5. DRUG AND EXCIPIENT PROFILE

5.1 DRUG PROFILE

5.1.1 Valsartan profile

Drug name: Valsartan
Innovator product: Diovan
IUPAC Name: 3-methyl-2-[pentanoyl-[4-[2-(2H-tetrazoyl-5-yl)phenyl] phenyl] methyl]amino]- butanoic acid

Molecular structure of valsartan

CAS No: 137862-53-4
Molecular formula: C24H29N5O3
Molecular weight: 435.5
BCS classification: BCS class-II

Physicochemical profile

State: White to practically white fine powder.
Melting point: 116-117°C
Solubility: Soluble in ethanol and methanol and slightly soluble in water. Valsartan has pH dependent solubility
Solubility in water at 25°C: 0.18 g/L
log P: 1.499
pKₐ: 3.9 and 4.7
Storage: Stored at 15-30°C (away from heat, moisture, and light)
Official status: USP
Pharmacological profile

Table 5 Pharmacological profile of valsartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Angiotensin II receptor inhibitor with selectivity for the Type I receptor subtype$^{101}$</td>
</tr>
<tr>
<td>Use</td>
<td>Anti – Hypertensive</td>
</tr>
<tr>
<td>Indication</td>
<td>Uncomplicated hypertension, Isolated systolic hypertension and left ventricular hypertrophy$^{102}$</td>
</tr>
<tr>
<td>Dose</td>
<td>20, 40, 80, 160 and 320 mg</td>
</tr>
</tbody>
</table>

Pharmacokinetic profile

Table 6 Pharmacokinetic profile of valsartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Bioavailability</td>
<td>23% with high variability$^{102}$</td>
</tr>
<tr>
<td>Absorption</td>
<td>Rapid after oral administration. Peak plasma concentration occurs 2-4 hours after oral dose</td>
</tr>
<tr>
<td>Protein binding</td>
<td>94-97% (mainly serum Albumin)</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>17 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>20% recovered as metabolites after oral administration</td>
</tr>
<tr>
<td>Excretion</td>
<td>Primarily recovered in feces (about 83% of dose) and urine (about 13% of dose)</td>
</tr>
<tr>
<td>Half life</td>
<td>The initial phase $t_{1/2\alpha}$ is $&lt; 1$ h while the terminal phase $t_{1/2\beta}$ is 5-9 h</td>
</tr>
<tr>
<td>Clearance</td>
<td>2 L/h (IV administration); Renal clearance 0.62 L/h</td>
</tr>
</tbody>
</table>
### Analytical profile

*Table 7 Analytical profile of valsartan*

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV spectroscopy</td>
<td>$\lambda_{\text{max}}$ - 250 nm; LOD – 0.295 µg/ml; LOQ – 0.895 µg/ml; Linearity – 4-40 µg/ml</td>
<td>151</td>
</tr>
<tr>
<td>UV Spectroscopy</td>
<td>$\lambda_{\text{max}}$ - 250 nm; LOD – 0.15 µg/ml; LOQ – 0.449 µg/ml; Linearity – 2-20 µg/ml</td>
<td>152</td>
</tr>
<tr>
<td>HPLC</td>
<td>Chromolith performance column (RP-18e, 100×4.6 mm); Fluorescence detector, excitation and emission wavelengths at 230 and 295 nm; 0.01 M disodium hydrogen phosphate buffer-acetonitrile (60:40 v/v); pH 3.5; Flow rate 2 ml/min; Linearity: 20-2000 ng/ml; RT – 3.3 min</td>
<td>132</td>
</tr>
<tr>
<td>HPLC</td>
<td>Inertsil ODS-3 C18 column (0.5 µm, 15 cm × 0.46 cm); UV detector at 247 nm. Acetonitrile and distilled water (6:4 v/v); pH 3; Flow rate 1 ml/min</td>
<td>106</td>
</tr>
<tr>
<td>Liquid chromatography/ mass spectrometry (LC/MS)</td>
<td>XTerra MS C18 column (2.1×50 mm, 3.5 µm); 0.1 % trifluoroacetic acid/ ethanol/ acetonitrile (45/30/25, v/v/v); Flow rate at 0.2 ml/min; Column temperature 50 °C. Spray voltage: 4.5 kV; sheath gas (N₂) pressure: 90 psi; auxiliary gas (N₂): 15 ml/min; capillary temperature: 225° C; collision energy: -20 V; and collision gas (Ar) pressure: ca.2.0 mTorr. The scan time for each analyte was set at 1.0 s.</td>
<td>153</td>
</tr>
<tr>
<td>HPTLC</td>
<td>Ethyl acetate-methanol-toluene-ammonia (7.5 : 3 : 2 : 0.8, v/v/v/v); UV detection at 242 nm</td>
<td>154</td>
</tr>
</tbody>
</table>
5.1.2 Telmisartan profile

