2. REVIEW OF LITERATURE

2.1 LITERATURE ON LIQUISOLID COMPACTS

Tayel SA et al. improved the dissolution rate of insoluble antiepileptic drug carbamazepine, by using the liquisolid compaction (LSC) technique. Avicel PH 102, and Aerosil 200 were used as the carrier and the coating materials. Propylene glycol as non-volatile vehicle and Explotab was used as disintegrant. The prepared liquid solid tablets showed good wettability, rapid disintegration and acceptable dissolution rate comparable to the generic product64.

Amrit B. Karmarkar studied, the effect of carrier on dissolution behaviour of fenofibrate from liquisolid tablets. The LSC tablets were prepared using Avicel PH 102 and Ceolus KG-802 as carrier material. The in vitro dissolution studies showed lower dissolution rates from the formulations prepared with Ceolus KG-802 compared to those prepared with Avicel PH 102. The authors explained the lower dissolution rates were due to high compactability of Ceolus KG-80250.

Tiong N and Elkordy A investigated the effect of non-volatile vehicle used in the formulation of liquisolid tablets on the dissolution profiles of naproxen. LSC tablets were prepared with three different non-volatile vehicles, Avicel PH 102 as carrier and Aerosil 200 as coating material. The dissolution studies performed in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) without enzyme revealed that the tablets prepared with Cremophor EL at 20 % w/ w drug concentration showed faster disintegration time, superior dissolution profile and acceptable tablet properties. This results indicate the viscosity and HLB value of non-volatile vehicle plays an important role in improving the dissolution profiles of poorly water-soluble drug from liquisolid formulations65.

Javadzadeh Y et al. compared the dissolution rate of piroxicam from LSC tablets, conventional capsules and directly compressed tablets containing micronized piroxicam. LSC tablets were prepared at various ratios of drug to Tween 80. The dissolution studies in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) showed significantly higher drug release from LSC tablets compared to
conventional capsules and directly compressed tablets containing micronized piroxicam.

**Hentzsche CM et al.** compared the dissolution rate of griseofulvin from liquisolid systems, aerogel formulations and directly compressed tablets containing crystalline griseofulvin. LSC were prepared by dissolving drug in PEG 300 and adsorbing on to Neusilin. They showed higher drug release from liquisolid compacts compared to other formulations. The authors concluded that the higher dissolution rates of griseofulvin from LSC were due to presence of drug in dissolved state in the non-volatile liquid. They also observed the higher liquid adsorption capacity of Neusilin reduced the tablet weight.

**Amal Ali Elkordy et al.** studied the release profile of spironolactone from LSC prepared with Capryol 90, Solutol HS-15 and Kollicoat SR 30 D as non-volatile solvents. The prepared tablets were within quality control limit according to British pharmacopoeia. Significant improvement in drug release was observed from liquisolid tablets compared to conventional tablets and plain drug. The formulation also found to be stable after storage at high humidity for one month.

**Boushra M et al.** studied bioavailability and biological activity of repaglinide from liquisolid compacts and determined its effect on glucose tolerance in rabbits. The relative bioavailability of repaglinide was found to be increased significantly from liquisolid compacts compared to that of marketed tablet. The decrease in blood glucose was also higher with LSC formulation compared to commercial product.

**Yousef Javadzadeh et al.** reported a new approach of the liquisolid technique to sustain the release of propranolol hydrochloride from tablets. The reduction in drug release was achieved by dissolving or dispersing the drug in a solvent with low solubility and then adsorbing on to a carrier and coat material. The drug was dispersed in Tween 80 and adsorbed on to Eudragit RS and silica gel. The formulation showed higher retardation compared to matrix tablets prepared using Eudragit and silica gel matrix in 0.1N HCl and pH 6.8 buffer.

**Nokhodchi A et al.** studied the effect of co-solvent and HPMC on release of theophylline from liquisolid compacts (LSC). LSC were prepared by mixing liquid medication with silica–Eudragit RL or RS followed by the compaction of the mixture.
Drug release from LSC containing different co-solvents and different concentrations of HPMC was analysed. The results suggested that the presence of non-volatile co-solvent had significant effect on drug release. The sustained release action of HPMC was enhanced in liquisolid compacts in comparison to simple sustained release matrix tablets. The authors concluded that liquisolid compacts has a potential to produce zero-order release kinetics for less water soluble drugs such as theophylline\textsuperscript{70}.

**Hentzschel CM et al.** investigated the influence of liquid drug content on the flowability and tabletability of various liquisolid powder blends. Tocopherol acetate (TA) was used as model drug and LSC were prepared with different excipients like Avicel, Fujicalin, Neusilin as carriers and Aerosil, Florite and Neusilin as coating material. The results indicated that Fujicalin and especially Neusilin are more effective carrier materials for liquid adsorption than Avicel, which is often used for liquisolid systems. Moreover, Florite and Neusilin turned out to be more suitable as coating materials than the commonly used Aerosil due to their better tableting properties\textsuperscript{71}.

**Fahmy R et al.** prepared LSC tablets of famotidine and investigated the in vitro and in vivo performance of the prepared liquisolid tablets. The dissolution profiles of the selected famotidine liquisolid tablet formulations was compared with that of famotidine conventional, directly compressed tablets. In vivo pharmacokinetic studies were performed in human volunteers. Dissolution studies indicated complete and faster release of drug from LSC compared to conventional and directly compressed tablets. No significant differences in pharmacokinetic parameters was observed between LSC formulation and marketed famotidine tablets\textsuperscript{72}.

**Singh S et al.** formulated glyburide liquisolid tablets and studied the influence of formulation parameters like type of non-volatile liquid vehicles and drug concentrations, on dissolution rates of glyburide from LSC. The liquisolid tablets were formulated with Propylene glycol, as liquid vehicle. Microcrystalline cellulose was used as a carrier material, silica as a coating material and croscaremelleose as a disintegrant. In vitro drug dissolution profiles of the liquisolid formulations were studied and compared with direct compressed non-micronized and micronized tablets of glyburide. The liquisolid tablets prepared with PVP showed a remarkably improved dissolution rate in comparison with DC tablet and other formulations. The authors
concluded that it is possible to load poorly soluble drug into liquisolid tablets by addition of PVP to the liquid vehicle\textsuperscript{73}.

