Synopsis
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Of the thesis titled

DEVELOPMENT OF ORAL CONTROLLED DRUG DELIVERY SYSTEMS FOR PAIN MANAGEMENT

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INTRODUCTION

Chronic pain is a major health problem that affects a significant number of patients, resulting in personal suffering, reduced productivity, and substantial health care costs. Musculoskeletal conditions such as low back pain, osteoarthritis, myofascial pain, peripheral neuropathic pain, and idiopathic chronic pain, joint pain are the leading causes of disability in individuals of working age. Acute pain is usually a consequence of an identifiable insult, such as surgery or other trauma or a consequence of a disease. There is, therefore, a need for optimised pharmacologic and non-pharmacologic treatment strategies for the management of chronic pain. Although there are many effective treatments for pain in most cases, pain is poorly managed and under-treated.

RATIONALE

Current pain management is symptomatic and directed primarily towards relief of pain, optimisation of function, and minimisation of disability. Non-pharmacologic management is frequently aimed at reducing inflammation (with ice and/or heat), rest, exercise, improving range of motion, increasing muscle strength, restoring favourable mechanics, and improving coping skills. Drug treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 selective inhibitors, paracetamol and opioid analgesics. Although NSAIDs, COX-2 selective inhibitors, and paracetamol are effective in ameliorating the symptoms of acute musculoskeletal pain and mild chronic pain, they are suboptimal when used alone for the treatment of moderate to severe pain. Paracetamol is another alternative non-opioid agent, but it’s analgesic efficacy is less than maximal doses of the NSAIDs and it lacks anti-inflammatory effects. Recent evidence suggests that long-term paracetamol use may significantly increase the risk of developing end-stage renal disease.

Opioids are effective analgesics for both nociceptive and neuropathic pain. When opioids are administered, pain is not eliminated, it is simply not acknowledged by the patient. Opioid analgesics are classified as strong agonists, mild to moderate agonists, mixed agonist-antagonists, and antagonists, according to their interaction with opioid receptors. Strong agonists are used to treat severe pain. Morphine is the standard in this group. Other opioids include tramadol (Ultracet, Ultram), hydromorphone (Dilaudid and others), codeine (Tylenol#3), hydrocodone (Vicodin, Lortab), methadone, meperidine (Demerol), Fentanyl (Sublimaze, Duragesic, Verafen), pentazocine (Talwin), propoxyphene (Darvon), and butorphanol (Stadol). Amongst these two opioid analgesic drugs were selected for development of formulations for management of acute and chronic pain. Opioid analgesic CN2011 interacts predominantly with opioid mu receptors but also binds to kappa and delta type receptors and CN1027 is a mixed agonist antagonist that exerts antagonistic and partially antagonistic...
effects at mu opiate receptor sites but is thought to exert it’s agonistic effect at the kappa and sigma opiate receptors. A number of strategies have been introduced to minimise the abuse of opioid analgesics. Primary among these schemes is a legal infra-structure that controls the manufacture, distribution and sale of such drugs. Hence we had to acquire FDA permission and license to procure the two selected actives CN2011 AND CN1027 for research purpose.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Continuous suppression of pain through the use of around the clock opioid analgesics is now recommended in chronic pain treatment guidelines. Conventional immediate release opioid analgesics have been demonstrated to provide short-lived plasma levels, thereby requiring dosing every 4-6 hours in chronic pain. In the case of CN1027, the duration of analgesic effect when administered parenterally or intranasally is approximately 2 to 4 hours. In contrast, twice-a-day (e.g., MS Contin™, OxyContin™) or once-a-day preparations of opioid analgesics (e.g., Avinza™, Jurnista™) are designed to maintain effective plasma levels throughout a 12 or 24-hour dosing interval.