Drug name: Telmisartan
Innovator product: Micardis
IUPAC Name: 4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

CAS No: 144701-48-4
Molecular formula: C_{33}H_{30}N_{4}O_{2}
Molecular weight: 514.617 g/mol
BCS classification: BCS class-II

Physico chemical profile
State: white to slightly yellowish crystalline powder.
Melting point: 261-263 °C
Solubility: Practically insoluble in water & in the pH range of 3-9, sparingly soluble in strong acid, and soluble in strong base
log P: 3.20 (n-octanol/phosphate buffer pH 7.4)
pK_{a}: 3.5, 4.1 and 6.0
Storage: Stored at room temperature and away from excess heat and moisture
Official status: USP

Pharmacological profile

Table 8 Pharmacological profile of telmisartan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>A potent and highly selective angiotensin II type-1 (AT1) receptor antagonist\textsuperscript{157,158}</td>
</tr>
<tr>
<td>Use</td>
<td>Anti-hypertensive</td>
</tr>
<tr>
<td>Dose</td>
<td>20 mg, 40 mg, 80 mg tablets</td>
</tr>
</tbody>
</table>
### Pharmacokinetic profile

**Table 9** Pharmacokinetic profile of telmisartan

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapidly absorbed; peak plasma concentrations (C\textsubscript{max}) are reached in 0.5–1 hour after single-dose administration\textsuperscript{110}</td>
</tr>
<tr>
<td>Distribution</td>
<td>Easily crosses biological membranes and highly bound to tissues</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Conjugation to glucuronic acid by UDP-glucuronosyltransferases\textsuperscript{110}</td>
</tr>
<tr>
<td>Elimination</td>
<td>Largely unchanged in the faeces, via biliary excretion; &lt;1% is excreted in the urine.</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>43 %</td>
</tr>
<tr>
<td>Clearance</td>
<td>30 L/h</td>
</tr>
<tr>
<td>Half-life</td>
<td>24 h</td>
</tr>
<tr>
<td>V\textsubscript{d}</td>
<td>7 L/kg</td>
</tr>
<tr>
<td>Protein binding</td>
<td>&gt; 99.0 %</td>
</tr>
</tbody>
</table>

### Analytical profile

**Table 10** Analytical profile of telmisartan

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV Spectroscopy</td>
<td>Absorbance maxima at 296 nm; Linearity 4–16 μg/ml</td>
<td>\textsuperscript{159}</td>
</tr>
<tr>
<td>HPLC</td>
<td>ACE 5 C18 column at 30\textdegree C; Ammonium acetate buffer-acetonitrile (60:40, v/v) of pH 5.5; Flow rate, 1 ml/min; Detection wavelength 260 nm.</td>
<td>\textsuperscript{160}</td>
</tr>
<tr>
<td>HPLC</td>
<td>Kromasil C\textsubscript{18} column (250 × 4.6 mm; 5μm) at 40 °C; solvent A (2.0 g of potassium dihydrogen phosphate anhydrous &amp; 1.04 g of Sodium 1-Hexane sulphonic acid monohydrate in 1L water, pH 3.0) solvent B (mixture of Acetonitrile: Methanol 80:20 v/v); Flow rate 1 ml/min; UV detection at 270 nm</td>
<td>\textsuperscript{161}</td>
</tr>
</tbody>
</table>
5.2 EXCIPIENT PROFILE

5.2.1 Avicel PH 102

Chemical Name: Cellulose

CAS Registry Number: [9004-34-6]