**Vittal GV et al.** prepared liquisolid compacts for dissolution improvement of ketoprofen. Optimization was performed using Box-Behnken design by selecting liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables; cumulative percentage drug release and angle of repose were considered as dependent variables. The optimized formulation yielded the response values, which were very close to the predicted values. Dissolution profiles indicated improvement in dissolution of ketoprofen from LSC compared to plain drug. The accelerated stability studies conducted showed that liquisolid tablets were not affected by ageing and there were no appreciable changes in the drug content\textsuperscript{74}.

**Khanfar M et al.** discussed the effect of formulation factors on the release of ezetimibe from different liquisolid compacts. Four liquid vehicles were used to prepare different LSC formulations. The dissolution studies showed that the dissolution rate was affected by the drug concentration, solubility of the drug in the liquid vehicle and type of carrier. In addition, authors also showed, the presence of the liquid vehicle has been found to affect the mechanical properties of the liquisolid formulations\textsuperscript{75}.

### 2.2 LITERATURE ON SOLID DISPERSIONS

**Win Loung Chiou and Sidney Riegelman** discussed the application of solid dispersion (SD) in pharmacy. They explained the historical background of the SD development along with the definition given by Mayersohn and Gibaldi. They also discussed about classification, different types of SDs and their manufacturing procedure in detail along with carrier materials used in the preparation of SDs\textsuperscript{56}.

**Win Loung Chiou** prepared chloramphenicol SDs using urea. He studied phase diagrams of chloramphenicol and urea and confirmed the formation of eutectic mixture rather than SD with the help of thermal analysis and X-ray diffraction (XRD) studies. The results showed improvement in the dissolution of chloramphenicol due to change in particle size of chloramphenicol crystals\textsuperscript{76}.
Hu L et al. compared the physical characters and dissolution profile of cilnidipine from SD formulations prepared using polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP) and Poloxamer. The interactions in the solid state were characterized by differential scanning calorimetry (DSC), XRD and Fourier transform infrared spectroscopy (FT-IR). Significant improvement in the dissolution rate of cilnidipine was observed from prepared SD compared to plain drug and its corresponding physical mixture. However, PEG solid dispersions showed the best results both on physical characterizations and dissolution studies.

Stavchansky S and Gowan WG studied the formulation of phenytoin SD in polyethylene glycol 6000 and compared the bioavailability of prepared SD with the commercial phenytoin sodium capsule in dogs. They observed that the prepared solid dispersion was bioequivalent to the commercial formulations available.

Shah N et al. discussed about the use of hypromellose acetate succinate (HPMCAS), as carrier in the formulation of vemurafenib amorphous SD by solvent-controlled precipitation process. The final product obtained was termed micro precipitated bulk powder (MBP). The improvement in the solubility of crystalline drug by 30-folds from SD indicates HPMCAS was most suitable polymer for preparing vemurafenib MBP.

Shailendra Kumar Singh et al. prepared clopidogrel SD with the hydrophilic carrier PEG 6000 at different ratios. A statistical design at two factor and three level was employed to quantify the influence of PEG 6000 concentration on the dissolution profile of clopidogrel from the SDs. Significant improvement in the dissolution rate and solubility of clopidogrel was observed from SD compared to plain drug.

Macheras PE and Reppas CI prepared SDs of dicumarol and sulfamethizole in defatted milk prepared by freeze-drying. XRD and DSC data showed that both drugs were dispersed in the formulations in amorphous state. Bioavailability studies conducted in four male volunteers showed significant differences in pharmacokinetic parameters compared to plain drug indicating superiority of the dicumarol-milk formulations.

Chiba Y et al. showed improvement in the dissolution rate and bioavailability of mebendazole from SDs prepared with PEG 6000 compared to the physical mixtures.
and plain drug after oral administration in rabbits. The dissolution rate of mebendazole was increased with the increasing amount of PEG 6000 in SD\textsuperscript{82}.

Ozdemir N and Ordu S discussed the effect of carrier properties on the dissolution of furosemide from SDs prepared using different grades of PEG (6000, 10,000 and 20,000). Stability of the complex formed and effect of particle size on dissolution rate of the drug were also studied. The studies showed that the molecular weights of different PEGs and the various proportions of active material/polymer complexes as well as the particle size of the SDs were not significant in the release rate of active material. The increase of the dissolution rate of drug was being a result of both wettability and solubility enhancing effects of PEG\textsuperscript{83}.

Koh PT et al. prepared ternary SDs of efavirenz using PEG 8000, PVP K30 alone and in combination by different methods. Tween 80 was incorporated to obtain a ternary SD system. The results showed significant (P < 0.05) improvement in dissolution rate of drug with both binary and ternary SD compared to plain drug. No significant difference (P > 0.05) was observed in dissolution of dispersions prepared by the two methods. The physicochemical characterization studies suggested that efavirenz exists in the amorphous form in all the solid dispersions\textsuperscript{84}.

Vyas V et al. studied the dissolution behaviour of a poorly water-soluble drug, tadalafil, from SDs prepared with Poloxamer 407 at different carrier to drug ratios. Dissolution results indicated preparations containing 1:0.5 proportion of tadalafil / Poloxamer 407 showed rapid dissolution of drug. No significant improvement was observed with higher concentration of Poloxamer. This was attributed to the altered rheological characteristics of the polymer at its higher concentration, which might have retarded the release rate of tadalafil\textsuperscript{85}.

Caroline Goddeeris and Guy Van den Mooter discussed, the effect of carrier physicochemical characteristics on dissolution behaviour of anti-HIV drug UC 781 in SD of Poloxamer 407 and TPGS 1000. The formulation containing TPGS 1000 / Poloxamer 407 in 80/20ratio showed better flow properties and improvement in drug release compared to plain drug\textsuperscript{86}.