Although oral extended release opioids such as morphine are widely utilized for the management of chronic severe pain, the occurrence of unmanageable adverse effects requires their discontinuation in many patients. Recent clinical experience suggests that patients who have failed to obtain adequate analgesia due to their intolerable and unmanageable side effects while taking one opioid may benefit from switching to an alternative opioid. Opioid analgesics like CN1027 is uniquely suited for use in opioid rotation regimens due to its receptor binding properties, which differentiate it from morphine. Furthermore, CN1027, a schedule IV opioid in the U.S. is associated with less abuse potential than the other Schedule II opioid agonists.

Extended release formulations are the standard of care in chronic pain. Such formulations of Opioid analgesic CN2011 and CN1027 have the potential to provide fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcome, and increased control over the management of their pain. In addition, they may provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects, compared with short acting opioids. When compared with intranasal administration, oral butorphanol may be associated with reduced peak to trough fluctuation in concentrations and clinical effects, such as drug craving.

Hence, the research project was undertaken with an objective to develop a formulation that can deliver such Opioid analgesic drugs for extended periods of time for once a day administration. This
may offer significant patient benefits by providing enhanced efficacy and reduced side effects and may also reduce the number of daily doses compared to conventional therapies. An attempt was made to incorporate these two opioid analgesics drugs as controlled release novel drug delivery systems as pellet systems, matrix diffusion formulations, osmotically controlled drug delivery systems (OCDDS) based on monolithic and push pull technology.

**OBJECTIVES:**

To design and develop once a day controlled release formulations of Opioid analgesics coded as CN2011 and CN1027 using approaches like pelletization, matrix formulations and osmotic pumps.

**PLAN OF WORK:**

The experimental work was planned as follows:

1. Selection of drug candidates
2. Standardization of drugs and polymers
3. Drug-excipients incompatibility studies using Differential Scanning calorimetry

6. Preparation and evaluation of Extended release formulations as follows:
   A) CN2011 extended release formulations:
      a) Pellet formulations  
      b) Matrix formulations (Wet granulation technique)
      c) Osmotic formulations (Push Pull Osmotic Pump).
   B) CN1027 extended release formulations:
      a) Matrix formulations (Wet granulation & Direct Compression technique)
      b) Osmotic formulations (Monolithic osmotic Pump).

7. Evaluation of developed formulations for in vitro drug release profiles using various mathematical models, membrane characterization, DSC, and other physicochemical parameters such as hardness, friability, angle of repose, bulk density. Investigations would also include process optimization and determination of osmotic pressure and coating membrane parameters like water diffusibility, water permeability, and volumetric flux.

8. Scale up and Pilot studies
9. Stability studies as per ICH guidelines
10. In-vivo studies using suitable animal models

**METHODOLOGY:**

1. **Selection and Procurement of drug candidates:** The actives were selected on the basis of their potency, safety and abuse potential in order to develop once a day formulations of opioid analgesic for pain management. The two actives being controlled substances, FDA permission and license was needed from FDA for research purpose. The opioid analgesics CN2011 and CN1027 belonging to
class schedule II and schedule IV drugs respectively had a molecular weight of 336.47g/mol and 327.473g/mol.

**PART I: PREFORMULATION STUDIES ON OPIOD ANALGESICS CN2011 & CN1027:**

1. **Standardization of Drug and Polymers:** CN2011 and CN 1027 were obtained from Rusan Pharma and Ivax Pharma respectively. The drugs were standardized as per the Certificate of Analysis. Cellulose acetate was procured from Sigma Chemicals. Various grades of HPMC, Eudrajit and Avicel were obtained from Colorcon Asia Pvt. Ltd, Degussa, Signet chemicals respectively. All the excipients were standardized as per the specifications and were found to be within the Pharmacopeial limits.

2. **Drug-Excipient compatibility studies:** To investigate the stability of CN2011 and CN1027 and their interaction with polymers and other excipients, DSC studies were carried out. Endotherm for drugs was obtained at 128.5°C and 234°C respectively. Endotherms of other excipients did not overlap with the drug indicating compatibility.

