CHAPTER 2

DRUG PROFILE

2.1 INTRODUCTION

Tapentadol is an FDA approved opioid analgesic with a central action, with a potency between morphine and tramadol. Tapentadol has been approved as immediate-release as well as controlled release tablets in formulations of 50 mg, 75 mg and 100 mg for every 4 to 6 hours. The drug is administered 3-4 times daily owing to high first-pass effect and oral bioavailability is 32 %.

It is a synthetic central acting analgesic and is indicated for the treatment of moderate to severe acute or chronic pain. It has a unique dual mode of action,as an agonist of the μ opioid receptor and as an inhibitor of nor-epinephrine reuptake. As a μ-opioid agonist, it binds and activates μ opioid receptors in the central nervous system (2). It modifies the sensory and affective aspects of pain, inhibits transmission of pain in the spinal cord and affects the activity in parts of the brain that control the perception of pain (3). Tapentadol also exerts its analgesic effect by increasing the level of nor-epinephrine in the brain. Itinhibits the re-absorption in nerve cells due to its inhibitory properties of nor-epinephrine reuptake in the sites of the central nervous system (4).

The physicochemical properties of Tapentadol and its unique mechanism of action led to the scientific inquiry to administer the drugintranasally to provide early relief from the pain.

2.2 DRUG PROFILE

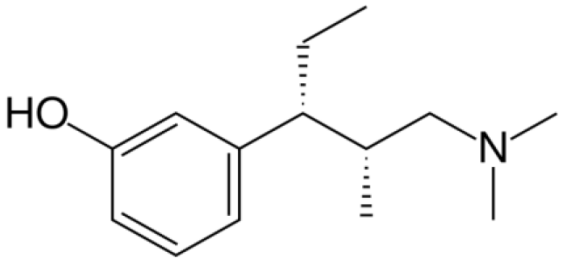
2.2.1 PHYSICOCHEMICAL PROPERTIES:

Table 2.1: Tapentadol base is characterized by various physicochemical properties.

S.No	Parameters	Description
1	Genericname	Tapentadol
2	IUPACname	3-[(2R,3R)-1-(dimethylamino)-2-methylpentan-3-yl]phenol
3	CASregistrynumber	175591-23-8
4	Empiricalformula	$C1_4H_{23}NO$
5	Molecularweight	221.33 (base)
6	Meltingpoint	90°C (base)
7	Appearances	White crystalline powder
8	LogP	2.87 (FDA), 3.47 (predicted)
9	pKa	9.34 - 10.45
10	WaterSolubility	It is less soluble in water (base), but its HCl salt is very soluble in water

2.2.2 CHEMISTRY:

Tapentadol has a molecular formula C14H23NO and mol. Wt. 221.3 g/molTapentadol. The chemical name for Tapentadol is (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol (5).



It is a weakly basic drug,the solubility of base increases as pH decreases. It exerts lower melting point and crystalline in nature. It also exhibits racemic nature due to rotatable bonds however potency remains the same.

- **DSC thermogram**

Drug shows lower melting point with Peak point 91.04°C.

