Chapter No. 3 Literature Review

The details of the drug profile of the selected drugs were shown below along with the current literature review and the references.

3.1 Drug Profile

3.1.1 Profile of Nicorandil

Category: - Vasodilator

Chemical name: -2-[(pyridin-3-ylcarbonyl) amino] ethyl nitrate

Molecular formula: \( \text{C}_8\text{H}_9\text{N}_3\text{O}_4 \)

Chemical structure of Nicorandil:-

![Chemical Structure of Nicorandil](image)

Physical properties

Molecular weight of Nicorandil:- 211.175 g/mol

Appearance and color: - white crystalline powder or white needles with a faint, characteristic odour

Solubility: - It is freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethyl acetate and chloroform; sparingly soluble in water; slightly soluble in ether.
Dosage: - Tablet

General Pharmacology:

Nitrate: Nicorandil stimulates guanylate cyclase to increase formation of cyclic GMP (cGMP). cGMP activates protein kinase G (PKG) which phosphorylates and inhibits GTPase RhoA and decreases Rho-kinase activity. Reduced Rho-kinase activity permits an increase in myosin phosphatase activity, decreasing the calcium sensitivity of the smooth muscle. PKG also activates the sarcolemma calcium pump to remove activating calcium. PKG acts on K+ channels to promote K+ efflux and the ensuing hyperpolarization inhibits voltage-gated calcium channels. Overall, this leads to relaxation of the smooth muscle and coronary vasodilation. K+ATP channel opener: Nicorandil activates K+ATP channel, causing K+ efflux. This hyperpolarizes the cell, which inactivates voltage-gated calcium channels and reduces free intracellular Ca$^{2+}$.

The effect of nicorandil as a vasodilator is mainly attributed to its nitrate property. Yet, nicorandil is effective in cases where nitrates, such as nitroglycerine, are not effective. Studies show that this is due to its K+ATP channel agonist action which causes pharmacological preconditioning and provides cardio protective effects against ischemia. Nicorandil activates K+ATP channels in the mitochondria of the myocardium, which appears to relay the cardio protective effects, although the mechanism is still unclear.

Indications and Usage:

- Nicorandil is used to prevent and treat chronic angina pectoris. It is a type of drug called a potassium channel activator with a nitrate component.
- It is used to maintain blood flow to the heart and prevent angina pain.
- In general this drug is used to increase blood flow through the blood vessels of the heart which prevents angina pectoris.
- Benefits of being on this drug can include prevention and/or reduction of complications that may arise from having angina pectoris.
• Studies have shown that the drug can reduce the risk of having a heart attack (myocardial infarction) and other complications such as coronary artery bypass graft for people with angina pectoris.

**Pharmacokinetics:**

After oral administration, nicorandil is absorbed rapidly and completely from the gastrointestinal tract. The absolute bioavailability is about 75%. There is no significant hepatic first-pass effect. Maximum plasma concentrations are reached after about 30-60 minutes. The plasma concentration (and the area under the curve) show a linear proportionality to the dose. The drug disposition processes (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain stable whatever the dose in the therapeutic range. Nicorandil is only slightly bound to human plasma proteins (free fraction estimated at about 75%). The decrease in plasma concentration reveals two different processes: 1. a rapid elimination phase with a half-life of about 1 hour, which covers about 96% of the plasma concentration 2. a slow elimination phase occurring between the 8th and the 24th hour following the oral dose. Metabolism takes place mainly via denitration of the molecule with the denitrated product then merging into the nicotinamide pathway. Nicorandil and its metabolites are mainly excreted by the kidney. About 21% of the administered dose is eliminated through the urine with about 1% as the unchanged compound and the remainder as mainly the denitrated metabolite (about 7%) and derivatives following denitration (eg. nicotinuric acid, nicotinamide, N-methylnicotinamide and nicotinic acid). Steady state is rapidly achieved during twice daily administration. No clinically relevant modifications of the nicorandil pharmacokinetic profile is evidenced in populations at risk such as elderly people, or patients with liver disease or chronic renal failure. Moreover, the metabolism of nicorandil does not appear to significantly interact with that of cimetidine, rifampicin, anticoagulants, digoxin or other antianginal treatments.
### 3.1.2 Profile of Olanzapine

**Category:** Atypical Antipsychotic

**Chemical name:** 5-methyl-8-(4-methylpiperazin-1-yl)-4-thia-2,9-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),3(7),5,8,10,12-hexaene

**Molecular formula:** \( C_{17}H_{20}N_4S \)

**Chemical structure of Olanzapine:**

![Chemical Structure of Olanzapine](image)

**Physical properties**

**Molecular weight of Olanzapine:** 312.4 g/mol

**Solubility:** Practically insoluble in water. Soluble in Alcohol. \( \log P = 2 \)

**Dosage:** Powder, for solution, Tablet, Tablet, orally disintegrating

**General Pharmacology:**
Olanzapine has a higher affinity for 5-HT\textsubscript{2A} serotonin receptors than D\textsubscript{2} dopamine receptors, which is a common property of all atypical antipsychotics, aside from the benzamide antipsychotics such as amisulpride. Olanzapine also had the highest affinity of any second-generation antipsychotic towards the P-glycoprotein in one \textit{in vitro} study. P-glycoprotein transports a number of drugs across a number of different biological membranes including the blood-brain barrier which could mean that less brain exposure to Olanzapine results from this interaction with the P-glycoprotein.

