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Mini Review

A mini-review of various analytical methodologies for quantitative analysis of tramadol hydrochloride and celecoxib in different matrices

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ABSTRACT

Any medicine that effectively reduces pain without interfering with nerve impulse conduction, significantly changing sensory experience, or influencing consciousness is regarded as an analgesic. One key difference between analgesics and anesthetics is their selectivity. Analgesics like tramadol (TRM) operate centrally by blocking neuronal absorption of noradrenalin and serotonin, which reduces pain in many ways. Osteoarthritis (OA), one of the leading causes of disability worldwide, is one of several illnesses and conditions for which celecoxib (CLX) is recommended to alleviate inflammation and discomfort. A recently developed co-crystal combining active pharmaceutical ingredient (API) and celecoxib is known as tramadol-celecoxib (CTC). The analgesic effects are exerted via both the peripheral and central routes by means of the co-crystal structure of TRM and CLX. Multimodal treatment relies heavily on the utilization of co-crystal compositions. In order to alleviate pain, multimodal treatment makes use of a wide variety of therapeutic approaches. Collectively, these medications impact a wide variety of pain

circuits. There are two main categories of analgesics: those that work on the central nervous system (the opioids) and those that reduce local inflammation (the anti-inflammatory medicines). Opioid analgesics were once known as narcotics due to their sedative properties. Opioid analgesics are useful for both the short- and long-term treatment of severe pain. On the other hand, anti-inflammatory drugs are prescribed for moderate to severe pain that won't last long, such aches and pains caused by arthritis, bruises, muscular strain, or headaches.

Keywords: Tramadol hydrochloride, Celecoxib, HPLC, Spectrophotometry, Analgesics.

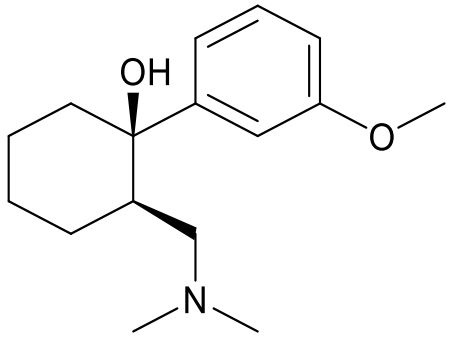
1. Introduction

Analgesics are drugs that specifically alleviate pain without impeding the transmission of nerve signals, significantly modifying sensory experience, or impacting consciousness. The selectivity mentioned is a crucial differentiation between an analgesic and an anesthetic (1). Analgesics may be categorized into two types: anti-inflammatory medications, which relieve pain by diminishing local inflammatory reactions, and opioids, which exert their effects on the brain. The opioid analgesics were formerly referred to as narcotic medications due to their ability to produce sedation (2). Opioid analgesics may be used for both acute and chronic alleviation of intense pain (3). Conversely, the anti-inflammatory substances are used to alleviate pain temporarily and to address mild discomfort, such as that caused by a headache, muscular strain, bruises, or arthritis (4). Analgesics may be categorized in the following manner:Non-opioid analgesic medications include acetaminophen and nonsteroidal anti-inflammatory medicines (NSAIDs) such as meloxicam and celecoxib. These medications provide efficient pain relief for mild to moderate pain and have become an essential component in managing both nociceptive and neuropathic pain. Regrettably, nonopioid analgesics are limited by a maximum effective dosage threshold and may cause notable adverse effects (1).

Opioids, sometimes referred to as "narcotics", include natural drugs such as morphine, semi-synthetic chemicals like hydrocodone, and synthetic substances such as tramadol. Opioids attach to opioid receptors located inside the neuron membrane, mainly in the central nervous system (CNS) and gastrointestinal tract. Positron emission tomography (PET) scans may be used

to map the brain regions that house opiate receptors, which are responsible for the effects of opiate drugs. The thalamus, responsible for pain processing, has the largest concentrations of mu opiate receptors in the human brain. The cerebral cortex and basal ganglia, which are involved in movement and emotions, have intermediate amounts of these receptors. The visual cortex, on the other hand, has the lowest levels (1).