3. **Analytical Method Development:** The analytical method for estimation of drug content was developed both by U.V and HPLC method of analysis as per U.S.P. The methods were validated and found to be reproducible, accurate and precise.

   i. **Development of U.V. Spectroscopy for CN2011:**
   Opioid analgesic CN2011 is sensitive to ultra violet radiation at wavelength of 254nm. The calibration curves were obtained in distilled water, pH7.4 and in dil HCL in methanol. The calibration curves exhibited linearity in all the dissolution media. However this method of analysis for CN2011 was found to be sensitive at concentrations higher than 100mcg/ml.

   Opioid analgesic CN1027 is sensitive to ultra violet radiation at wavelength of 280nm. The calibration curve was obtained in distilled water, buffer pH1.2, pH6.8 and pH7.4. The calibration curve exhibited linearity in all the dissolution media. CN1027 was found to be sensitive at a concentration less than 100mcg/ml. However a drug -excipient interference was observed at this wavelength. Hence, HPLC Method of analysis was also developed.

   ii. **Development of HPLC Methods:**
   HPLC method was developed using 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 a 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 $r^2 = 0.9997$. The analysis was carried out on HPLC system Thermofischer with U.V.Detector.
HPLC method was developed using Hypersil C18 gold column (250 X 4.6mm, particle size 5micron) using buffer pH 6.8 and Acetonitrile (40:60) as mobile phase. The method was found to be sensitive in the concentration range of 0.34-45.6mcg/ml. The linearity was obtained with $r^2 = 0.9998$. The developed method was validated for linearity, precision, accuracy, LOD, LOQ and robustness.

PART II: EXPERIMENTAL STUDIES ON DEVELOPMENT OF OPIOID ANALGESICS CN2011 & CN1027 CONTROLLED RELEASE FORMULATIONS

II.a.1) Formulation development and characterization of controlled release Pellets:
The pellets are multiparticulate systems with the advantages like reduced risk of dose dumping, reduced risk of local irritation in the gastro-intestinal tract and less variable bio-availability. Particles of 1mm or less behave more like liquids in terms of gastric emptying, even distribution over the gastro-intestinal tract. The developmental work was initiated using a model drug 5-ASA. This drug was selected on the basis of it's solubility. The pellets were developed using extrusion spheronisation technique incorporating polymers like HPMC, Eudrajit, ethyl cellulose and spheronising agent microcrystalline cellulose.

A. Optimization of proportion of Spheronising Agents (MCC: Lactose):
Pellet formulations with varying ratios of MCC and Lactose (100:0, 80:20, 70:30, 50:50, 40:60, and 30:70) were prepared using Spheroniser S-120, (Umang Pharmatech).

B. Selection of Binders: Controlled release pellet formulations with different binders (ethyl cellulose, guar gum, Eudragit S) were prepared.

C. Optimization of Spheronisation time and speed:
The process of pellet formulations using selected ratios of spheronising agents was optimized in terms of spheronising time (1, 2.3,4,5,6 mins) maintaining the speed constant.
Pellet formulations with optimized ratios of spheronising agents and residence time were then prepared t varying spheronisation speeds (600-1500 rpm) in order to optimize the spheronising speed.

Optimised process parameters
1) Diluent & Spheronising agent: MCC and Lactose in ratio of 80:20, 2) Binder: Ethyl cellulose, 3)Spheronising time : 2mins, 4) Spheronising speed: 900 rpm

Preparation of CN2011 Pellets: The optimized formula obtained for controlled release pellets of model drug 5-ASA was used to develop the pellets of drug CN2011. The pellets were prepared using
the optimized ratios of spheronising agents and process variables like binders, residence time and spheronising speed.

Evaluation of developed controlled release pellet formulations: The developed pellets were evaluated for physicochemical parameters such as appearance, moisture content, density, hardness, angle of repose, friability and flow properties.

