6.1. Pain Management

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage”. Pain management is a broad category of medical science that incorporates multiple disciplines, assessment tools, diagnostic strategies, therapeutic modalities, and treatment philosophies. The present research work has focused on practical applications of only one therapeutic tool, Opioid medications for pain management.

Chronic pain remains a prevalent, challenging, and expensive problem. When treating patients whose pain is not adequately managed with non opioids, in the absence of good evidence for a specific, curative treatment for a given pain problem including physical, psychological, pharmacological and surgical options, opioid analgesics are prescribed with appropriate monitoring. A key principle in the treatment of all types of pain with opioids is to control the dosing schedules.

Opioids are narcotic pain medication. These drugs work by binding to opioid receptors in the brain, spinal cord, and other areas of the body. They reduce the transmission of pain signals to the brain and reduce sensation of pain. They are used to treat moderate to severe pain that may not respond well to other pain medications.

Continuous suppression of pain through the use of around the clock opioid analgesics is recommended in chronic pain treatment guidelines. Conventional opioid analgesics usually require dosing every 4-6 hours in chronic pain. According to IMS Health, the 2011 U.S. market for opioid analgesics was $8.5 billion, of this, extended release opioids accounted for approximately $4.8 billion. Literature states that controlled release formulations of Opioid analgesics also reduce the risk of abuse potential (Charles Hsiao, 2000).

Extended release formulations, “sustained release” or “controlled release” are the standard of care in management of chronic pain. Extended release opioids can provide fewer interruptions in sleep, reduced dependence on caregivers, improved compliance and enhanced quality of life outcomes. In addition, such dosage forms may provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects, compared with short acting opioids. Hence an attempt was made to develop and evaluate pharmaceutically acceptable once a day oral controlled release formulations of opioids CN1027( belongs to schedule IV) and CN2011(belongs to schedule II) for round the clock chronic pain management.
therapy using various approaches such as extended release swelling controlled matrices, osmotic delivery systems, osmocolonic formulations and pellets.

**CN1027** is a centrally acting opioid analgesic used in severe acute or chronic pain management. It is a water soluble drug with half life around 4-5hrs. It is a partial agonist with antagonist activity at the \( \mu \) opioid receptors and agonist activity at the \( \kappa \) opioid receptors.

**CN2011** is a potent, synthetic opioid analgesic with a rapid onset and short duration of action. It is a strong agonist at the \( \mu \)-opioid receptors. Historically it has been used to treat breakthrough pain and is commonly used in pre-operative procedures as a pain reliever as well as an anesthetic in combination with a benzodiazepine. It is approximately 100 times more potent than morphine, with 100 micrograms of CN2011 approximately equivalent to 10 mg of morphine and 75 mg of pethidine analgesic activity.

It is a sparingly soluble drug with a half-life of 1.5hrs. CN2011 binds \( \mu \)-opioid G-protein-coupled receptors, which inhibit pain neurotransmitter release by decreasing intracellular \( \text{Ca}^{2+} \) levels. According to the DEA, C-III to C-V opioids have a low potential for abuse relative to Schedule II (C-II) opioids. This lower abuse potential includes reduced risk for physical dependence and reduced “liking” by recreational drug users. "In addition to the low risk of abuse, C-III opioids have practical advantages over C-II opioids. Considering the half-lives of both the drugs, there is a strong clinical need and market potential for delivery systems that will deliver CN1027 and CN2011 in controlled and prolonged release manner. The rationale, objectives and the plan of the research work are described in Chapter 1.

The project was undertaken with an objective to develop the novel extended release formulations of potent opioid analgesics. A number of strategies were planned for formulation development and evaluation of the novel oral controlled release drug delivery systems such that they demonstrate robust stability and *in vitro-in vivo* performance.

### 6.2. Preformulation Studies

**6.2.1. Procurement of drugs:** In order to procure CN1027 and CN2011, both being opioids, initially FDA permission was mandatory. Drug licenses were obtained by the licensing procedure discussed in Chapter 2 under section 2.2. Drugs CN1027 and CN2011 were then procured from Ivax Pharma and RusanPharma.
6.2.2. Standardization of drugs and excipients: Opioids CN1027 and CN2011 were standardized as per monographic specifications and Certificates of Analysis. Tables 2.1 and 2.3 illustrate various tests and observations and specifications for both the drugs. The drugs passed the tests for identity, purity and the results were found to comply with the pharmacopoeial standards and hence were used for further incorporation in the formulation of controlled drug delivery systems.