Waghmare A et al. developed SDs using different hydrophilic polymers to improve the dissolution rate of zaleplon. SDs and physical mixtures of zaleplon were prepared
with Poloxamer F68, PVP K30, and PEG 6000 each at 1:1, 1:3 and 1:5 ratios. No significant difference in dissolution rate was observed among the polymers used when compared statistically. However, the analysis of drug release in terms of dissolution efficiency from different polymers showed following order (Poloxamer F68 (1:5) SD > PVP K30 (1:5) SD > PEG 6000 (1:3) SD)\(^87\).

2.2.1 Literature on Gelucire based dispersions

**Dhumal RS et al.** studied the formulation of cefuroxime axetil (CA) SD in Gelucire 50/13, Aerosil 200 and PVP prepared by spray drying process. They compared solubility and bioavailability of both formulations with that of amorphous CA produced by spray drying the drug alone. The results indicated improvement in the bioavailability of CA from SD containing Gelucire 50/13 compared to SD containing PVP and amorphous CA\(^88\).

**Faisal W et al.** formulated a novel lipid (Gelucire 44/14) based SDs to improve the dissolution and thereby bioavailability of poorly soluble drug lycopene. SDs were prepared by solvent evaporation method. Bioavailability studies conducted in female landrace pigs showed marked increase in the absorption and bioavailability of lycopene from SDs in comparison to marketed formulation\(^89\).

**Fini et al.** prepared SDs of diclofenac and its N-(2-hydroxyethyl) pyrrolidine salt with PEG 6000 and Gelucire 50/13. The authors used different analytical tools to elucidate the structure of the dispersion and to detect possible drug/carrier interactions. The results indicate no chemical decomposition of the drug and excipient, showing compatibility and formation of homogeneous systems up to 10 % w/w composition. The dissolution studies showed a better solubilization of diclofenac and its salt form in PEG than Gelucire 50/13\(^90\).

**Potluri RH et al.** showed improvement in solubility of carvedilol from Gelucire 50/13 based SDs. Carvedilol solubility was increased linearly with increasing concentration of Gelucire 50/13. The improvement in solubility was attributed to change in crystalline form of drug to amorphous form as confirmed by scanning electron micrographs (SEM) and XRD studies\(^91\).
Elbadry M et al. discussed the formulation of SDs to improve the solubility and dissolution of indomethacin using Gelucire 50/13 and PEG 4000 by melt method. About 3.5 and 4 folds of improvement in dissolution rate of indomethacin was observed at pH 1.2 and 7.4 from SDs prepared in PEG and Gelucire (at 1:4 ratio) compared to pure drug and physical mixture. 

EL-Badry M prepared meloxicam SD in Gelucire 50/13 by spray drying method and evaluated anti-inflammatory activity of resulting dispersion using rat paw model. SD showed 2.5-fold higher dissolution rate compared to corresponding physical mixture and 4 fold higher dissolution rates compared to plain drug in phosphate buffer pH 7.4. SDs also exhibited a 4-fold higher anti-inflammatory activity on the paw oedema of rats in comparison to the plain drug.

2.2.2 Literature on solid dispersions prepared with adsorbent

Donald CM and Lach JL discussed the use of adsorbents in enhancing the dissolution of insoluble drugs. The study was performed using a series of insoluble drugs. They concluded that, the increase in dissolution rate was accomplished by equilibration of the drug in an organic solvent (acetone) on an insoluble excipient with an extensive surface (fumed silicon dioxide).

Komal RP et al. investigated the use of SDs technology combined with surface adsorption in improving the dissolution of a poorly soluble drug ezetimibe. PEG (4000, 6000), Gelucire 44/14 were used as hydrophilic carriers and lactose as surface adsorbent. Phase solubility studies revealed linear relationship between drug solubility and carrier concentrations. Dissolution studies showed an improvement in drug release from prepared formulations compared to plain drug. The release mechanism was best described by the Korsmeyer–Peppas model, with Fickian diffusion as the possible drug-release mechanism.

Gupta MK et al. reported improvement in the dissolution rate of BAY 12-9566 by combining SD and surface adsorption techniques. The drug was dispersed in molten mass of Gelucire 50/13 and adsorbed on to the Neusilin US2 (magnesium alumino silicate). The flow and compressibility properties of dispersion granules were improved significantly when compared to the drug alone or the corresponding
physical mixture. The dispersion granules were compressed easily into tablets with up to 30% w/w drug loading.

**Pranav V. Patelet al.** reported improvement in the dissolution rate of sirolimus by SDs in combination with surface adsorbent. The combination of melt and adsorption techniques employed for the preparation of SDs resulted in free-flowing final product. All prepared SDs showed significant improvement in dissolution compared to plain drug.

### 2.2.3 Literature on Eudragit solid dispersions

**Janssens S et al.** formulated amorphous itaconazole SDs with Eudragit E100 by spray drying and film casting method. The authors also evaluated for drug, polymer miscibility level by both the process. The experimental miscibility level was found to be 27.5 % w/w, 15 % w/w for spray drying and film casting respectively indicating considerable degree of super saturation below Tg.

**He H et al.** compared the *in vitro* and *in vivo* performance of fenofibrate SDs in Eudragit E 100 and polyvinylpyrrolidone-vinyl acetate (PVP-VA) copolymer S630 prepared by hot melt extrusion. Fenofibrate was found to be present in amorphous form in both dispersions. Eudragit SDs showed better dissolution compared to PVP-VA dispersions in both the dissolution media. The difference in dissolution was related to difference in polymer solubility and gelling tendency in the given solvents. The relative bioavailability of fenofibrate was found to be 177 % from Eudragit dispersion (1:4) compared to commercial marketed product.

**Huiju Liu et al.** prepared SDs of indomethacin in Eudragit EPO and evaluated effects of extrusion process parameters like set mixer temperature, screw rotating speed and residence time on the drug–polymer mixing. The results indicated that the dissolution rate can be enhanced by increasing set temperature and screw rotating speed. The results also showed that the dissolution of drugs in polymeric melt is a convective diffusion process.

