CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

The pharmaceutical industry is facing problems in development of new drug molecule for prevention and treatment of existing and newer diseases. Additionally, the development cost for NCEs is very high and escalating, and today the cost is more than 1 billion US $ for developing one NCE and bring it to market. Drug delivery system helps in providing competent drug product of existing drugs. The earliest studies in the field of controlled drug delivery date back to the 1950s. Since then, a large number of drug products with controlled release characteristics, have been introduced. The incredible growth can be attributed to several advantages that these products offer, including improved patient compliance, better therapeutic efficiency, potential for cost saving, patentability and opportunity for extending product life-cycle. Various technologies have been investigated in order to achieve different kinds of modified release, e.g. sustained, delayed, pulsatile, targeted and programmed release. Regardless of the delivery type, the main mechanisms associated with drug transport in these systems include diffusion, swelling, erosion, ion exchange, and osmotic effect. Figure 1.1 shows schematic of plasma profiles attained through different types of delivery systems

BENEFITS OF EXTENDED RELEASE DRUG DELIVERY SYSTEMS

By improving the way in which drugs are delivered, an extended release drug delivery system is capable of achieving the following benefits.

1. Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations for extended period of time.
2. Predictable and reproducible release rates for extended duration.
3. Enhancement of activity duration for short half-life drugs.
4. Elimination of frequent dosing, inconvenience of night time administration of drug.
5. Optimized therapy and better patient compliance.
6. Improve efficacy/safety ratio
7. Reduction total dose
8. Uniform drug effect
9. Reduction of the incidences and degree of toxic and side effects such as irritation of gastro-intestinal tract caused by some orally administrated drugs.

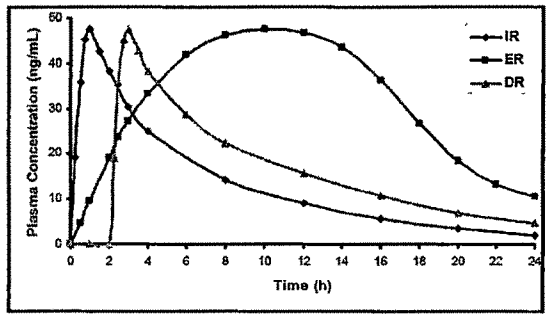

Figure 1.1 Schematic IR – Immediate Release; ER – Extended Release; DR – Delayed Release

Acute pain is usually a consequence of an identifiable situation, such as surgery or other trauma, or a consequence of a disease, e.g. mechanical low back pain, sprain, strain, stone etc. The treatment of acute pain, including post-surgical pain has not significantly improved despite the growing recognition that adequate pain relief is a foremost important for improving patient's life. Better pain management is supreme need. Chronic non-cancer pain is a major health problem that afflicts a significant number of patients, resulting in personal suffering, reduced productivity and substantial health care costs. Musculoskeletal conditions such as low back pain, osteoarthritis, and peripheral neuropathic pain and idiopathic chronic pain joint pain are the leading causes of disability in individuals of working age. Patient who undergoes surgery has more fears about post-surgical pain rather any other concern, including whether or not the surgery would be effective. Survey data indicate that chronic pain is poorly managed and that many patients experience moderate to severe pain and reduced activities of daily living despite seeking the assistance of clinicians. In the absence of established medical or surgical procedures to significantly influence many conditions that result in acute and chronic pain, current management is symptomatic and directed primarily towards relief of pain, optimisation of function and minimization of disability.

Non-pharmacologic management of pain is expected to reduce inflammation (with ice and/or heat), rest, exercise, improving range of motion, increasing muscle strength, restoring favourable mechanics and improving coping skills. There is, therefore, a need for optimised pharmacologic and non-pharmacologic treatment strategies for the management of chronic non-cancer pain.

Drug treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 selective inhibitors and opioid analgesics.

Although NSAIDs like COX-2 selective inhibitors and paracetamol are effective in ameliorating the symptoms of acute musculoskeletal pain and mild chronic pain. The inhibition of COX-1 during long-term NSAID therapy is believed to be responsible for a number of common and severe adverse effects, including coagulopathies, gastrointestinal injury and renal impairment.

