Review Article

ANALYTICAL METHOD FOR DETERMINATION OF THIOCOLCHICOSIDE IN MARKETED PHARMACEUTICAL PREPARATION: A REVIEW

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ABSTRACT:

Thiocolchicoside is a natural anti-inflammatory glycoside. It is the semi-synthetic derivative of the colchicine which has effect on muscle relaxant with anti-inflammatory and analgesic effects. It works through selective binding to the GABA-A receptor. It prevents muscle contractions by activating the GABA inhibitory motor pathway. The article summarizes analytical method including the chromatographic method, LC-MS (Liquid Chromatography-mass spectroscopy), HPLC, GC-MS (Gas chromatography-mass spectroscopy), HPTLC and UV-Visible spectrophotometry techniques for estimation of Thiocolchicoside in biological samples, bulk and pharmaceutical formulation.

KEYWORDS: Thiocolchicoside (THC); UV-Spectrophotometry; HPLC; HPTLC; LC-MS; GC-MS.

1. INTRODUCTION:

Thiocolchicoside is originates from the flower seeds of S*uperba Gloriosa*. It has potent convulsant activity and should not be administered to individuals prone to seizures. It is used in the treatment of arthritis. It is mainly used in the treatment of painful muscle contractures and is indicated in acute spinal pathology. Furthermore it has effect on muscle tone, stiffness, contractures, and soreness.

1.1 Chemistry:

This compound are phenolic glycosides belongs to the class of organic compounds containing a phenolic structure attached to a glycosyl moiety. Natural glycosides consist of sugar units like L-Fructose, D-glucose, and L rhamnose. IUPAC name is N-[(10S)-3,4-dimethoxy-14-(methylsulfanyl)-13-oxo-5-{[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2 yl]oxy}tricyclo[9.5.0.0^{2},^{7}] hexadeca1(16) ,2,4,6,11,14-hexaen-10-yl] acetamide. The chemical formula of Thiocolchicoside is $C_{27}H_{33}NO_{10}S$ and molecular weight is 563.6 g/mol.

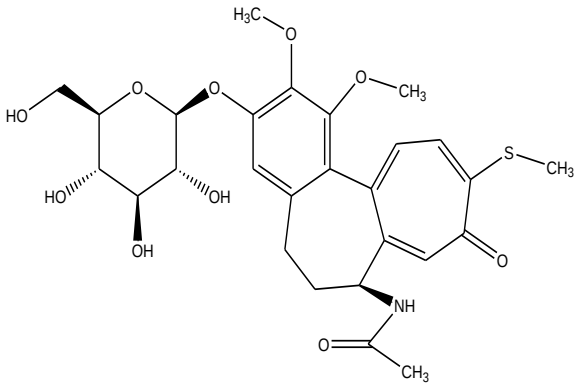

Figure no. 1: Structure of Thiocolchicoside.

1.2 Mechanism of Action:

Thiocolchicoside acts on muscular contractures by activating the GABA inhibitory pathways because it has a selective and potent affinity for g-amino butyric acid A (GABA-A) receptors thereby behaving as a potent muscle relaxant. In human cortex the main inhibitory neurotransmitter is Gamma-amino butyric acid (GABA). GABAergic neurons are involved in the anesthetics, myorelaxation, sedation, also in the treatment of anxiolytic. GABA can also modulate heart rate and blood pressure. It acts as a muscle relaxant because it has an affinity for the inhibitory glycine receptors i.e. glycomimetic and GABA mimetic activity. Glycine is an inhibitory neurotransmitter and acts as an allosteric regulator of NMDA (N-methyl-D-aspartate) receptors. It regulates the movement, vision by processing the motor and sensory data.

1.3 Pharmacology:

A) Pharmacokinetic properties:

1) Absorption- Thiocolchicoside C_{max} occurs in 30 min and reach values of 113 mg/mL after a 4 mg dose and 175 mg/mL after an 8 mg dose after IM administration.

2) Distribution- After an IM administration of 8 mg, the apparent volume of distribution of thiocolchicoside is estimated around 42.7 L.

