PHARMACOLOGICAL VALUES OF POTENT DRUGS

DR. VIVEKANAND ANKUSH KASHID

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INDEX

19	ALPRAZOLAM:- A BENZODIAZEPINE USED IN ANXIETY MANAGEMENT Aradhana Purushottam Dakle*, Shiwani Bharat Aurange, Anjali Satish Ugalmugle, Komal Sukhdev Solankar, Pallavi Dhondiram Puri	
20	LAZERTINIB FOR EGFR-MUTANT LUNG CANCER: A DETAILED REVIEW OF HOW IT WORKS, ITS BENEFITS, AND MEDICAL USE Ghotekar Priyanka Yogesh, Rupali Vasant Nirmal, Borude P.G., Hinge K.M.	
21	METHYL GALLAT : THE POTENT DRUG Sayyed Mahereen Akram, Salunke Vaishnavi Bhushan, Sangapal Siddhika Yogesh, Shaikh Juveriya Zakir, Kartiki Bhandari , Dr. S. V. Amrutkar	
22	DEVELOPMENT AND EVALUATION OF HERBAL GUMMIES FOR FEMALE HORMONAL BALANCE AND FERTILITY HEALTH Dr.Sonia Singh, Ms. Madhuri Kawade, Gaurav Nagmoti, Vicky Kushwaha, Shravani Maggirwar	
23	INCRETIN BASED DRUGS FOR TYPE 2 DIABETES Madhuri Kawade, Sonia Singh, Samarth Kulkarni, Gireeraj Kulkarni, Krishna Kumawat	
24	ZICONOTIDE: A MARINE-DERIVED NON-OPIOID ANALGESIC WITH EXCEPTIONAL PHARMACOLOGICAL VALUE Kiran Kotade, Charushila Bhangale, Krutika Hadole*, Samruddhi Jagdale, Simran Nemane, Ashwini Dhase	
25	PHARMACOLOGICAL POTENTIAL OF TIRZEPATIDE: A REVOLUTIONARY TREATMENT EXPANDING BEYOND TYPE 2 DIABETES Niketan Tambe, Omkar Kulkarni, Abhay Kakade, Vidya Bade	
26	PHARMACOLOGICAL VALUES OF WARFARIN - BALANCING EFFICACY (INR THERAPY) Vinoth Jeevanesan*, Senthilkumar Chelladurai, Naveen Nandhakumar, Aathiraga Ramesh, Mohamed Thasrik, Ahamed Hussain	
27	METFORMIN: EMERGING ANTI-AGING DRUG Piyush N. Jangam, Arya Shaligram*, Yogesh Bafna, Shravan Yadav, Adesh Zende	
28	"ATORVASTATIN: A STATIN WITH ANTICANCER PROPERTIES IN GLIOBLASTOMA" Piyush N. Jangam, Aarati Shinde*, Yogesh Bafna, Nusratfatema Shaikh, Dhanashri Avhad	
29	PHARMACOLOGICAL VALUES OF ANTI-PSYCHOTIC MEDICINES: Pradeep Kumar Yadav, Dr A.K. Singhai, Piyush Kashaundhan, Tanishq Agrawal, Rupali Shukla	
30	BLOCKBUSTER EMPAGLIFLOZIN: REDEFINING POTENCY IN CARDIOVASCULAR AND RENAL PROTECTION Pratima Patel1*, G.S. Chakraborthy2, Savi Ahirrao3, Om Mahajan3, Shubham Gunjal3	
31	HYDRO METHYLTHIONINE MESYLATE (HMTM): A BREAKTHROUGH TAU- TARGETING THERAPY IN ALZHEIMER'S DISEASE Panchal Khushbu, Shah Khushi, Polepali Manideep	
32	THE POTENT POWER OF CLONAZEPAM IN NEUROLOGICAL AND PSYCHIATRIC CARE Mahalakshmi G., Senthil Kumar C., Guhan R., Abarna S., Gowtham K., Farjith Aswan S.	
33	PHARMACOLOGICAL VALUE OF OMADACYCLINE: A COMPREHENSIVE REVIEW Gauravi Kherde*, Pooja Akoshkar, Pratiksha Katkade, Dr. Rahul D. Khaire, Dr. Chaurshila J Bhangale	
34	ASPIRIN: MORE THAN JUST A PAINKILLER Ashwini Donode, Arti Meshram, Apeksha Gupta. Roshni Agrawal. Dr. T.P. Nimbekar	
35	PHARMACOLOGICAL PROFILE AND THERAPEUTIC POTENTIAL OF PIVMECILLINAM Rushikesh A Kashid*, Sahil D Sanap, Mayur S Vare , Prof. Shruti A Salve, Dr. V. A. Kashid	
36	A COMPREHENSIVE REVIEW OF APROCITENTAN: PHARMACOLOGICAL ADVANCES IN BLOOD PRESSURE REGULATION Yogesh B. More*, Vaibhav S Dhanwate, Chetan C Kadam, Shruti A Salve	
37	FINERENONE: THE SILENT GUARDIAN OF KIDNEYS AND HEART Shetal B. Desai, Shreyas Khale*, Dr. Sachin B. Narkhede, Dashrath Prajapati, Preeti Tiwari, Om Sadrani	
38	A POTENT OPIOID ANALGESIC Charmi Bhagat*, Fancy Bhandari, Zahabia Bhavnagarwala, Mrs. Shetal B. Desai, Dr. Sachin B. Narkhede	
39	EFFECTIVE AND BENEFICIAL SAFFRON ON ANTI-CANCER Ms. Shweta. R. Agrawal, Aditi Thorat, Uzaifa Shaikh	