**Kojima T et al.** evaluated the stabilization mechanism of a supersaturated solution of mefenamic acid (MFA) from SDs prepared with Eudragit EPO. The prepared SD was characterized by FTIR, XRD, and NMR spectroscopy, *in vitro* dissolution test and *in*
vivo oral absorption study. The dissolution in acetate buffer (pH 5.5) showed > 200-fold higher concentration of MFA from SD compared to plain drug. Supersaturated solution was stable over 1 month and exhibited 7.8 fold higher AUC and improved oral bioavailability in rats. The NMR studies revealed that MFA was almost mono molecularly dispersed in the EPO polymer matrix\textsuperscript{101}.

\textbf{Feng Jet al.} studied the oral bioavailability of SDs containing bifendate in different polymers. Bifendate SDs were prepared in Plasdone S-630, Eudragit EPO and Kollidon VA 64 by hot melt extrusion. The oral bioavailability of three SDs were compared with that of commercially available bifendate pills. The relative bioavailability of bifendate was found to be 110 ± 62\% from Eudragit EPO dispersion compared to commercial pills\textsuperscript{102}.

2.3 LITERATURE ON VALSARTAN

\textbf{Nam Sung HA et al.} discussed the use of pH modifiers to improve the dissolution of poorly soluble ionisable drugs like valsartan and aceclofenac. SDs were prepared in Poloxamer with different alkalizers by melt method. The drug release from SD containing sodium carbonate was found to be drastically increased compared to plain drug and commercial product\textsuperscript{103}.

\textbf{Cao QR et al.} developed novel mucoadhesive pellets for improving the bioavailability of valsartan by dry powder coating technique. The studies revealed that, the use of solubilizer and pH modulator in the pellet preparation gave considerably faster drug release than the valsartan plain drug. No significant difference in the release rate was observed by coating the pellets with HPMC and carbomer at different ratios. However, coated pellets showed high AUC and \textit{C}_{\text{max}} compared to core pellets and valsartan suspension due to better mucoadhesion property \textit{in vivo} and delayed GI transit\textsuperscript{104}.

\textbf{Ahad A et al.} prepared nano transferosomes of valsartan for improved transdermal delivery and compared skin permeation with conventional liposomes. Optimization of formulation was carried out using experimental design. The drug permeation through skin was increased by 34 \% from nano transferosomes compared to rigid liposomes. \textit{In vivo} antihypertensive activity conducted in rats also showed better activity in comparison to liposomes due to increased permeation of drug\textsuperscript{105}.
Yan YD et al. reported improvement in the bioavailability of valsartan from novel SDs prepared using HPMC and SLS. The prepared dispersions were found to have relatively rough surface with no change in crystalline form of the drug. Improvement in the dissolution rate was due to change in hydrophobic surface of the drug to hydrophilic by the attachment of hydrophilic molecules. The solubility was improved by 43 folds compared to plain drug and bioavailability was improved by 2.2 and 1.7 folds compared to valsartan powder and the commercial product, respectively.

Dixit AR et al. prepared self-micro emulsion of valsartan and estimated its oral bioavailability in rabbits. Valsartan SMEDDS was prepared using Capmul MCM (oil), Tween 80 (surfactant) and polyethylene glycol 400 (co-surfactant). The particle size, size distribution and zeta potential were found to be 12.3 nm, 0.138 and −0.746 mv, respectively. Valsartan SMEDDS showed maximum drug release when measured by in vitro dialysis bag method using phosphate buffer pH 6.8 compared to plain drug and marketed formulation with significant improvement in the bioavailability.

Tapas AR et al. reported improvement in the solubility and dissolution rate of valsartan by spherically agglomerated SDs. Solid dispersions were prepared using methanol, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The prepared agglomerated SDs with different polymers exhibited marked increase in solubility, dissolution rate and micrometric properties (bulk density, flow property, compactability) compared to valsartan plain drug.

Ibrahim HK et al. formulated and characterized valsartan orodispersible tablets by freeze-drying technique. The optimization of the procedure was done using 3³ full factorial design. The oral bioavailability of prepared dispersible tablets was compared to the marketed tablets after single dose administration to four healthy volunteers. The relative bioavailability calculated as the ratio of mean total area under the plasma concentration–time curve for the orodispersible tablets relative to the conventional tablets was found to be 135%.

Soakar MS et al. designed pulsatile core-in-cup valsartan tablets by direct compression of homogenous mixture containing valsartan, Avicel PH-101, croscarmellose sodium, magnesium stearate and Aerosil. The floating behaviour,
water uptake and drug release from the prepared formulations were evaluated. The lag time can be changed based on the plug material and polymer concentration\textsuperscript{110}.

**Poudel BK et al.** investigated the interaction and the quadratic effects of formulation variables on the performance of self-microemulsifying drug delivery system (SMEDDS) of valsartan using design of experiment. Box-Behnken design (BBD) with 3-factors and 3-levels, including 5 replicates at the centre point, was used for fitting a 2nd-order response surface. The dependent factors (responses) were particle size, polydispersity index, dissolution after 15 min and equilibrium solubility. The results demonstrated marked main and interaction effects of independent factors on responses. The optimized formulation showed average micelle size of 90.7 nm and 0.246 PDI, 91.2% dissolution after 15 min and 226.7 mg/g equilibrium solubility. The optimized formulation gave more than 2-fold higher area under curve (AUC) and about 6-fold higher $C_{\text{max}}$ in rats than valsartan powder ($p<0.05$)\textsuperscript{111}.

