CHAPTER – 3

OBJECTIVE AND PLAN OF WORK

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3. OBJECTIVE AND PLAN OF WORK

The enhancement of bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Together with the permeability, the solubility behavior of a drug is key determinant of its oral bioavailability. In preformulation studies, polymorphs solubility has represented a dispute for the creation of a most suitable and stable dosage forms administrated by orally. The number of poorly soluble drug candidates was raised quickly and the development of low soluble substances for an oral route was one of the most happening and interested challenges to formulative people in the pharmaceutical industry. Amlodipine besylate, Entacapone & Lomeloxacin hydrochloride comes under poorly water soluble drugs. The above given introduction highlights the importance of crystal forms of drug substances in pharmaceuticals, physical state of the active constituents is of paramount importance in pre-formulation studies and also for getting better bioavailability of the active ingredients.

The present work was undertaken with the aim to study crystal forms of Amlodipine besylate, Entacapone & Lomeloxacin hydrochloride, their formulative and evaluation studies etc.

3.1. Characterization of polymorphs

For the characterization of polymorphs there are number of tools to be used as like scanning electron microscopy (SEM) analysis to identify the shape of polymorphs, from the infra red studies the functional groups of each polymorphic form and also to ensure the compatibility between the drugs and solvents. In the other side to observe the un even structures of crystal forms, maximum diffracted angle on 2-theta scale and percentage crystalline of active ingredient comparatively amorphous form to be reported by powder x-rd studies and also many thermal analytical methods such as differential scanning colorimetry (DSC) and thermal gravimetric analysis (TGA) to ensure the purity in terms of melting point, heat of fusion, and also phase transition of prepared polymorphs.
3.2. PLAN OF WORK

The present research work includes the following steps:

- Preparation of different crystal forms of Amoldepine besylate, Entacapone and Lomefloxacin hydrochloride using suitable solvents.

- Characterization of prepared crystals by using:
  - Scanning electronic / Optical microscopic analysis.
  - Differential scanning calorimetry.
  - IR spectroscopy.
  - Powder x-ray diffraction spectroscopy.

- Preformulation studies
  - Determination of solubility of prepared crystal forms
  - Construction of standard graphs of selected insoluble drugs
  - Evaluation of pre-compressional parameters such as bulk density, tapped density, angle of repose, carr’s index and hausner’s ratio

- Formulation studies
  - Development of Amlodepine besylate, Entacapone & Lomefloxacin hydrochloride crystal tablet by using direct compression method.

- Evaluation studies
  - Evaluation of post compressional parameters of crystal tablet such as thickness of tablet, tablet hardness, friability, weight variation and drug content uniformity
  - *In-vitro* drug release

- Stability studies for optimized formulation

- Determination of the antimicrobial activity of Lomefloxacin hydrochloride crystal forms by agar well diffusion method

- To conduct the *In-vivo* bioavailability studies for optimized formulation in healthy animal subjects.
3.3. DRUG PROFILE

3.3.1. Amlodipine besylate [106]

**Brand name**: Norvasc, Amaday-10

**Category**: Amlodipine besylate is a selective calcium channel blocker in hypertensive disorder.

**Chemical name**: 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-Pyridine di-carboxylate benzene sulphonate.

**Description**: White, Bitter and Odorless powder.

**Molecular formula**: C_{20}H_{25}ClN_{2}O_{5}, C_{6}H_{6}O_{3}S

**Molecular weight**: 567.1 Daltons.

**Melting point**: 195 -204°C.

**pK\text{a}**: 9.02 at 23.5°C.

**Molecular structure**: [Image of molecular structure]

**Figure: 3.1. Molecular structure of Amlodipine besylate**

**Solubility**: partially solubilise in water and ethanol.

**Mechanism of action**: Amlodipine is a derivative of dihydropyridine. Calcium antagonist (calcium ion antagonist slow-channel blocker). It acts as slow calcium channel blocker that inhibits the entry of calcium elements from transmembrane to cardiac muscle.
Absorption

After oral administration of therapeutic doses of Amlodipine besylate retains maximum concentration of plasma between 6 to 12 hrs.

Distribution & Metabolism

It is bound to approximately 93% proteins of plasma.

Excretion

Studies have shown that elimination of drug from the plasma is two phasic with half-life 30-50 hr.

Dose & Administration

Initial dose of Amlodipine besylate is 5 mg once daily was suggested in hypertension and angina pectoris.