3) Biotransformation- Thiocolchicoside is first metabolized in the aglycon 3-dimethyltiocolchicine after oral administration. It is mainly occurs by intestinal metabolism.

4) Elimination- The apparent $t_{1/2}$ of thiocolchicoside is 1.5 hr. and the plasma clearance 19.2 L/h after IM administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20% in oral administration.

B) Pharmacodynamics:

Thiocolchicoside act into contractures with a central cause as well as in the contractures of reflex type and rheumatic. Thiocolchicoside inhibits glycine receptors by acts as a competitive GABA receptor antagonist. It used in combination with glafenine and meprobamate to tranquilize patients undergoing hysterosalpingography; also it is used in the treatment of painful muscle spasms. It has powerful convulsant activity and should not be used in individuals at risk for seizures.

1.4 Side effects:

Itching and skin rash, Swelling of face, lips, eyelids, tongue, hands and feet, Fainting and drowsiness, Nausea and Vomiting, Diarrhoea, Yellowing of skin and eyes Photosensitivity, Dry mouth, Headache.

1.5 Dosage Forms and Recommended Dose:

THC is available in India in the form of Parenteral, Oral, and topical formulations which having recommended oral dose is 8 mg every 12 hours. The maximum intramuscular dose should be 4 mg every 12 hours, for up to 5 days.

2. ANALYTICAL METHODS:

This all are method which are used for determination of Thiocolchicoside in Pharmaceutical formulation and in biological fluids. This are all analytical method are reported during the literature survey. This all reported analytical method with specific condition. The literature reports vast number of analytical methods for the determination of thiocolchicoside in biological matrices, bulk material and the pharmaceutical dosage formulation.

2.1 Spectrophotometry:

In the literature survey were found that 25 UV-Spectrophotometric methods have been reported for estimation of Thiocolchicoside single and in combined dosage form.

Table no. 1 shows the summery of reported UV-Spectrophotometric methods indicating sample matrix used, lambda Max., Solvent used in it.

Table no. 1: Summary of UV-Spectrophotometric methods of Thiocolchicoside.

Sr. no.	**Name of drug**	**Sample**	**Method**		**Wavelength(nm)**		**Solvent**	**Ref. no.**
					Thio-colchi-coside	Other		
1.	Thiocolchico-side	Tablets		Spectrophotometric	410	-	Distilled water	1
2.	Thiocolchico-side + Ketoprofen	Tablets		Simultaneous equation	372	251.5	Methanol	2
3.	Thiocolchico-side + Etodolac	Tablets	A	Simultaneous equation	259.4	223	Methanol	3
			B	Q-value analysis				
4.	Thiocolchicoside	Capsule	A	Zero order	259.8	-	Methanol	4
			B	Area Under Curve (AUC)	269.8-259.8			
5.	Thiocolchico-side + Deslora-tadine + Fexo-fenadine HCL + Etodolac + Moexipril HCL	Capsule		Area Under Curve (AUC)	607	-	Distilled water	5
6.	Thiocolchico-side	Capsule		Zero order	257.0	-	Methanol	6
7.	Thiocolchico-side	Capsule	A	Zero derivative spectrum	259.0	-	0.1N NaOH	7
			B	First derivative spectrum	252.0			

			C	Second derivative spectrum	260.0			
			D	Area Under Curve (AUC)	254.0-264.0			
8.	Thiocolchicoside + Diclofenac Potassium	Tablets	A	Ratio Derivative	268.78	355.6	Methanol	8
			B	Dual Wavelength	263.22	301.65		
9.	Thiocolchicoside + Hydro-chloro thiazide	Tablets		Q-absorption ratio	282.60	271	Methanol	9
10.	Thiocolchicoside + Aceclofenac	Tablets		Second order derivative	278.2	215.1	Methanol	10
11.	Thiocolchicoside + Dexketoprofen + Trometamol	Tablets		Dual wavelength data processing program	368	284.60	Methanol	11
12.	Thiocolchicoside + Diclofenac Potassium	Capsule		Multicomponent Method	254,259,265,271,286	254,259,265,271,286	Methanol	12
13.	Thiocolchicoside + Paracetamol + Aceclofenac	Tablets		Multicomponent Method	258	249, 276	Methanol	13
14.	Thiocolchicoside + Aceclofenac	Tablets		Area Under Curve (AUC)	264.5-254.5	279.0-269.0	Methanol	14
15.	Thiocolchicoside + Etodolac	Tablets		Multivariate calibration methods	240–440	240-440	Methanol	15
16.	Thiocolchico-side + Diclofenac sodium	Capsule	A	Absorbance correction	276.6	372.8	Methanol	16
			B	First order derivative	278.6	243.2		
			C	Dual wavelength	244	269		
17.	Thiocolchico-side + Dexketoprofen	Tablets	A	Absorbance correction method	370	255	Methanol	17