**Beg S et al.** prepared solid self-nanoemulsifying drug delivery systems (SNEDDS) of valsartan using porous carriers by response surface methodology employing $3^3$-Box–Behnken design. SNEDDS were prepared using blends of oil (Capmul MCM), surfactant (Labrasol), and cosurfactant (Tween 20). Optimized liquid SNEDDS were formulated into free flowing granules by adsorption on the porous carriers like Aerosil 200, Sylysia (350, 550, and 730) and Neusilin US2, and compressed into tablets. In vitro dissolution studies of S-SNEDDS revealed 3–3.5-fold increase in dissolution rate of the drug due to enhanced solubility. In vivo pharmacodynamic studies showed significant reduction in mean systolic BP by S-SNEDDS vis-à-vis oral suspension ($p < 0.05$) owing to the drug absorption through lymphatic pathways\textsuperscript{112}.

**Pardeshi CV et al.** formulated HPMC-based spray-dried mucoadhesive microspheres for intranasal delivery of valsartan. A $2^3$-factorial design was used for the assessment of influence of three independent variables, namely inlet temperature, feed-flow rate and drug-polymer ratio on production yield, particle size and in vitro drug diffusion. The prepared formulations showed good mucoadhesion with no severe sign of damage on nasal mucosa. In vivo animal studies in dexamethasone-induced hypertensive rat model suggested the suitability of developed formulations for intranasal administration\textsuperscript{113}.  

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2.4 LITERATURE ON TELMISARTAN

Tran PH et al. investigated the potential of self-assembled gelatin–oleic acid (GO) nanoparticles for solubility improvement and controlled release of poorly soluble drugs like telmisartan, valsartan and aceclofenac. The particle size of the drug-loaded nanoparticles was in the range of 200–250 nm. Formulations containing nanoparticles showed enhanced solubility compared to plain drug and further the release profiles of the model drugs were modified in a controlled manner\textsuperscript{114}.

Cho HJ et al. developed self-microemulsifying drug delivery system (SMEDDS) for enhanced water solubility and bioavailability of telmisartan using the Box-Behnken design. The formulation consisted of the mixture of oil (Peceol), surfactant (Labrasol), co-surfactant (Transcutol), drug and triethanolamine. A three-level experimental design was applied to explore the main effect, interaction effect and quadratic effect of three independent variables, including the amount of Peceol (X1), Labrasol (X2) and Transcutol (X3). The actual values from the optimized formulation showed good agreement with predicted values. The optimized telmisartan SMEDDS formulation showed faster drug dissolution and higher bioavailability compared to telmisartan pure drug\textsuperscript{115}.

Tran PH et al. discussed about the modulation of micro environmental pH and crystallinity of anionizable drug telmisartan to enhance the dissolution rate using alkalizers in solid dispersions. Dissolution rate of telmisartan was improved in presence of alkalizers and structural change in drug crystallinity to an amorphous form was further contributed to the enhanced dissolution of telmisartan from solid dispersion formulations\textsuperscript{116}.

Sangwai M and Vavia P showed, significant enhancement in the solubility and reduced pharmacokinetic variability of telmisartan from amorphous ternary cyclodextrin nanocomposites. They have combined both the techniques namely ternary β-cyclodextrin complexation and top-down nanonization in a unit process. In vitro dissolution studies showed significant improvement in drug release compared to plain drug and marketed formulation. In vivo studies conducted in male Wistar rats showed reduced variability among pharmacokinetic parameters at fed and
fasted states with significant improvement in the bioavailability compared to plain drug and marketed formulation\textsuperscript{117}.

\textbf{Lepek P et al.} studied the effect of melt quench technique and cryogenic grinding method on the amorphization of telmisartan, its solubility, compression process and on the stability of the amorphous form compared to crystalline form of telmisartan. The solubility of telmisartan prepared by both techniques showed enhancement in solubility compared to their crystalline counterpart. The compression process functioned much better with the tablet blends made from the amorphous form of telmisartan\textsuperscript{118}.

\textbf{Vasanthakumar S and Chellan VR} investigated, the use of super disintegrants in the preparation of telmisartan IR tablets and evaluated stability of prepared formulations according to ICH guidelines. The results showed improvement in the dissolution of telmisartan from tablets containing Polyplasdone XL-10 as super disintegrant. No significant difference in dissolution profile was found between initial and six months stored samples\textsuperscript{119}.

\textbf{Londhe, VY and Umalkar, KB} prepared a fast dissolving film containing telmisartan to improve the onset of action, therapeutic efficacy, patient compliance and convenience. Fast dissolving films were formulated using hydroxypropyl methylcellulose, polyvinyl alcohol, glycerol, sorbitol, menthol and an alkalizer by solvent casting method. The prepared films showed improved dissolution profile along with elegant appearance and other physical characteristics like tensile strength, \% elongation, folding endurance\textsuperscript{120}.

\textbf{Patel B et al.} reported enhancement in dissolution of telmisartan by formulating surface solid dispersion (SSD) using polymers like Poloxamer 407, PEG 6000 by solvent evaporation method. A $2^2$ full factorial design was used to investigate for each carrier the joint influence of formulation variables. The drug was solubilized by surfactants and/or polymers then adsorbed onto the surface of extremely fine carriers to increase its surface area and to form the SSD which give the more surface area for absorption of the drug\textsuperscript{121}.

\textbf{Bansode SD et al.} formulated telmisartan microspheres by emulsion solvent evaporation technique. Microparticles were prepared with ethyl cellulose as polymer
and poly vinyl alcohol as stabilizer. The authors also studied the effect of polymer concentration on the drug loading and drug release from microspheres. The selected method produced hollow microspheres that showed floating time up to 10 hrs with constant and prolonged drug release\textsuperscript{122}.

**Chauhan K et al.** prepared fast dissolving tablets of telmisartan by using crosscarmellose sodium, Doshion, sodium starch glycolate as super disintegrants to increase the dissolution rate and hence its bioavailability. The tablets were prepared by Direct Compression methods and the prepared blend and tablets were evaluated for their physicochemical properties and in-vitro dissolution study. The prepared tablets showed improved disintegration time and wetting and enhanced dissolution rate compared to pure telmisartan\textsuperscript{123}.