The in vitro drug release profile of the developed controlled release pellets of CN2011 was investigated by pH change method. The pellets exhibited 9.5% drug release in 2hrs, 33.2% in 4hrs, 41% in 8hrs and 65% in 24hrs. Since high drug loss occurred during the spheronisation and there was increased risk of drug exposure to body, this formulation development was not taken up for further investigations. The further research work was focused on formulation development of CN2011 using the following approaches:

1. Controlled release diffusion matrix based formulations.
2. Push Pull Osmotic formulations

II.a.2) Formulation development and characterization of diffusion matrix based sustained release tablets: A series of formulations were tried using combinations of swellable, hydrophilic and hydrophobic polymers with diluents like lactose monohydrate, MCC101, polymers (HPMC 4M, HPMC K15M, different grades of ethyl cellulose), lubricant magnesium stearate, glidant talc and binders like ethanol and alcoholic solutions of ethyl cellulose. Initially the formula optimized for model drug, 5-ASA was used to develop Sustained release matrix diffusion controlled tablets. Drug and excipients were blended together and granulated using ethanol and PVP solution. The formula was further modified to get an optimum formulation for once a day release of opioid analgesic CN2011.

Evaluation: The matrix tablets were evaluated for physicochemical properties like hardness, friability, thickness and weight variation.

In-vitro release kinetics: It was studied by pH change method (pH 1.2 HCL buffer for first 2hrs followed by phosphate buffer pH 6.8 upto 24hrs) at agitation rate of 50 rpm and temperature 37°C using USP Dissolution rate test apparatus II.

The optimum formula was selected on the basis of the invitro drug release profile studied by pH change method. The developed tablets exhibited 20% drug release in 2hrs, 37.5% in 4hrs, 46% in 8hrs and 74% upto 24hrs thus indicating a sustained release profile following Higuchi diffusion mechanism and first order release kinetics.
II.a.3] **Formulation development and characterization of Push Pull based osmotic drug delivery systems**

Osmotic delivery systems utilize osmotic pressure as driving force for controlled delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent, and it is possible to modulate the release characteristics of the drug by optimizing the composition of the system. Delivery of drugs takes place in solution form, which is ready for absorption. Thus they form an in-situ prepared liquid dosage form. It is possible to design an osmotic pump for drugs with wide range of water solubilities.

Currently various products for osmotic delivery are available in the market but they all use laser drilling technology which is expensive and time consuming. Hence the major objective of the project was to develop cheap and cost effective formulations which do not require sophisticated laser drilling technology. Instead novel controlled porosity membrane coated push pull osmotic tablets were developed.

Hence the objective of this part of research work was to develop a once a day dosage form based on osmotic pump technology. This will reduce dose frequency and severity of plasma level fluctuations caused due to conventional dosage forms. Osmotic delivery system of CN2011 for pain management is not yet available commercially.

**Push–pull osmotic pump (PPOP):**

In this technology, the bilayer tablets are coated with a semi permeable membrane. Drug along with osmogents is present in the upper compartment whereas lower push compartment consists of polymers and osmotic agents. The delivery system for CN2011 was developed wherein a semi-permeable rate-controlling membrane, cellulose acetate surrounded an osmotic core. It contained a push layer (composed of swelling polymer and osmotic agents, 110 mg) and a drug layer (composed of CN2011 and diluents, 140 mg).

**Preparation of core tablets:** Core tablets were prepared by wet granulation method. Various formulations were developed using osmogents like sodium chloride, sodium bicarbonate, fructose, lactose and mannitol. Swelling polymers like different grades of HPMC like HPMCK4M and HPMCK100M were incorporated. Tablets were punched using 8 mm deep concave punch fitted to a single punch tablet machine.

**Coating of core tablets:** The core tablets were coated using film former such as cellulose butyrate, cellulose acetate containing the chanelling agents such as PEG 400 & glycerol to form a controlled porosity semi permeable membrane.

