valsartan in human urine. Urine samples were diluted on the extraction mobile phase (1:4, v/v) and a volume of 20 µL of this mixture were directly injected onto the HPLC system. The analytes were extracted from the matrix using an on-line solid phase extraction procedure involving a precolumn packed with 25 µ C18 alkyl-diol support (ADS), and a solution 2% methanol in 5mM phosphate buffer (pH 3.8) at a flow-rate of 0.8 ml/min for isolation and preconcentration of losartan, telmisartan, and valsartan. The enriched analytes were back-flushed after, onto the analytical column with a mixture of 5mM phosphate buffer (pH 3.8)–acetonitrile–methanol (65:20:15, v/v/v) at a flow-rate of 3.0 ml/min and detected by fluorescence at 259 and 399 nm as excitation and emission wavelength respectively. The estimated calibration range was 0.001–2.5µg/ml with excellent coefficient of determination (>0.9981). The detection limits for losartan, telmisartan, and Valsartan at a signal-to-noise ratio of 5:1were 0.002, 0.0002 and 0.001µg/ml. The developed procedure allows efficient extraction of losartan, telmisartan, and valsartan from urine samples and provides high sensitivity for their fluorescence detection.

**Krishnaiah and coworkers**\(^6^6\) developed a stability-indicating UPLC method for determination of valsartan and their degradation products in active pharmaceutical
ingredient and pharmaceutical dosage forms. A simple, precise, accurate stability-indicating gradient reverse phase ultra-performance liquid chromatographic (RP-UPLC) method was developed for the quantitative determination of purity of Valsartan drug substance and drug products in bulk samples and pharmaceutical dosage forms in the presence of its impurities and degradation products. The method was developed using Waters Aquity BEH C$_{18}$ column with mobile phase containing a gradient mixture of solvents A and B. The solvent A contained a mixture of 1.0% acetic acid buffer, Acetonitrile in the ratio 90:10 (v/v); and the solvent B contained a mixture of 1.0% acetic acid buffer and acetonitrile in the ratio 10:90 (v/v), respectively. The flow rate of mobile phase was 0.3 ml/min. The UPLC gradient program (T/%B) was set as 0.01/20, 1.0/40, 3.5/55, 6.5/80, 8.5/80, 8.9/20 and 9.5/20. The column temperature was maintained at 27°C and the detection was monitored at a wavelength 225 nm. The injection volume was 1.0ml, the run time was within 9.5 min, which Valsartan and its seven impurities were well separated. Valsartan was subjected to the stress conditions of oxidative, acid, base, hydrolytic, thermal and photolytic degradation. Valsartan was found to degrade significantly in acid and oxidative stress conditions and stable in base, hydrolytic and photolytic degradation conditions. The degradation products were well resolved from main peak and its impurities, proving the stability indicating power of the method. This method is suitable for the assay determination of Valsartan in pharmaceutical dosage forms.

Patro and coworkers$^{67}$ have developed stability indicating RP-HPLC method for determination of valsartan in pure and pharmaceutical formulation. The method was developed using Shimadzu HPLC LC 2010 CHT series system with quaternary constant flow pump, auto injector, Photo Diode array detector, LC Solution Version 1.22 SP1 software, 0.01 M ammonium dihydrogen orthophosphate buffer and methanol in the ratio of 50:50 (v/v) used as a mobile phase and detection wavelength 210 nm. The flow rate was 1ml/min and the drug valsartan eluted at 11.04 min. The standard curve was linear over a range of 50-175 ng/ml and gave an average correlation coefficient of 0.9998 during validation. Forced degradation studies were performed to evaluate the stability indicating properties and specificity of the method. Intentional degradation was carried out by exposing the 20 mg of samples in three different 20 ml volumetric flasks.
containing acid (0.1 N HCl, at 40 °C), basic (0.1 N NaOH, at 40 °C) and hydrogen peroxide (3% \( \text{H}_2\text{O}_2 \)) and kept for 2 h. These sample solutions were injected and analyzed. The developed method was simple, linear, accurate, sensitive and reproducible, and stability indicating assay. This method can be easily used for the routine quality control of bulk and tablet form.