All the excipients viz. HPMC K4M, Eudragit RLPO, HPMCK100M, HPMCK100MCR, Carbopol71G NF, Ethyl cellulose N7, Guar gum, Microcrystalline cellulose 101, Aerosil200, Sodium chloride, Sodium bicarbonate were standardized and complied as per the tests given in the respective monographs and Certificates of Analyses provided by the manufacturers and were used in formulation development of proposed oral controlled release drug delivery systems.

6.2.3. Analytical Method Development and Validation:

The analytical methods for estimation of drug content in formulations were developed both by U.V and HPLC methods of analysis as per Pharmacopoeial procedures. The methods were validated and found to be reproducible, accurate, precise, specific, robust and precise.

i. U.V. Spectroscopy for CN1027 and CN2011:

Opioid analgesic CN1027 is sensitive to ultra violet radiation at wavelength of 280nm. Initially an UV visible spectrophotometric method for determination of CN 1027 was developed. The calibration curve was obtained in distilled water and buffers of pH1.2, pH6.8 and pH7.4. The calibration curves exhibited linearity in all the dissolution media, Fig. 2.14. CN1027 was found to be sensitive to U.V. spectroscopy at concentrations less than 100µg/ml. Linear calibration curve in pH 6.8 phosphate buffer was obtained within a concentration range of 50 to 150 µg/ml. LOQ was found to be 50 µg/ml, Table 2.23. Hence UV spectrophotometric method developed was not found very sensitive to determine the low drug content of dissolution aliquots in an initial (1-4) hours and hence HPLC methods were also developed.

Opioid analgesic CN2011 is sensitive to ultra violet radiation at wavelength of 254nm. The calibration curves were obtained in distilled water, buffer pH7.4 and in diluteHCl in methanol. The calibration curves exhibited linearity in various dissolution media. Fig.2.18. This method of analysis for CN2011 was found to be sensitive at concentrations higher than 100mcg/ml.
ii. HPLC method development for CN1027 and CN2011:

HPLC method was developed for CN1027 using Hypersil C18 gold column (250 X 4.6mm, particle size 5micron). For HPLC analysis of drug, the mobile phase consisted of phosphate buffer solution pH 6.8: acetonitrile (60: 40 v/v). The retention time for CN1027 was 5.4 mins.

The method was found to be sensitive in the concentration range of 0.34-45.6µg/ml. The linearity was obtained with $r^2 = 0.9998$. The developed method was validated for linearity, precision, accuracy, LOD, LOQ and robustness. HPLC analytical method for determination of CN 1027 was also developed and validated, Table.2.24. Calibration curves in pH 6.8 buffer and pH 1.2 buffer, Fig.2.16 were developed with excellent linearity within a concentration range of 1 to 40 µg/ml for routine analysis of CN 1027 matrix formulations during in vitro dissolution studies.

A validated HPLC method was developed for determination of CN 2011using a HPLC system Thermofischer with U.V Detector. Calibration curves were linear as depicted in the Fig. 2.20. HPLC method was developed for CN2011using Hypersil C18 gold column (250 X 4.6mm, particle size 5micron) using 1% ammonium acetate: mixture(Methanol: Acetonitrile: Glacial acetic acid (400 : 200 : 0.6))in ratio of 4:6 as mobile phase. The pH was adjusted to 6.6. The method was found to be sensitive in the concentration range of 2.5-12.5mcg/ml. The linearity was obtained with $r^2 = 0.999$.

Drug excipients compatibility studies

To investigate the stability of CN1027 and CN2011 and their interaction with polymers and other excipients, DSC studies were carried out. Endotherms for drugs were obtained at 234°Cand128.5°C respectively. Endotherms of other excipients did not overlap with those for drugs indicating compatibility. Drug contents of excipient admixtures stored at 55°C for 1 month were determined, and there was no significant difference in drug content after storage. FTIR spectra of the tablet blend and placebo premix further confirmed compatibility of CN 1027 and CN 2011 with the selected excipients.