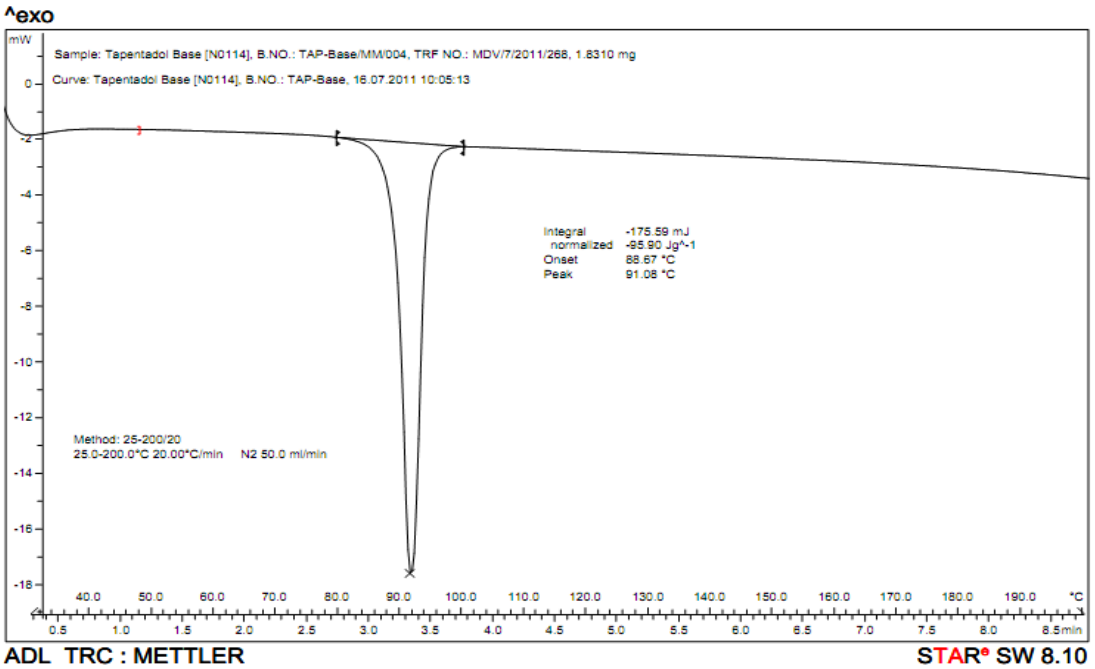


Figure 2.1: DSC thermogram of Tapentadol base

- **Solubility**

Tapentadolexhibits pH dependent solubility. However,the saturated solubility of drug was carried out by shake flask method.

Table 2.2: Saturated solubility data of Tapentadol base

Drug Saturated solubility	
Temperature: 37°C	
Shake Flask method (48 hrs.)	
Media	Solubility
In pH 4.5 Acetate buffer	4.1 mg/ml
In pH 6.0 Phosphate buffer	7.9 mg/ml
In pH 7.4 PBS	2.2 mg/ml

2.3 MECHANISM OF ACTION

Tapentadol is a synthetic, centrally acting analgesic. Although its exact mechanism is unknown, analgesic efficacy is believed to be due to the activity of the μ-opioid agonist and the inhibition of nor-epinephrine reuptake. As a μ-opioid agonist, it binds and activates μ opioid receptors in the central nervous system. It modifies the sensory and affective aspects of pain, inhibits the transmission of pain in the spinal cord and affects the activity in parts of the brain that control the perception of pain. Tapentadol also exerts its analgesic effect by increasing the level of nor-epinephrine in the brain by inhibiting its re-absorption in nerve cells due to its inhibitory property of nor-epinephrine reuptake in the sites of the central nervous system.

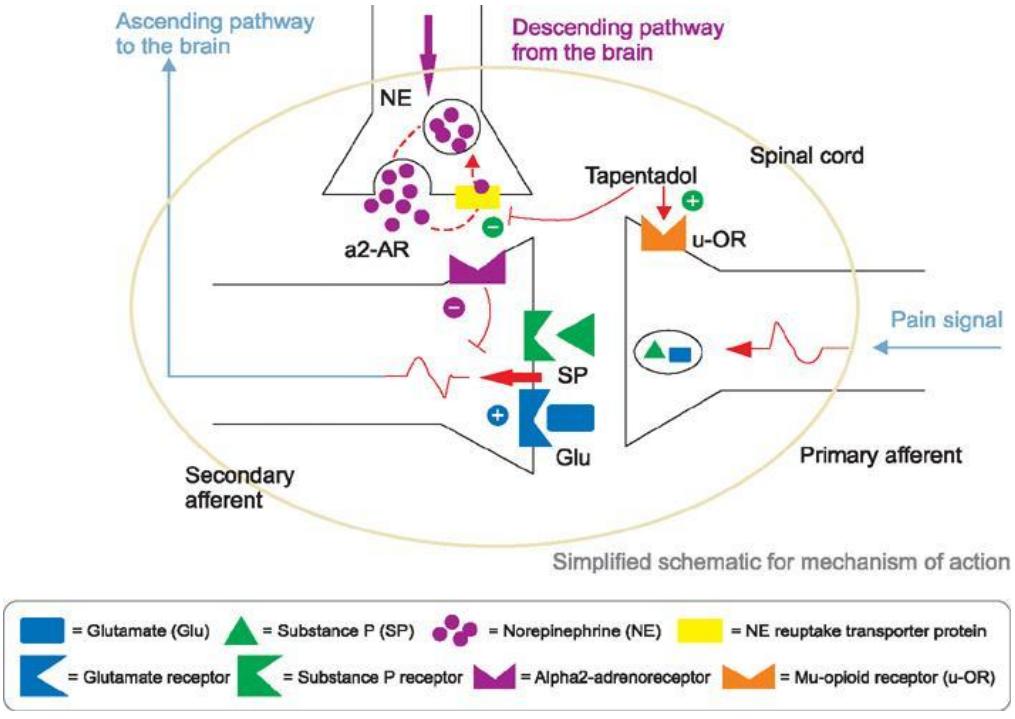


Figure 2.2: Neuronal and receptor pathway for the Tapentadol, Image Courtesy (4)