40	PHARMACOLOGAL VALUES OF ZOLMITRIPTAN Shubham S Bhalerao*, Pratik S Pagar, Akash S Gangurde, Prof. Smita P Mali	
41	PHARMACOLOGICAL VALUES OF PAXLOVID Suvarna S Borade*, Sakshi D Vyapari, Mayur S Vare, Prof. Smita P Mali, Dr.V. A. Kashid	
42	SEEING THE WORLD RIGHT AGAIN: EXPLORING HOW SUMATRIPTAN AFFECTS ALICE IN WONDERLAND SYNDROME Ms. Snehal Tuse, Dr. Sanjay G. Walode, Prerna Solanki, Kashmira Shaikh, Rekha Solanki	
43	THE ROLE OF AZATHIOPRINE IN IMMUNOSUPPRESSIVE THERAPY: UPDATE Nehe Sneha S.*, Kanade Arti J., Laware Vaishanvi V., Navale Sonali U., Dr. Mansuk Avinash G	
44	THE ROLE OF NIRAPARIB IN ADVANCED OVARIAN CANCER: A REVIEW OF ITS CLINICAL APPLICATIONS AND FUTURE DIRECTIONS Kakad Saish P*, Gaikwad Gayatri S, Gahire Pratiksha D, Navale Sonali U, Dr. Urmilesh Jha	
45	A REVIEW ON PHARMACOLOGICAL VALUES OF CISPLATIN: AN ANTINEOPLASTIC AGENT Shilbi Saxena, Sourya Rahangdale, Swapnil Mishra, Steffi Thomas	
46	PHARMACOLOGICAL VALUES OF ATAZANAVIR: A POTENT ANTIRETROVIRAL AGENT Dr. A. K. Singhai, Swati Burungale, Mayuri More, Shivnath Shinde, Ashwini Pawar, Srushti Chame	
47	DOES IT REALLY WORK FOR INFERTILITY? Deeksha D. Karadi, Samiksha S. Kasar, Harshal R. Kasar	
48	DONEPEZIL: THE MEMORY BOOSTER Seema Shamarao Khot*, Shruti Bhima Kamble, Sakshi Satish Khamkar, T.S. Khamkar, A.P. Gadad	
49	AZILSARTAN IN FOCUS: ASSESSING ITS POTENCY AND EFFECTIVESNESS IN CARDIOVASCULAR THERAPY Unmesh Gulabrao Bhamare, Pranjal Balu Phadol, Aaditya Kishor Shewale, Kishan Subhash Yadav	
50	FENTANYL – A DOUBLE EDGED SWORD IN PAIN THERAPY Vanitha Devi Rajendran*, Senthilkumar Chelladurai, Arun Vengadesh, Jayasri Jayabalan, Santhosh Rajapandiyan, Madhavan Selvakumar	

PREFACE

This book is a result of extensive literature survey done by students of pharmacy, and other science fraternity from different colleges all over India. It covers the pharmacological values of potent drugs.

The information in this book is not intended to be a substitute for professional medical advice. Do not use this information to diagnose any disease; also the book should not be used for the treatment of any disease.

Students/academicians/industry persons should go through it in order to get research ideas which can be transformed into the product. Thus this book will serve as a guide for people wishing to do research on the subject covered in this book.

We are thankful to all the contributors as without their help publishing this book would have not been possible. We are also thankful to the editors of this book for timely completing the work and helping us to publish this book on time.

The book ensures that the readers acquire a good fundamental understanding of the subject. We wish all our readers knowledgeable and research oriented reading.

50 FENTANYL – A DOUBLE EDGED SWORD IN PAIN THERAPY

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ABSTRACT

Fentanyl is a synthetic opioid analgesic known for its extraordinary potency—approximately 50 to 100 times greater than morphine. Its high efficacy arises from strong binding affinity to μ-opioid receptors, leading to rapid and profound analgesia. The drug's lipophilic nature allows swift penetration of the blood-brain barrier, resulting in a fast onset of action, depending on the administration route. Clinically, fentanyl is extensively used for managing severe pain, especially in cancer patients, post-operative care and as an adjunct in anaesthesia. However, these same pharmacological properties contribute to its risk profile. The narrow therapeutic window poses a significant risk of accidental overdose, particularly with misuse, inappropriate dosing or co-administration with other central nervous system (CNS) depressants. Adverse effects include respiratory depression, rigid chest syndrome, bradycardia and potentially fatal respiratory failure. Moreover, the emergence of illicit fentanyl analogues has fuelled a sharp rise in opioid-related overdose deaths, making it a central player in the ongoing global opioid crisis. Understanding fentanyl's pharmacokinetics and pharmacodynamics is essential for safe prescribing and effective pain management. Novel interventions—such as opioid vaccines, monoclonal antibodies, abuse-deterrent formulations and receptor-biased agonists—offer hope in mitigating its misuse without compromising analgesia. Greater emphasis on prescriber education, patient screening and public health surveillance is critical to balance therapeutic use with harm reduction. This chapter critically explores fentanyl's dual role as both a cornerstone in modern pain therapy and a major contributor to opioid-related morbidity and mortality.

DISCOVERY & FURTHER HISTORY

Fentanyl, a synthetic opioid, was first synthesized in 1960 by Dr. Paul Janssen of Janssen Pharmaceutica during a focused effort to develop potent and rapid-acting analgesics superior to morphine. The discovery stemmed from structural modifications of meperidine, a phenylpiperidine-based opioid, ultimately resulting in fentanyl citrate—a compound exhibiting analgesic potency nearly 100 times greater than that of morphine.[1] This extraordinary potency was attributed to its high affinity for μ-opioid receptors and its pronounced lipophilicity, which facilitated rapid central nervous system (CNS) penetration and onset of action.

Following its synthesis, fentanyl was introduced into clinical practice in the mid-1960s under the trade name Sublimaze for intravenous use as an anaesthetic adjunct. Its rapid onset, short duration of action and minimal cardiovascular effects made it particularly advantageous for surgical and anaesthetic procedures, including cardiac surgery.[2] Over the next several decades, pharmaceutical interest in fentanyl expanded, leading to the development of a broad range of formulations, including transdermal patches, buccal tablets, oral lozenges, nasal sprays and sublingual tablets. These dosage forms extended fentanyl's utility from hospital-based anaesthesia to outpatient pain management, notably in oncology and palliative care settings.

The release of the transdermal patch formulation (Duragesic®) in 1990 marked a significant advancement in chronic pain therapy.[3] This delivery system allowed sustained drug release over 72 hours and enabled patients with chronic malignant and non-malignant pain to achieve consistent analgesia. However, the extended-use formulations also introduced new risks, including accidental exposure, misuse and diversion. Even used patches retained a substantial amount of active drug, making them susceptible to extraction and abuse.

The increased emphasis on aggressive pain management during the late 20th century, particularly in the United States, led to an exponential rise in opioid prescriptions, including fentanyl. Pain was increasingly recognized as a critical vital sign and long-acting opioids were promoted for chronic non-cancer pain despite limited long-term safety data. This environment, combined with misjudgements about the addiction potential of prescription opioids, contributed to widespread opioid overuse.

The early 2000s witnessed a transition in the fentanyl landscape with the emergence of illicitly manufactured fentanyl and its analogues. While pharmaceutical fentanyl was stringently regulated, clandestine laboratories began synthesizing chemically similar derivatives such as acetylfentanyl, butyrylfentanyl, sufentanil and carfentanil—many of which exhibited potencies far exceeding that of fentanyl itself.[4] These substances were often mixed with heroin, cocaine or counterfeit tablets and distributed through illicit drug markets. Because of their extreme potency, even microgram-level dosing errors were sufficient to cause fatal respiratory depression.