6.3.1. Dose Titration studies of CN1027

CN1027 is an investigational extended release opioid analgesic with a significantly reduced potential for physical and psychic dependence. Till date there are no marketed formulations of CN1027 available for oral use. Thus, efficacy studies were carried out
to assess the potential of the test article (CN1027) to provide anti-nociceptive effect in rats on oral administration. The data presented constitute the first time study examining the effects of oral CN1027 analgesics on established diabetes and chemotherapy-induced pain models. The pharmacodynamic studies in rats were carried out in two parts. As described in Chapter 3.1. Orally effective dose of the CN1027 was titrated by using models of chronic neuropathic pain viz. DPN (Diabetes Peripheral Neuropathy), VIPN (Vincristine induced Peripheral Neuropathy) and TIPN (Taxol Induced Peripheral Neuropathy). The oral doses selected for the studies were 1, 3, 10 and 30 mg/kg. It was observed that the effect of analgesia was pronounced in rats when oral dose given was 10 mg/70 kg and also revealed no significant difference in the analgesic activity with doses 10 and 30 mg/70 kg.

6.3.2. Controlled Porosity Membrane Based Monolithic Osmotic Drug Delivery Systems

Osmotically controlled release dosage formulations have gained considerable interest due to distinct and practical advantages compared with other oral controlled delivery systems such as matrices and reservoirs. Since osmotic drug delivery systems utilize osmotic pressure as the energy source and driving force, drug release can be controlled at a constant rate. In addition, drug release may not be affected by gastric motility, pH, or the presence of food.

CN1027, a short-acting investigational multimodal opioid analgesic has a reduced potential for physical and psychic dependence in experimental models of addiction. In this study, a CPOP dosage form of CN1027 was developed to release drug over 24 hours suitable for once a day administration.

Unlike the elementary osmotic pump (EOP) and push pull osmotic pumps (PPOP), which require a laser drilled drug delivery orifice through the semipermeable membrane, controlled porosity osmotic pumps (CPOP) form an in-situ microporous membrane after imbibing water. The membrane consisted of cellulose acetate as coating polymer and pore forming channeling agent PEG400 in the coating solution avoiding the need for laser drilling of an orifice in the tablets. The effect of polymers, osmogents, channeling agent and loading on in-vitro drug release was investigated. The effects of external variables such as pH and agitation intensity on drug release were also investigated. Scanning electron microscopic studies were carried out to confirm the microporous structure and the coating membrane characteristics. The
membranes formed were characterised in terms of their water permeability, diffusivity and volumetric flux. Osmotic pressure generated was determined using 3D3 freezing point osmometer. Optimized CN1027 dosage forms were placed on stability at 25 deg C/60% RH for 12 months and 40 deg C/75% RH for 12 months. The drug release was inversely proportional to the concentration of polymer (cellulose acetate) in the coating membrane and insoluble pore former, (Dibutylphtalate). The drug release was directly proportional to the concentration of pore formers and osmotic agents. The drug release from the monolithic tablets was found to be directly proportional to the osmotic pressure generated within the tablets as the drug release increased with the increase in osmotic pressure. This may be due to cellulose acetate membrane, which imbibes water and dissolves the osmotic agent present in the core generating osmotic pressure, which serves as the driving force for drug release. The developed monolithic tablets were found to exhibit pH independent release kinetics indicating that the release of CN1027 was through osmotic process. There was no significant change in drug release rate at different agitation intensity. Hence, it can be concluded the release rate of drug from CPOP tablets was independent of agitational intensity. SEM studies confirmed pore formation in CPOP through which the drug was released at constant rate. Pores were formed in situ due to dissolution of hydrophilic pore former embedded in the osmotic pump. SEM studies also revealed that the porosity of the coating membrane was inversely proportional to the concentration of polymer in coating solution used. Drug release from monolithic tablets was linearly proportional to osmotic pressure generated. The formulation provides robust in vitro release over 24 hours, consistent with a once-a-day dosage form. Drug release data from CN1027 formulations fitted well into zero-order kinetics, indicating the release to be drug load independent.

