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In-Depth Investigation of Analytical Methods for the Determination of sildenafil citrate and Tramadol hydrochloride in Synthetic mixture: a Review

Yuvrajsinh solanki, Priyanka malani, Dr Umesh Upadhyay

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ABSTRACT
Sildenafil citrate and Tramadol hydrochloride used in treatment of Premature ejaculation. Tramadol HCl is thought to exert its therapeutic action in PE patients through one or more of the following mechanisms: weak μ-opioid effect, 5-HT2 receptor antagonist effect, N-methyl-D-aspartate receptor antagonist effect, serotonin and norepinephrine reuptake inhibitory effect, and acetylcholine receptor antagonist effect. On the other hand, Sildenafil citrate is thought to play a therapeutic role in treating PE though the following mechanisms: peripheral delay of ejaculation through modulation of contractions of the vas deferens, seminal vesicles, prostate and urethra, increasing the duration of erection , central decrease of the sympathetic output via modulation of NO activity in the medial pre-optic area , peripheral analgesic effect, peripheral analgesic effect, increasing patient confidence, and improving the perception of ejaculation control and sexual satisfaction.

I. INTRODUCTION[1-3]

- premature ejaculation (PE) is one of the most common male sexual disorders and has been estimated to occur in **4-39%** of men in the general community.The World Health Organization (WHO) 2nd International Consultation on Sexual Health defined it as "...persistent or recurrent ejaculation with minimal stimulation before, on or shortly after penetration and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and / or his partner bother or distress..."Ejaculation occurs during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it, during all or almost all sexual activity (75% to 100% of the time).
- Ejaculation occurs during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it, during all or almost all sexual activity (75% to 100% of the time). Symptoms must persist for at minimum 6 months and cause clinically significant distress to the individual. The dysfunction is not explainable by a nonsexual mental disorder, medical conditions, the effects of a drug or medication, or severe relationship distress, or other significant stressors.
- Premature ejaculation is treated with different types of medicines like Daily treatment with selective serotonin reuptake inhibitors, On-demand treatment with selective serotonin reuptake inhibitors, On-demand treatment with tramadol, Anaesthetic topical ointments, Phosphodiesterase inhibitors.

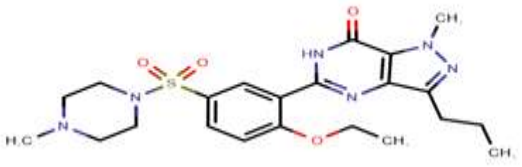

Fig 1: - chemical structure of sildenafil citrate

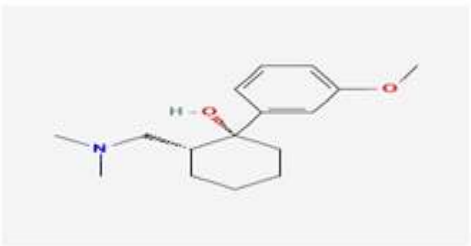

Fig 2: - chemical structure of tramadol hydrochloride

INTRODUCTION OF SILDENAFIL CITRATE [4]

Sildenafil was the first phosphodiesterase-5 (PDE5) inhibitor approved for usein erectile

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

dysfunction by US Food and Drug Administration on March 27, 1998. Method for determination of sildenafil citrate official methods.(Table 1)

MECHANISM OF SILDENAFIL CITRATE [4]

Sildenafil is a selective inhibitor of cGMP-specific phosphodiesterase (PDE-5). Penile erection involves relaxation of the corpus cavernosum, an event mediated by NO and cGMP. The biological actions of cGMP are terminated by phosphodiesterase enzymes and PDE-5 is the major cGMP metabolizing enzyme in this tissue.

INTRODUCTION OF TRAMADOL HYDROCHLORIDE[5]

Tramadol is a centrally-acting opioid agonist and SNRI (serotonin/norepinephrine reuptake inhibitor) used for the management of moderate to severe pain in adults. It is considered a class IV drug by the FDA in July 7th, 2014. Method for determination of tramadol hydrochloride official methods.(Table 2)

MECHANISM OF TRAMADOL HYDROCHLORIDE [5]

Tramadol is an opioid and, like other opioids, selectively bind to different opiate receptors in the central nervous system. The liver enzyme, CYP2D6, converts tramadol to its active metabolite M1, which has a stronger affinity for the mu receptor compared to the inactive form. Tramadol does not bind to the mu receptor as much as morphine. Unlike other opioids, tramadol does not reverse its course completely after the administration of naloxone. Along with the partial agonist activity on the opioid receptors, it also inhibits the reuptake of serotonin and norepinephrine.