Abdel naser and coworkers\(^{68}\) compared the bioavailability of two Valsartan tablets in 24 healthy male volunteers. An open, randomized, two periods cross over study design was performed under fasting conditions. The selected volunteers were divided into two groups of 12 subjects. One group was treated with the reference formulation (Diovan\(^{®}\)) and the other one with the generic Valzan\(^{®}\), with a cross-over after the drug washout period of 14 days. Blood samples were collected at fixed time intervals and Valsartan concentrations were determined by a validated HPLC assay method. The pharmacokinetic parameters \( \text{AUC}_{0-48} \), \( \text{AUC}_{0-\infty} \), \( C_{\text{max}} \), \( T_{\text{max}} \), \( K_e \) and \( T_{1/2} \) were determined for both the tablets and were compared statistically to evaluate the bioequivalence between the two brands of valsartan, using the statistical model recommended by the FDA. The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90% confidence intervals (CI) fell within the acceptable range for bioequivalence. Based on this statistical evaluation it was concluded that the test tablets (Valzan\(^{®}\)) is well formulated, since it exhibits pharmacokinetic profile comparable to the reference brand Diovan\(^{®}\).

Ana Cristina Franco Spínola and coworkers\(^{69}\) compared the bioavailability of valsartan 160-mg tablets in 24 healthy male volunteers. An open label single-cent single-dose, randomized-sequence, 2-way crossover study with a minimum washout period of 7 days drug was administered to healthy volunteers under fasting conditions. Blood samples were collected up to 36 h post administration, and valsartan levels were gauged from plasma by reverse liquid chromatography and tandem mass spectrometry. Pharmacokinetic parameters were calculated from valsartan concentration data using non compartmental analysis. \( \text{AUC}_{\text{last}} \), \( \text{AUC}_{\infty} \), and \( C_{\text{max}} \) were analyzed. The 90% CIs of the ratios of the test versus-reference pharmacokinetic parameters (\( \text{AUC}_{\text{last}} \), \( \text{AUC}_{\infty} \), and \( C_{\text{max}} \)) were obtained by ANOVA on Intransformed data. The 90% CIs were required to be within 80.00% to 125.00% of the 90% CI to meet the criteria for bioequivalence.
Tolerability was monitored using physical examination (including vital-sign measurements) and ECG performed at screening, as well as laboratory analysis, including biochemistry tests, hematology tests, and urinalysis, which were performed at screening and during the study period.

2.2. Ranolazine

Asaduzzaman and coworkers\textsuperscript{70} designed and evaluated sustained release matrix tablet of ranolazine based on Methocel K4M CR as the retardant polymer. Tablets were prepared by wet granulation technique. Dissolution studies were performed in 0.1 HCL at 50 rpm for 8 h. The release kinetics was analyzed using the zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. \textit{In vitro} release studies revealed that percent drug release decreased with increase of polymer loading. Based on the dissolution data, the formulation contain 16\% Methocel K4M CR w/w of drug was elected as the best formulation. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model (R2 = 0.99) and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation. All the formulations were checked for stability as per ICH guidelines and formulations were found stable during the study.

Gowda and coworkers\textsuperscript{71} Prepared microparticles of Ranolazine to minimize the unwanted toxic effects of anti-anginal, it was entrapped into biodegradable Eudragit (EU) and ethyl cellulose (EC) binary blend using phase separation method. The prepared microparticles were characterized for micromeritic properties, polymer drug compatibility by FT-IR and DSC, and surface morphology by SEM. The obtained angle of repose, percentage Carr’s index and tapped density values were within the limits indicating good flow properties. The prepared microparticles were evaluated for percentage yield, encapsulation efficiency and \textit{in vitro} release studies. The \textit{in vitro} drug release studies were carried out using pH 1.2 acid buffer and pH 7.4 phosphate buffer. The drug release kinetics followed different transport mechanisms. Increasing the weight fractions of EU and decreased EC helped to control the drug release from the particles.
Murthy and coworkers\textsuperscript{72} designed extended release tablets of ranolazine employing hypromellose phthalate grade HP-55, ethocel standard 7FP premium ethyl cellulose, Surelease E-7-19040, Klucel HF pharm and Natrosol Type 250 HHX as matrix forming agents using wet granulation method. The formulated tablets were evaluated for uniformity of weight, assay, water content, \textit{in vitro} drug release studies and stability studies. The drug release followed first order kinetics with both erosion and diffusion as the release mechanism. It was concluded that the desired drug release pattern can be obtained by using natrosol type 250 HHX compared to other polymers.