Empirical Formula: (C₆H₁₀O₅)ₙ

Synonyms: Cellets; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur

Functional Category

Adsorbent; Suspending agent; Tablet and capsule diluent; Tablet disintegrant

White, odourless, tasteless, crystalline powder composed of porous particles. Different grades of microcrystalline cellulose (MCC) are commercially available that differ in their method of manufacture, particle size, flow and other physical properties. The larger particle size and higher density grades generally provide better flow properties. Low-moisture grades are used with moisture-sensitive materials. It is widely used in oral pharmaceutical formulations and food products and is generally regarded as relatively nontoxic and non-irritant material. MCC is not absorbed systemically following oral administration and thus has little toxic potential.

Density: 1.420–1.460 g/cm³

Melting point: Chars at 260–270°C

Particle size: 100 µm

Specific surface area: 1.21–1.30 m²/g

Oral LD₅₀: > 5,000 mg/kg (rat)

Moisture content: ≤ 5%

Storage: Stored in a well-closed container in a cool, dry place

Incompatibilities: Incompatible with strong oxidizing agents

Regulatory Status: GRAS listed; Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database
5.2.2 Aerosil 200

Chemical Name: Silica  
CAS Registry Number: [7631-86-9]
Empirical Formula: SiO₂  
Molecular Weight: 60.08

Synonyms

Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide

Functional Category

Adsorbent; anti-caking agent; Emulsion stabilizer; Glidant; Suspending agent; Tablet disintegrant; Thermal stabilizer; Viscosity increasing agent

Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white colored, odourless, tasteless, amorphous powder. These products are stable indefinitely at room temperature if kept dry. Their tendency to adsorb moisture suggests an effective shelf-life of about two years. Fumed silica will form dispersions in water, glycerine, butyl alcohol, mineral oil and a variety of other liquids causing them to thicken or form gels. The dispersions often have thyrotrophic properties, i.e., viscosity that varies with rate of stirring. Several grades of colloidal silicon dioxide are commercially available, which are produced by modifying the manufacturing process.

Bulk Density: 0.029–0.042g/cm³
Melting point: 1600°C
Specific surface area: 200 m²/g
Storage: Stored in a well-closed container; Hygroscopic but adsorbs large quantities of water without liquefying
Incompatibility: Incompatible with diethylstilbestrol preparations
Regulatory Acceptance: GRAS listed. Included in the FDA Inactive Ingredients Database
Safety: Generally regarded as an essentially non-toxic and non-irritant excipient.
5.2.3 Croscarmellose Sodium

Chemical Name: Cellulose, carboxymethyl ether sodium salt, crosslinked

CAS Registry Number: [74811-65-7]

Synonyms
Ac-Di-Sol; carmellosummatricumconexum; crosslinked carboxymethylcellulose sodium; Explocel;

Functional Category
Tablet and capsule disintegrant.

Croscarmellose Sodium is an odourless, white or greyish-white powder. It should be Stored in a well-closed container in a cool, dry place. Not compatible with strong acids or with soluble salts of iron and some other metals such as aluminium, mercury, and zinc\footnote{\textsuperscript{164}}.

Bulk Density: 0.529 g/cm\textsuperscript{3}

Tapped Density: 0.819 g/cm\textsuperscript{3}

True Density: 1.543 g/cm\textsuperscript{3}

Regulatory Status: Included in the FDA Inactive Ingredients Database

5.2.4 Lactose monohydrate

Chemical Name: O-\(\beta\)-D-Galactopyranosyl-(1,4)-\(\beta\)-D-glucopyranose

CAS Registry Number: [63-42-3]

Empirical Formula: \(\text{C}_{12}\text{H}_{22}\text{O}_{11}\) \(\text{H}_{2}\text{O}\)  Molecular Weight: 360.30

Functional Category
Directly compressible tablet excipient; dry powder  inhaler carrier; lyophilisation aid; diluent and filler.