When this system comes in contact with G.I fluids, the osmotic agents present in the push layer dissolve generating osmotic pressure at the same time swelling polymer swells and pushes the drug
layer to release the drug in a controlled manner through the pores formed in situ due to simultaneous dissolution of channeling agents. Thus this system avoids the use of laser drill making it a cost effective formulation.

a) Optimization of Coating Process and Formulation Parameters
i. The coating membranes of different types were prepared and characterized to select a suitable film former. Cellulose acetate in varying concentrations with plasticisers was used to prepare Dense coating, or Controlled porosity membrane or Asymmetric membrane.

ii. The parameters of controlled porosity membrane which can affect the delivery of water soluble compounds such as Bursting strength, Percent elongation, Membrane thickness were investigated.

iii. Coating process was carried out on Aquacoater and optimized for parameters like speed of rotation, spray rate, distance of spray gun, temperature and pressure of spray.

b) Effect of following on performance of osmotic delivery system was investigated:
Concentration of osmotic agents on in-vitro drug release profile. Types of swelling polymers and coating composition on in-vitro drug release. The developed osmotic tablets were evaluated for,

i. In-vitro release kinetics: In-vitro release profiles were studied in different dissolution media (phosphate buffer pH1.2, 6.8, and 7.4) at different agitation rates (50, 75 and 100 rpm). Physicochemical properties of tablets like hardness, thickness, weight gain after coating were also noted.

ii. Determination of Osmotic pressure: The osmotic pressure generated within developed formulations was investigated using 3D3 Freezing point osmometer. The readings were obtained in mosmol/kg which was then converted to mmHg and atmospheric pressure.

Results & discussions:

i. The rate of drug release from developed osmotic systems was found to be independent of agitation rate and pH of dissolution media.

ii. The optimised formula was selected on the basis of the in-vitro drug release profile studied in phosphate buffer pH 6.8. It exhibited 13% drug release in 2hrs, 29.5% in 4hrs, 33% in 8hrs and 68.2% in 24hrs thus indicating a sustained release profile.

iii. The osmotic pressure developed in osmotic tablet was in range 11-70 mosmol/kg. The drug release was found to be linear with increase in osmotic pressure.

iv. Characterisation of Controlled Porosity Membranes
Among the three coating membranes, (dense coating, controlled porosity membrane and asymmetric membrane), the controlled porosity membrane was selected on the basis burst strength, percent elongation and membrane thickness.
The pore formation in controlled porosity membrane was confirmed by Scanning Electron Microscopy.

**STABILITY STUDIES:**
The selected batches of developed formulations were subjected to stability studies at room temperature. No significant changes were observed up to a period of 6 months of storage.

**PART II.b: Studies on Opioid analgesic CN1027:** Major objective of this study was to prepare pH independent sustained release dosage form that will slowly release its active ingredient so as to maintain therapeutically effective levels of the active drug in the blood stream for prolonged period of time suitable for once a day administration.

**II.b.1) Formulation development of diffusion matrix based sustained release tablets:**
Based on the trial batches developed for preparation of matrix tablets of CN2011 and the solubility of opioid analgesic CN1027, a number of formulations were tried using combinations of swellable, hydrophilic and hydrophobic polymers with diluents like lactose monohydrate, MCC101, polymers (HPMC K4M, HPMC K15M, different grades of ethyl cellulose), lubricant magnesium stearate, glidant talc and binders like ethanol, alcholic solutions of ethyl cellulose. In addition, novel polymers Polyox WSR301, Polyox WSR303 were also tried.

Both the Wet granulation and Direct compression methods were attempted.
A series of formulations were prepared and investigated for in vitro release profile in order to select an optimum formulation. Two prototypes each were developed using the wet granulation technique and the Direct compression method to get an optimum formulation for controlled release of active CN1027.

**Evaluation:** The dissolution rate studies was conducted using USP Dissolution rate apparatus II (Electrolab attached to an autosampler model).