Mohammad Nezab and coworkers\textsuperscript{73} designed and evaluated sustained release matrix tablets of ranolazine using HPMC as the retardant polymer and to study the effect of formulation factors such as polymer proportion and polymer viscosity on the release of drug. The release kinetics was analyzed using the zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. \textit{In vitro} release studies revealed that the release rate decreased with increase in polymer proportion and viscosity grade. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. The developed controlled release matrix tablets of ranolazine prepared with high viscosity HPMC extended release up to 12 h.

Mofizur Rahman and coworkers\textsuperscript{74} studied the effect of various grades of HPMC on ranolazine sustained release drug delivery systems. Different grades of HPMC (E50, K100LV, Methocel K4M, and K15M) were used as retarding polymer. Matrix tablets were prepared by direct compression method. The USP paddle method was selected to perform the dissolution profiles carried out by USP apparatus 2 (paddle) at 100 rpm in 900 ml 0.1 N HCl and phosphate buffer. Drug release was analyzed according to their kinetic models. A One way analysis of variance (ANOVA) was used to interpret the result. Statistically significant differences were found among the drug release profile from different matrices. At a fixed polymer level, drug release from the higher viscosity grades (K15M) was slower as compared to the lower viscosity grades (E50). The best-fit release kinetics was achieved with the Higuchi model followed by the zero-order plot, Korsmeyer and Hixson Crowell equations. The data obtained proved that the
formulations are useful for a sustained release of ranolazine. From these formulations corresponded more controlled of the drug release by the higher viscosity grade of HPMC. **Jagdish Bidada and coworkers** developed extended release matrix tablets of ranolazine containing polyacrylic and ethylcellulose polymer. The matrix tablets were prepared by wet granulation method. *In vitro* dissolution studies were conducted using paddle method at 100 rpm for 12 h. The amount of drug dissolved in the medium was determined by HPLC. The effect of varying the Carbopol-Ethocel ratio, as well as the drug-polymeric matrix ratio, was evaluated by simple factorial design using two independent factors. The results showed the suitability of Carbopol-Ethocel mixtures as matrix forming material for ranolazine extended release formulations. Combination of the swelling properties of Carbopol with the plastic properties of the more hydrophobic Ethocel allowed suitable modulation of ranolazine release. Mathematical analysis of the release kinetics indicated that the nature of the drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. The factorial study indicates a good correlation coefficient. The effect was dependent on both the independent factors of hydrophilic and hydrophilic polymer.

**Yuan Wang and coworkers** developed a sensitive LC-MS/MS assay for simultaneous quantitation of ranolazine and its three metabolites in human plasma. A rapid, sensitive and reliable LC–MS/MS method was developed and validated for the simultaneous determination of ranolazine and its three metabolites, CVT-2514, CVT-2738, and CVT-4786, in human plasma. The plasma samples were prepared by protein precipitation. Chromatographic separation was achieved on a Gemini C18 column using methanol and ammonium acetate as the mobile phase with gradient elution. Mass detection was carried out by electro spray ionization in both positive and negative ion multiple reaction monitoring (MRM) modes. The calibration curves were linear over a concentration range of 4–2000 ng/ml for ranolazine, 4–1000 ng/ml for CVT-2514 and CVT-2738 and 8–1000 ng/ml for CVT-4786. The intra-day and inter-day accuracy and precision were within the acceptable limits of ±15% at all concentrations. The method was successfully applied for the simultaneous estimation of ranolazine and its three metabolites in human plasma for a clinical pharmacokinetics study.
Xingping Luo and coworkers\textsuperscript{77} developed an Analytical and semi preparative resolution of ranolazine enantiomers by liquid chromatography using polysaccharide chiral stationary phases. A New HPLC method was developed for the analytical and semi preparative resolution of new antianginal drug ranolazine enantiomers. Good baseline enantioseparation was achieved using cellulose tris (3,5-dimethyl phenylcarbamate) (CDMPC) chiral stationary phases (CSPs) under both normal-phase and polar organic modes. The validation of the analytical methods including linearity, LODs, recovery, and precision, and the semi preparative resolution of ranolazine racemate were carried out using methanol as mobile phase without any basic and acidic additives under polar organic mode, using CDMPC CSPs. At analytical scale, the elution times of both enantiomers were less than 7.5 min at 208C and 1.0 ml/min, with the separation factor 1.88 and the resolution factor 2.95. At semi preparative scale, about 14.3 mg/h enantiomers could be isolated and elution times of both enantiomers were less than 13 min at 2.0 ml/min. To increase the throughput, the technique of overlapping injections was used. The first eluted enantiomer was isolated with a purity of 99.6% enantiomer excess (e.e.) and A99.0% yield. The second enantiomer was isolated with a purity of 98.8% e.e. and A99.0% yield. In addition, optical rotation and circular dichroism spectroscopy of both ranolazine enantiomers isolated were also investigated.