			B	First order derivative spectroscopic	332	242		
18.	Thiocolchicoside + Diclofenac	Capsule	A	Simultaneous equation	260	276.5	NaOH	18
			B	Absorbance Correction method	373	276.5		
19.	Thiocolchicoside	Injection		Spectrofluorimetry	289 & 366.	-	-	19
20.	Thiocolchicoside	Capsule	A	Zero order	259.8	-	Distilled water	20
			B	Area under Curve	269.8-259.8			
21.	Thiocolchicoside + Paracetamol + Aceclofenac	Tablets		Multicomponent mode	258	256, 270	Methanol	21
22.	Thiocolchicoside + Diclofenac	Capsule	A	Q-value/Analysis	264	259	Methanol	22
			B	Simultaneous equation				
23.	Thiocolchicoside + Diclofenac	Tablets	A	Absorption correction	264.99	373.8	Methanol	23
			B	Area Under Curve (AUC)	278.51-285.53	252.5-260.5		
24.	Thiocolchicoside + Diclofenac	Capsule		Simultaneous equation	259	277	Methanol	24
25.	Thiocolchicoside + Diclofenac	Capsule	A	Simultaneous equation	260.0	276.5	Methanol	25
			B	Absorbance Correction	373.0	276.5		

2.2 Chromatographic Methods:

The High performance liquid chromatography (HPLC) for residue determination of single and combined drug and also used in impurity profiling.

Table no. 2 shows the summarized reported chromatographic method indicating sample, method, mobile phase and wavelength.

Table no. 2: Summary chromatographic methods of Thiocolchicoside.

Sr. no.	Drug Name & Combination	Sample	Column	Mobile Phase	Mode of analysis	Wavelength (nm)	Retention time in min.	Ref. No.
1.	THC+ ETO	Tablets	C-18 (Inertsil)	Acetonitrile: 0.05M ammonium acetate (80:20) pH 6.5	Isocratic	240	THC-9.04, ETC-5.01	26
2.	THC+ GF	Tablet MIX-I	C18 (Waters symmetry)	Methanol : 0.035 M phosphate buffer (50:50, v/v) pH 4.5	Isocratic	400	THC-2.56, GF-4.5	27
3.	THC+ ACE	Tablets	C18 (Inertsil)	Acetonitrile: Water: Methanol (70:20:10, v/v)	Gradient	260	THC-3.36, ACE-4.12	28
4.	THC+ ETO DOL AC	Tablets	C18 (ZODIAC)	Methanol: Acetonitrile: Water 20:60:20 (v/v/v)	Isocratic	274	THC-5.49, ETD-7.86	29
5.	THC+ ACE	Tablets	C18 (Thermo)	Acetonitrile: Water: 0.025M pot. Dihydrogen OPB (pH 3.0 (70:10:20, v/v)	Isocratic	260	THC-2.70, ACE-4.76	30
6.	THC+ ACE	Tablets	C18 (Waters symmetry)	Phosphate buffer :Acetonitrile (40:60 v/v)	Isocratic	261	THC-2.17, ACE-4.80	31
7.	THC+	Tablets	C18 (Thermo	Acetonitrile: buffer	Isocratic	261	THC-	32