### 2.5 LITERATURE ON VALSARTAN ANALYTICAL METHODS

**Gupta et al.** described analysis of valsartan in bulk drugs and tablets. The standard and samples were dissolved in methanol, and the determination of analytes in samples was performed by comparing with standards and value of A (1%, 1 cm). Comparison with standards was performed by using two methods, i.e., zero-order absorption (at 250 nm) and second-order spectra (at 241 nm). Calibration ranges were linear in the range of 10–50μg/mL ($r^2 = 0.999$). Recovery studies were in the range of 99.08–100.31%. A statistical evaluation showed no significant difference among three methods of estimation\textsuperscript{124}.

**Tatar S and Saglik** developed a UV spectroscopic and high-performance liquid chromatographic methods for the determination of valsartan in pharmaceutical formulations. The authors showed that valsartan exhibits maximum absorbance at 205.6 nm in UV absorption spectra with linearity in the range of 2.0–10.0 μg/ ml in ethanol. Limit of detection and limit of quantitation were 0.5 and 2 μg/ ml, respectively. HPLC separation of valsartan was performed on C18 column by isocratic system using mixture of 45% acetonitrile and 55% phosphate buffer solution (pH 2.7) as mobile phase at a flow rate 1.3 ml/ min. Detection was at 265 nm and retention times were 6.14. Limit of detection and limit of quantitation were 0.2 and 1 μg/ ml, respectively\textsuperscript{125}. 

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Dinc et al. reported two simultaneous spectrophotometric determination of valsartan and hydrochlorothiazide in tablets. The first method applied ratio derivative method. In this case, first amplitude derivate were at $\lambda$ 231.5 and 260.5 nm (valsartan) and 270.6 nm (hydrochlorothiazide). Mean recover for valsartan was 100.4% (RSD = 1.76%). Second method applied inverse least square absorbance matrix of zero-order spectra in the range of 225–280 nm ($\Delta\lambda =$ 5 nm, at 12 wavelengths). Spectra were measured in various binary mixtures; in this case, recovery of valsartan was 101.2% (RSD = 1.58%)\textsuperscript{126}.

Akiful Haque et al. developed stability indicating HPLC method for estimation of valsartan in tablet dosage form. Valsartan was estimated using a C18 column, methanol & phosphate buffer pH 3.0 in ratio of 65:35(v/v) as mobile phase at a flow rate of 1 ml/min. The effluent was monitored at 210 nm. Retention time was found to be 6.22 min. The minimum concentration level at which the analyte can be reliably detected & quantified were found to be 0.02 & 0.06 $\mu$g/ml respectively\textsuperscript{127}.

Subhajit Ghanty et al. developed a RP- HPLC method for the estimation of valsartan in solid dosage form. The chromatographic separation of valsartan was achieved using ODS C18 column, mobile phase containing acetate buffer (pH4.6): acetonitrile: methanol in (38:24:38 %, v/v) ratio at a flow rate of 1.2 ml/min. Valsartan was analyzed at 248 nm and the retention time of valsartan was found to be 4.6±0.06 min. Linearity was detected in the concentration range of 10-30 $\mu$g/ml. Limit of detection and limit of quantitation were 0.17 and 0.56 $\mu$g/ ml, respectively\textsuperscript{128}.

Kepekci Tekkeli SE reported an HPLC-UV method for the analysis of drugs used for combined hypertension therapy in pharmaceutical preparations and human plasma. The separation was achieved by using an RP-CN column, and acetonitrile-methanol-10 mmol orthophosphoric acid pH 2.5 (7:13: 80, v/v/v) as a mobile phase. The detector wavelength was set at 235 nm. Linearity for valsartan was reported in the range of 0.3–15.5 $\mu$g/ml and the authors showed that the developed method was reproducible and accurate with relative standard deviation (RSD) $\leq$ 6.9% and relative mean error (RME) $\leq$ 6.5%\textsuperscript{129}.

Imam S et al. Reported a RP-HPLC method for simultaneous determination of propranolol and valsartan in bulk drug and gel formulation. The separation was
achieved on Hypersil ODS C-18 column (250*4.6 mm, i.d., 5 μm particle size) with isocratic flow with UV detector. The mobile phase at a flow rate of 1.0 mL/min consisted of acetonitrile, methanol, and 0.01 M disodium hydrogen phosphate (pH 3.5) in the ratio of 50:35:15 v/v. A linear response was observed over the concentration range 5-50 μg/mL of propranolol and the concentration range 4-32 μg/mL of valsartan. Limit of detection and limit of quantitation for propranolol were 0.27 μg/mL and 0.85 μg/mL, and for valsartan were 0.45 μg/mL and 1.39 μg/mL, respectively. The authors concluded that the method was selective for simultaneous estimation of propranolol and valsartan can be potentially used for the estimation of these drugs in combined dosage form.\textsuperscript{130}

**Galande VR et al.** discussed about simultaneous UV spectrophotometric method for the estimation of amlodipine besylate, valsartan and hydrochlorothiazide in combination in bulk mixture and tablet. Method was validated according to ICH guidelines with respect to specificity, linearity, range, accuracy, precision, LOD, LOQ, robustness, ruggedness and can be applied for routine analysis of tablet dosage forms. Valsartan was estimated at a wavelength of 250 nm. Beer Lambert's law obeyed in the concentration range of 5-25 μg/ml. The validation of method with reference to all above parameters showed % RSD less than 2% with LOD 1.57 μg/ml and LOQ 4.77 μg/ml for valsartan. The method was found to be simple, accurate, precise, economic and specific for determination and quantitation of these drugs in bulk mixture and tablet formulation\textsuperscript{131}.