The effect of the volume of dissolution media (100, 250 and 500ml) on drug release from the developed formulations was investigated. The machine was run at multi-rpm using multi-dissolution media and the drug release rate from the developed formulations was determined.

1. Phosphate buffer, pH 6.8 at 50 and 100 rpm, USP-2 apparatus.
2. Acetate buffer, pH 4.5 at 50 rpm
3. pH 1.2 HCL for the first 2 hours, then pH 6.8 for the remaining 22 hours at 50 rpm and 100 rpm.

Forced degradation studies under stress conditions such as acidic medium, basic medium, u.v.exposure, oxidation, high temperature and humidity were also conducted.

**Results and discussions:**
The optimum formula was selected on the basis of invitro drug release profiles studied in phosphate buffer pH 6.8 and at gradient pH.
Formulations prepared by Direct compression technique:
The two optimized prototype formulations prepared by Direct compression & Wet granulation technique exhibited 15-18% drug release in 2hrs and 78-84% in 24hrs.

Effect of agitation intensity on Drug release:
No significant differences were observed in the drug release profiles at 50rpm and 100rpm of stirrer.

Effect of volume of dissolution media on Drug release:
Significant differences in the drug release profiles were observed when studied using 100ml and 250ml of dissolution media. This could be due to poor solubility of CN1027 and saturation solubility of the media in low volume. No significant differences in the drug release profiles were observed when studied using 250ml and 500ml of dissolution media.

Effect of pH change on Drug release:
As the pH of dissolution media increased, the drug release was found to be further retarded. It could be due to less solubility of drug at higher pH.

II.b.2. Formulation of Monolithic based Controlled Porosity Osmotic Pumps:
Microporous membrane coated monolithic osmotic tablets of CN1027 were prepared by conventional wet granulation technology.
Drug and excipients were blended together in geometric proportion. The alcoholic solution of PVP K30M was added for granulation and the wet mass was passed through #22 sieve and dried in hot air oven at 60°C for 2 hrs. The dried granules were then passed through #36 and mixed with lubricants. The precompression mix was evaluated for physicochemical properties, like moisture content, angle of repose and bulk density results. The tablets were compressed at an average weight of 250mg using 8mm deep concave tablet compression machine.

Coating process Optimization and Formulation Parameters:
Coating process was optimized for parameters like speed of rotation, spray rate, spray gun distance, temperature and pressure. Various factors modifying osmotic drug delivery and their effect on in vitro drug release profile were investigated. The influence of varying the concentration and different types of osmotic agent, swelling polymers, film formers and poreformers were investigated. The coating membranes were optimized for volumetric flux, water permeability and water diffusibility. These factors play a vital role in drug release. The osmotic tablets were evaluated as described earlier.

Results & discussions:
The optimum formula was selected on the basis of the invitro drug release profile studied in phosphate buffer pH 6.8.

Prototype formulations A, B & C exhibited 13-15% drug release in 2hrs and 76-85% in 24hrs.
Process Optimization and Formulation Parameters:
The drug release was found to be increased with increase in the concentration of pore formers and osmotic agents.
The drug release was found to be retarded with increase in the thickness coating membrane and concentration of polymers like cellulose acetate, cellulose butyrate and on addition of insoluble pore formers.
The developed monolithic tablets was found to exhibit pH independent release kinetics rate indicated that the release of CN1027 was through osmotic process.
There was no significant change in drug release rate at different agitation intensity of stirrer and thus 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 insitu due to dissolution of hydrophillic poreformer embedded in the osmotic pump.
The drug release from the osmotic system was found to be linear with the osmotic pressure generated in monolithic system.

Water permeability: Permeability of water through the membrane was calculated from the eq. \( \frac{dv}{dt} = \frac{A}{h} L_p (\sigma \Delta \pi - \Delta p) \). For 20% of pore former (PEG 400) the water permeability was found to be \( 5.3 \times 10^{-5} \). As permeability of membrane increased drug release was found to increase. Hence concentration of pore former was optimized to 20% w/w of cellulose acetate.