	ACE		Hypersil BDS)	of pH 6 (42:58,v/v)			4.15, ACE-4.88	
8.	THC+ DCF	Capsules	C18 (Inertsil)	Acetonitrile: Methanol: Water (35:15; 50, v/v), pH adjusted to 3.5 with Orthophosphoric acid.	Gradient	286	THC-3.3, DCF-4.0	33
9.	THC+ DCF	Tablets	C18 (Waters Symmetry)	Water (pH 9.2adjusted with di- Potassium hydrogen Phosphate) (60: 40, v/v)	Isocratic	223	DCF-3.229, THC-4.999	34
10.	THC+ LOR	Tablets	C18 (Waters Symmetry)	Methanol: THF: acetate buffer (60: 10: 30, v/v); pH adjusted to 5.5 with glacial acetic acid	Isocratic	250	LOR-4.08, THC-3.36	35
11.	THC+ LOR	Tablets	C18 (Varian)	Methanol: Acetate buffer (PH4.6) :THF(50:35:15, v/v)	Isocratic	375	LOR-400, THC-2.92	36
12.	THC+ LOR	Tablets	C18 (Inertsil ODS 3V)	Ammonium Dihydrogen Phosphate buffer (pH 7.3 with TEA): Methanol (45:55,v/v)	Isocratic	290	LOR-9.40, THC-2.96	37
13.	THC+ LOR	Tablets	C8 (X terra)	Sodium Phosphate buffer (pH 6.8 adjusted with NaOH): ACN (35:65% v/v)	Isocratic	298	LOR-4.50, THC-3.40	38
14.	THC+	Tablets	C18	Acetonitrile: Water: Phosphate	Isocratic	260	THC-	39

	KET		(Thermo scientific)	buffer (pH 3.0) (60:30:10, v/v)			2.70, KET-4.90	
15	THC+ KET	Tablets	C18	Acetonitrile: Water (60:40,v/v)	Isocratic	300	THC-3.7± 0.1, KET-7.90± 0.1	40
16.	THC+ DXKET	Tablets	C18 (HS, HiQ sil)	Methanol: Sodium acetate buffer (pH 5 with Glacial acetic acid) (70:30, v/v)	Isocratic	265	THC-3.013, DXKET-6.013	41
17.	THC+ DXKET	Tablets	RP-18e (Purosphere STAR)	Methanol: Phosphate buffer (pH adjusted to 4.5 with OPA) (65:35 v/v)	Isocratic	260	THC-3.02, DXK-8.91	42
18.	THC+ ETR	Tablets	C-18 (BDS Hypersil)	Trifluoroacetic acid buffer (pH 2.6): Acetonitrile (75:25, v/v)	Isocratic	220	ETR-6.6, THC-3.1	43
19.	THC+ ETR	Tablets	C18 (RP-select B Lichrospher)	1 mL TFA in 2 litre milli-Q water) and Acetonitrile (75:25 v/v)	Isocratic	258	THC-3.37, ETR-8.62	44
20.	THC+ ETR	Tablets	C18 (Inertsil ODS3)	Phosphate buffer (PH 6, adjusted with Orthophosphoric acid) and Methanol (30:70 v/v)	Isocratic	255	THC-2.50, ETR-4.60	45
21.	THC+	Tablets	C-18 (Phenom	Methanol and Phosphate buffer	Isocratic	259	ETD-4.39±	46

	ETD		enex)	pH 6, (85:15 v/v)			0.10, THC-3.52± 0.10	
22.	THC+ ETD	Tablets	C18 (HiQ sil HS)	Acetonitrile: 20mM potassium dihydrogen phosphate buffer (65:35 v/v)	Isocratic	257	THC-2.240, ETD-7.141	47
23.	THC+ ETORICOXIB	Tablets	C18 (Inertsil)	Acetonitrile: 0.05M ammonium acetate (80:20) pH 6.5	Isocratic	240	THC-9.04, ETC-5.01	48
24.	THC+ ETD	Tablets	C18 (Symmetry)	Acetonitrile: Potassium dihydrogen phosphate buffer (pH 3.0) (50:50, v/v	Isocratic	255	ETD-4.27, THC-2.6	49
25.	THC+ PCM	Tablets	C18 (BDS Hypersil)	Potassium Dihydrogen phosphate: Methanol (40:60, v/v)	Isocratic	247	PCM-3.27, THC-5.50	50
26.	THC+ ACE+ PCM	Tablets	C18 (HiQ Sil)	Acetonitrile: Water (30: 70, v/v)	Isocratic	263	PCM-2.51 THC-3.55 ACE-5.20	51
27.	THC+ ACE+ PCM	Tablets	C18 (Inertsil ODS)	Buffer of pH 6.5 and Acetonitrile in Gradient elution.	Gradient	300	PCM-2.70, THC-3.95, ACE-9.91	52

ABBREVIATIONS:

The following abbreviations are used in the tables.