White to off-white crystalline particles or powder. Sparingly soluble in 95\% ethanol, ether (40 g/100ml at 25\(^\circ\)C), and soluble in water. Stored in a well-closed container in a cool & dry place. It may develop brown coloration on storage, the reaction being accelerated by warm and damp conditions\footnote{\textsuperscript{165}}. Incompatible with strong oxidizers;
Interact with primary and secondary amines (Millard reaction) under high humid conditions

True Density: 1.589 g/cm³
Bulk density: 0.71 g/cm³
Tapped density: 0.88 g/cm³
Regulatory Status: GRAS listed. Included in the FDA inactive ingredients database

5.2.5 Magnesium Stearate

Chemical Name: Octadecanoic acid magnesium salt

CAS Registry Number: [557-04-0]

Empirical Formula: C₃₆H₇₀MgO₄ Molecular Weight: 591.24

Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin. Practically insoluble in 95% ethanol, ether and water; slightly soluble in warm benzene and warm ethanol. It is stable and should be stored in a well-closed container in a cool, dry place. Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. It cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

True Density: 1.092 g/cm³
Bulk density: 0.159 g/cm³
Tapped density: 0.286 g/cm³
Regulatory Acceptance: GRAS listed. Accepted as food additive in USA and UK. Included in the FDA Inactive Ingredients Database
5.2.6 Polyethylene Glycol

Chemical Name: \( \alpha \) Hydro-\( \omega \)-hydroxypoly (oxy-1,2-ethanediyl)

CAS Registry Number: [25322-68-3]

Empirical Formula: \( \text{HOCH}_2(\text{CH}_2\text{OCH}_2)_m\text{CH}_2\text{OH}; (m - \text{average number of oxyethylene groups}) \)

Synonyms

Carbowax; Lipoxol; Lutrol E; Pluriol E; macrogola; PEG; Polyoxyethylene glycol.

Functional Category

Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

Polyethylene glycol (PEG) is an addition polymer of ethylene oxide and water. PEG is available in different grades, 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades occur as clear, colourless or slightly yellow colored, viscous liquids with slight but characteristic odour and a bitter, slightly burning taste\(^{167}\). PEG 600 can occur as a solid at ambient temperatures. Solid grades (PEG >1000) are white or off-white in colour, and range in consistency from pastes to waxy flakes. All grades of PEG are soluble in water and miscible in all proportions with other PEG. Liquid PEG’s are soluble in acetone, alcohols, benzene, glycerine, and glycols. Solid PEG’s are soluble in acetone, dichloromethane, ethanol (95%), and methanol. PEG’s are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. PEG do not support microbial growth, and do not rancid. Generally, they are regarded as nontoxic and non-irritant materials. They are included in the FDA inactive ingredients database.

5.2.7 Propylene Glycol

Chemical Name: 1,2-Propanediol

CAS Registry Number: [57-55-6]

Empirical Formula: \( \text{C}_3\text{H}_8\text{O}_2 \)

Molecular Weight: 76.09

Synonyms

1,2-Dihydroxypropane; methyl glycol; methyl ethylene glycol; propane 1,2-diol; 2 hydroxypropanol; E1520;
**Functional Category**

Antimicrobial preservative; disinfectant; Humectant; plasticizer; Solvent; stabilizing agent; water-miscible co-solvent

Propylene glycol (PG) is a clear, colourless, viscous, practically odourless liquid, with a sweet, slightly acrid taste resembling that of glycerine. It is miscible with acetone, chloroform, ethanol (95%), glycerine, and water. PG is stable at cool temperatures when stored in a well-closed container, but at high temperatures, and in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. It is incompatible with oxidizing reagents such as potassium permanganate. GRAS listed, nontoxic, accepted for use as a food additive in Europe and included in the FDA Inactive Ingredients Database.

**5.2.8 Eudragit E100**

**Chemical name:** Poly (butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1: 2: 1

**Synonyms:** Acryl-EZE; acidimethacrylicetethylisacrylatispolymerisatum, polymeric methacrylate, Kollicoat MAE; polyacrylatisdispersio 30 per centum.