**Afshin Zarghi et al.** developed a rapid high-performance liquid chromatographic (HPLC) method using a monolithic column for determination of valsartan in human plasma. The assay was based on protein precipitation using acetonitrile and fluorescence detection. The separation was carried out in reversed phase conditions using a Chromolith Performance (RP-18e, 100×4.6 mm) column, an isocratic mobile phase consisting of 0.01 M disodium hydrogen phosphate buffer-acetonitrile (60:40 v/v) adjusted to pH 3.5. The excitation and emission wavelengths were set at 230 and 295 nm, respectively. Linearity was observed over the concentration range 20-2000 ng/ml. The coefficients of variation for inter-day and intra-day assay were found to be less than 6%. The method was successfully developed and applied for analysis of biological samples in pharmacokinetic valsartan research\textsuperscript{132}.
Daneshtalab N et al. developed an easy assay for the quantitation of the angiotensin II receptor antagonist valsartan in human plasma using a liquid extraction procedure. An isocratic HPLC equipped with reverse phase column and a fluorescence detector was used at room temperature. The method involves acid extraction from 1 ml human plasma with methyl-tert-butyl ether followed by back-extraction into a basic medium. Linearity was observed in the range of 10–2000 ng / ml. The method was found to be suitable for pharmacokinetic studies of valsartan.

Dixit R et al. reported an HPLC method for determination of valsartan from rat plasma samples to determine the oral bioavailability of valsartan from SMEDDS formulation. Methanol was used for protein precipitation and extraction of drug from the plasma samples. Losartan potassium was used as internal standard. HPLC analysis was performed on a reverse-phase C-18 column (250 × 4.6 mm, 5 μm, Hypersil BDS) triethylamine buffer (pH adjusted 3.0 with orthophosphoric acid) and acetonitrile with ratio of 60:40 pumped at a flow rate of 0.7 mL/min. The column temperature was kept at 25°C. The detector was set at 215 nm.

Yan YD et al. reported a HPLC method for pharmacokinetic determination of valsartan from solid dispersion formulations. Valsartan from plasma samples was analyzed by HPLC equipped with an Inertsil ODS-3 C18 column and a UV detector. The mobile phase consisted of acetonitrile and distilled water (6:4, volume ratio), and the pH was adjusted to pH 3.0 with 10% phosphoric acid. The effluent was monitored at a UV absorption wavelength of 247 nm and a flow rate of 1.0 ml/min.

Ibrahim HK et al. discussed an analytical method based on HPLC for determining valsartan from human plasma samples for pharmacokinetic determination of drug from orodispersible tablets. A thermo BDS hypersil C18 column and a mobile phase consisting of 0.02 M phosphate buffer (pH3.2): acetonitrile (55:45v/v) mixture were used. The flow rate was 1 ml/min, and the effluent was monitored at 225 nm using an ultraviolet visible detector. Diclofenac sodium was used as an internal standard.

2.6 LITERATURE ON TELMISARTAN ANALYTICAL METHODS

Palled MS et al. developed a difference spectrophotometric method for the estimation of telmisartan in bulk drug and in pharmaceutical formulations. Telmisartan exists in two different forms in acidic and basic mediums that differ in their UV spectra.
Difference spectrum, obtained by keeping telmisartan in 0.01 N NaOH in reference cell and telmisartan in 0.01 N HNO₃ in sample cell, showed two characteristic peaks at 295 and 327 nm with positive and negative absorbance, respectively. Difference of absorbance between these two maxima was calculated to find out the amplitude, which was plotted against concentration. The method was found to be linear in the range of 2–12 μg/ml\(^{134}\).

**Tatane S** has developed a UV spectrophotometric (\(A_{\text{max}}\)) method for determination of telmisartan in tablet formulation. The wavelength (\(\lambda_{\text{max}}\)) selected for the telmisartan was 230 nm. The linearity was observed in the range of 1-8 μg/ml. Beer’s law was obeyed in this concentration range with correlation coefficient of 0.999\(^{135}\).

**Ajit Pandey et al.** developed and validated a simple, precise, and accurate UV spectrophotometric method for the estimation of telmisartan in bulk and tablet dosage form. The zero-order spectra of telmisartan in 0.1 N NaOH shows \(\lambda_{\text{max}}\) at 234.0 nm and estimation was carried out by (\(A_{1%_{\text{cm}}}\)) and by comparison with standard. Calibration graph was found to be linear (\(r^2 = 0.999\)) over the concentration range of 4–24 μg/ml\(^{136}\).

**Sunil Singh et al.** developed UV first derivative spectrophotometric methods for the determination of telmisartan in pharmaceutical formulation. They prepared the solutions of standard and sample in 0.1 M sodium hydroxide. They carried in the UV spectrophotometric method, the quantitative determination of the drug at 295 nm, and they found the linearity range to be 4–20 μg/ml. They were determined the drug at 311 nm for the first-order derivative spectrophotometric method, with the linearity ranges of 4–20 μg/ml\(^{137}\).

**Qin Z et al.** developed new method for the estimation of based on the formation of red colored chromogen when it is reacted with congo red in presence of buffer solution in pH 2.50 HCl–NaAc, which has the maximum absorbance at 593 nm in the spectrophotometric experiment. Under this wavelength, the Beer’s law was obeyed within the concentration range of \(1.08 \times 10^{-6} – 2.24 \times 10^{-5}\) M. The linear regression equation was \(A = -0.1913 \times 10^{5}c + 0.0286\) (C:M). The regression coefficient \(r\) was 0.9986. The apparent molar coefficient \(\varepsilon_{593}\) was \(1.63 \times 10^{4}\) l/mol/cm and the detection limit was \(5.66 \times 10^{-7}\) M\(^{138}\).
Gonzalez L et al. optimized a capillary zone electrophoretic method for the separation of telmisartan and four other ARA-IIs (losartan, irbesartan, valsartan, and eprosartan) and their metabolites by means of experimental design methodologies. Successful results were obtained with a 50 mM potassium dihydrogen phosphate:boric acid (25:75, v/v) buffer at pH 5.5 in the presence of 5% methanol and application of a 25 kV voltage. Analysis time was 8 min in a conventional fused-silica capillary (50 cm effective length) in a normal cationic mode (anode at the inlet and cathode at the outlet) after hydrostatical sample injection for 30 s\textsuperscript{139}.