Lornoxicam, is a short-acting nonsteroidal anti-inflammatory drug (NSAID) from the oxicam group with analgesic, anti-inflammatory and antipyretic properties. It works like other NSAIDs, the inhibitory action on prostaglandin synthesis, via inhibition of cyclo-oxygenase(COX) activity. It is used in the form of injectable, suppository, tablet formulations for relieving postoperative pain following gynaecological or orthopedic surgery, and as effective as other NSAIDs after oral surgery. Lornoxicam was also as effective as other NSAIDs in relieving symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. Patients suffering from diseases such as acute pain, mild to moderate pain and/or inflammatory conditions and/or related conditions very often require a dosage and a formulation which enable a fast onset of the therapeutic effect of the non-steroidal anti inflammatory drugs (NSAID)
The twice daily dosing regimen for immediate-release Lornoxicam tablets is well tolerated with few incidences of adverse events which are proportionate to the drug plasma level and therefore for improving the therapeutic efficacy, reducing incidences of adverse events and enhancing patient compliance an extended release once-daily regimen is needed. 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 to be given before the effects of the previous dose dilapidates.

The objective here is to provide an extended release pharmaceutical composition of lornoxicam, which upon ingestion results in blood plasma levels having pharmacological effect for an extended period of time. It is needed to produce a pharmaceutical composition which releases Lornoxicam in predetermined manner. It is also needed to provide extended release pharmaceutical composition of Lornoxicam for once daily dosage regimen.

Extended therapeutically effective plasma levels over a twenty four hour period with lesser incidences of adverse events by eliminating the troughs and peaks of drug concentration in a patient blood plasma, which comprises administering orally to a patient in need thereof, an

extended release tablet that provides a peak blood plasma level of Lornoxicam for extended duration.

The use of high viscosity grade hydrophilic and the hydrophobic polymers to produce extended or controlled release pharmaceutical composition is very well known. For extending the release, the tablet comprising the drug also comprises of high viscosity grade hydrophilic polymer. On contact with gastric fluid, it enters the tablet core and results into the hydration of the polymer which also controls the release of the drug. Control of the rate of release benefits therapy by producing constant blood plasma levels of the active ingredient and by decreasing the frequency of administration, thereby improving the patient compliance to the dosage regimen. It is imminent to develop pharmaceutical composition of extended release tablets of Lornoxicam suitable for once daily administration with immediate burst effect.

Like most of the NSAIDs, lornoxicam is very sparingly soluble in water. Since lornoxicam is a weak acid (pKa of 4.7), the aqueous solubility of acidic lornoxicam is pH dependent. Fast absorption of drugs into the circulating blood is generally required in managing pain relief, like in the case of lornoxicam. Therefore, for oral dosage forms it is of utmost importance to have the drug dissolved, completely or partially, already when present in the gastric fluid. Thus, in the event where the drug is not absorbed from the gastric mucosa, it may be ready for being absorbed already when entering the upper intestinal tract, such as duodenum. Duodenum itself has a limited amount of liquid, thus resulting in slow dissolution of the drug in duodenum, although the weak acid may be more soluble in the intestinal fluid. Concordantly, the major problem associated with the formulation and effectiveness of the lornoxicam is its variable oral absorption due to insufficient aqueous solubility at gastrointestinal pH, thus making solubility the rate-determining step in the gastric absorption of it followed by controlled rate of release to produce constant blood plasma levels leading to decreasing the frequency of administration, thereby improving the patient compliance to the dosage regimen.

Presently Lornoxicam is administered to adults as conventional immediate release tablets. The current dosing regimen includes twice daily administration. Lornoxicam is available as an immediate release and is approved for sale in various countries.

Opioid analgesics are highly effective in treating moderate to severe pain. Although the role of opioid analgesics in cancer pain is now well established, there is continued resistance to their use in acute, and particularly, chronic non-cancer pain, due to a perceived lack of

efficacy, concerns about analgesic tolerance, side effects, addiction and adverse regulatory sanctions. Many clinicians utilize opioid analgesics half-heartedly, often at suboptimal doses in patients with significant pain that is only partially responsive to non-opioid analgesics.

A major snag in the evaluation of opioid analgesic therapy for non-cancer pain is the possible risk of addiction. The perception that patients with chronic pain receiving opioid analgesics are at high risk of addiction has significantly influenced the approach to treatment for many painful chronic non-cancer conditions. The terms physical dependence, psychological dependence (addiction) and tolerance are often used inconsistently, resulting in considerable misunderstanding among clinicians, patients and regulators. Physical dependence is characterised by an abstinence syndrome following the abrupt cessation of an opioid or following administration of opioid antagonists. Physical dependence to opioids is to be expected with long-term opioid therapy at therapeutic doses. In such patients, symptoms of opioid withdrawal can be avoided or minimised by gradually tapering the dose of an opioid. Psychological dependence (addiction), on the other hand, is a behavioural syndrome that is characterised by an intense desire for the opioid, evidence of compulsive use, and acquisition of opioids by manipulation of the medical system or from a non-medical source. According to the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, addiction is a neurobiological disease that is characterised by behaviours with at least one of the following: impaired control over drug use, compulsive use, use despite harm and craving for the drug. Tolerance is a phenomenon resulting from continued exposure to the drug, resulting in a decreased pharmacological effect over time.