**Functional Category:** Film-forming agent; Tablet binder; Tablet diluent

**LD$_{50}$ (mouse, oral):** 5.2g/kg

Eudragit E100 is a cationic polymer that is soluble in gastric fluid up to pH 5.0, swellable and permeable above pH 5.0. Glass Transition Temperature (Tg): ~ 48 °C. Available as colourless to yellow tinged granules with a characteristic amine like odour. One gram is soluble in 7 g of methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride or 1 N hydrochloric acid to give clear to slightly cloudy solutions. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30 °C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance. Included in the FDA inactive ingredients database.
5.2.9 Gelucire 50/13

**Synonyms:** Stearoyl macrogol-32 glycerides EP, Stearoyl polyoxyl-32 glycerides NF, Stearoylpolyoxylglycerides

**Physical Form:** Semi-solid block  
**Administration Route:** Oral

**Hydrophilic-Lipophilic Balance (HLB):** 13

**Field of use:** Human pharmaceutical products, veterinary products excluding food producing animals (EU)

A non-ionic, water dispersible surfactant composed of well-characterized PEG-esters, a small glyceride fraction and free PEG. Able to self-emulsify on contact with aqueous media forming a fine dispersion. The surfactive power improves the solubility and wettability of active pharmaceutical ingredients *in vitro* and *in vivo*. The improved *in vivo* drug solubilization facilitates absorption. It is used binder in melt processes due to its good thermoplasticity\textsuperscript{170}. Gelucire is used in melt granulation (thermoplastic palletisation) and melt extrusion techniques. Suitable for hard gelatine capsule moulding, for adsorption onto neutral carrier powders for use in tablets, capsule filling and sachets\textsuperscript{171}.

5.2.10 Transcutol HP

Highly purified diethylene glycol monoethyl ether EP/NF

**Physical Form:** liquid  
**Administration Route:** Oral

**Field of use:** Human pharmaceutical products, veterinary products excluding food producing animals

Highly purified powerful solvent for poorly water soluble active pharmaceutical ingredients. Hydrophilic co-solvent for use in self-emulsifying lipid formulations to obtain a coarse dispersion\textsuperscript{172}. Suitable for adsorption onto neutral carrier powders for use in tablets, capsule filling and sachets. Suitable for hard gelatine and soft gelatine capsules in association with other compatible excipients.
Table 11 List of equipment used in the preparation and analysis

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Equipment</th>
<th>Model</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Weighing balance</td>
<td>CA-223</td>
<td>Contech Instrument Ltd., India</td>
</tr>
<tr>
<td>2</td>
<td>Weighing balance</td>
<td>Analytical balance</td>
<td>Sartorius GK Germany</td>
</tr>
<tr>
<td>3</td>
<td>Incubator shaker</td>
<td>SI-300</td>
<td>Jeio Tech Co. Ltd., Korea</td>
</tr>
<tr>
<td>4</td>
<td>Vortex shaker</td>
<td>Spinix</td>
<td>Tarsons products Pvt.Ltd., India</td>
</tr>
<tr>
<td>5</td>
<td>UV Spectrophotometer</td>
<td>V-650</td>
<td>JASCO, Inc., USA</td>
</tr>
<tr>
<td>6</td>
<td>Dissolution Test Apparatus</td>
<td>LABINDIA DS-8000</td>
<td>Lab India Instrument Pvt. Ltd. India</td>
</tr>
<tr>
<td>7</td>
<td>Ultra Sonicator</td>
<td>Power Sonic 405</td>
<td>Huwashin Technology, Korea</td>
</tr>
<tr>
<td>8</td>
<td>pH meter</td>
<td>pH Tutor</td>
<td>Eutech Instruments, India</td>
</tr>
<tr>
<td>9</td>
<td>HPLC</td>
<td>Prominence UFLC</td>
<td>Shimadzu Analytical India Pvt. Ltd.</td>
</tr>
<tr>
<td>10</td>
<td>Zeta Sizer</td>
<td>Ver. 6.01MAL1004428</td>
<td>Malvern Instruments Ltd., United Kingdom</td>
</tr>
<tr>
<td>11</td>
<td>FTIR</td>
<td>Spectrum RX1</td>
<td>Perkin Elmer, USA</td>
</tr>
<tr>
<td>12</td>
<td>Refrigerated Centrifuge</td>
<td>Heareus multifuge X3R</td>
<td>Thermo Fisher Scientific Inc., USA</td>
</tr>
<tr>
<td>13</td>
<td>Centrifuge</td>
<td>REMI, R-24</td>
<td>Remi Elektrotechnik Ltd., India</td>
</tr>
</tbody>
</table>
6. MATERIALS AND METHODS