As a result, fentanyl and its analogues have become central contributors to the global opioid crisis, with mortality data reflecting a sharp increase in synthetic opioid-related deaths. Many affected individuals were unaware that their consumed substances contained fentanyl, underscoring the high lethality of contamination and substitution in unregulated drug supplies. This crisis presented a multifaceted challenge involving toxicology, public health, forensic science and international regulation.[5]

In response, regulatory agencies worldwide implemented various measures to limit the distribution and misuse of fentanyl and its analogues. The U.S. Drug Enforcement Administration (DEA) enacted temporary and permanent scheduling of numerous fentanyl-related substances under Schedule I and Schedule II of the Controlled Substances Act. Countries such as Canada, Australia and members of the European Union adopted similar classification frameworks. In India, fentanyl and its analogues are regulated under the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985, which was amended to strengthen control over synthetic opioids. The Narcotics Control Bureau (NCB), in collaboration with the Central Bureau of Narcotics (CBN), oversees the monitoring and licensing of fentanyl-related substances and their precursors. In recent years, India has taken steps to enhance border surveillance, monitor pharmaceutical manufacturing and restrict the diversion of opioid precursors such as N-phenethyl-4-piperidone (NPP) and 4-anilino-N-phenethylpiperidine (ANPP), both of which are listed under the Controlled Substances Rules, 2013. Internationally

organizations including the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB) have called for coordinated monitoring of fentanyl precursors and trafficking patterns.[6]

Pharmaceutical research continued to evolve with the development of second-generation fentanyl analogues optimized for specific clinical contexts. Compounds such as sufentanil and alfentanil were designed with modifications to onset and duration profiles, while remifentanil was engineered for rapid metabolism by non-specific esterases, making it suitable for continuous infusion in short procedures. These derivatives provided greater flexibility in anaesthetic planning and pain control, particularly in critical care and procedural sedation.[7]

Meanwhile, the rise in fentanyl misuse prompted interest in designing formulations that minimize abuse potential. Abuse-deterrent technologies have aimed to prevent mechanical manipulation, extraction or chemical alteration of fentanyl dosage forms. Additionally, innovations in transdermal systems—such as iontophoretic patches and rate-controlling membranes—have been investigated to optimize delivery kinetics and safety profiles.

The broader implications of fentanyl misuse extended into domains of epidemiology, pharmacovigilance and social medicine. Surveillance data revealed increasing concentrations of synthetic opioids in overdose toxicology reports, often in polydrug contexts. Naloxone, a μ-opioid receptor antagonist, has emerged as an essential emergency intervention to reverse fentanyl-induced respiratory depression. Consequently, its distribution to first responders and high-risk populations has become a cornerstone of harm reduction strategies.[8]

Emerging research efforts are exploring immunotherapeutic approaches, including fentanyl-specific vaccines and monoclonal antibodies, to neutralize circulating drug molecules before they reach the CNS. These strategies aim to prevent relapse in opioid use disorder and protect against overdose. Additionally, there is growing interest in biased μ-opioid receptor agonists that retain analgesic efficacy with reduced risk of respiratory depression and euphoria, potentially decoupling therapeutic benefit from abuse liability.

The historical trajectory of fentanyl—from a revolutionary anaesthetic agent to a central figure in the opioid epidemic—illustrates the complex interplay between scientific innovation, clinical application, regulatory oversight and societal impact. While fentanyl remains indispensable in modern pain management, its potential for harm underscores the need for meticulous risk-benefit assessment, ongoing pharmacological innovation and robust public health infrastructure.

PHYSICOCHEMICAL PROPERTIES

Fentanyl (N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide) is a potent synthetic opioid belonging to the phenylpiperidine class. It exists as a white to off-white crystalline powder with a molecular formula $C_{22}H_{28}N_2O$ and molecular weight 336.47 g/mol.

The compound exhibits high lipophilicity, with a log P value of ~4.05–4.2, which contributes to its rapid absorption across biological membranes and penetration of the blood-brain barrier (BBB). The pKa of fentanyl is approximately 8.4, indicating that, at physiological pH (7.4), it exists predominantly in ionized form, although its lipophilic nature ensures sufficient membrane permeability for rapid central action.

Fentanyl is sparingly soluble in water (~1.4 mg/mL at 25°C) but highly soluble in organic solvents including ethanol, methanol, chloroform and acetonitrile, which are frequently used in formulation and analytical methods. The drug exhibits a melting point of approximately 87–88°C, which is relatively low and poses a sublimation risk under inappropriate storage or handling conditions.

UV-visible spectroscopy reveals fentanyl's strong absorbance in the 200–230 nm region due to its aromatic rings and conjugated system. In infrared (IR) spectroscopy, characteristic absorption bands include:

~3300 cm^{-1} (N–H stretching),
~1650 cm^{-1} (C=O stretching from the amide group),
~1500–1600 cm^{-1} (aromatic C=C stretching) and
~750–800 cm^{-1} (monosubstituted benzene ring).

Fentanyl is relatively chemically stable under normal storage conditions but is susceptible to oxidation and hydrolysis under extreme pH or temperature. It is usually packaged in light-resistant, air-tight containers to preserve integrity. The compound is known to exist primarily in an anhydrous form, with limited evidence of polymorphism affecting pharmaceutical performance.[9]

Analytically, fentanyl can be reliably quantified using HPLC, GC-MS or LC-MS/MS techniques. These methods exploit its UV absorbance and volatility, as well as its high sensitivity to mass spectrometric detection. In pharmaceutical preparations, its low aqueous solubility necessitates the use of solubilizers, penetration enhancers or specialized delivery systems, particularly in transdermal, buccal and parenteral formulations.

Its molecular structure—comprising a lipophilic phenethyl side chain, a piperidine ring and an amide linkage—confers high μ-opioid receptor affinity. These structural features also enable structural modifications, giving rise to potent analogues such as sufentanil, remifentanil and alfentanil.

PHARMACOKINETIC PROPERTIES

Fentanyl exhibits complex pharmacokinetics governed by its high lipophilicity, extensive tissue distribution and route-dependent absorption kinetics. Understanding its absorption, distribution, metabolism and excretion (ADME) is critical for both clinical applications and risk management.[10]

Absorption

Fentanyl is efficiently absorbed via multiple routes, including intravenous (IV), transdermal, intranasal, buccal, sublingual and intramuscular (IM). IV administration results in immediate systemic availability and rapid onset (1–2 minutes), making it ideal for anaesthesia. Bioavailability varies widely across non-parenteral routes due to first-pass metabolism:

- Transdermal: ~92%
- Buccal: ~50–65%
- Sublingual: ~54%
- Intranasal: ~70–90%
- Oral (swallowed): ~33% (due to extensive first-pass hepatic metabolism)

The onset and duration of action depend on both formulation and route. For example, transdermal patches begin action within 12–24 hours and last up to 72 hours, while buccal and sublingual forms act within 5–15 minutes with shorter durations.

