Chapter 3

LITERATURE REVIEW
3.0. LITERATURE REVIEW

The most preliminary step for the initiation of Research work is the collection of Literature and it gives a full background of various technologies relevant to our research work. The main literature related to the current research work was given below.

3.1. Review on Modified release dosage forms:

Ahmed abdelbary, et al., 2010, has revealed trimetazidine dihydrochloride extended release floating tablets and prepared by dry coating technique by various hydrophilic polymers and tablets were performed in-vitro drug release studies, in-vivo and stability studies. All formulations shows zero order kinetics in drug release studies and T8 formulation shows improvement in the bioavailability than immediate release tablets.31

Y.S.R.Krishnaiah, et al., 2002, has developed a controlled release guar gum based trimetazidine dihydrochloride matrix tablets and the tablets were prepared by wet granulation technique. The drug release studies were carried out at different time intervals and drug concentration was estimated by HPLC method and results shows that guar gum was a suitable carrier for the preparation of a trimetazidine dihydrochloride three layer matrix tablets.32

Y.S.R.Krishnaiah, et al., 2002, was performed in-vivo drug release studies for guar gum based trimetazidine dihydrochloride matrix tablets. The study was conducted in six healthy volunteers by two way cross over design and plasma concentration was estimated by reverse phase HPLC and the pharmacokinetic parameters were
calculated. The results found that, slow and prolonged drug delivery with minimum fluctuations than commercially available IR tablets.\textsuperscript{33}

D.Parekh, \textit{et al.}, 2006, has developed a trimetazidine dihydrochloride controlled release tablets by using various polymers in different proportions. The drug and polymer was blended by melt granulation technique and tablets were prepared by direct compression technique. The \textit{in-vitro} results shown that the formulation were concordant with theoretical release profile and follows a first order kinetics, meant for drug was suitable for once daily administration.\textsuperscript{34}

Rajkumar. Marikanti, \textit{et al.}, 2010, was formulated a controlled release trimetazidine dihydrochloride tablets with a rate controlling polymer such as Polysaccharide B-1459. The tablets were prepared, coated and carried out dissolution studies in 0.1N HCl. The results found that the drug release was inversely proportional to the polymer concentration and indicates that the appropriate concentration of non cellulosic hydrophilic polymer was used to retard the drug release.\textsuperscript{35}

David karhu, \textit{et al.}, 2010, has developed a once daily single and multiple dose administration of tramadol extended release tablets and compared with IR product in two separate studies. The results found that AUC parameters met bioequivalence in both single and multiple studies and tramadol ER provides a rapid rise in plasma concentrations and tramadol IR shows a reduction in peak plasma concentrations.\textsuperscript{36}
Sandip B. Tiwari, et al., 2003, was studied the effect of concentration of hydrophilic and hydrophobic polymers on the release of tramadol. Hydrophilic matrix tablets were prepared by wet granulation method and hydrophobic matrix tablets were prepared by melt granulation technique. The results found that hydrophobic matrix tablets showed a sustained drug release than hydrophilic matrix tablets and the tablets prepared with hydrogenated castor oil are better suitable for modulating the delivery of tramadol hydrochloride.\textsuperscript{37}

Deepthi kodam, et al., 2011, were developed tramadol HCl SR tablets with Hydrophilic and hydrophobic polymers such as HPMC, Poly ethylene oxide, ethyl cellulose and Eudragit. The prepared tablets were evaluated for Physical parameters, drug content and \textit{in-vitro} drug release studies; and concluded that HPMC based formulation shows more sustained drug release than other polymers.\textsuperscript{38}

M. Hite, et al., 2003, was designed a simple monolithic tramadol CR tablets by direct compression technique and \textit{in-vitro} studies were conducted by using a paddle type dissolution apparatus. The tablets were prepared with different drug loadings and shown a zero order and bimodal drug release. The drug release was similar in various media when formulation composition changes and Results found that tramadol was suitable drug for CR monolithic delivery system.\textsuperscript{39}

R. Gendle, et al., 2010, was designed tramadol HCl SR tablets by wet granulation technique using Hydrophilic polymers and drug
release studies were carried out in dual media. The results found that the drug release was similar after three months of the storage and tramadol HCl was suitable drug for SR dosage forms.\textsuperscript{40}

**Jaleh Varshosaz, et al., 2005,** was prepared tramadol HCl SR matrix tablets by direct compression technique using natural polymers (Xanthan gum, guar gum) and hydrophilic polymers (HPMC, CMC). *In-vitro* drug release studies were performed in pH 7.4 phosphate buffer and the results found that the combination of Xanthan gum and HPMC based tablets could control the drug release than guar gum alone.\textsuperscript{41}