THC = Thiocolchicoside, ACN = Acetonitrile, ACE = Aceclofenac, DCFS = Diclofenac Sodium, DCFP = Diclofenac Potassium, DPs = Degradation products, DXKET= Dexketoprofen, ETD = Etodolac, ETR = Etoricoxib, FN = Floctafenine, GF = Glafenine, IM = Intra-muscular, KET = Ketoprofen, M = concentration (mol/L), MP = Mobile Phase, nm = nanometre, OPA = Orthophosphoric Acid, PCM = Paracetamol, TEA = Triethylamine, TFA = Trifluoroacetic Acid, ETO = Etoricoxib.

2.3 HPTLC Methods for Determination of Thiocolchicoside:

Table no.3 shows the summarized reported HPTLC method indicating sample, wavelength, mobile phase, linearity and retention factor.

Table no. 3: Summary HPTLC methods of Thiocolchicoside.

Sr. no.	Drug Name & Combination	Sample	Mobile Phase	Linearity	Wave length (nm)	Rf	Ref. No.
1.	THC+ ACE	Tablets	Methanol: Chloroform: Water (9.6: 0.2: 0.2 v/v)	THC 30-180 ng/band ACE 750-4500 ng/band	254	THC- 0.70 ± 0.05, ACE- 0.83 ± 0.05	53
2.	THC+ DXKET	Tablet	Toluene: Ethyl acetate: Methanol (5:3:2 v/v)	THC-50-350 ng/band DXKET-100-700 ng/band	286	THC- 0.10, DXKET- 0.40	54
3.	THC+ DCF	Capsule	Toluene: Acetone: Methanol: Formic acid (5:2:2:0.01 v/v/v/v)	THC 160-800 ng/band DCF 1000-5000 ng/band	280	THC- 0.29±0.02, DCF- 0.71±0.02	55
4.	THC+ ETR	Tablet	Ethyl acetate: Methanol (8 :2 v/v)	THC 100–500 ng/band ETR 50–250 ng/band	290	THC- 0.17, ETR- 0.70	56
5.	THC+ DCF	Capsule	Toluene: Ethyl acetate: Methanol (5:3:2 v/v)	50-300 ng/band for both	285	THC- 0.17, DCF- 0.53	57

6.	THC+ DXKET	Tablet	Toluene: Methanol: Ethyl Acetate (6: 2.5: 0.5, v/v)	THC-100-800 ng/band DXKET-600-4800 ng/band	280	THC- 0.33± 0.011, DXKET-0.61± 0.007	58
7.	THC+ LOR	Tablet	Methanol: Chloroform: Water (9.6:0.2:0.2 v/v)	THC 30-180 ng/band LOR 60-360 9ng/ban	377	THC- 0.58±0.05, LOR- 0.85±0.05	59
8.	THC+ ACE	Tablet	Methanol: Chloroform: Water 9.6:0.2:0.2 v/v)	30–180 ng/band THC 750–4500 ng/band ACE	254	THC- 0.70 ± 0.05, ACE- 0.83 ± 0.05	60
9.	THC+ ACE	Tablet	Toluene: Ethyl acetate: Methanol: Glacial acetic acid (4: 6: 2: 0.5 v/v).	THC 6–21 ng/band ACE 10-35 ng/band	255	THC- 0.16, ACE- 0.79	61

2.4 Stability-Indicating HPLC and HPTLC Methods for Determination of Thiocolchicoside.

Table no.4 shows the summarized reported Stability-indicating High Performance Liquid Chromatography & High Performance Thin Layer Chromatography method indicating sample, mobile phase, wavelength and Retention time.