Distribution

Fentanyl is highly lipophilic, allowing rapid distribution into the central nervous system. The volume of distribution (Vd) ranges from 3 to 6 L/kg, indicating extensive tissue binding. It accumulates in adipose tissue with repeated dosing or continuous infusions, which can prolong terminal elimination.

Fentanyl is 90–94% bound to plasma proteins, mainly alpha-1-acid glycoprotein, which may affect free drug levels in patients with hepatic impairment or inflammation.

Metabolism

Fentanyl is extensively metabolized in the liver, primarily by cytochrome P450 3A4 (CYP3A4), to the major inactive metabolite norfentanyl, which lacks opioid activity. Other minor metabolites include hydroxyfentanyl and despropionylfentanyl. The biotransformation may be affected by enzyme-inducing or -inhibiting drugs, posing risks for overdose or subtherapeutic effects.

Co-administration with CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, erythromycin) can significantly elevate plasma fentanyl levels, increasing the risk of respiratory depression. Conversely, enzyme inducers (e.g., rifampicin, carbamazepine) may reduce efficacy.

Excretion

Fentanyl and its metabolites are mainly excreted via the renal route. Around 75% of a dose is recovered in urine, mostly as norfentanyl and other hydroxylated derivatives, while 9% is excreted unchanged. A smaller proportion is eliminated via faeces. Renal clearance is not the primary route for active drug removal, but renal impairment may affect metabolite accumulation.

Elimination Half-Life and Clearance

The terminal elimination half-life (t½) of fentanyl varies with route and duration of administration:

- IV bolus: ~2–4 hours
- Transdermal: 17–27 hours
- Buccal/sublingual: ~6–12 hours

Prolonged infusions or repeated dosing may lead to context-sensitive half-life increases due to redistribution from peripheral compartments. Systemic clearance ranges between 8–20 mL/min/kg, reflecting efficient hepatic metabolism.

Bioavailability and BCS Classification

Fentanyl falls under Biopharmaceutics Classification System (BCS) Class I or sometimes Class II, due to its high permeability but low aqueous solubility, depending on the formulation. This impacts formulation strategies for non-parenteral routes and supports the use of lipid-based systems and permeation enhancers.

The summary of various pharmacokinetic parameters in various routes are given in table.50.1.

Table 50.1 Pharmacokinetics Across Routes

Route	Bioavailability	Onset	Duration	Cmax/Tmax
IV	100%	1–2 min	30–60 min	Cmax immediate
IM	~92%	7–15 min	1–2 hours	Cmax ~20 min
Transdermal	~92%	12–24 hrs	~72 hrs	Tmax ~24–36 hrs
Buccal/Sublingual	50–65%	5–15 min	1–2 hours	Tmax ~20–60 min
Intranasal	70–90%	<10 min	1–2 hours	Tmax ~15–30 min

PHARMACODYNAMICS

Fentanyl is a highly potent μ-opioid receptor (MOR) agonist, exerting analgesic, sedative and respiratory depressant effects. MOR activation leads to inhibition of adenylyl cyclase, decreased cAMP, blockade of presynaptic calcium channels and activation of postsynaptic potassium efflux, resulting in suppressed nociceptive transmission and neuronal hyperpolarization.

Its high lipophilicity enables rapid CNS penetration, producing a quick onset of analgesia—1–2 minutes after IV administration, 5–15 minutes via transmucosal and 12–24 hours with transdermal delivery. Duration varies by route: IV (30–60 minutes), transmucosal (1–2 hours) and transdermal (up to 72 hours). The brief action of IV fentanyl is due to redistribution, not metabolism.[11]

Fentanyl selectively targets μ-receptors with negligible activity at δ- or κ-receptors. It does not cause histamine release, reducing the risk of pruritus and hypotension seen with morphine. However, rigid chest syndrome—a potentially life-threatening muscular rigidity—may occur with high doses or rapid IV injection.

Respiratory depression is the most serious effect, resulting from μ-receptor activation in the brainstem. It is dose-dependent and may be sudden or prolonged. This effect has a narrow therapeutic window, as the dose required for analgesia is close to that causing respiratory compromise.

Response to fentanyl varies between individuals due to differences in μ-receptor density, genetic polymorphisms, CNS sensitivity, co-administered drugs and tolerance. CYP3A4 interactions also affect fentanyl's action by altering its metabolism. Elderly, opioid-naïve and patients with hepatic/renal impairment show increased sensitivity.

Repeated exposure leads to tolerance to analgesia and euphoria but not proportionally to respiratory depression, increasing overdose risk. Dependence arises via mesolimbic dopaminergic pathways.

Fentanyl may show biased agonism, favouring G-protein signalling over β-arresting recruitment. This may influence its efficacy versus adverse effect profile, although clinical implications are still being studied.

MECHANISM OF ACTIONS

Fentanyl produces its pharmacological effects by acting as a full agonist at the μ-opioid receptor (MOR), a G-protein-coupled receptor (GPCR) predominantly expressed in the central and peripheral nervous systems. The receptor is located on presynaptic terminals of

primary afferent neurons and postsynaptic membranes of secondary neurons in key pain-processing regions, including the periaqueductal gray (PAG), thalamus, spinal cord dorsal horn and brainstem.

Upon binding, fentanyl induces a conformational change in the MOR, leading to activation of Gi/o proteins, which in turn:

- Inhibit adenylyl cyclase, reducing intracellular cAMP levels;
- Close voltage-gated calcium channels on presynaptic neurons, decreasing neurotransmitter release (e.g., glutamate, substance P);
- Open inward-rectifying potassium channels on postsynaptic membranes, causing hyperpolarization and reduced neuronal excitability.

This dual pre- and postsynaptic inhibition diminishes nociceptive transmission in both ascending (sensory) and descending (modulatory) pain pathways, resulting in potent analgesia.

Fentanyl's high lipid solubility accelerates its passage across the blood-brain barrier, allowing rapid receptor engagement and onset of effect. Its binding is characterized by high affinity and efficacy, enabling strong receptor activation even at low concentrations.

In addition to analgesia, MOR activation by fentanyl affects other CNS functions. In the brainstem respiratory centres, particularly the pre-Bötzinger complex, fentanyl suppresses respiratory rhythmogenesis, leading to respiratory depression—a major risk in overdose scenarios. Similarly, activation of MORs in the mesolimbic dopaminergic pathway enhances dopamine release in the nucleus accumbens, producing euphoria and reinforcing behaviours that contribute to dependence and addiction.[12]

While fentanyl exhibits limited activity at δ- and κ-opioid receptors, its clinical effects are overwhelmingly mediated by MOR. It may also exhibit biased agonism, preferentially activating G-protein signalling while minimizing β-arrestin recruitment, which may influence side effect profiles, though the clinical significance remains under investigation.