**Suhas S Khandave, et al., 2010,** was designed a comparative bioequivalence studies in healthy volunteers for test and reference products. Single dose studies were conducted under fasting and fed conditions and multiple dose studies were conducted under fasting conditions. The serial blood samples were collected and analyzed by a validated LC/MS analytical method. Based on single and multiple dose studies, it concluded that test product is bioequivalent to reference product.\textsuperscript{42}

**E. Pastorini, et al., 2009,** was developed HPLC method for determination of glucosamine in human synovial fluid. The samples were collected and analyzed after a protein precipitation step with trichloro acetic acid using a polymer based amino column with a mobile phase at 0.3mL/min flow rate and detection was performed by tandem mass spectrometry with electro spray source. The method was successfully developed and validated by measuring the Glucosamine
concentration in synovial fluid collected from osteoarthritis patients at the dose of 1500mg/day for 14 consecutive days.\textsuperscript{43}

\textbf{Aldo Roda, et al., 2006,} was developed and validated a sensitive and specific HPLC-ESI-MS/MS method for the direct determination of glucosamine in human plasma. Plasma samples were analyzed by HPLC and detection was carried out by MS using an electro spray source and reactions was monitored separately with internal standard and concluded that the precision and accuracy were found to be 13.8 and 4.0\% and the mean recovery of glucosamine at three concentration levels was found to be 101.6\(\pm\) 5.7\%.\textsuperscript{44}

\textbf{Yunqi Wu, et al., 2005,} was designed glucosamine MR matrix tablets and drug release studies were carried out by using type II dissolution apparatus and samples were collected at periodic intervals and reaction was carried out with Ninhydrin reagent and purple color was developed and measured the concentration of Glucosamine at 570nm using UV visible spectrophotometer. It indicates that the developed UV method was easy and cost effective for routine studies than HPLC method.\textsuperscript{45}

\textbf{Pravit Akarasereenont, et al., 2009,} was conducted Bioequivalent study for two different formulations having two different salt forms (KCl & NaCl) of Glucosamine sulfate in twenty four healthy volunteers by two sequence cross over design and Pharmacokinetic parameters were determined by non compartment model and the plasma samples were analyzed by LC-MS method. The results
indicates that both formulations shows bioequivalent in two different salt forms.\textsuperscript{46}

\textbf{Yu Bing Zhu, et al., 2009,} was compared the pharmacokinetics and relative bioavailability of a test and reference formulation of glucosamine sulfate 500mg after single oral administration in healthy Chinese subjects. The study was carried out by healthy male volunteers at 1:1 ratio to receive single dose of 500mg test and reference capsule formulation with 1week of wash out period. The samples were collected and analyzed by LC tandem mass spectrometry. They concluded that a single dose of 500mg test formulation was bioequivalence to reference formulation and both test and reference formulations were well tolerated.\textsuperscript{47}

\textbf{M. Basak, et al., 2004,} was developed a comparative bioavailability study for pellet filled gelatin capsule and powder filled gelatin capsule in twelve healthy male subjects and samples were collected and measured the concentration upto 24hours. They concluded that both formulations are comparable when reduction in the dose by 33% in pellet filled gelatin capsule than powder filled gelatin capsule and two pellet filled capsules can be used instead of three immediate release powder filled capsules per day.\textsuperscript{48}

\textbf{Santanu Ghosh and B. B. Barik, 2009,} were developed Matrix tablets of Aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to \textit{in-vitro} drug release studies. The results of the \textit{in- vitro}
studies in pH 7.5 phosphate buffer medium showed that F7 tablets were shown controlled release compared with marketed sustained release formulation. Based on the results of the in-vitro studies, it was concluded that the HPMC was best suitable for controlled release matrix tablets of Aceclofenac.\textsuperscript{49}

\textbf{Harris shoaib, M, et al., 2006,} have been developed once-daily SR matrix tablet of ibuprofen using HPMC as release controlling polymer and evaluated drug release parameters as per various release kinetic models. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity. The drug release data fit well to the Higuchi expression.\textsuperscript{50}

\textbf{Deepak Sahu, et al., 2010,} were developed sustained release matrix tablets of quetiapine fumarate using different polymers viz. HPMC and PVP K30. The in-vitro drug release studies were performed in 0.1N HCl for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. Dissolution data was analyzed by Higuchi expression. It was observed that matrix tablets contained polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs. Stability studies (40±2°C/75±5%RH) for 6 months indicated that Quetiapine Fumarate was stable in Accelerated condition.\textsuperscript{51}