Aniruddha Chabukswar et al. described an HPTLC method for the simultaneous determination of telmisartan and amlodipine besylate from tablet dosage form. This employs a precoated silica gel 60 F 254 (0.2 mm thickness) on aluminium sheets and a mobile phase ethyl acetate:1,4 dioxane:methanol:25% ammonia in the ratio of 15:1.5:3:1.5 (v/v), having chamber saturation for 30 min at room temperature. The developing chamber was run up to 8 cm. The Rf values were found to be 0.16 and 0.33 for telmisartan and amlodipine, respectively. The plates were scanned and quantified at 323 nm. The linear detector response was observed between 100–500 μg/ml and 200–1000 μg/ml for telmisartan and amlodipine, respectively. The method so developed was validated for its accuracy and precision. The LOD and LOQ were found to be 0.025, 0.0747 μg/ml and 0.0236, 0.0714 μg/ml, respectively, for telmisartan and amlodipine\textsuperscript{140}.

Sujana K et al. developed and validated a simple, selective, precise, and stability-indicating reverse phase high-performance liquid chromatographic (RP-HPLC) method of an analysis of telmisartan in pure and pharmaceutical dosage form. The chromatographic conditions comprised of a reversed phase C8 column, with a mobile phase composed of buffer and methanol (40:60, v/v, adjusted the pH to 3.0 with ortho phosphoric acid). Flow rate was 0.5 ml/min, detection was carried out at 230 nm. The retention time of telmisartan was 2.6 min. The linear regression analysis data for the calibration plots showed good linear relationship in the concentration range of 20–100μg/ml. The values of correlation coefficient, slope, and intercept were 0.9998, 2.326, and -6.708, respectively\textsuperscript{141}.

Wankhede S et al. described a validated RP-HPLC method for simultaneous estimation of telmisartan and hydrochlorothiazide in tablet formulation.
Chromatography was performed on an ODS Hypersil C18 (25 cm×4.6 mm I.D.) column in isocratic mode with mobile phase containing acetonitrile:0.05 M KH2PO4, pH 3.0 (60:40). The flow rate was 1.0 ml/min and the eluent was monitored at 271 nm. The selected chromatographic conditions were found to effectively separate telmisartan (RT: 5.19 min) and hydrochlorothiazide (RT: 2.97 min). Linearity for telmisartan and hydrochlorothiazide were found in the range of 4.1–20.48 and 1.28–6.4 μg/ml, respectively. The proposed method was found to be accurate, precise, reproducible, and specific and can be used for simultaneous analysis of these drugs in tablet formulation\textsuperscript{142}.

**Charde MS et al.** developed and validated a simple, rapid, precise, sensitive, and reproducible RP-HPLC method for determination of telmisartan in tablet dosage form. Chromatographic separation was achieved on a 250×4.6 mm, 5 μm, Waters symmetry column in gradient mode, with mobile phase consisting of a mixture of solution (10 mM potassium dihydrogen phosphate, pH 3.5±0.01):acetonitrile (64:40). The quantitation performed at flow rate of 1.0 ml/min at 230 nm and run time was 12 min. The analytical method was validated as per ICH guideline for linearity, accuracy, precision, specificity, limit of detection limit of quantification, robustness, and stability, and method can be extended to the analysis of telmisartan in tablet formulations. The relative standard deviation values for precision was less than 2%, and % recovery was greater than 98% for telmisartan\textsuperscript{143}.

**Li et al.** developed a rapid, selective, and sensitive method for the determination of telmisartan, in human plasma. Telmisartan and the internal standard, diphenhydramine, were extracted from plasma using diethyl ether–dichloromethane (60:40, v/v), and separated on a Zorbax extend C18 column using methanol–10 mM ammonium acetate (85:15, v/v) adjusted to pH 4.5 after mixing with formic acid as mobile phase. Detection was carried out by multiple reactions monitoring on a Q-trap\textsuperscript{TM} LC–MS/MS system with an ESI interface. The assay was linear over the range 0.5–600.0 ng/ml with a limit of quantitation of 0.5 ng/ml and a limit of detection of 0.05 ng/ml. Intra- and interday precision were <6.7% and <8.1%, respectively, and the accuracy was in the range of 88.9–111.0%. The assay was applied to a pharmacokinetic study of telmisartan given as a single oral dose (80 mg) to healthy volunteers\textsuperscript{144}.
Zhang H et al. developed a rapid HPLC method using a monolithic column with fluorescence detection has been for determination of telmisartan in human plasma. Sample preparation was done by protein precipitation with acetonitrile and naproxen was used as internal standard. The compounds were detected by fluorescence detection, using an excitation wavelength of 300 nm and emission wavelength of 385 nm. Calibration curves of telmisartan were linear in the range of 1–200 ng/ml. The assay was high throughput, sensitive, and precise, and it was applied to a bioequivalence study of two formulations of telmisartan\textsuperscript{145}.

Londhe SV et al. developed a sensitive and reproducible HPLC method for quantitative analysis of telmisartan. The drug was separated from its degradation products on a C18 column at ambient temperature with methanol–water 80:20 (v/v), pH 4.0 (adjusted by addition of orthophosphoric acid), as mobile phase at a flow rate of 1.0 ml/min. Under these conditions, the retention time of telmisartan was 4.85±0.05 min. Quantification on the basis of peak area was achieved by UV detection at 225 nm; calibration plots were linear in the concentration range 10–60 μg/ml. When the method was applied to a pharmaceutical formulation, there was no chromatographic interference from tablet excipients\textsuperscript{146}.

Bhat et al. developed a simple, selective, and precise RP-HPLC method for the simultaneous determination of telmisartan and hydrochlorothiazide from pharmaceutical formulation. The mobile phase consisted of methanol and acetonitrile (70:30, v/v) at a flow rate of 1 ml/min and the wavelength of detection was 270 nm. Rabeprazole was used as an internal standard. The retention times of telmisartan, hydrochlorothiazide and rabeprazole were 1.79±0.01, 2.80±0.01, and 3.19±0.01 min, respectively. The developed method was validated according to ICH guidelines. The method can be used for determination of these drugs in combined dosage forms\textsuperscript{147}.