METHODS OF SYNTHESIS

Fentanyl synthesis is based on modification of the phenylpiperidine scaffold, with several synthetic routes developed for both industrial and illicit purposes. The classical and most widely accepted laboratory method is the Janssen method, first reported in 1960 by Paul Janssen and forms the basis for most pharmaceutical production.[13]

Janssen Route (Classical Synthetic Route)

This multi-step synthesis involves the following key intermediates and transformations:

- N-Phenethyl-4-piperidone (NPP) is the central starting material.
- Reductive amination of NPP with aniline gives 4-anilino-N-phenethylpiperidine (ANPP).
- ANPP is acylated with propionyl chloride (or propionic anhydride) to yield fentanyl base.
- The base is converted to fentanyl citrate, the pharmaceutically active salt form, by treatment with citric acid.

Overall Reaction Sequence: NPP + Aniline → ANPP → [Propionylation] → Fentanyl → [Salt formation] → Fentanyl citrate

This route is efficient and scalable, with good overall yield and selectivity. Both NPP and ANPP are currently listed as controlled precursor chemicals under international drug control treaties due to their association with illicit fentanyl synthesis.

Alternate Routes and Analog Development

To bypass restricted precursors, clandestine laboratories have developed modified synthetic pathways, including:

- Starting from 4-piperidone hydrochloride monohydrate instead of NPP;
- Use of phenylmagnesium bromide with piperidone intermediates to avoid direct access to ANPP;
- Modular synthesis of fentanyl analogues (e.g., carfentanil, acetylfentanyl) by changing the acyl group or N-aryl substitution in the final step.

These non-traditional routes aim to circumvent regulatory controls but often result in impure, variable and highly toxic products, contributing to the global opioid crisis.[14]

Green and Safer Synthetic Approaches (Research Stage)

Recent advances explore greener synthesis approaches, such as:

- Enzymatic reductive amination of NPP analogues;
- Microwave-assisted reactions to reduce reaction time;
- Flow chemistry techniques for controlled micro-scale synthesis, which enhances safety and scalability.

However, these methods remain largely investigational and are not yet adopted at industrial scale.

MEDICINAL USES

Fentanyl is a versatile opioid analgesic used across multiple medical disciplines due to its high potency, rapid onset and favourable pharmacokinetics. Its therapeutic applications are largely guided by formulation, route of administration and severity of pain.[15]

Acute Pain Management

1. Anaesthesia and Perioperative Analgesia:

Fentanyl is extensively used as an adjunct in general and regional anaesthesia, owing to its rapid onset (1–2 minutes) and short duration of action (30–60 minutes). It facilitates sedation, blunts sympathetic responses during intubation and provides analgesia during and after surgical procedures.

2. Procedural Sedation and Analgesia:

Used in emergency departments, ICUs and endoscopic suites for short-term analgesia in settings like cardioversion, fracture reduction and bronchoscopy.

Chronic Pain Management

1. Cancer Pain:

Fentanyl is a first-line opioid for moderate-to-severe cancer pain, particularly in opioid-tolerant patients. It is preferred in transdermal patch form for continuous baseline analgesia, offering 72-hour duration and bypassing gastrointestinal metabolism.

2. **Palliative Care:**

Transdermal and transmucosal fentanyl are valuable in end-of-life care for managing intractable pain, with advantages including ease of use, steady plasma levels and minimal GI side effects.

Breakthrough Pain (BTP)

In opioid-tolerant individuals, transmucosal fentanyl formulations (buccal tablets, lozenges, nasal sprays, sublingual tablets) are used for episodic breakthrough cancer pain due to their rapid onset and short duration, typically acting within 5–15 minutes. These are titrated individually and contraindicated in opioid-naïve patients.

Postoperative Pain

Short-acting IV fentanyl is used in patient-controlled analgesia (PCA) systems post-surgery. Its predictable pharmacokinetics and minimal histamine release reduce risks of hypotension and allergic reactions, offering a safer alternative to morphine in sensitive patients.

Labor Analgesia and Obstetrics

Though less commonly used due to neonatal respiratory depression risk, fentanyl is administered via epidural or intrathecal injection in combination with local anaesthetics for labour analgesia. Careful dosing ensures maternal comfort with minimal foetal impact.

Adjunct in Cardiac Anaesthesia

Due to its cardiovascular stability, fentanyl is used in high doses during cardiac surgeries to provide analgesia without depressing myocardial function.

Neurologically Sensitive Patients

Fentanyl is often preferred in patients with head injuries, elevated intracranial pressure or hemodynamic instability, where agents causing histamine release or hypotension must be avoided.

ADVERSE EFFECTS

Fentanyl's adverse effects are closely linked to its μ-opioid receptor agonism, high potency, rapid CNS penetration and narrow therapeutic index. While its safety profile is favourable under controlled medical use, even small dosing errors or drug interactions may result in life-threatening complications.[16]

Respiratory Depression

The most critical adverse effect of fentanyl is dose-dependent respiratory depression, mediated via inhibition of respiratory centres in the brainstem. It may present as delayed-onset apnea even after transient exposure and is more severe compared to morphine. High doses, rapid IV bolus or concurrent CNS depressants (e.g., benzodiazepines, alcohol) markedly increase the risk. In overdose, this is the primary cause of mortality.

Chest Wall Rigidity (Wooden Chest Syndrome)

A fentanyl-specific adverse reaction, particularly with rapid IV administration or high doses, is rigid chest syndrome, characterized by truncal muscle rigidity, including laryngeal and thoracic wall stiffening. This may impede ventilation, requiring neuromuscular blockade and mechanical support.

Bradycardia and Hypotension

Fentanyl induces bradycardia via vagal stimulation, especially in high doses or in combination with other sedatives. Severe hypotension is rare due to lack of histamine release but may occur in volume-depleted or elderly patients.

Tolerance, Dependence and Addiction

Prolonged use leads to tolerance—requiring higher doses for the same analgesic effect—and physical dependence, marked by withdrawal symptoms upon cessation. Psychological addiction is driven by fentanyl's strong euphoric effect and dopaminergic reinforcement, with a high potential for abuse.

Hyperalgesia

Paradoxically, opioid-induced hyperalgesia (OIH) may occur with chronic fentanyl use, leading to increased sensitivity to pain. The mechanism involves NMDA receptor activation and neuroplastic changes in pain pathways.

Endocrine Dysregulation

Long-term fentanyl use may suppress the hypothalamic-pituitary axis, causing hypogonadism, reduced libido, fatigue and menstrual irregularities. Adrenal insufficiency has also been reported, though rarely.

Neurotoxicity

Chronic exposure may result in cognitive impairment, drowsiness, dysphoria or delirium, particularly in elderly or renal-impaired patients. High doses may provoke seizures, though this is uncommon and typically related to excipient toxicity or drug interactions.