Uttam Bhaumik and coworkers\textsuperscript{78} reported determination of ranolazine in human plasma LC-MS/MS and its application in bioequivalence study. A simple, sensitive and specific liquid chromatography–tandem mass spectrometry (LC–MS/MS) method was developed and validated for quantification of ranolazine in human plasma. The analytical method consists in the precipitation of plasma sample with methanol, followed by the determination of ranolazine by an LC–MS/MS. The analyte was separated on a Peerless Cyano column (33mm×4.6mm,3μ) an isocratic mobile phase of methanol–water containing formic acid (1.0%, v/v) (65:35, v/v) at a flow rate of 1.0 ml/min. Protonated ions formed by a turbo ion spray in positive mode were used to detect analyte and internal standard (IS). The MS/MS detection was made by monitoring the fragmentation of \textit{m}/z 428.20\rightarrow279.50 for ranolazine and \textit{m}/z 448.30\rightarrow285.20 for internal standard on a triple quadrupole mass spectrometer. The method was validated over the concentration range of 5–2000 ng/ml for ranolazine in human plasma with
correlation coefficient of 0.9937 (S.D.: ±0.00367, range: 0.9895–0.9963). The accuracy and precision values obtained from six different sets of quality control samples analyzed in separate occasions ranged from 94.53 to 117.86 and 0.14% to 4.56%, respectively. Mean extraction recovery was 82.36–94.25% for three quality control (QC) samples and 88.37% for IS. Plasma samples were stable for three freeze thaw cycles, or 24 h ambient storage, or 1 and 3 months storage at −20°C. Processed samples (ready for injection) were stable up to 72 h at auto sampler (4°C). The developed method was successfully applied for analyzing ranolazine in plasma samples for a bioequivalence study.

Vivek nalawade and coworkers\textsuperscript{79} developed a liquid extraction-HPLC method for the determination of ranolazine in human plasma. The analytical method was developed by using experimental design and quantitation was accomplished with the internal standard method. The standard curves of ranolazine in human plasma were linear over the range of 200-5000 ng/ml and the regression coefficients were over 0.9988. The intraday and interday precision and accuracy (measured by relative standard deviation, RSD, and relative error, RE, respectively) were always lower than 6% (RSD) and 4% (RE). The recovery of ranolazine was assessed at three different concentrations. The results were found to be 102.04% at 500 ng/ml, 103.21% at 2500 ng/ml and 101.93% at 4000 ng/ml. Stability studies showed that ranolazine stock solutions are stable for at least 1 month when stored at -20°C and plasma samples containing the drug were stable at least during the whole analytical method. The method offers an alternative detection method for the analysis of ranolazine. The developed method was inexpensive and easy to use with excellent reproducibility and is suitable for both routine analysis and clinical studies.