6.1 MATERIALS

Table 12 List of materials used in the experiments throughout the work

<table>
<thead>
<tr>
<th>Drug/Excipient</th>
<th>Gifted by / Procured from</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan &amp; Telmisartan</td>
<td>Aurobindo Pharmaceuticals, Hyderabad, India</td>
</tr>
<tr>
<td>Avicel PH102</td>
<td>Signet Chemicals Corporation, Mumbai, India</td>
</tr>
<tr>
<td>Pluronic F68</td>
<td>Sigma-Aldrich Co., USA</td>
</tr>
<tr>
<td>Eudragit E100</td>
<td>Evonik Industries AG, Germany</td>
</tr>
<tr>
<td>Gelucire 50/13 &amp; Transcutol HP</td>
<td>Gattefosse India Pvt. Ltd., Mumbai, India</td>
</tr>
<tr>
<td>Tween 20, Tween 80, Propylene glycol (PG)</td>
<td>Sd Fine-Chem Ltd., Mumbai, India</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG 200, 400, 600, 4000 and 8000)</td>
<td></td>
</tr>
<tr>
<td>Sodium hydroxide, Magnesium stearate</td>
<td>Nehal traders, Hyderabad, India</td>
</tr>
<tr>
<td>Potassium dihydrogen orthophosphate</td>
<td></td>
</tr>
<tr>
<td>Aerosil 200, Lactose mono hydrate</td>
<td>Merck India ltd., India</td>
</tr>
<tr>
<td>Dicalcium phosphate (DCP) di hydrate</td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td></td>
</tr>
<tr>
<td>Acetonitrile, Methanol (HPLC grade)</td>
<td></td>
</tr>
<tr>
<td>Valzaar 40 mg (Torrent Pharmaceutical Ltd., Ahmadabad)</td>
<td>Local Pharmacy</td>
</tr>
<tr>
<td>Telma 20 mg (Glenmark Pharmaceutical Ltd., Himachal pradesh)</td>
<td></td>
</tr>
</tbody>
</table>
6.2 METHODS

The study was divided into four sections

Experiment I: Liquisolid compacts of valsartan and telmisartan

Experiment II: Melt dispersion granules of valsartan and telmisartan

Experiment III: Polymeric solid dispersions of valsartan and telmisartan

Experiment IV: In vivo studies on selected formulations

Experiment I: Liquisolid Compacts

Liquisolid compacts of valsartan and telmisartan were prepared by direct compression. The drug excipient interactions and solid state characterization was performed by the using FT-IR, DSC and XRD analysis. The prepared tablets were evaluated for hardness, friability, content uniformity, disintegration and in vitro dissolution. The dissolution profile of the optimized formulation was compared with plain drug and marketed formulation. The optimized liquisolid formulations were subjected to accelerated stability studies for 3 months.

Experiment II: Melt dispersion granules

Melt dispersion granules of valsartan and telmisartan were prepared using carriers, PEG 8000, Pluronic F68 and Gelucire 50/13 and lactose as surface adsorbent. The prepared granules were characterized by FT-IR, DSC, XRD and in vitro dissolution studies. The dissolution profiles of the optimized formulations were compared with that corresponding physical mixture, plain drug and marketed formulations. The optimized formulations were subjected to accelerated stability studies for 3 months.

Experiment III: Polymeric solid dispersions

Polymeric solid dispersions of valsartan and telmisartan were prepared using Eudragit E 100. The prepared dispersions were characterized by FT-IR, DSC, XRD and in vitro dissolution studies. The dissolution profiles of optimized formulations were compared with physical mixture, plain drug and marketed formulation. The optimized polymeric dispersions were subjected to accelerated stability studies for 3 months.
Experiment IV: In vivo studies on selected formulations

The optimized formulations of valsartan were subjected to in vivo pharmacokinetic studies. The formulations and plain drug was administered to male Wistar rats. The plasma drug concentration versus time profiles were obtained and bioavailability of the formulations was calculated and compared relative to plain drug. All animal experimentation were carried out with prior approval from institutional animal ethical committee.
6.3. ANALYTICAL METHOD DEVELOPMENT

Analytical method to quantify the samples were developed for valsartan and telmisartan by UV spectroscopy. HPLC method was also developed to quantify the valsartan in plasma samples.