Table no.4: Summary of Stability-indicating HPLC and HPTLC methods of Thiocolchicoside.

Sr. no.	Drug Name & Combination	Sample	Mobile Phase	Wavelength (nm)	Retention time in min.	Ref. No.
1.	THC+ ACE	Tablets	methanol and 0.1% ortho phosphoric acid of 75:25 (v/v)	275	THC- 1.93, ACE- 3.76	62
2.	THC	Capsule	Acetonitrile: Water (70:30)	286	3.35 min.	6
3.	THC+ DCF	Tablet	Solvent A (5 mM sodium dihydrogen phosphate, pH 2.5) and Solvent B (Methanol)	258	THC- 5.8 min., DCF- 11.0 min	64

4.	THC	Capsule	Acetonitrile: Phosphate Buffer pH 3.5, (70:30 % v/v	260	2.24 min.	65
5.	THC+ ACE	Tablet	(A) 10mM Ammonium acetate pH 5.00 buffer and (B) Acetonitrile: Water (70:30 v/v)	265	THC- 13.29 min, ACF- 2.20 min	66
6.	THC+ PCM + DCF	Capsule	Acetonitrile: Phosphate buffer adjusted pH 3 with OPA	228	PCM - 5.3, THC- 9.61, DCF- 21.47	67
7.	THC+ ACE	Tablet	Potassium phosphate monohydrate buffer (pH-5.0): Acetonitrile: Methanol in (40:20:40 % v/v)	263	THC- 2.8 min., ACE- 4.2 min.	68
8.	THC+ ACE	Tablet	Methanol: Acetonitrile: THF: Acetate buffer (56:4:10:30 v/v) pH adjusted to 6.5 with Acetic acid	312	THC- 4.7 min., ACE- 6.3min.	69
9.	THC+ KET	Tablet	Methanol: Toluene: Benzene (2.5:3.5:4 v/v)	260	THC- 0.35, KET- 0.65 min.	70
10.	THC+ DCF	Tablet	Methanol: Acetonitrile : Phosphate buffer (40:20:40 v/v at pH 5.0)	263	THC- 2.8 min., ACE- 4.2 min	71
11.	THC+ ACE	Tablet	5% ammonium acetate buffer and methanol (40:60 v/v) pH 5 with OPA	276	THC- 0.697 min., ACE- 1.125 min.	72
12.	THC	Capsules	methanol: water(70:30v/v)	377	THC- 0.60 ± 0.02	73

2.5 LC-MS (Liquid chromatography-mass spectroscopy) Method:

A highly sensitive Liquid Chromatography–tandem Mass Spectrometry (LC-MS-MS) method has developed to determine 3-desmethylthiocolchicine in human plasma to evaluate the bioequivalence of thiocolchicoside after oral administration. It shows that thiocolchicoside is rapidly converted to 3-desmethylthiocolchicine during absorption and during the first-pass effect through the liver.[74]

2.6 GC-MS (Gas chromatography - mass spectroscopy) Method:

A capillary gas chromatography-mass spectrometry (GC-MS) method has developed for THC with enzymatic hydrolysis of thiocolchicoside occurs to its aglycon i.e. 3- dimethyl thiocolchicine. The paper shows oral bioavailability of the capsule formulation was 1.06 +/- 0.39 relative to the tablet formulation. [76]

3. CONCLUSION:

This reviews articles presented the analytical methods for the estimation of thiocolchicoside & its combination in pharmaceutical dosage form and biological sample like Blood, serum or plasma the literature survey of analytical data exhibit that HPLC methods are primarily for the analysis of Thiocolchicoside in single and in combination with other drugs in various formulation type of dosage form the other analytical methods like RP-HPLC, HPTLC, LCMS, GC-MS, UV-Spectrometry, Spectrofluorimetry and stability indicating methods by HPLC used for the estimation of Thiocolchicoside in single and its combined dosage form, biological sample like serum or plasma as well as blood. The presented information is useful for future prospective study for researcher in formulation development, Bio analytical research and Quality control of Thiocolchicoside.

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5. CONFLICT OF INTEREST:

The author shows that there is no conflict of interest.

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