\textbf{PG yeole, et al., 2006,} has revealed that sustained release matrix tablets of diclofenac sodium were developed by using Xanthan gum as a polymer in different ratios and MCC as diluents. The formulation F1 shows 89.67% of drug releases at 12 hours and
stability studies were carried out for formulation F1 for a period of 3 months and result complies with standard. Thus, Xanthan gum can be used as an effective matrix former to extend the release of Diclofenac sodium.52

**S. Siddique, et al., 2008,** was developed SR matrix tablets for highly soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Hydrophilic polymers have become product of choice as an important ingredient for formulation SR formulations of highly water soluble drugs. Drug release through matrix system is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs such as Metoprolol tartrate, Diltiazem, Tramadol, Ranitidine has been formulated as SR matrix tablets.53

**Hongtao L, et al., 2008,** deals with drug solubility on polymer hydration and drug dissolution from MR matrix tablets of poly ethylene oxide. Different PEO matrix tablets were prepared using acetaminophen and ibuprofen as study compounds and Polyox WSR 301 as primary hydrophilic matrix polymer. Tablet dissolution was tested using the USP Apparatus II and the hydration of PEO polymer during dissolution was recorded using a texture analyzer. The mathematical correlation was also proven to be valid and adaptable to a series of study compounds.54
3.2. Review on Selected model drugs:

3.2.1. Trimetazidine Dihydrochloride\textsuperscript{55-58}

![Figure 2.1: Structure of Trimetazidine dihydrochloride](image)

**Category**: Anti anginal agent

**Empirical Formula**: $\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_{3}\cdot 2\text{HCl}$

**Chemical Name**: 1-(2, 3, 4-Trimethoxybenzyl) piperazine dihydrochloride.

Trimetazidine Hydrochloride contains not less than 98.5 % and not more than 101.5 %, calculated on the dried basis.

**Molecular Weight**: 339.26 g/mol

**Appearance**: White crystalline powder

**Melting Point**: Between 225\degree C and 227\degree C

**Solubility**: Soluble in water, sparingly soluble in ethanol & practically insoluble in ether.

**Pharmacokinetic data**: Bioavailability : 87%

Metabolism : Myocardial, free fatty acid.

Half life : 6 hrs

Protein binding : 16%

Excretion : Renal
**Pharmacodynamic Properties**

Class III drug is a unique anti-ischemic drug, which protects the myocardial cell from the harmful effects of ischemia.

**Mechanism of Action:**

Drug inhibits fatty acid oxidation secondary to an inhibition of long-chain 3-ketoacyl CoA thiolase (KAT), resulting in an increase in glucose oxidation. This results in switching energy substrate preference from fatty acid oxidation to the more efficient glucose oxidation which explains the anti anginal properties. Drug prevents intracellular metabolic changes such as depletion of adenosine triphosphate (ATP) and phosphor creatinine accumulation of protons, and toxic free radical generation which result from ischaemia and reperfusion in the myocardium.

**Therapeutic Uses:**

Trimetazidine dihydrochloride is indicated in the treatment of ischemic heart disease (angina pectoris, sequelae of infarction).

**3.2.2. GLUCOSAMINE HCL:**

**Description:**

Glucosamine is commonly used as a treatment for osteoarthritis, although its acceptance as a medical therapy varies. It is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids.
Structure:

![Glucosamine Structure](image)

Figure 2.2: Structure of Glucosamine hydrochloride

**Trade name**: 2-Amino-2-deoxy-D-glucopyranose; chitosamine hydrochloride; D-glucosamine hydrochloride; D-(+)-glucosamine hydrochloride

**CAS Number**: 3416-24-8

**Mol. Formula**: $C_6H_{13}NO_5.HCl$

**Mol. Wt**: 215.63

**Structural class**: Amino sugar

**Solubility**: Soluble in water, 0.1 g/ml

**Melting point**: 190-194°C or 300°C

**Mechanism of Action**: Glucosamine is a precursor for glycosaminoglycans and is a major component of joint cartilage, supplemental glucosamine may help to rebuild cartilage and treat arthritis.

### 3.2.3. Tramadol HCl: 61-63

**Description**: Tramadol is a narcotic analgesic proposed for moderate to severe pain. It may be habituating.
Structure:

Figure 2.3: Structure of Tramadol hydrochloride

Synonyms: Tramadol, Tramadol Hydrochloride
Brand names: Tramal, Ultram, Ultram ER, Ryzolt
Categories: Narcotics, Analgesics, Opioid analgesics
CAS Number: 27203-92-5
Chemical formula: C$_{16}$H$_{25}$NO$_2$.HCl
IUPAC Name: (1R,2R)-2-[(dimethylamino)

Mechanism of Action:

Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and nor adrenaline is inhibited.
**Pharmacokinetics:**

**Absorption:**

Racemic Tramadol is rapidly and almost completely absorbed after oral administration.

**Metabolism:**

The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver.