Storage condition

Store at 15-30°C & protect from light.
3.3.2. Entacapone [107]

**Brand name** : COMTAN, COMTESS

**Category** : Catechol–O–methyltransferase inhibitor.

**Systemic (IUPAC) name** :
\((E)-2\text{-Cyano-3-(3, 4di-hydroxy-5nitrophenyl-N, Ndiethyl-2-propenamideN-diethyl-3, 4-dihydroxy5nitrocinnamamide}\)

**BCS class** : Entacapone is assigned BCS Class –IV, i.e. low soluble & low permeable.

**Description** : Entacapone is a yellow or greenish yellow, non-hygroscopic powder.

**Solubility** : It is practically insoluble in water

**Molecular formula** : \(C_{14}H_{15}N_3O_5\)

**Molecular weight** : 305.286 g/mol.

**pKa** : 4.5 at 25°C

**Melting point** : 163°C

**Structural formula** :

![Molecular Structure of Entacapone](image)

**Figure: 3.2. Molecular structure of Entacapone**

**Mechanism**
Entacapone is a selectively and reversible inhibitor of catechol-O-methyltransferase (COMT), which is mainly responsible for stimulation dopaminergic level in the brain.

**Absorption**
Poor absorption through via oral cavity, peak plasma concentration reached within to 2-3 hour. Oral bioavailability was found to be 35%. The concentration of blood not affected by the food.
Distribution
Entacapone has more affinity to bound serum albumin proteins i.e. 98%, so it is not widely distributed in body tissues.

Metabolism and Elimination
This is completely metabolized by oxidisable enzymes present in the liver with glucuronidation step. More ever 90% of unchanged drug eliminated from feces.

Strength & Administration
200 mg with to a maximum of 8 times/day (maximum daily dose: 1600mg/day) taken by oral route in the treatment Parkinson's disease.

Storage condition
Store at 25-30°C & protect from light.
3.3.3. Lomefloxacin hydrochloride [108]

**Brand name**: Maxaquin, Uniqin

**Category**: Fluoroquinolone class of Antimicrobial drug.

**Chemical name**: It is 1- Ethyl - 6, 8 - difluoro - 1, 4 – dihydro – 7 - (3- methyl -1-piprazinyl)-4- oxoquinoline-3-carboxylic acid

**Description**: White crystalline powder, odorless and bitter in taste

**Molecular formula**: C₁₇H₂₀O₃N₃F₂Cl

**Molecular weight**: 387.85 gm/ml

**Melting point**: 290°C-300°C

**Solubility**: slightly soluble in water, ethanol and methanol.

**pKₐ**: 6.75

**Molecular structure**

![Structure of Lomefloxacin hydrochloride](image)

**Figure: 3.3. Structure of Lomefloxacin hydrochloride**

**Mechanism of action**

Lomefloxacin is member of Fluoroquinolone class of Antimicrobial drugs. It is active against wide range of gram-positive and gram-negative organism. It inhibits DNA-gyrase in susceptible organisms there by inhibits relaxation of supercoiled DNA and promotes breakage of DNA strand. DNA-gyrase (topoisomer II) is an essential bacterial enzyme that maintains the super helical structure DNA and is required for DNA replication and transcription, DNA repair, recombination and transposition.
Pharmacokinetics Data

Lomefloxacin is rapidly and almost completely absorbed following oral administration, peak plasma concentration of 3ug/ml being attained in about 1-1.5 hrs after 400mg dose. When Lomefloxacin and food were administered concomitantly, the rate of drug absorption was delayed. Peak plasma concentration is increased to 2hrs. $C_{\text{max}}$ decreased by 18% and extent of absorption was decreased by 12%. Lomfloxacin is approximately 10% bound to plasma proteins. It is widely distributed into body tissue including lungs and prostate. Lomefloxacin is minimally metabolized to major metabolite i.e. Glucuronides (about 9% of administered dose). The elimination half-life of Lomefloxacin is about 7-8 hrs and it is prolong in patient with renal impairment. Lomefloxacin is excreted in urine mainly as unchanged drug, but also in small amount as the glucuronide and other metabolites. Small amount are also excreted unchanged in the faeces.

Indication and Treatment

Lomefloxacin is indicated for treatment of adult with mild to moderate infection caused by susceptible strain of designated microorganism in the below condition like,

- Acute bacterial exacerbation of chronic bronchitis.
- Pulmonary and extra pulmonary tuberculosis.
- Uncomplicated urinary tract infection(cystitis)
- Complicated urinary tract infection and
- Lower respiratory tract infection etc.,

Dosage form and administration

Lower respiratory and urinary tract infection 200mg – 400mg once daily for 10-14 days (Adults). Uncomplicated cystitis by *Escherichia Coli* - 400mg once daily for 3 successive days(Female).Complicated UTI caused by E.coli, Klebsiella, Pnuemoniae , Pseudomonas aeruginosa – 400mg once daily for 14 Successive days taken through oral route.

Storage condition

Store at 15-30°C & protect from light.