Table no.1 official method for sildenafil citrate

SR.NO	Official Method	Description	Reference
1	**HPLC(USP2021 NF39)**	**Mobile phase:**Buffer: Methanol: Acetonitrile (58:25:17%v/v/v) **Flow rate:** 1mL/min **Injection volume:** 20 µL **Detection wavelength:** UV 290nm	**6**
2	**HPLC(BP 2020 VOLUME 2)**	**Stationary phase:** End-capped octadecyl silyl silica gel for chromatography R (0.25m×4.6mm,5µm) **Mobile phase:** – Mobile phase A: Acetonitrile for chromatography R, Buffer solution (20:80 % V/V) Mobile phase B**:** Buffer solution: Methanol R1: Acetonitrile: Chromatography R (20:20:60% V/V/V) **Flow rate:** 1.5 mL/min **Injection volume:** 10 µL **Detection wavelength:** 230 nm.	**7**
3	**HPLC(IP volume 3 2018)**	**Stationary phase:** A stainless-steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µg) (such as Hypersil ODS) **Mobile phase**: A. dissolve 3.85 g of Ammonium acetate in 1000 ml of Water, adjusted to pH 7.5 with Ammonia solution B. Acetonitrile **Flow rate: -** 1 mL/min **Injection volume**: 20 µL **Detection wavelength:** 240 nm.	**8**
4	**HPLC(EP2017)**	**Stationary phase:** End-capped octadecyl silyl silica gel for chromatography R (0.25m×4.6mm,5µm)	**9**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

		Mobile phase: – Mobile phase A: - Acetonitrile for chromatography R: Buffer solution (20:80 % V/V), Mobile phase B: - Buffer solution, methanol R1, Acetonitrile for chromatography R (20:20:60% V/V/V) **Flow rate: -** 1.5 mL/min **Injection volume:**10 µL **Detection wavelength:** 230 nm.

Table 2 : official methods for Tramadol hydrochloride

SR.NO	Method	Description	Reference
1	**HPLC[USP2021(NF39)]**	**Stationary phase:** 4.6-mm×25cm;5µmpackingL1 **Mobile phase:** Acetonitrile: Solution A (30:70)%v/v **Solution A:** Dissolve 2 mL of Trifluoroacetic acid in 1000 mL of water. **Flow rate:** 1 ml/min **Injection volume:**20 µL **Detection wavelength:** 210 nm	**10**
2	**HPLC(JP 2021)**	**Stationary phase:** A stainless steel column, packed with octylsilanized silica gel **(**4×25, 5µm) **Mobile phase:**A mixture of Diluted Trifluoroacetic acid (1 in 500) : Acetonitrile (141:59)%v/v **Flow rate:** Adjust so that the retention time of tramadol is about 5 minutes **Detection wavelength:** 270 nm	**11**
3	**HPLC(BP 2020 Vol. 2)**	**Stationary phase:** End-capped base-deactivated octyl silyl silica gel for chromatography (0.25m×4.6mm,5µm) **Mobile phase:** Acetonitrile: 295 volumes of Acetonitrile R :705 volumes of a mixture of 0.2 mL of Trifluoroacetic acid R :100 mL of Water R. **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 270 nm.	**12**
4	**HPLC(IP 2018 Vol.3)**	**Stationary phase:** Stainless steel column 25 cm x 4.0 mm packed with end capped octyl silane bonded to porous silica (5 µm) **Mobile phase:** A mixture of 29.5 volumes of Acetonitrile : 70.5 volumes of a mixture of 0.2 ml of Trifluoroacetic	**13**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

		acid: 100 ml of Water **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 270 nm.	
5	**HPLC(EP 2017)**	**Stationary phase:** End-capped base-deactivated octyl silyl silica gel for chromatography R (5µm). **Mobile phase:** 295 volumes of Acetonitrile R and 705 volumes of a mixture of 0.2 mL of Trifluoroacetic acid R and 100 mL of water R. **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 270 nm.	**14**

Table no.3 : Methods for determination of sildenafil citrate and Tramadol hydrochloride single and combination with other drugs by UV Spectroscopy, chromatography and other techniques.