Volumetric Flux: It shows influx of G.I fluids through the coating membrane. It was calculated from the eq. \( \frac{dv}{dt} = \frac{1}{C} \frac{dm}{dt} \). For 20% of pore former (PEG 400) the volumetric flux was found to be \( 8.7 \times 10^{-4} \) ml/hr.

Water diffusivity: The effective or “equivalent diffusivity” of water through the walls of the controlled porosity osmotic pump was computed using eq. \( \frac{dV}{dt} = AKD_{w,eq} \Delta C_w/h \).
The nominal equivalent diffusivity of water through void free cellulose acetate was \( 1.04 \times 10^{-7} \) cm\(^2\)/sec. It was found to increase to \( 7.205 \times 10^{-5} \) cm\(^2\)/sec with increase in PEG 400 (20% w/w).

Effect of Osmotic pressure generated within the system: The osmotic pressure developed in osmotic tablet was in range 8-65 mosmol/kg. The drug release was found to be linear with osmotic pressure.
Membrane characteristics:

<table>
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<tr>
<th>S.no</th>
<th>Membrane</th>
<th>Burst strength (kg/cm²)</th>
<th>Percent elongation (%)</th>
<th>Membrane thickness (µm)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Dense coat</td>
<td>4.5±0.3</td>
<td>1.2±0.25</td>
<td>40±1.8</td>
</tr>
<tr>
<td>2</td>
<td>Controlled porosity membrane</td>
<td>3.7±0.4</td>
<td>4.7±0.8</td>
<td>40±2.5</td>
</tr>
<tr>
<td>3</td>
<td>Asymmetric membrane</td>
<td>2.9±0.5</td>
<td>7.5±0.7</td>
<td>40±2.2</td>
</tr>
</tbody>
</table>

PART III. SCALE UP AND REPRODUCIBILITY STUDIES:

The optimized formulations were scaled up to 5 times of the original batch size. The reproducibility of manufacturing process was validated by preparing the same batch in triplicate. Effect of compression speed, pressure, and rotation speed on tablet weight and hardness was assessed. The coating process for large scale up batch was also optimized using the Aquacoater. The developed formula was found to be scalable and reproducible during the pilot plant study without any significant changes in physicochemical parameters such as friability, hardness, thickness, and moisture content.

STABILITY STUDIES:

The optimized formulations (both matrix and osmotic) were packed in HDPE Bottles, 50cc with an induction seal and subjected to stability studies at temperature and humidity conditions as per ICH Guidelines:

25°C ± 2°C and 60% ± 5% RH, withdrawal time points at 1, 2, 3, 6, 9, and 12 Months
40°C ± 2°C and 75% ± 5% RH, withdrawal time points at 1, 2, 3, and 6 Months.

The matrix and osmotic formulations of active CN1027 indicated no appreciable changes in appearance, colour, %drug content, hardness, weight, drug release profile, and the formulations were stable at all storage conditions at the end of 12 months.

PART IV: IN VIVO STUDIES:

The pharmacokinetic and behavioural studies were conducted as per the animal protocol approved by the Animal Ethic Committee.

a) Pharmacokinetic studies: Pharmacokinetics of developed formulations was studied in Wistar rats. The rats were anaesthetized and at different time intervals the blood was collected and concentration
of drug in blood was estimated by developed bioanalytical method using HPLC. Various pharmacokinetic parameters like $C_{\text{max}}$, $T_{\text{max}}$, AUC, bioavailability and $t_{1/2}$ were determined.

**b) Behavioural studies:** The analgesic activity of developed opioid analgesic CN1027 was carried out using the following Pain models.