6.3.3. Colon Targeted Delivery Systems of CN1027 based on Osmotic Technology

An attempt was further made to develop an osmocolon system of CN1027 wherein the osmotic tablet B25 was coated with colon specific polymers such as Eudragits S100 and L100 so as to target the osmotic system to colon. This system consisted of osmotic core (drug, osmotic agent and wicking agent), coated with semi-permeable membrane (SPM) containing PEG 400 as pore former, coated cores were then further functionally coated with enteric coating to protect the system from acidic environment of stomach thereby increasing the oral bioavailability of poorly bioavailable drug
CN1027 with extensive hepatic first pass metabolism. The objective of this study was to evaluate the effect of two factors (ratio of Eudragit S100 and Eudragit L100 and the coating level) on CN1027 release from Osmocolon tablets in order to optimize coating formulations for colonic delivery. The ratios of the coating solutions were optimized. For optimization, the ratios of Eudragit S100: Eudragit L100 (1:4, 1:1 and 1:0) were used and the levels of coatings selected were (10%, 15% and 20%, w/w), respectively. The coating process was optimized as shown in Table 3.3.5. Dissolution test was carried out in media with different pH (1.2, 6.8 and 7.2). The formulation showing a lag time of 5hrs and exhibiting the drug release profile as tabulated in Table 3.3.3 was considered potentially viable for the colonic delivery of the formulation. The dissolution data as given in Table 3.3.7 revealed that the level of coating and the ratio of polymers are very important to achieve optimum formulation. The results of the study revealed that factorial design is a suitable tool for optimization of coating formulations to achieve colon delivery. It was confirmed that coating formulation consisting of Eudragit S100: Eudragit L100 in 4:1 ratio at 20% coating level has potential for colonic delivery of CN1027. The optimized formulation produced dissolution profiles that were close to predicted values.

6.3.4. Water Penetration Controlled Swellable Matrices

One of the most common approaches used for prolonging and controlling the rate of drug release is to incorporate the drug in hydrophilic colloid matrices such as hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), Carbopol, ethylcellulose, alginites and gelatin. The mechanism and release kinetics of the drug incorporated in these polymer matrices are dependent on the type and amount of polymer as well as on the physicochemical properties of the drug. Thus attempts were made to develop and evaluate Controlled swellable matrices of CN1027, 10mg using various release retardants such as HPMCK4M, HPMCK15M, HPMCK100M, HPMCK100MCR with swelling controlled mechanism to achieve the desired sustained release profile i.e. 15 to 20% drug release in 2h, 30 to 35% in 6h, 35 to 45% in 8h and 75 to 80% in 24 h. Factors affecting the drug release such as polymer viscosity, polymer ratios, combination of hydrophilic as well as hydrophobic polymers, ratio of swelling agent to the swelling medium and mechanical strength of the polymer were also investigated. The effect of process variables such as tablet hardness, manufacturing techniques on drug release through swellable matrices,
effects of hydrodynamic conditions on drug release such as multi-rpm, multi-dissolution media, multiple dissolution volume on drug release were also studied. Drug release kinetics of the developed and optimized formulation was investigated using mathematical models. Impact of reducing the dose strength on the in vitro release studies was also explored.

From the experimental studies on developed formulations, S1-S13, Formulation S12 with HPMC K100MCR exhibited better sustained effect suitable for once a day administration as compared to HPMC K4M, HPMC K15M, and HPMC K100M. The drug release profiles were not affected by agitational intensity viz. 50 rpm and 100 rpm. No significant differences in the drug release profiles in varying volumes viz. 250ml and 500ml of dissolution media were observed. However, significant differences in the drug release profiles when studied in 250ml and 100ml of dissolution media were observed may be as a result of saturation solubility of the drug. As the pH increased, the drug release was found to be sustained. Formulation S12 showing desired in vitro release profile was considered to be the optimum and taken up for stability studies. Data applied to (a) Higuchi & (b) KorsmeyerPeppas release kinetic models with higher value for $r^2$ confirmed the diffusion controlled drug release mechanism.

Drug release profiles of 5 mg and 10 mg controlled swellable matrices showed comparable release profiles under varying dissolution conditions and indicated robustness of the compositions of optimized formulations.