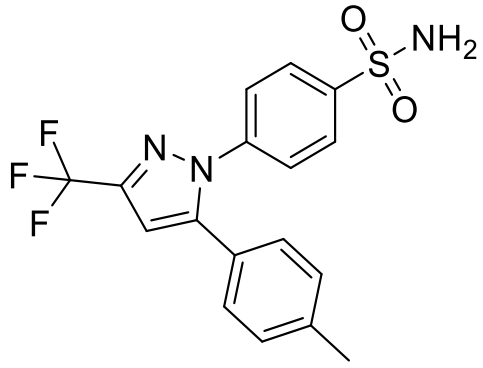
Tramadol (TRM), (1R,2R)-2-[(dimethylamino)methyl]-1-(3methoxyphenyl) cyclohexan-1-ol;hydrochloride as seen in **Figure 1a**, is a systemically acting opioid receptor antagonist. It alleviates pain by inhibiting the reuptake of noradrenaline and serotonin by neurons (5). TRM is white to yellow solid and soluble in methanol (MeOH); sparingly soluble in ethanol; and very slightly soluble in isopropanol and water. Celecoxib (CLX), 4-[5-(4-Methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid as shown in **Figure 1b**, is administered as a remedy for pain and inflammation, which are the main symptoms of several diseases and conditions, particularly osteoarthritis, a major global contributor to disability. CLX is Pale yellow solid and poorly soluble in H2O and freely soluble in MeOH, ethanol and methylene chloride.



Tramadol

(1*R*,2*R*)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexan-1-ol

(A)



Celecoxib

4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide

(B)

Figure 1: Chemical structures of (A) TRM, and (B) CLX.

2. Analytical techniques

2.1. Official and reported analytical methods for the analysis of TRM

2.1.1. Official analytical method

TRM is an official drug in BP (6) and USP (7). It is determined in BP potentiometrically, Dissolve 0.180 g in 50 mL of ethanol (96 percent) R. Titrate with 0.1 M ethanolic sodium hydroxide, determining the end-point potentiometrically I mL of 0.1 M ethanolic sodium hydroxide is equivalent to 29.98 mg of TRM (6). In addition, TRM was determined in USP by HPLC where the mobile phase is trifluoroacetic acid: acetonitrile (70:30, v/v), column C_{18}, UV 270 nm and flow rate of 1 mL/min (7).

2.1.2. Reported analytical methods

a. Spectroscopic methods

UV spectrophotometric methods

For the quantitative estimation of TRM, a direct UV spectrophotometric approach has been designed. TRM measured at 270.5 (8), 270 nm (9) and at 273.5 (10) in bulk and capsule dosage forms.

Using zero-order, first-order, and second-order derivative spectrophotometric techniques, TRM was analyzed in methanol and water at wavelengths ranging from 240 to 290 nm (11).

TRM was also quantified by employing the area under the curve and second order derivative techniques. We values obtained at 272 and 280 nm for this analysis , respectively (12).

Colorimetric method uses a special dye called wool fast blue to create a chloroform extractable complex with TRM. This complex has a maximum absorbance at 590, which helps us measure the TRM concentration (13). There's another method that involves using the Folin-Ciocalteu (F-C) reagent and TMH in an alkaline solution. This technique results in the creation of a blue color that absorbs light at 760 nm (14).

TRM was mixed with Eriochrome Black T and acetate buffer at pH 3.5, it produces a colored complex. The measurement of this complex was compared to a reagent blank at 520 nm. (15)

Spectrofluorimetric method

A method based on NBD-Cl derivatization has been reported. In ethyl acetate, the product had an absorbance maximum at 460 nm and a fluorescence emission peak at 520 nm (16).

b. Electrochemical methods

TRM was measured in urine, milk, and medicinal formulations employing two improved carbon paste electrodes (17).

Two TRM-determining plastic membrane electrodes were designed and manufactured, and their composition, lifetime, useable pH range, and working concentration range were thoroughly studied (18).

Based on the ion-association of TRM with phosphomolybdic acid (TD-PM), a potentiometric measurement of TRM was published, which relies on a selective electrode (19).

An ion-to-electron transducer layer composed of polyaniline nanoparticles has been used to construct an ion-selective electrode that can detect TRM was also reported (20).

Carbon nanotube electrodes were implemented to measure TRM in bulk, pharmaceutical formulations, and spiked human plasma and urine. These electrodes were compared to coated platinum wire and carbon paste selective electrodes (21).