The use of opioids for non-medical purposes has existed throughout recorded human history. Pharmaceutical dosage forms containing opioids have been used for non-medical purposes like by patients with pain who had a pre-existing addiction disorder; by patients with an addiction disorder seeking opioids for their non-analgesic properties; and by recreational drug users looking for periodic mood-altering effects of opioids.

Experience with the use of opioid analgesics in cancer pain and, more recently, in patients with chronic non-cancer pain indicates that in patients with no prior history of drug abuse, the risk of addiction to opioids is low. In depth understanding of the clinical pharmacology of opioids and well-controlled clinical trials data resulted in their more widespread use in patients with non-cancer pain in regulated market. This, in turn, has led to concerns about the

increased non-medical use of opioids through both licit and illicit channels. For instance, unsuspecting clinicians may prescribe opioids for pain to individuals with an addiction disorder or individuals with pain who divert a portion of their prescribed dose to other persons. There have also been documented cases of inappropriate prescribing or dispensing of opioids by physicians and pharmacists, with its eventual diversion into the non-medical marketplace. In addition, the non-medical supply of pharmaceutical-grade opioids is often achieved through prescription forgeries and theft from pharmacies. Non-medical users of opioids analgesics are either recreational drug users who may use such agents episodically, or individuals with an addiction disorder who may require frequent maintenance doses. Opioid analgesics may be ingested whole, crushed and ingested, crushed or vaporised and inhaled, or injected intravenously after attempted extraction of the active pharmaceutical ingredient.

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. Excessive controls on the manufacture, distribution and particularly the sale of opioids has the unintentional effect of causing physicians, fearful of being accused of permitting opioid overuse, to prescribe suboptimal doses of opioids to patients. This phenomenon is described in the literature as opiophobia or narcophobia. It is also evident that controls on the manufacture, distribution and sale of opioids alone are not adequate to deter the abuse of opioid analgesics.

There is greater resistance on the part of physicians and patients to the use of the more potent opioid analgesics for non-cancer pain. There is also a greater risk of drug abuse and drug diversion with the full opioid agonists, such as morphine, fentanyl, meperidine, methadone, oxycodone and hydromorphone.

Butorphanol is a unique synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. Unique characteristic of butorphanol is that it is an agonist at the κ opioid receptor and an antagonist at the μ opioid receptor which is not the case for commercially available opioid analgesics morphine, hydromorphone, oxycodone, hydrocodone, fentanyl and pethidine. Butorphanol was pioneered in the U.S. as an injectable analgesic and as an intranasal formulation later. Both injection and nasal spray formulations of butorphanol tartrate are approved in the U.S. for the management of pain when the use of an opioid analgesic is appropriate. The injection formulation is also indicated as a

preoperative or pre-anesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

Butorphanol is not a controlled substance in most countries, including India and it is not a listed drug in Schedules I and II of the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol Amending the Single Convention. The International Narcotics Control Board (INCB), an independent and quasi-judicial control organ monitoring the implementation of the United Nations drug control conventions does not monitor its import or export.

At the time of its commercial introduction in the U.S., butorphanol was an unscheduled narcotic. In 1997, as a result of increased rates of abuse, it was reclassified in the U.S. as a Schedule IV controlled substance. According to the Drug Enforcement Administration (DEA), which enforces the controlled substances laws and regulations of the United States, a Schedule IV drug has a low potential for abuse relative to other substances in schedule III, II or I. For comparison purposes, morphine, fentanyl, meperidine, methadone, oxycodone and hydromorphone, the most commonly used opioids are all Schedule II opioids.

The agonist properties of butorphanol at the κ opioid receptor and antagonist properties at the μ opioid receptor give rise to its unique pharmacological profile when compared with μ opioid receptor agonists such as morphine, fentanyl, meperidine, methadone, oxycodone and hydromorphone, including:

1. A "ceiling" to the respiratory depressant effects of butorphanol;
2. A reduced propensity to produce physical dependence;
3. Significantly reduced reinforcing properties in subjects;
4. Reduced drug liking by drug addicts and recreational drug users;
5. Different opioid receptor binding profile

It will not be wrong to conclude that butorphanol provides a safer alternative to the μ-opioid receptor agonists, both in terms of opioid effects and in terms of the risk of physical dependence, addiction and drug diversion.