6.4.1. Controlled Porosity Membrane Based Push Pull Osmotic Drug Delivery Systems

Initially various formulations were tried with different concentrations of osmotic agents in push as well as pull layers. The formulation was optimized using response surface methodology by $3^2$ Factorial designs. It was evident that both the independent variables, namely the concentration of sodium chloride (A1) and sodium bicarbonate (B2) have interactive effects on both the responses, e.g., $Y_1$-drug release in 12hrs, $Y_2$-drug release in 24hrs. PPOP osmotic tablets, Batch B2 exhibited the desired controlled release profiles over a period of 24hrs, suitable for once a day administration. The drug release was found to be increased with increase in the concentration of poreformers and osmotic agents. The drug release was found to be retarded with increase in the concentration of polymer in coating membrane and use
of insoluble poreformer. The developed monolithic tablets exhibited pH independent release kinetics concluding that the release of CN1027 was through osmotic process. There was no significant change in drug release rate at different agitation intensities, hence it can be concluded the release rate of drug from PPOP tablets was independent of agitational intensity. SEM studies confirmed pore formation in PPOP through which the drug was released at constant rate. Pores were formed in-situ due to dissolution of hydrophilic poreformer embedded in the osmotic pump. Drug release from monolithic tablets was linearly proportional to osmotic pressure generated in them.

6.4.2. CN2011 Extended Release Matrix Tablets

From the preliminary experience of the various grades of HPMC on the in vitro drug release of water soluble drug CN1027, we attempted to formulate extended release matrix tablets of CN2011 using putative hydrophilic matrix material HPMC,(HPMCK15M) in combination with hydrophobic polymer, Ethyl cellulose N10 and to study the in vitro release characteristics and release rate kinetics of the prepared formulations. The kinetics of the dissolution process was studied by application of two kinetic equations to the dissolution studies viz. KoresmeyerPeppas equation and Higuchi square root equations.

A Central composite design was employed to get an optimum formulation suitable for once a day administration. The amounts of HPMC K 15M (A) and ethyl cellulose (B) were selected as the factors, studied at three levels each. Table.3.3.2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. The % of drug released in 2hrs (rel2hr),(Y1), % of drug released in 12hrs (rel12hrs),Y2 and % of drug released in 24hrs (rel24hrs),Y3 and 50% drug release ( t50%), Y4 were taken as the response variables. The in vitro release profile was assessed by dissolution study in 250 ml of dissolution media at 50 rpm by pH change method (i.e. pH 1.2 buffer for 2 hrs followed by pH 6.8 phosphate buffer for remaining 22 hrs). Optimized formulations successfully provided minimum release in initial 2 hrs (about 25%) and extended release upto 20 to 24 hrs (52.3% in 12hrs, 88.7% in 24hrs). Physicochemical evaluation of the precompression blend and tablets was carried out for various parameters and results are shown in the Tables 4.2.3. and 4.2.4 respectively. Physicochemical parameters were within limits corresponding to
good flow property of the precompression blend. To assess the effect of agitation speed and change in pH of the buffer media on the \textit{in vitro} release profiles, dissolution studies were carried out by pH change method at 100rpm and in pH 6.8 phosphate buffer as well as in pH 4.5 acetate buffer. The \textit{in vitro} drug release profile was found to be independent of variations in the rpm i.e. agitation speed and pH of the dissolution media. Due to the pH sensitive polymers, the \textit{in vitro} drug release was sustained with increasing pH, (pH 6.8<pH4.5<pH1.2). \textit{In vitro} drug release data of the optimized formulations was applied to various drug release kinetic models. The drug release from the swelling-controlled release systems which swell to a moderate equilibrium degree of swelling prepared by incorporation of a drug in a hydrophilic, initially glassy polymers(Various higher viscosity grades of HPMC and Carbopol) followed non Fickian diffusion layer controlled first order release mechanism.

6.4.3. Controlled Release Pellets

As discussed in Chapter 4.3, the application of the multiple unit dosage principle eliminates the dependency of the depot on gastric emptying, since the sub-units are sufficiently small (i.e less than 2mm diameter) to pass the human pylorus even when the sphincter is closed. It has been suggested that the greatest advantage of the controlled release pellets formulation lies in the reproducible gastrointestinal transport of this multiple pellet preparation (Bechgaard H, 1982). Due to many other advantages as elaborated in Chapter 4.3, our objective was to formulate and evaluate the controlled release pellets of CN2011 using extrusion spheronisation technique incorporating polymers guar gum as release retardant and microcrystalline cellulose as spheronising agent.