Serotonin Syndrome

Concomitant use with SSRIs, SNRIs, MAO inhibitors or other serotonergic agents can precipitate serotonin syndrome, presenting with agitation, hyperthermia, tremors and altered mental status. Fentanyl has weak serotonergic activity but may potentiate this effect when combined with serotonergic drugs.

Accidental Exposure and Paediatric Toxicity

Transdermal patches, if improperly disposed or applied, pose a risk of accidental exposure, especially in children, leading to fatal respiratory depression even from a single contact.

TREATMENT OF FENTANYL OVERDOSE

Fentanyl overdose is a medical emergency characterized primarily by severe respiratory depression, often accompanied by bradycardia, hypotension, unconsciousness and cyanosis. Given its high potency, rapid onset and prolonged effect due to redistribution, management requires prompt and sustained intervention.[17]

Immediate Supportive Care

- Airway, Breathing, Circulation (ABCs): The cornerstone of management involves maintaining a patent airway, ensuring adequate ventilation and supporting hemodynamic.
- Oxygen supplementation via nasal cannula or face mask is initiated immediately. In cases of apnea or hypoventilation, bag-valve-mask ventilation or mechanical intubation may be required.
- Chest wall rigidity, if present, may necessitate neuromuscular blockade and controlled ventilation.

Naloxone Administration

Naloxone, a competitive μ-opioid receptor antagonist, is the antidote of choice.

- Route & Dosing:
- Initial IV dose: 0.4–2 mg, may be repeated every 2–3 minutes.
- In severe cases or unknown exposure: start with 2 mg IV/IM/SC or 4 mg intranasally and titrate.
- Continuous infusion (0.4–2 mg/hour) may be necessary for sustained reversal, especially after high-dose or long-acting formulations like transdermal patches.
- Challenges:

Fentanyl's lipophilicity and receptor affinity can make it less responsive to standard naloxone doses compared to morphine. Re-narcotization is common due to fentanyl's longer duration versus naloxone's short half-life (~30–90 minutes), necessitating prolonged monitoring and repeat or continuous dosing.

Removal of Source

- Transdermal patch should be removed immediately in suspected overdose to prevent continued absorption.
- Skin should be cleansed thoroughly to eliminate residual fentanyl.

Adjunctive Measures

- Activated charcoal has limited utility due to rapid absorption and is generally not indicated unless co-ingestants are involved.
- Benzodiazepines may be required in cases of seizures or co-toxicity.
- IV fluids may support blood pressure; vasopressors are rarely needed unless profound hypotension occurs.

Monitoring and Observation

Patients require continuous cardiorespiratory monitoring for at least 6–12 hours post-reversal. Those exposed to transdermal, extended-release or illicit fentanyl analogues may need 24 hours or more of observation due to rebound toxicity.

Advanced and Emerging Therapies

- Nalmefene, a longer-acting opioid antagonist, is under consideration in some settings, especially for fentanyl analogue overdose.
- Investigational approaches, including fentanyl-binding antibodies and opioid vaccines, are in development to neutralize fentanyl in circulation.

INTERACTIONS OF FENTANYL

Fentanyl is prone to clinically significant drug interactions due to its CYP3A4-mediated metabolism and potent CNS depressant effects. These interactions may enhance toxicity, reduce efficacy or precipitate life-threatening conditions such as respiratory depression, serotonin syndrome or cardiovascular collapse.[18]

Pharmacokinetic Interactions

1. CYP3A4 Inhibitors

Fentanyl is metabolized primarily by cytochrome P450 3A4 (CYP3A4) into inactive norfentanyl. Co-administration with strong CYP3A4 inhibitors can significantly increase plasma fentanyl concentrations, heightening the risk of sedation and respiratory depression.

Examples:

- Antifungals: ketoconazole, itraconazole
- Macrolides: clarithromycin, erythromycin
- Protease inhibitors: ritonavir, lopinavir
- Grapefruit juice

2. CYP3A4 Inducers

Drugs that induce CYP3A4 may accelerate fentanyl metabolism, reduce its analgesic effect and require dose adjustments.

Examples: rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort

Pharmacodynamic Interactions

1. CNS Depressants

Concurrent use with other central nervous system depressants amplifies the risk of profound sedation, bradycardia and life-threatening respiratory depression.

Examples:

- Benzodiazepines (e.g., midazolam, lorazepam)
- Alcohol
- Barbiturates
- Sedating antihistamines
- General anaesthetics
- FDA mandates boxed warnings for combined use of opioids with benzodiazepines due to high mortality risk.

2. Serotonergic Agents

Although fentanyl is a weak serotonin reuptake inhibitor, when combined with other serotonergic drugs, it can precipitate serotonin syndrome.

Risk increased with:

- SSRIs (e.g., fluoxetine, sertraline)
- SNRIs (e.g., venlafaxine)
- MAO inhibitors (contraindicated)
- Tramadol, linezolid, triptans

3. Monoamine Oxidase Inhibitors (MAOIs)

Use of fentanyl within 14 days of MAO inhibitors is contraindicated. This interaction may lead to hypertension, serotonin toxicity or exaggerated CNS depression.

Other Notable Interactions

- Beta-blockers or calcium channel blockers: May exacerbate fentanyl-induced bradycardia.
- Anticholinergics: Combined use may increase the risk of urinary retention and constipation.
- Naltrexone or naloxone: These opioid antagonists can abruptly reverse fentanyl's effects, potentially triggering acute withdrawal syndrome in dependent individuals.

DRUG OPTIMISATION AND INDIVIDUALISED THERAPY OF POTENT FENTANYL

Drug optimisation in fentanyl therapy is of paramount importance due to its extremely high potency, rapid onset, narrow therapeutic window and substantial inter-individual variability in response. Precise dose optimisation is critical to achieve effective analgesia while preventing serious complications such as respiratory depression, bradycardia or fatal overdose. A one-size-fits-all approach is not suitable for fentanyl, as the balance between efficacy and toxicity is tightly constrained. Effective individualisation requires careful assessment of patient-specific factors including age, weight, comorbidities, organ function, pharmacogenetic profile and history of opioid use.[19]

In paediatric populations, fentanyl dosing must be approached with heightened caution. Children exhibit distinct pharmacokinetics and may have increased sensitivity to opioids due to immature hepatic enzyme systems and central nervous system development. Neonates and infants in particular have reduced metabolic capacity via CYP3A4, leading to prolonged drug action and increased vulnerability to respiratory depression. Therefore, dosing should always be weight-based and titration must be done slowly with continuous cardiorespiratory monitoring. Intranasal and buccal fentanyl may be used in selected paediatric settings, but only in opioid-tolerant patients and under expert supervision. The use of fentanyl in paediatrics remains largely restricted to intensive care and procedural sedation environments.[20]