**Indications and Usage:**

Olanzapine is indicated for the:

- For the acute and maintenance treatment of schizophrenia and related psychotic disorders, as well as acute treatment of manic or mixed episodes of bipolar 1 disorder.
- Intramuscular Olanzapine is indicated for the rapid control of agitated patients.
- Olanzapine, an atypical antipsychotic agent, is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia
- Future uses may include the treatment of obsessive-compulsive disorder and severe behavioral disorders in autism

**Pharmacokinetics:**

Olanzapine is well absorbed with approximately 40% of the dose metabolized before reaching the systemic circulation. The volume of distribution is 1000L. The protein binding is 93%. Hepatic metabolism is observed. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.
3.1.3 Profile of Cyclobenzaprine

**Category:** Skeletal Muscle Relaxant And CNS Depressant

**Chemical name:** - dimethyl ([3-(2E)-tricyclo[9.4.0.0^3,8]pentadeca-1(11),3 (8), 4, 6, 9, 12, 14- heptaen-2-ylidene]propyl)amine

**Molecular formula:** - C_{20}H_{21}N

**Chemical structure of Cyclobenzaprine:**

![Chemical Structure of Cyclobenzaprine](image)

**Physical properties**

**Molecular weight of Cyclobenzaprine:** - 275.4 g/mol

**Solubility:** - Practically insoluble in water. Soluble in Alcohol. Log P =5.2 and Pka = 8.47

**Dosage:** oral tablet

**General Pharmacology:**

Like other tricyclic antidepressants, cyclobenzaprine exhibits anticholinergic activity, potentiation of norepinephrine, and antagonism of reserpine. Cyclobenzaprine does not directly act on the neuromuscular junction or the muscle but relieves muscle spasms through a central action, possibly at the brain stem level. Cyclobenzaprine binds to the
serotonin receptor and is considered a 5-HT2 receptor antagonist that reduces muscle tone by decreasing the activity of descending serotonergic neurons.

**Indications and Usage:**

Cyclobenzaprine is indicated for the:

- For use as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.
- Cyclobenzaprine, closely related to the antidepressant amitriptyline, is used as a skeletal muscle relaxant to reduce pain and tenderness and improve mobility.
- Unlike dantrolene, cyclobenzaprine cannot be used to treat muscle spasm secondary to cerebral or spinal cord disease

**Pharmacokinetics:** It is slowly but well absorbed after oral administration. The protein binding is 93%. It is extensively metabolized by gastrointestinal and hepatic metabolism. Cyclobenzaprine is extensively metabolized, and is excreted primarily as glucuronides via the kidney.

### 3.1.4 Profile of Candesartan

**Category:** Anti hypertensive

**Chemical name:** 2-ethoxy-1-([4-[[2-(2H-1,2,3,4-tetrazol-5 yl)phenyl]phenyl]methyl]-1H-1,3-benzodiazole-7-carboxylic acid

**Molecular formula:** C_{24}H_{20}N_{6}O_{3}

**Chemical structure of Candesartan:**

![Chemical Structure of Candesartan](image-url)
Physical properties

**Molecular weight of Candesartan**: - 440.5 g/mol

**Solubility of Candesartan**: Practically insoluble in water. Soluble in Methanol.

\[ \text{Log P} = 4.02 \quad \text{Pka} = 7.3 \]

**Dosage**: - Tablet

**General Pharmacology**:  
Candesartan selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Candesartan is greater than 10,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion

**Indications and Usage**:  
It may be used as a first line agent to treat uncomplicated hypertension, isolated systolic hypertension and left ventricular hypertrophy. It may be used as a first line agent to delay progression of diabetic nephropathy. Candesartan may be also used as a second line agent in the treatment of congestive heart failure, systolic dysfunction, myocardial infarction and coronary artery disease in those intolerant of ACE inhibitors

**Pharmacokinetics**:  
The absolute bioavailability of candesartan was estimated to be 15%. Food with a high fat content has no affect on the bioavailability of candesartan from candesartan cilexetil. The volume of distribution 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The prodrug candesartan cilexetil undergoes rapid and complete ester hydrolysis in the intestinal wall to form the active drug, candesartan. Elimination of candesartan is primarily as unchanged drug in the urine and, by the biliary route, in the feces. When candesartan is administered
orally, about 26% of the dose is excreted unchanged in urine. Candesartan is mainly excreted unchanged in urine and feces (via bile).