6.3.1 UV SPECTROSCOPIC METHOD FOR VALSARTAN

Calibration curves of valsartan was prepared in different media i.e., 0.1 N hydrochloric acid (HCl), 0.001 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. All solutions were freshly prepared before use.

6.3.1.1 Preparation of media/buffer solutions

Preparation of 0.1 N HCl

Aliquots of 8.5 ml of concentrated HCl was transferred into a 1000 ml of volumetric flask and diluted to 1000 ml with distilled water\textsuperscript{173}.

Preparation of 0.001 N HCl

Aliquots of 10 ml of 0.1 N HCl was pipetted into a 1000 ml volumetric flask and diluted to 1000 ml with distilled water.

Preparation of acetate buffer pH 4.5

Accurately weighed 2.99 g of sodium acetate trihydrate was placed in a 1000 ml volumetric flask. Aliquot of 14 ml of 2 N acetic acid was added and volume was made up to 1000 ml with distilled water.

Preparation of 0.2 M potassium dihydrogen phosphate solution

Accurately weighed 27.218 g of potassium dihydrogen phosphate was dissolved in some amount of water and diluted with distilled water to 1000 ml.

Preparation of 0.2 M sodium hydroxide solution

About 8 g of sodium hydroxide (NaOH) was dissolved in some amount of water and diluted with distilled water to 1000 ml.
Preparation of phosphate buffer pH 6.8

Aliquots of 250 ml of 0.2 M Potassium dihydrogen orthophosphate was transferred to a 1000 ml of volumetric flask and 112 ml of 0.2 M NaOH was added to it. The volume was made up to 1000 ml with distilled water. The pH was adjusted to 6.8 using 0.2 M Potassium dihydrogen orthophosphate or sodium hydroxide.

6.3.1.2 Preparation of standard solutions of valsartan

Stock solution – I: Accurately weighed amount (100 mg) of valsartan was placed in a 100 ml volumetric flask and small amount of methanol was added to dissolve the drug. The volume was made up to 100 ml using methanol to give 1000 μg/ml solution.

Stock solution – II: One ml aliquot from stock solution -I was taken and diluted to 10 ml with 0.1N HCl in a volumetric flask to get 100 μg/ml.

Stock solution – III: One ml aliquot from stock solution -II was taken and diluted to 10 ml with 0.1N HCl in a volumetric flask to get 10 μg/ml.

The same procedure was repeated using 0.001 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8.

6.3.2 UV SPECTROSCOPIC METHOD FOR TELMISARTAN

Calibration curves of telmisartan was prepared in different media i.e., 0.1 N HCl, acetate buffer pH 4.5 with 0.5 % sodium lauryl sulphate (SLS) and phosphate buffer saline pH 7.4 with 0.5 % SLS. All the solutions were freshly prepared before use.

6.3.2.1 Preparation of media/buffer solutions

Preparation of acetate buffer with 0.5 % SLS

Accurately weighed 5 g of sodium lauryl sulphate was dissolved in some amount of acetate buffer and the solution was made up to 1000 ml with buffer.
Preparation of phosphate buffer saline (PBS) pH 7.4

Dissolve 2.38 g of disodium hydrogen phosphate, 0.19 g of potassium dihydrogen phosphate and 8.0 g of sodium chloride in sufficient water to produce 1000 ml. The pH was adjusted if necessary.

Preparation of PBS with 0.5 % SLS

About 5 g of sodium lauryl sulphate was dissolved in some amount of PBS and the solution was made up to 1000 ml with PBS.

6.3.2.2 Preparation of standard solution of telmisartan

Stock solution – I: Accurately weighed amount (100 mg) of telmisartan was placed in a 100 ml volumetric flask and small amount of methanol was added to dissolve the drug. The volume was made up to 100 ml using methanol to give 1000 μg/ml solution.

Stock solution – II: One ml aliquot from stock solution -I was taken and diluted to 10 ml with 0.1 N HCl in a volumetric flask to get 100 μg/ml.