In the present study, guar gum was used in the concentration range of 5%-20%w/w. MCC: DCP in various proportions (55:45 to 64:32) were tried and it was observed that as the proportion of DCP was reduced, the pellets became more spherical. DCP alone gave spherical but brittle pellets. With MCC dough of right consistency was obtained as it is finer and has a greater surface area. However, with all the formulations the pellets obtained were more or less spherical. From the \textit{in vitro} release profiles of the developed formulations as shown in Fig.4.3.1 it was observed that all the formulations containing guar gum exhibited total drug release in 10-12hrs. Thus to get an optimum controlled release multiparticulate system of CN2011, further formulation development was carried out by coating the formulation G4 with.
different ratios of Eudragit RLPO and ethyl cellulose in combination. The formulation optimization was finalised using $3^2$ experimental factorial design. The effect of independent formulation variables i.e. concentration of Eudragit RLPO and ethyl cellulose on the dependent response variables such as drug release after 24 hrs and $t_{50\%}$ was assessed. Polymers were coated onto the drug loaded pellets using the pan coater. It was observed that the concentrations of polymers used directly affected the drug release profile. Eudragit RLPO and ethylcellulose showed opposite effects on drug release profiles. Mathematical models were generated for each response parameter to predict the values at selected levels of formulation variables. The effect of the variables and behavior of the system was investigated using response surface plots. The optimized formulation showed drug release of 96.22% in 24 hr and $t_{50\%}$ of approximately 12hrs. The results of this study revealed that the pellets of CN2011 coated with 1:5 ratio of Eudragit RLPO: Ethyl cellulose showed optimum controlled release.

6.5. Preclinical studies

Once the dose of drug, CN 1027 was titrated as discussed in Chapter.3.1, water penetration controlled swellable matrix formulation of CN1027 was developed and optimized. Further, efficacy of the developed formulations was assessed using two behavioural tests viz, Hot Plate Analgesiometer and Tail Flick Test and chronic neuropathic pain models. Following oral administration in rats, the tail flick test and hot plate test were useful for quantifying the duration of nociceptive effect, and helped to differentiate between the effects of various dose strengths of CN1027. The results of the Hot plate test are as shown in Table 5.4 and Fig 5.3 whereas those of Tail flick study are summarized in Table 5.5 and Fig 5.4. In models of chronic neuropathic pain, CN1027 oral formulation showed full analgesic efficacy by successfully reversing the pronounced mechanical and cold allodynia induced in the STZ, VIPN and TIPN models of neuropathic pain as assessed in terms of the mechanical withdrawal threshold test and cold allodynia score test results (Tables 5.6-5.11).

Pharmacokinetic Studies

Pharmacokinetics of the developed oral CN1027 formulation was initiated in Wistar rats to investigate the time course of systemic absorption of CN1027 from oral formulations when compared to intravenous CN1027 in rats. HPLC-UV is the most
sought and inexpensive technique used for bioanalysis. Hence, using this technique, development of analytical method of CN1027 was attempted. From the calibration curve as shown in Fig. 5.2, it was observed that though the curve was linear, the concentration of 1μg/ml showed area of 10.2Mv which is too low to estimate the drug from rat plasma. Thus, this method was found to be less sensitive to detect the drug levels in nanograms. Due to poor UV absorptivity of CN1027, the estimation of CN1027 in plasma was found to be difficult using the HPLC-UV technique. The poor absorptivity necessitated the use of high end analytical technique viz. LCMS-MS. Due to unavailability of this instrument, the pharmacokinetic studies for the system were not undertaken. However, it was concluded that pharmacokinetic evaluation of solid oral dosage forms of such low dose, highly potent opioid analgesic like CN1027 (5-7 times more potent than morphine) needs to be investigated in beagle dogs which was not feasible at Institute level and hence the study was discontinued.

**Toxicity Studies**

The optimized water penetration controlled swellable matrix formulation of CN1027 was subjected to toxicity studies. Acute dose toxicity studies were conducted for 14 days as per OECD guidelines using Wistar rats as animal model. During the acute toxicity studies, the animals were dosed at three dose levels viz 5, 10 and 15 mg/70kg of formulations CN1027 WPCS A, CN1027 WPCS B and CN1027 WPCS C respectively. Animals were observed for presence of tremors, convulsions, salivation, diarrhoea, lethargy, and loss of body weight and food intake. Various haematological and biochemical parameters were also assessed and all the parameters were found to be within the normal limits at all the three dose levels during acute dose toxicity studies. All the rats undergoing treatment in acute dose toxicity studies were subjected to full gross necropsy. Histopathology of all major organs such as liver, kidney, heart, brain and spleen did not reveal any distinct pathological alterations (Fig 5.11-5.15).