**Experimental conditions:** Wistar rats of either sex (equally distributed among groups) weighing 250±20g maintained on standard laboratory diet having free access to tap water were employed in the present study. They were housed in the departmental animal house and were exposed to 12 hr cycle of light and dark and the animals were divided in Vehicle control group and four treatment groups of Orally administered CN1027 at four dose levels with three animals in each group.

i). **HOT PLATE TEST:** The wistar rats were placed into a glass cylinder on a hot plate adjusted to 52°C and the latency of the first reaction. (Lick, shake, jump) was recorded (cut off for the first trial 30 seconds).

ii) **TAIL FLICK TEST:** The wistar rats were submitted during which the ventral surface of their tail was immersed into a glass cylinder containing water adjusted to 52°C and the latency of the first reaction. (Lick, shake, jump) was recorded (cut off for the first trial 30 seconds).

**Following Neuropathic Pain models were developed to assess the analgesic effect of developed formulations:**

The induction of neuropathy was assessed in terms of tactile allodynia using von frey filaments and cold allodynia using acetone drop test.

i) **DIABETES INDUCED NEUROPATHIC RATS:** A single injection of streptozotocin (STZ) (40-70 mg/kg, i.p.) was used to induce diabetes in rats.

ii) **PACLITAXEL INDUCED NEUROPATHIC RATS:** The rats were administered paclitaxel (2 mg/kg, i.p.) every second day until five such doses were delivered to the rats.

iii) **VINCRISTINE INDUCED NEUROPATHIC RATS:** The rats were administered vincristine (200 µg/kg, i.p.) every second day until five such doses were delivered to the rats.

**c) Toxicity Studies:** To prove the safety of the developed opioid analgesic formulations, the toxicity studies were carried out as per OECD guidelines. The potential of developed formulations to induce acute toxicity was investigated in Wistar rats.

**Acute Toxicity:** The acute toxicity of the developed matrix formulations was assessed at three dose levels. The rats were observed for 14 days and at the end of 14th day hematological profile and serum biochemistry was determined. The histopathological examination of vital organs was performed. No mortality was observed. No significant change in any of the biochemical and histological parameters was observed. The results obtained from histopathological studies indicated that the developed formulations were safe for oral administration.
One of the challenges with the development of oral extended release dosage forms is that unlike immediate release oral or parenteral dosage forms, the dose cannot be modified for testing on non-human species. In the case of opioids, emesis, obtundation, significant psychomotor retardation, inactivity or cardiac depression could ensue with the use of human doses, thereby affecting the PK of the drug. In addition, the prolonged sampling times result in increased sample volume, which can also add to PK variability. As a first step, we have dosed dogs to determine whether we will need to concurrently dose the dogs with the opioid antagonist, naltrexone.

The behavioural studies for CN1027 in two dogs: The developed formulation (CN1027 dose: 10mg) was administered to two dogs weighing 25-30kg and 12-15kg weight.

**Results & discussions:**

The studies investigated the analgesic efficacy of formulation CN1027 in diabetes induced, paclitaxel induced and vincristine induced neuropathic rats. The drug showed full analgesic efficacy against the neuropathic pain condition as assessed in terms of the mechanical withdrawal threshold test and cold allodynia score test results.

In both the animals mild sedation began 20 minutes after dosing and peaked by 50-60 minutes after dosing. No other signs of opioid toxicity were observed (one dog was of 25-30 kg weight, while the other was 12-15 kg weight.

Further Pharmacokinetic profile in Dogs needs to be investigated.

**CONCLUSION:**

The developed Controlled porosity membrane based monolithic osmotic tablets would provide cost benefit as compared to conventional laser driven osmotic drug delivery system.

It was concluded that patent non-infringing controlled release osmotic and matrix formulations have been successfully developed and characterized. Since once a day formulation for opioid analgesics CN2011 and CN1027 is much needed for treatment and management of acute and chronic pain, the developed formulations have a great market potential.

**KEY REFERENCES:**


Makhija SN, Vavia PR, “Controlled porosity osmotic pump-based controlled release systems of Pseudoephedrine I.


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