Patel and coworkers\textsuperscript{80} reported estimation of ranolazine by spectrometric and RP-HPLC in tablet dosage forms. A UV spectrometric method and reverse phase high performance liquid chromatography were developed for the estimation ranolazine in bulk and pharmaceutical dosage forms. For UV spectrophotometric method ranolazine shows maximum absorbance at 273 nm with the concentration ranges of 20-150 μg/ml. The limit of detection and limit of quantification were found to be 1 and 4 μg/ml, respectively, while for reverse phase high performance liquid chromatography method, Inertsil ODS C18 column consisting of 10 cm x 4.6mm i.d., 3μ particle size in isocratic mode, with mobile phase containing buffer: acetonitrile (60:40 v/v, 1.0 ml of triethylamine in 1000ml
milli-Q water) adjusted to pH 6 using ortho phosphoric acid. The flow rate was 1.0 ml/min and the sample injection volume was 10 μl, the effluent was monitored at 224nm. The retention time was 5.09 min. The method was validated in terms of linearity, accuracy and precision. The linearity curve was found to be linear over 20-150 μg/ml. Limit of detection and limit of quantification were found to be 1 and 4 μg/ml, respectively. The RP-HPLC and UV spectroscopy methods are simple, rapid, accurate and sensitive.

Limei zhao and coworkers\(^8\) reported determination of ranolazine in human plasma by liquid chromatographic-Tandem mass spectrometric assay. The analyte and internal standard tramadol are extracted from plasma by liquid–liquid extraction using diethyl ether–dichloromethane (60:40 v/v), and separated on a Zorbax extend C\(_{18}\) column using methanol–10mM ammonium acetate (60:40 v/v, pH 4.0) at a flow of 1.0 ml/min. Detection is carried out by multiple reaction monitoring on a QtrapTM LC–MS–MS system with an electrospray ionization interface. The assay was linear over the range 10–5000 ng/ml with a limit of quantitation of 10 ng/ml and a lower limit of detection (S/N > 3) of 1 ng/ml. Intra- and inter-day precision are < 3.1% and < 2.8%, respectively, and the accuracy is in the range 96.7–101.6%. The validated method was successfully used to analyze the drug in samples of human plasma for pharmacokinetic studies. The method was flexible and requires only 50 μl of plasma, making it suitable for pharmacokinetic studies of Ranolazine.
Drug profile

Valsartan

Chemical name: (2S)-3-methyl-2-[N-({4-[2-(2H-1, 2, 3, 4-tetrazol-5-yl) phenyl] phenyl}methyl) pentanamid] butanoic acid

Molecular formula: \( C_{24}H_{29}N_{5}O_{3} \)

Description
A white or almost white, crystalline powder, practically insoluble in water, soluble in alcohol. Stored in air tight containers.

Uses
Valsartan used as antihypertensive Agents, Angiotensin II Receptor Antagonists. The drug is available commercially as conventional tablets 40, 80, and 160 mg. Trials were done to formulate valsartan as a transdermal dosage form to overcome its low oral bioavailability.

Pharmacokinetics
Valsartan is an Angiotensin II receptor antagonist used in the management of hypertension. It treats the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin1 receptor in many tissues. Valsartan is rapidly absorbed following oral administration, with a bioavailability of about 23%. It is 95% protein bound and is mostly excreted as unchanged drug via the bile. Peak plasma concentrations of valsartan occur 2 to 4 h after an oral dose.

Adverse effects
Most commonly, headache and dizziness sometimes fatigue.

Marketed products in India
Diovan, Valnet, Valzaar.
Ranolazine

Chemical name: (2S)-3-methyl-2-[N-{4-[2-(2H-1, 2, 3, 4-tetrazol-5-yl)phenyl] phenyl}methyl) pentanamido] butanoic acid

Molecular formula: $C_{24}H_{33}N_3O_4$

Description
Ranolazine is a white to off-white solid. Ranolazine is soluble in dichloromethane and methanol. Sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Uses
Ranolazine belongs to the category of Anti anginal drug. Ranolazine affects the sodium-dependent calcium channels during myocardial ischemia. Ranolazine, a novel anti-anginal agent belonging to the group of piperizine acetamide has been widely used in the treatment of cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction.

Pharmacokinetics
Ranolazine is extensively metabolized in the gut and liver and its absorption is highly variable. Oral bioavailability is in the range of 30% to 55%. Peak plasma concentrations occur between 2–5 h and the terminal half-life is approximately 7 h.

Adverse effects
Nervous system side effects include dizziness and headache. Gastrointestinal side effects include constipation, nausea and diarrhea. Respiratory side effects have included cough and dyspnea.

Marketed products in India
Caroza, cartinex, Ranexa.