Thus, extended release formulations of CN1027 were developed and their physicochemical parameters were investigated and pharmacodynamic efficacy was explored as described in chapters 3 and 5.

**6.6. Conclusion**

Controlled release formulations are preferred over conventional multidose delivery systems, particularly for long-term therapeutic effect. Oral extended release formulations of opioid analgesics may be more beneficial for chronic pain
management. An attempt has been made to develop and evaluate the oral controlled release formulations by applying various strategies such as swellable controlled osmotic pumps, matrix diffusion systems, colon specific, and controlled release pellets.

Controlled swellable matrices of CN1027 and CN2011 were prepared using various viscosity grades of Methocel, Ethocel and Carbopols individually and in combination. The formulations were optimized using varying formulation factors and processing parameters using Central Composite Design. Swellable matrices of CN 1027 and CN 2011 prepared by wet granulation technique gave minimum drug release in 2hrs (15 to 25%) and drug release to the extent of 90% was successfully extended up to 18–24 hrs.

Osmotic drug delivery systems of both the drugs CN1027 and CN2011 were prepared based on novel controlled technologies like monolithic and push pull osmotic pumps respectively. The drug release was found to be increased with increase in the concentration of poreformers and osmotic agents. The drug release was retarded with increase in the concentration of coating polymer and use of insoluble poreformers. The developed monolithic and push pull osmotic formulations were found to exhibit pH independent release kinetics indicating the release of both the drugs through osmotic process. There were no significant changes in the drug release rate at different agitation intensities. Hence, it can be concluded the release rate of drug from monolithic osmotic systems of CN1027 and push pull osmotic pumps of CN2011 were independent of agitational intensities of the dissolution media. SEM studies confirmed pore formation in monolithic osmotic systems and push pull osmotic pumps through which the drug was released at constant rate. Pores were formed in-situ due to dissolution of hydrophilic poreformers embedded in the osmotic pump membrane coat. Drug release from the osmotic system was linearly proportional to Osmotic pressure generated in monolithic tablets.

The multiparticulate pellets of CN2011 were successfully developed using a combination of Eudragit RLPO and ethyl cellulose in 5% w/v and 1% w/v respectively. The formulations were optimized by 3² factorial design. The mathematical models generated during this optimization process were found to be valid on the basis of ANOVA.

The colonic delivery of CN1027 based on osmotic technology was further targeted to colon using pH sensitive polymers such as Eudragits viz. Eudragit S100 and
EudragitL100. Developed formulations exhibited the desired controlled release profiles with a lag time of 5hrs and further extended release over a period of 24hrs, suitable for once a day administration.

The optimized controlled swellable and monolithic osmotic formulations of CN1027 and CN2011 were found to be stable up to a period of 12months under accelerated storage conditions. The in vivo pharmacodynamic and histopathological studies indicated that the swellable controlled drug delivery systems of CN1027 were non-toxic and safe for oral administration. These formulations showed physico-chemical stability and marked antinociceptive activity in Wistar rats. All experiments were conducted with appropriate safety precautions and minimal exposure to the opioid drugs to minimize the drug associated risks.

As against Osmotic systems, the developed swellable controlled matrix based formulations were found to be cost effective avoiding functional coating for retarding drug release with great market potential. The developed optimised formulations might fulfill the biopharmaceutical requirement for once a day oral extended release delivery systems of opioid analgesics.

6.7. Future Scope of the Research Work:

Extended release formulations could also be developed using other novel nanocarriers such as nanoparticles, liposomes, nanostructured lipid carriers could be explored in an attempt to target the opioids to specific pain receptor sites and to minimize the side effects. Such novel particulate carrier based delivery systems may also achieve enhanced oral bioavailability.

Although the developed formulations were found to be promising based on in vitro release profiles and pharmacodynamic efficacy studies, they need to be further investigated by in vivo bioavailability studies in suitable animal models like beagle dogs and human volunteers to assess their in vivo performance.