3.1.5 Profile of Hydrochlorothiazide

**Category:** Calcium-sparing diuretic

**Chemical name:** 6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzo thiadiazone-7-sulfonamide 1, 1-dioxide

**Molecular formula:** $C_7H_8ClN_3O_4S_2$

**Chemical structure of Hydrochlorothiazide:**

![Chemical Structure of Hydrochlorothiazide](image)

**Figure No. 25 Chemical Structure of Hydrochlorothiazide**

**Physical properties**

**Molecular weight of Hydrochlorothiazide:** 297.7 g/mol

**Solubility of Hydrochlorothiazide:** Slightly or very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dimethylformamide; n-butylamine; and solutions of alkali hydroxides; insoluble in ether, chloroform, and dilute mineral acid. Pka = 7.9  Log P = -0.16

**Dosage:** Tablet

**Mechanism of Action:**

Hydrochlorothiazide is a thiazide diuretic which acts as by inhibiting fluid-expelling and blood pressure-lowering agent which increases the tubular re-absorption of sodium in the cortical diluting segment.
It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

**General Pharmacology:**

Hydrochlorothiazide acts directly on the kidney, increasing the excretion of sodium chloride and potassium and consequently water, mainly in the distal tubule.

**Indications and Usage:**

Hydrochlorothiazide is a diuretic which reduces the reabsorption of electrolytes from the renal tubules.

Used to treat hypertensive disease and to manage the oedema due to mild-to-moderate congestive heart failure. Oedema due to chronic hepatic or renal disease may also respond favorably.

It may also be used in patients with diabetes insipidus, due to a paradoxical effect.

May be used in the treatment of hypercalciuria in patients who have recurrent urinary calculi composed of calcium salts.

The use of hydrochlorothiazide has been indicated for the oedema of the premenstrual tension, if there is evidence of fluid retention.

**Pharmacokinetics:**

Oral absorption of hydrochlorothiazide is relatively rapid. The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (Tmax) varies between 1.5 and 5 hours, with a mean of about 4 hours. Protein binding is approximately 40%. The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours. Hydrochlorothiazide is eliminated rapidly by the kidney and excreted unchanged (> 95%) in the urine. At least 61% of the oral dose is eliminated unchanged within 24 hours. In renal and cardiac impairment, as in the elderly, the renal clearance
of hydrochlorothiazide is reduced, and the elimination half-life increased. Elderly subjects also show increased peak plasma concentrations.

3.2 Reported Bio-analytical Methods.

3.2.1 Reported Bio-analytical Methods of Nicorandil.

1. Routine and sensitive method for determination of nicorandil in human plasma developed for liquid chromatography with ultraviolet and mass spectrometric detection.


4. HPLC method for stability and pharmacokinetic studies of nicorandil.


7. Rapid and simple determination of nicorandil in rat plasma using a solid-phase extraction column.

3.2.2 Reported Bio analytical Methods of Olanzapine.

1. Simultaneous determination of Clozapine, coanzepine and mirtazapine in human plasma by LC-MS/MS.
6. A Bioequivalence Evaluation of Two Different Olanzapine Orodispersible Tablet Formulations.
3.2.3 **Reported Bio analytical Methods**\(^{134-138}\) of Cyclobenzaprine.

1. GLC determination of Cyclobenzaprine in plasma and urine.
4. Quantitative determination of Cyclobenzaprine in human plasma by high-pressure liquid chromatography.
5. Development and comparison of high-performance liquid chromatographic methods with tandem mass spectrometric and ultraviolet absorbance detection for the determination of Cyclobenzaprine in human plasma and urine.

3.2.4 **Reported Bio analytical Methods**\(^{139-145}\) of Candesartan and Hydrochlorothiazide

1. LCMS determination of Candesartan in Human plasma.
2. Bio analytical method development and its validation for determination of Candesartan cilexetil by high performance liquid chromatography with UV detection.
3. Determination of Candesartan cilexetil, Candesartan and a metabolite in human plasma and urine by liquid chromatography and fluorometric detection.
4. Liquid chromatography coupled with mass spectrometry method for the simultaneous quantification of Irbesartan and hydrochlorothiazide in human plasma.

7. Direct analysis of Valsartan or Candesartan in human plasma and urines by on-line solid phase extraction coupled to electrospray tandem mass spectrometry.

8. Optimization and validation of a SPE-HPLC-PDA-fluorescence method for the simultaneous determination of drugs used in combined cardiovascular therapy in human plasma.