In geriatric patients, dose individualisation is equally critical. Age-related changes such as decreased hepatic and renal function, altered body composition (increased fat-to-lean ratio) and heightened CNS sensitivity contribute to prolonged drug action and enhanced susceptibility to side effects. Fentanyl's lipophilicity leads to deeper and prolonged distribution in adipose tissue, often resulting in extended duration of sedation and respiratory depression in the elderly. Initial doses should be conservative and titration must be slow and closely guided by clinical response. Long-acting formulations such as transdermal patches should be used with caution, as impaired thermoregulation and skin changes in elderly patients can unpredictably alter absorption.[21]

Formulation selection is central to optimised therapy. Intravenous fentanyl is suitable for acute, controlled analgesia in surgery and critical care. Transdermal patches are preferred for stable, chronic cancer pain in opioid-tolerant individuals, while transmucosal and intranasal formulations are reserved for rapid-onset management of breakthrough pain. Epidural or intrathecal fentanyl may be used in regional analgesia, such as obstetrics, under precise dosing control. When switching between formulations, accurate equianalgesic dose conversions and cross-tolerance reductions are essential to prevent underdosing or overdose.

In routine clinical practice, therapeutic drug monitoring is limited; therefore, reliance on clinical endpoints such as sedation scores, respiratory rate, oxygen saturation and patient-reported pain relief is vital. Risk mitigation includes minimizing concomitant CNS depressants, avoiding CYP3A4 inhibitors and using opioid conversion calculators when transitioning between routes or formulations. Co-prescription of naloxone in high-risk individuals, especially those with polypharmacy or comorbid respiratory disease, enhances safety and preparedness in overdose scenarios.

Personalised approaches are increasingly being explored. Pharmacogenomic testing—particularly for polymorphisms in CYP3A4 and OPRM1 genes—may eventually guide dose prediction and therapeutic decisions. Novel technologies such as AI-guided dosing algorithms, smart infusion systems and digital health monitoring platforms may further refine fentanyl use by adapting real-time dosing to the patient's physiological parameters. As the complexity of pain management grows, precise dose optimisation tailored to individual characteristics will remain central to unlocking the therapeutic potential of fentanyl while safeguarding against its inherent dangers.

DRUG INTERRUPTION AND WITHDRAWAL CONSIDERATION

Interruption or discontinuation of fentanyl therapy, particularly after prolonged use, must be approached with clinical vigilance due to the risk of opioid withdrawal syndrome. Fentanyl, though potent and short-acting in intravenous form, exhibits prolonged effects in transdermal or depot formulations due to extensive lipid tissue accumulation and slow redistribution. Sudden cessation, especially in opioid-dependent individuals, may precipitate a constellation of withdrawal symptoms including anxiety, restlessness, mydriasis, rhinorrhea, diaphoresis, piloerection, abdominal cramps, nausea, vomiting, insomnia and tachycardia. The onset and severity of withdrawal symptoms depend on the duration of exposure, dose, formulation used and degree of physical dependence. Notably, withdrawal following transdermal fentanyl may be delayed by 12–24 hours after patch removal and symptoms may persist for several days.

To mitigate these effects, fentanyl therapy should be tapered gradually rather than abruptly discontinued. Dose reductions of 10–25% every 2–3 days are commonly recommended, though tapering must be individualised based on patient response, underlying condition

and concurrent medication use. In patients unable to tolerate tapering or exhibiting significant withdrawal, pharmacological support using clonidine, lofexidine or short-acting opioids may be employed to ease symptoms.

Furthermore, careful monitoring is essential when transitioning patients from fentanyl to other opioids or analgesics, as cross-tolerance may be incomplete, increasing the risk of overdose or inadequate analgesia. In cases involving non-compliance, abrupt interruption due to drug supply issues or overdose reversal with antagonists such as naloxone, the abrupt elimination of fentanyl can result in intense withdrawal and a rapid return of severe pain. These scenarios require immediate clinical attention and often necessitate reinitiation of opioid therapy under supervision or use of multimodal analgesic strategies. Effective planning for fentanyl discontinuation—especially in chronic pain, palliative care or critical care contexts—demands a structured and supportive approach to minimise patient distress and preserve therapeutic continuity.[22]

TAPERING STRATEGIES

Tapering fentanyl requires a carefully structured and patient-specific approach to safely discontinue therapy while minimizing withdrawal symptoms and preserving functional pain control. Given fentanyl's potency, lipophilicity and variable pharmacokinetics across formulations, abrupt cessation is contraindicated in opioid-dependent individuals, especially those on long-term transdermal or high-dose regimens. The tapering process should be gradual, with typical dose reductions of 10% to 25% every 2 to 3 days, adjusted based on the patient's clinical response, psychological state and comorbid conditions. In cases of long-standing opioid use, especially at higher doses, a slower taper—reducing by 5% to 10% every 1 to 2 weeks—may be more appropriate to avoid withdrawal and emotional destabilization.

Transdermal fentanyl tapering often involves switching to a lower patch strength sequentially, followed by transition to a short-acting opioid for finer dose adjustments before complete discontinuation. Alternatively, patients may be rotated to an equivalent oral morphine regimen using equianalgesic dose conversions to facilitate more precise titration and eventual tapering. Close monitoring of withdrawal symptoms is essential throughout the process, with pharmacologic support such as clonidine, lofexidine, antiemetics, antidiarrheals and non-opioid analgesics provided as needed. Psychological support, counselling and use of multimodal pain management strategies—such as cognitive behavioural therapy, physical therapy or adjuvant analgesics—can aid in reducing opioid reliance and improving overall outcomes. A patient-cantered, flexible tapering plan that includes regular reassessment is essential to balance withdrawal management with effective pain control, particularly in individuals with chronic non-cancer pain, history of substance use disorder or psychiatric comorbidities.[23]

MARKETED FORMULATION

The marketed formulations of fentanyl, with details on dosage form, brand name, manufacturer, strength, price per pack (₹) and pack size was given in Table.50.2.