The oral route of administration (i.e., oral ingestion) is the most widely used and most widely preferred method of drug administration. It is simple, reliable and readily accessible. Under

most conditions of use, particularly outside the hospital setting, it is the recommended method of drug administration. Even in settings of skilled nursing care, where there are technical and human resources to initiate and manage parenteral therapy, the goal is to rapidly transition patients from parenteral medications to oral medications. Some generally cited exceptions to the use of the oral route include: (i) drugs with poor oral bioavailability; (ii) drugs requiring a rapid onset of effect; (iii) where venous access already exists (e.g., in the peri-operative or intensive care setting); and (iv) where the oral route provides unreliable or inconsistent clinical effects.

Administration of butorphanol by the oral route provides significantly greater flexibility in dosage form design, clinical utility and patient acceptability. 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. Furthermore, in many cases, such dosage forms may have a reduced potential for abuse and diversion than intranasal solutions of butorphanol, thereby reducing subsequent abuse by the intravenous route.

Well controlled clinical trials also demonstrate the efficacy of oral immediate release butorphanol.

Oral extended release opioids such as morphine are widely utilized for the management of chronic severe pain (Babul et al., J Clinical Pharmacol, 1998) but due to adverse effects they required discontinuation (Bruera et al., Journal of Clinical Oncology, 1998). Recent clinical experience suggests that patients who have failed to obtain adequate analgesia due to intolerable and unmanageable side effects while taking one opioid may benefit from switching to an alternative opioid. Clinicians can exploit this variability in drug response by empirically offering sequential trials of different opioids in order to optimize analgesia and minimize side effects (opioid rotation). Butorphanol is uniquely suited for use in opioid rotation regimens due to its receptor binding properties, which differentiate it from other morphine like molecules.

The apparent low bioavailability of butorphanol (about 17%) has also been referred as a barrier to effective oral therapy and has short half life. However, by developing an extended

release formulation activity duration for short half-life drugs can be enhanced. Several clinical trials have established efficacy of oral immediate release butorphanol for different pain i.e. moderate to severe musculoskeletal pain, postsurgical pain dose from 2 mg to 16 mg. Additionally, low oral bioavailability with the parent drug is usually associated with higher concentration of its principal metabolite. For butorphanol, both hydroxybutorphanol and norbutorphanol appear to be pharmacologically active and may contribute disproportionately to the analgesic efficacy of oral butorphanol. Some parallels can be drawn between the low oral bioavailability of butorphanol and the low oral bioavailability of oral oxymorphone, a μ opioid receptor agonist, which has an oral bioavailability of less than 10 % and has demonstrated robust oral efficacy in acute and chronic pain in immediate release and extended release forms.

The duration of analgesic action of intranasal and injectable butorphanol is approximately 2 to 4 hours. Previous well controlled clinical trials in chronic cancer and non-cancer pain with other opioids have demonstrated that scheduled administration of extended release analgesic results in significant reductions in pain intensity, breakthrough pain and pain related disability, when compared with "unlimited" analgesic administration of immediate release formulation.

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 to be given before the effects of the previous dose dilapidates. Uninterrupted pain suppression through the day use of opioid analgesics is recommended in chronic pain treatment guidelines (American Pain Society, 2002; American Pain Society, 2005). Conventional release so called "immediate-release", "short acting" or "normal release" opioid analgesics have been demonstrated to provide in consistent plasma levels leads to dosing interval of 4-6 hours for treatment of chronic pain. In the case of butorphanol, the duration of analgesic effect when administered parenterally or intranasally is approximately 2 to 4 hours. In contrast, twice-a-day Morphine Sulphate & Oxycodone respectively MS Contin™ controlled release, OxyContin™ timed release or once-a-day Morphine Sulphate preparations of opioid analgesics vinza™ and Extended release Hydromorphone capsule, Jurnista™ prolonged-release tablets are designed to maintain effective plasma levels throughout a 12 or 24-hour dosing interval using various modified release drug delivery systems.

Extended release formulations are the standard in chronic pain. An extended release formulation of butorphanol has the potential to provide better sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of their pain. In addition, such a formulation may provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects, compared with short acting opioids. Furthermore, butorphanol, a schedule IV opioid associated with less abuse potential than the Schedule II opioid agonists like morphine, fentanyl, meperidine, methadone, oxycodone and hydromorphone molecules.