Stock solution – III: One ml aliquot from stock solution -II was taken and diluted to 10 ml with 0.1 N HCl in a volumetric flask to get 10 μg/ml.

The same procedure was repeated using acetate buffer pH 4.5 and PBS pH 7.4 containing 0.5 % SLS.

6.3.2.3 Determination of absorption maxima (λ_max)

A 10 μg/ml standard solutions (stock solution III) of valsartan and telmisartan was scanned on a double beam spectrophotometer against their respective media blanks in the range of 200-400 nm. The wavelength where it shows maximum absorption was determined.
6.3.2.4 Preparation of calibration curve

Valsartan

From the valsartan stock solution-II containing (100 μg/ml), aliquots of 0.5, 1, 1.5, 2, 2.5 and 3 ml were diluted to 10 ml with 0.1 N HCl to obtain concentrations 5, 10, 15, 20, 25 and 30 μg/ml. The absorbance of solutions was determined at respective $\lambda_{\text{max}}$ against corresponding media blank. The experiment was repeated 6 times and mean with standard deviation was reported. Similar procedure was repeated using 0.001 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8.

Telmisartan

From the telmisartan stock solution-II (100 μg/ml), aliquots of 0.4, 0.6, 0.8, 1, and 1.2 ml were diluted to 10 ml with 0.1N HCl to obtain concentrations 4, 6, 8, 10 and 12 μg/ml. The absorbance of solutions was determined at respective $\lambda_{\text{max}}$ against corresponding media blank. The experiment was repeated 6 times and mean with standard deviation was reported. The same procedure was repeated using acetate buffer pH 4.5 and PBS pH 7.4 containing 0.5 % SLS.

6.3.3 HPLC METHOD FOR VALSARTAN

HPLC analysis was developed for plasma samples to determine the concentration of valsartan from the plasma samples.

6.3.3.1 Apparatus and chromatographic conditions

HPLC analysis was performed on Schimadzu system equipped with isocratic pump, UV detector and a rheodyne injector holding 20 μL loop. The separation of the compounds was carried out using Grace C18 column (250×4.6mm; 5μm) with isocratic elution. The mobile phase consisted of a mixture of acetonitrile and water in ratio of (60:40 % v/v) and pH was adjusted to 3.2 with dilute orthophosphoric acid or triethanolamine. The eluents were monitored at a wavelength of 225 nm and 250 nm at a flow rate of 0.7 ml/min. Data acquisition was performed using Shimadzu LC solution software.
6.3.3.2 Preparation of mobile phase

The mobile phase was freshly prepared, filtered through 0.45 µm membrane filter and degassed prior to use. Acetonitrile and water of HPLC grade were mixed in 60:40 v/v ratios and pH was adjusted to 3.2 using orthophosphoric acid or triethanolamine.

6.3.3.3 Preparation of plasma samples

Prior to HPLC analysis, plasma samples were removed from frozen storage, allowed to equilibrate to room temperature and processed using acetonitrile protein precipitation method\textsuperscript{174,175}. A measured volume of plasma 40 µl was transferred to a micro centrifuge tube and spiked with 10 µl of internal standard (10 µg/ml diclofenac sodium solution) was mixed and vortexed for 2 min. A volume of 450 µl of acetonitrile was added to precipitate the proteins and vortexed for 5 min. The mixture was centrifuged at 5000 rpm for 5 min. The supernatant was separated and filtered through 0.45 µ filter and 20 µl of the this solution was injected into the system\textsuperscript{176}.

6.3.3.4 Preparation of calibration curve of valsartan by HPLC method

About 10 mg of valsartan was dissolved in 100 ml of mobile phase prepared as discussed in section 6.3.3.2 to obtain a concentration of 100 µg/ml. From this stock solution, concentrations of 10, 20, 30, 40, 50 and 60 µg/ml were prepared by appropriate dilution with mobile phase. These solutions were spiked with 40 µl of plasma containing 10 µl internal standard (10 µg/ml diclofenac sodium solution) and processed as described in section 6.3.3.3 to yield concentrations of 200,400,600,800, 1000 and 1200 ng/ml. Plot of ratio of areas of valsartan and internal standard versus valsartan concentration was obtained wherein each value as a mean of 3 experiments.