Table 50.2 Market Formulations of Fentanyl

Formulation	Brand Name	Manufacturer	Strength / Release Rate	Approx. Price
Transdermal Patch	Durogesic / Duragesic	Johnson & Johnson (Janssen)	25 µg/h (3pack)	₹1,485
	Durogesic / Duragesic	Johnson & Johnson (Janssen)	50 µg/h (1 patch)	₹953
	Fenstud	Rusan Healthcare	25 µg/h, 50 µg/h	₹415–₹795
	Fentrans	6ipain Healthcare	50 µg/h (3pack)	₹940
	Fendrop	Sun Pharma	25 µg/h (1 patch)	~₹590
IV/IM Injectable	Fenilate (Fentanyl Citrate)	Svizera Healthcare	50 µg/ml (2 ml ampoule)	₹35
	Fent (Neon Laboratories)	Neon Laboratories	50 µg/ml (2 ml ampoule)	₹50
	Fent (Neon Laboratories)	Neon Laboratories	50 µg/ml (10 ml vial)	₹125
	Trofentyl	Troikaa Parenterals	50 µg/ml (ampoule)	₹175–₹625
	San Fent	Sandor Medicaids	50 µg/ml (2 ml ampoule)	₹42.50 (₹21.25/ml)
Transmucosal Lozenge	Actiq	Cephalon (J&J)	200–1,600 µg lozenge	US$92–271 each

PATENTS

The development and commercialization of fentanyl have been protected by numerous patents that span from the original compound synthesis to advanced delivery systems. These patents not only reflect scientific innovation but also show how pharmaceutical formulations evolved to optimize pain relief while trying to reduce misuse potential.[24]

The first and foundational patent for fentanyl was granted to Dr. Paul Janssen in 1964 (US Patent 3143417A) for the compound N-(1-phenethyl-4-piperidyl) propionanilide, now known as fentanyl. This invention introduced a potent synthetic opioid analgesic with potency over 50–100 times that of morphine. The patent expired in 1981, opening the way for formulation advancements.

In 1989, ALZA Corporation patented a transdermal therapeutic system for delivering fentanyl steadily over 72 hours (US 4795591A), which later became the branded product Duragesic®. This innovative patch allowed controlled release through the skin, improving long-term pain management. The patent expired in 2006, but the technology influenced multiple transdermal analgesic systems.

ACTIQ®, developed by Anesta Corp., was a novel oral transmucosal lozenge containing fentanyl citrate. Patented under US 5145684A in 1992, this "lollipop-like" formulation enabled buccal absorption for rapid pain relief in cancer patients. It expired in 2009, but remains a reference formulation for opioid delivery.
Cephalon Inc. advanced transmucosal delivery with FENTORA®, a buccal tablet utilizing effervescent agents to enhance mucosal absorption. The patent (US 6455081B1) was granted in 2002 and expired in 2019. The tablet was designed for breakthrough cancer pain in opioid-tolerant individuals.
A sublingual spray formulation of fentanyl, SUBSYS®, was patented by Insys Therapeutics in 2011 (US 8075920B2) and is set to expire in 2028. This spray rapidly delivers fentanyl under the tongue, providing faster onset than tablets or lozenges.
Similarly, LAZANDA®, an intranasal fentanyl spray patented in 2010 by Archimedes Pharma (US 7842695B2), offered an alternative route for breakthrough cancer pain, especially for patients unable to use oral formulations. The patent will expire in 2026.
IONSYS®, an iontophoretic transdermal system, was another breakthrough by ALZA Corporation, patented in 2004 (US 6749867B2) and expired in 2023. It allowed hospital patients to self-administer fentanyl for acute post-operative pain without needles, using a mild electric current.
Hisamitsu Pharmaceutical developed a rate-controlled fentanyl patch (US 7201932B2), granted in 2007 and expiring in 2025, which included a layered adhesive system to prevent dose dumping and support stable fentanyl plasma levels.
Further innovations included injectable biodegradable microparticles containing fentanyl for sustained release (US 6565882B1, 2003–2021) by Robert Langer et al. and fentanyl prodrugs (US 8318758B2, 2012–2030) from Xenon Pharmaceuticals, which aimed at reducing abuse by modifying pharmacokinetics.
Insys Therapeutics also patented a pH-modulated sublingual tablet (US 8460731B2) in 2013, designed to enhance fentanyl's solubility and mucosal absorption. This patent remains active until 2031.
Lastly, Alexza Pharmaceuticals introduced an inhalable fentanyl formulation using thermal aerosolization (US 7037541B2, 2006–2024), which enabled ultra-rapid systemic delivery via the lungs.
The summary of important fentanyl related patent details is given in table.50.3.

Table 50.3 Key Patents on Fentanyl and Its Formulations

Patent Number	Invention	Inventor/Company	Grant Year	Expiry Year	Key Highlights
US3143417A	Fentanyl synthesis	Dr. Paul Janssen	1964	1981	First synthesis of fentanyl compound
US4795591A	Transdermal patch (Duragesic®)	ALZA Corporation	1989	2006	72-hour controlled skin delivery
US5145684A	Oral transmucosal lozenge (ACTIQ®)	Anesta Corp.	1992	2009	Buccal "lollipop" for breakthrough pain
US6455081B1	Buccal tablet (FENTORA®)	Cephalon Inc.	2002	2019	Effervescent buccal fentanyl tablet
US8075920B2	Sublingual spray (SUBSYS®)	Insys Therapeutics	2011	2028	Fast-onset sublingual spray
US7842695B2	Nasal spray (LAZANDA®)	Archimedes Pharma	2010	2026	Intranasal delivery for cancer pain
US6749867B2	Iontophoretic patch (IONSYS®)	ALZA Corporation	2004	2023	Needle-free, patient-controlled delivery
US7201932B2	Rate-controlled adhesive patch	Hisamitsu Pharma	2007	2025	Multi-layer patch to avoid dose dumping
US6565882B1	Injectable microparticles	Robert Langer (Alkermes)	2003	2021	Sustained injectable release
US8318758B2	Fentanyl prodrug	Xenon Pharmaceuticals	2012	2030	Modified-release, abuse-deterrent design
US8460731B2	pH-modulated sublingual tablet	Insys Therapeutics	2013	2031	Improved mucosal solubility
US7037541B2	Inhalable fentanyl aerosol	Alexza Pharmaceuticals	2006	2024	Rapid lung absorption via thermal aerosol

CONCLUSION

In conclusion, fentanyl stands as a double-edged sword in modern pain management and anaesthesia due to its exceptional potency and rapid onset of action. Its high lipid solubility enables swift penetration of the central nervous system, making it highly effective in surgical settings and for managing breakthrough cancer pain. These pharmacological strengths have driven the development of diverse and sophisticated patented delivery systems—ranging from transdermal patches, buccal tablets and sublingual sprays to nasal and inhalable forms—each designed to optimize its therapeutic potential.
However, these innovations have also contributed to broader accessibility, inadvertently fuelling the risk of misuse, overdose and addiction. The narrow therapeutic index of fentanyl necessitates precise dosing and vigilant monitoring, as even minor deviations can result in life-threatening respiratory depression. While key patents have expired, ushering in generic formulations, this has further complicated regulatory oversight and safety.

Thus, the history of fentanyl patents mirrors its clinical profile: highly beneficial when used judiciously, yet perilous when misused. As the medical and scientific communities strive to balance efficacy with safety, ongoing research focuses on developing safer analogues, abuse-deterrent formulations and advanced monitoring strategies. These efforts aim to preserve fentanyl's essential role in pain therapy while minimizing its potential harms, ensuring that innovation serves both therapeutic advancement and public health protection.

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