Sr no	Method	Description	Reference
1	Validation of Simple and Rapid UV-Spectrophotometric Method with Stress Degradation Study For Sildenafil Citrate	**Solvent:** Methanol **Linearity:** 10-50 µL **Detection wavelength:** 228 nm	**15**
2	Development of analytical method and its validation for sildenafil citrate by UV Spectrophotometry	**Solvent:** HCL(0.1N) **Linearity:** 8-60 µL **Detection wavelength :**293.2 nm	**16**
3	UV-analytical method development and validation for simultaneous estimation of dapoxetine hydrochloride and sildenafil citrate in tablet dosage form	**Solvent:** Methanol **Linearity:** 10-60 µg/mL **Sildenafil citrate**: 2-12 µg/mL **Dapoxetine hydrochloride:** 2-12 µg/mL **Detection wavelength:** Sildenafil citrate:293nm Dapoxetine hydrochloride:231 nm	**17**
4	Development and Validation Method for the Determination of Sildenafil Citrate Tablets by using UV-Spectrophotometer in Pharmaceutical Formulation	**Solvent:** HCL **Linearity:** 5-40 µg/mL **Detection wavelength:** 295 nm	**18**
5	Development and Validation of UV Spectrophotometric Area Under Curve (AUC) Method for Sildenafil Citrate in Pharmaceutical Formulation	**Solvent:** Water **Linearity:**5-30 µg/mL **Detection wavelength:** 295 nm	**19**
6	A Simple Spectrophotometric Assay of Sildenafil in Pure and Pharmaceutical Preparations	**Solvent:** Methanol **Linearity:** - 3-70 mg /L (3-70 µg/mL) **Detection wavelength:** 410 nm	**20**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

7	Development of new and rapid method for UV spectrophotometric Determination of sildenafil in marketed formulations	**Solvent:** HCL **Linearity:**4-10 µg/ml **Detection wavelength:**233.6 nm	**21**
8	Validated HPLC method for determination of sildenafil in pharmaceutical dosage forms	**Stationary phase:** Hypersil BDS-C18 (125 x 4 mm, 5 mm) **Mobile phase:** Phosphate buffer (20 mM, pH 2.8)-Acetonitrile (71:29, % V/V) **Flow rate:** 1.5 mL/min **Injection volume**: 25 µL **Detection wavelength:** 285 nm.	**22**
9	HPLC determination of Sildenafil in tablets	**Stationary phase:** LiChrosorb RP-18 (150 x 4.0 mm, 5 µm) **Mobile phase:** Acetonitrile: Methanol: 0.5% Triethylamine (15: 26: 59% v/v/v) **Flow rate:** 1ml/min **Injection volume:** 20µL **Detection wavelength:** 290 nm.	**23**
10	Development and validation of RP-HPLC method for sildenafil citrate in rat plasma-application to pharmacokinetic studies	**Stationary phase:** C18 column **Mobile phase:** Methanol: Water (85:15 % v/v). **Flow rate:**1ml/min **Injection volume**: 20 µL **Detection wavelength:** 230 nm.	**24**
11	RP-HPLC Method Development for Estimation of Sildenafil Citrate in Tablets and in Seminal Fluid	**Stationary phase:** Waters Spheris orb C18 bonded silica, (5 µm, 4.6 x 250 mm) **Mobile phase:** Trifluoroacetic acid (0.2%) (pH 3 adjusted with Orthophosphoric acid): Acetonitrile (60:40%v/v) **Flow rate:** 1.0mL/min **Detection wavelength:**230 nm	**25**
12	Analytical Method Development and Validation of Sildenafil Citrate by RP HPLC ABS TRACT	**Stationary phase:** C18 column [C18, 250 X 4.6mm, 5µ] **Mobile phase:** Acetonitrile: Phosphate buffer (35:65 % v/v) **Flow rate:** 1mL/min **Detection wavelength:**230 nm	**26**
13	New simple RP-HPLC Method for the estimation of Sildenafil citrate in Pharmaceutical dosage form	**Stationary phase:** C18 Column (150 X 4.6 mm, 5µ particle size) **Mobile phase:** Methanol and Buffer (50:50 % v/v) **Flow rate:** 1.5 mL/min **Detection wavelength:** 290 nm	**27**
14	Validation and stability indicating RP-HPLC method for the Determination of Sildenafil citrate in Pharmaceutical	**Stationary phase:** C18 Column (150 X 4.6mm, 5µ particle size) **Mobile phase:** Acetonitrile: Phosphate buffer (70:30, % v/v,	**28**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