**Excretion:**

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by kidneys.

**Protein Binding**: 20%

**Half life**: 5.5 hours
3.3. Review on Selected Excipients:64-66

3.3.1. HYDROXY PROPYL METHYLCELLULOSE (HPMC)

Different viscosity grades of HPMC are available in the market. HPMC is chemically O-methylated and O-(2-hydroxypropylated) cellulose. Grades are distinguished by with the apparent viscosity, in mpa, of a 2% w/w aqueous solution at 20°C. Higher viscosity grades are mostly used to control the drug release from a matrix. 10-80%w/w level of HPMC is used as a controlling release.

**Synonyms:**

Benecel MHPC; E464; Methocel, Metolose, Pharmacoat, Spectracel and tylopur.

**Chemical name:** Cellulose, 2-Hydroxypropyl methyl ether

**Empirical formula:**

HPMC is a partly o-methylated and o- (2-hydroxypropylated)

**Structural formula:**

![Figure 2.4: Structure of Hydroxy Propyl Methyl Cellulose](image)

where R is H, CH₃, or CH₂CH(OH)CH₃

**Molecular weight:** Approximately 10000-1500000
**Description:**

HPMC is an Odorless, tasteless, white or creamy white fibrous or granular powder.

**Aqueous viscosity:** HPMC K 15 - 15000 mPas.

**Solubility:**

Soluble in cold water, insoluble in alcohol, ether and chloroform but soluble in a mixture of methylene chloride and methanol.

**Functional category:**

Bioadhesive, Emulsifying agent, release modifying agent, sustained release agent, suspending agent, tablet binder, viscosity-increasing agent, film forming agent.

**Stability and storage condition:**

Stable in dry condition from pH 3.0 to 11.0 although it is hygroscopic in nature. Should be store in well closed container, in a cool and dry place.

**Typical properties of HPMC K200M:**

- **Viscosity:** 2% solution at 20°C, 150,000-280,000cps
- **pH:** 5-8
- **Loss on drying:** <5%
- **Gelation temperature:** 75-85°C
3.3.2. Polyethylene oxide – Polyox WSR 303:

Polyethylene oxide is a nonionic homo polymer of ethylene oxide, represented by the formula \((\text{CH}_2\text{CH}_2\text{O})_n\), here \(n\) is the average number of oxyethylene groups. The higher molecular weight grades controls the drug release by formation of hydrophilic matrix.

**Synonyms**: Polyox; Polyoxirane; Polyoxyethylene.

**Chemical Name**: Polyethylene oxide

**CAS Registry Number**: [25322-68-3]

**Molecular Weight**: 7,000,000

**Description**: White to off-white, free-flowing powder and slight ammonical odor.

**Functional Category**: Muco adhesive; tablet binder; thickening agent.

**Solubility**: Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol and most alcohols.

**Stability and Storage Conditions**: Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.
3.3.3. **Xanthan Gum:**

Xanthan gum as a high molecular weight polysaccharide gum and it contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium, or calcium salt.

**Synonyms:**

Corn sugar gum E415; Keltrol; polysaccharide B-1459; Rhodigel; Xantural.

**Chemical Name** : Xanthan gum  
**CAS Registry Number** : 11138-66-2  
**Empirical Formula** : \((C_{35}H_{49}O_{29})_n\)  
**Molecular Weight** : Approximately \(2 \times 10^6\)

**Description:**

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

**Typical Properties:**

- **Acidity/alkalinity** : pH = 6.0–8.0 for a 1% w/v aqueous solution.
- **Freezing point** : 08ºC for a 1% w/v aqueous solution.
- **Heat of combustion**: 14.6 J/g (3.5 cal/g)
- **Melting point** : chars at 270ºC.

**Solubility:**

Xanthan gum is practically insoluble in ethanol and ether; soluble in cold or warm water.
Stability and Storage Conditions:

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range pH 3–12, although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C.

3.3.4. Kollidon SR

Synonyms:

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Chemical name:

Poly vinyl acetate/Poly vinyl pyrrolidone

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value Povidones are manufactured by drum drying and occur as plates.

Empirical Formula : \((C_6H_9NO)_n\)

Molecular Weight : 2500 – 3 000 000

Typical Properties

Acidity/alkalinity

- pH :3.0–7.0 (5% w/v aqueous solution);
- pH :4.0–7.0 (5% w/v aqueous solution) for Povipharm K90

Bulk density : 0.29–0.39 g/cm³ for Plasdone
Tapped density: 0.39–0.54 g/cm$^3$ for Plasdone

True density: 1.180 g/cm$^3$

Melting point: Softens at 150°C.

Moisture content: Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic):

The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Stability and Storage Conditions:

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.