An electrochemical sensor was utilized for the voltammetric determination of TRM in real samples. The sensor was based on magneto LDH/Fe3O4 nanoparticles and was integrated with a glassy carbon electrode (22). An electrochemical imprinted sensor was also constructed to enable sensitive and selective determination of TRM (23).

A potentiometric sensor was developed and manufactured for the purpose of determining TRM in different real samples (24) .

A nano-sensing layer has been developed by incorporating synthesized TRM-imprinted polymer nanoparticles, which served as an effective sensing agent. This layer was utilized for the measurement of TRM (25).

An electrochemical method was successfully established for the quantification of TRM in pure solutions and pharmaceuticals. In order to accomplish this, we utilized a coated-wire electrode detector (26).

A voltammetric technique was successfully developed using nanoparticles of antimony oxide (Sb2O3NPs) and multiwalled carbon nanotubes (MWCNTs) (27).

A nanocomposite of graphitic carbon nitride and Fe3O4 (g-C3N4/Fe3O4) was incorporated into a carbon paste electrode. This electrode was then utilized as a sensor with high sensitivity for the voltammetric determination of TRM in an aqueous solution (28).

A quantitative measurement technique for TRM was proposed using an electrochemical detection approach. This method involves the use of an electrode made of pencil graphite (PGE) containing multi-walled carbon nanotubes (MWCNTs) and gold nanoparticles (AuNPs). The electroanalysis of TRM was conducted using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) strategies (29).

A glassy carbon electrode (GCE) was modified with hierarchical graphene oxide nanoplatelets (H-GONPs) and proposed as an electrochemical sensor platform to detect TRM (30).

potentiometric ion-selective PVC membrane sensor was developed based on tramadol-(tetraphenylborate) as the sensing element (31).

Factionalized CeO_2/Al_2O_3 nanocomposite membrane sensor was presented to assess TRM in marketable products (32)

Voltammetric methodology were established to analyze TRM using CuO NPs/MWCNT as a working electrode. The produced nanocomposite showed high selectivity for TRM analysis (33).

c. Chromatographic methods

High-performance thin-layer chromatography (HPTLC)

HPTLC technique for TRM was established on an aluminium-backed layer of silica gel 60F254 employing ethyl acetate: methanol: ammonia (25%) (9.0: 1.0 :0.5, v/v/v) as mobile phase. Densitometric detection at 271 nm was developed (34).

TLC determination of TRM employing a developing liquid containing a mixture of ethyl acetate: methanol: ammonia (9:0.8:0.5, v/v/v). Densitometric quantification of TRM was relied on reflectance–absorbance mode at 271 nm (35).

High-performance liquid chromatography

Table 1: The reported chromatographic methods for simultaneous determination of TRM

Assay method	Column	Mobil phase	Detection	Sample matrix	Ref.
HPLC-UV detection	Zorbax SB-C_{18} column	Potassium dihydrogen phosphate (KH_2PO_4) (pH 5): acetonitrile (ACN) (60:40, v/v)	218 nm	Human saliva	(36)
	Phenomonex-Gemini, C_{18} column	KH_2PO_4 (pH 5.5) : MEOH: ACN (40:40:20, v/v/v)	280 nm	Pharmaceutical formulation	(37)
	Waters Aquity BEH C_{18} column	KH_2PO_4 (pH 2.8): ACN (60 : 40, v/v)	226 nm	Pharmaceutical formulation	(38)
	Acquity BEH C_{18} column	Gradient elution solvent A (trifluroacetic acid buffer) and solvent B (MEOH: ACN)	270 nm	Pharmaceutical formulation Impurities	(39)
	XTerra RP-C_8 column	ACN : phosphate buffer (pH 3) (20:80 v/v)	218 nm	Rabbit plasma	(40)
HPLC-FLD	Phenomenex Luna® C_{18} ODS2 column	ACN: 20 mM NaH_2PO_4 (pH 3.9) (40:60, v/v)	Excitation at 275 nm, emission at 300 nm	Dog urine	(41)
	ChromolithTM Performance C_{18} column	Water (H_2O: MEOH (81:19, v/v)	Excitation at 200 nm, emission at 301 nm	Human urine	(42)
	Kromasil® C_{18}column	ACN : 0.1% formic acid (20:80, v/v)	Excitation at 280 nm, emission at 310 nm	Human plasma	(43)