2.4 PHARMACOKINETICS

After oral administration, approximately 32% of the drug was absorbed. It was widely distributed in the body. The binding to plasma proteins was low and amounted to approximately 20%. The activity of Tapentadolwas independent of metabolic activation and resided in the active moiety itself which readily crossed the blood-brain barrier. The half-life was 4 hours and the maximum effect reached after 1 hour. The duration of the action was 4-6 hours. The drug underwent extensive first-pass liver metabolism of approximately 97% (6). The main metabolic pathway for elimination was phase II glucuronidation. Phase I bio-transformations such as hydroxylation and N-demethylation played a secondary role hence TAP hada low potential for drug-drug interactions and inter-individual variability. 99% of the drug wasexcreted through the kidney.

2.4.1 Indications and use: The drug is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

2.4.2 Adverse reactions: Tapentadol, a centrally acting oral analgesic, although generally well tolerated, has the following adverse effects:

- Gastrointestinal side effects: Incidencesof constipation, nausea, vomiting areminimum with Tapentadol as compared to the class effect.
- Respiratory effects: Due to its μ-opioid receptor agonism, respiratory depression is a rare possibility howsoever it must beused under careful medical supervisionfor patients identified at risk.
- CNS effect: As with other CNS agents, drowsiness, dizziness/vertigo, headache, and somnolence.
- Drug overdose: Experience withan overdose of Tapentadol is limited. Treatment of overdose should focus on the treatment of symptoms of an opioid agonist.
- Potential drug abuse: The abuse of Tapentadol poses a risk of overdose and death. This risk is increased with the concurrent abuse of Tapentadol with alcohol and other drugs.

2.5 CONCENTRATION-EFFICACY RELATIONSHIPS

The minimal effective plasma concentration of Tapentadol for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids.

2.6 CONCENTRATION-ADVERSE EXPERIENCE RELATIONSHIPS

There is a general relationship between increased plasma opioid concentration and increasedthe frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression (7).

2.7 PRESENT COMMERCIAL FORMULATIONS OF TAPENTADOL

Available formulations:

IR tablet (Approved in US- 2008, India 2011)

ER tablet (Approved in US-Aug 2011)

Table 2.3:Pharmacokinetics of the present IR formulation (7, 8)

Parameters	Oral IR formulation
Absolute bioavailability	Approximately 32%
T_{max}	Around 1.25 hours
Linearity	50 to 150 mg dose range
Elimination $t_{1/2}$	About 4 hours
Metabolism	97% of the parent compound is metabolized.
Elimination	Exclusively (99%) via the kidneys

Basically, Oral immediate release formulation has low oral bioavailability and delayed $T_{max.}$

2.8 NEED AND RATIONALE FOR A NASAL SPRAY

- Intravenous administration, in general, provides rapid action; Howsoever, the maximum effect of morphine with T_{max}ranging between 5 to 10 minwithi.v NSAIDs, the peak effect is slow, with T_{max}ranging between 15 to 30 min. Rectal

administration usually provides a faster, but unreliable action, when compared to the oral route.

- Alternatively,marketed intranasal Fentanyl offers T_{max}ranging between 5 to 16 min with avery short half-life of 65 mins but treatment modalities are often complicated due tothe risk of respiratory depression, hence cannot be administered without the healthcare staff.
- Thus, the use of semi-opioid analgesics with established safety and proven efficacy such as Tapentadol may be a beneficial alternative and amenable treatment option for acute pain management. The desirable attributes of the current work include:
    - Fast onset of action (early T_{max}) as compared to Oral solution
    - Higher or comparable C_{max} and AUC to Oral solution
    - Non-invasive
    - No risk of infection
    - No needle stick risks
    - Appropriate for baseline as well as breakthrough pain management

2.9 ADVANTAGES OF TAPENTADOL HClNASAL SPRAY

The absolute bioavailability after administration of a single dose of immediate release formulation of TapentadolHCl (fasting) is approximately 32% due to extensive first-pass metabolism (9). The rich vessel plexus of the nasal cavity should help Tapentadolreach bloodstreamand brain through the olfactory pathway to provide faster pain relief. Hence to test the hypothesis, Oral drug solution, Intra-nasal solutionand drug encapsulated in Solid Lipid Nano particles as CR fraction suspended inan aqueous vehicle comprising of IR fraction were administered to characterize the PK profile in New-Zealand rabbits to confirm the hypothesis. Repeat dose Pharmacokinetics was done by simulation studies (Win-Nonlin) carried out to ascertain the accumulation potential by nasal route.

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