HPLC-MS/MS detection	HyPRITY C_{l8} column	H_2O : MEOH (65:35, v/v)	m/z at 58.2→264.40 (TRM) m/z at 58.2→ m/z 250.3758 (M1) m/z 250.3124 (M2) m/z 236.3976 (M3) m/z 222.5361 (M4) m/z 236.4475 (M5)	Human Urine Metabolites	(44)
	Phenomenex Luna® C_{18} ODS2 column	MEOH with 0.1% formic acid: ammonium acetate buffer(pH 4.5) (30:70, v/v)	m/z 30–500	Dog urine	(41)

2.2. Official and reported analytical methods for the analysis of CLX

2.2.1. Official analytical method

CLX is an official drug in USP (7). CLX was determined in USP by a liquid chromatographic method using phenyl column and mobile phase was (methanol: acetonitrile: potassium dihyrogen phosphate buffer (pH 3) (30:10:60, v/v/v) at 1.5 ml/min using UV detection at 215 nm (7).

2.2.2. Reported analytical methods

a. Spectroscopic methods

UV spectrophotometric methods

Two zero-order techniques were established for estimation of CLX in tablet form based on acetylation of CLX using acetyl chloride in methanol and acetyl derivative of CLX was determined at 270 nm (45). Another First derivative method using methanol as solvent and detection was reported at 252 nm (46).

CLX was reacted with methylene blue and iodine the produced complexes were measured at 665 nm and 511 nm, respectively (47).

Spectrofluorimetric method

Using methanol as solvent and β-cyclodextrin as fluorescence enhancer determination was at 390 nm after excitation at 290 nm (48).

b. Electrochemical methods

Cyclic voltammetry based on molecularly imprinted poly(vinylidene fluoride) membrane doped by gold nanoparticles was reported for CLX determination (49). Adsorptive stripping voltammetry using mercury electrode as working electrode was also reported for CLX determination (50).

c. Chromatographic methods

High-performance thin-layer chromatography

HPTLC method for estimation of CLX in bulk and its pharmaceutical formulation developed using Toluene: Ethyl acetate: Methanol (8:2:1, v/v/v) as the mobile phase and densitometric scanning was achieved at 254nm (51).

High-performance liquid chromatography

Table 2: The reported chromatographic methods for simultaneous estimation of CLX.

Assay method	Column	Mobil phase	Detection	Sample matrix	Ref.
HPLC-UV detection	IdLiChrospher c_{18} column	MEOH: H_2O (72:28,v/v)	251 nm	Different layers of skin	(52)
	L11 column	MEOH: ACN: phosphate buffer (pH 3) (30:10:60, v/v/v)	249 nm.	Pharmaceutical formulation	(53)
	Chiralpak IA-3 column	ACN: H_2O (45:55, v/v)	250 nm	Seven process-related impurities	(54)

2.3. Recently reported analytical methodologies for the estimation of TRM and CLX in binary mixtures

a. Spectroscopic methods

UV spectrophotometric methods

concurrent quantification of TRM by spectrophotometric methods with CLX by mathematical simultaneous equation and ratio difference methods (55) and by second derivative spectrophotometry technique, dual-wavelength resolution technique and induced dual-wavelength technique (56). TRM and CLX was determined simultaneously with 4-metyl actophenone as a process related impurity of CLX by third derivative and Fourier method (57).

b. Spectrofluorometric methods

TRM and CLX was determined simultaneously using a synchronous method (58).

3. Conclusion

The current study provides an overview of the many analytical approaches for TRM and CLX detection in various matrices, including pharmaceutical formulations and serum and plasma samples, that have been reported in the literature. Analytical methods such as spectroscopy, chromatography, and electrochemical processes were used to quantify TRM and CLX both individually and in bulk tablet formulation. According to the results of this study, various methodologies were reported for estimation of TRM and CLX as a single in addition just a few analytical techniques based on UV-Vis spectrophotometry and HPLC are accessible for estimation of the binary mixture. HPLC with UV detection is also the method most frequently used to assess both medicines in the pharmaceutical matrix and other biological matrices since it delivers correct findings with minimal effort, according to the data for TRM and CLX analysis.

- **Conflict of Interest**

The Authors declare no conflict of interest.

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