	Formulations	pH7.0) **Flow rate:** 0.8ml/m **Detection wavelength:** 228 nm.	
15	Stability indicating HPLC method for Simultaneous Quantification of Sildenafil citrate and Dapoxetine hydrochloride in Pharmaceutical Products	**Stationary phase:** C18(150x4.6mm ID, 5µm) **Mobile phase:** Acetonitrile and 0.2M ammonium acetate buffer **Flow rate:** 1.2ml/min **Injection volume:**25µL **Detection wavelength:** 228 nm	**29**
16	Development and Validation of HPTLC Method for Simultaneous Estimation of Sildenafil Citrate and Dapoxetine Hydrochloride in Combined Dosage Form	**Stationary phase:** Silica gel 60 F254 **Mobile phase:** Hexane: Methanol: Diethyl amine 9.2:1.6:1.2 (% v/v/v) **Detection wavelength:** 241nm **R_f Value :** Sildenafil citrate: 0.21 ± 0.02 Dapoxetine Hydrochloride: 0.72 ± 0.02	**30**
17	Method development and validation of visible spectroscopic method for the estimation of tramadol hydrochloride in pure and bulk dosage form	**Solvent:** Water **Linearity:** 10-50µg/ml **Detection wavelength:** 749 nm	**31**
18	Development of UV spectrophotometric methods and validation for Estimation of Tramadol hydrochloride in bulk and Tablet dosage form by Absorbance maxima and area under the curve method	**Solvent:** Methanol:Water (60:40 % v/v) **Linearity:** 30-150µg/ml **Detection wavelength:** 271 nm	**32**
19	Validated UV spectrophotometric method for quantitative analysis of Tramadol in bulk and pharmaceutical dosage form	**Solvent:** Water **Linearity:** 10-50 µg /mL **Detection wavelength:** 273.5 nm	**33**
20	Analytical Method Development and Validation of Tramadol Hydrochloride by Pharmaceutical Dosage Form by Ultraviolet Spectroscopy	**Solvent:** 0.1N HCL **Linearity:** 20-160 µg/ml **Detection wavelength:** 270nm	**34**
21	Validated Spectrophotometric Method for the Determination of Paracetamol and Tramadol Hydrochloride in Tablet dosage form	**Solvent:** Water **Linearity:** 2-14 µg/ml **Detection wavelength:** Paracetamol: 264 nm Tramadol:224.06nm	**35**
22	UV spectrophotometric method for Simultaneous Estimation of Tramadol hydrochloride and Aceclofenac in bulk and tablet dosage form	**Solvent:** Methanol: Water (60:40)%v/v **Linearity:** 5–30 µg/ml **Detection wavelength:** Tramadol hydrochloride:	**36**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

		214.8 nm Aceclofenac: 275.6 nm	
23	Development and validation of UV spectrophotometric Method for Simultaneous Estimation of Tramadol hydrochloride and Quercetin in niosomes formulation	**Solvent:** Methanol **Linearity:** 0 – 20 µg/ml and 2-20 µg/ml **Detection wavelength:**Tramadol HCl: 271nm Quercetin (Dihydrate): 372 nm	**37**
24	Validated spectrophotometric Methods for Simultaneous Estimation of Paracetamol, Domperidoneand Tramadol HCl in pure and tablet dosage form	**Solvent:** 0.1N NaOH **Linearity:** 0-25 µg/mL **Detection wavelength:** **Method I**:Paracetamol :256 nm, Domperidone: 289.6 nm, Tramadol hydrochloride: 218.4 nm **Method** II: 200-400 nm	**38**
25	Development and validation of UV Visible spectrophotometric method for estimation of Aceclofenac and Tramadol in bulk and dosage form	**Solvent:** Methanol **Linearity:** Aceclofenac: 2-25µg/mL Tramadol:2-10µg/mL **Detection wavelength:** Aceclofenac: 203 nm Tramadol : 241 nm	**39**
26	Determination of Dexibuprofen and Tramadol HCL by simultaneous UV spectroscopic method from bulk and pharmaceutical dosage form	**Solvent:** Ethanol **Linearity:** Dexibuprofen:100-500µg/mL Tramadol:20-120µg/mL **Detection wavelength:** Dexibuprofen: 264nm Tramadol:271nm	**40**
27	Development and validation of RP-HPLC method for Estimation of Tramadol in extended release tablet pharmaceutical dosage form	**Stationary phase:** Zorbax C18 (150 X 4.6 mm, 5µ) **Mobile phase:**5mM Ammonium acetate buffer (pH 4.0 ± 0.3): Acetonitrile (15: 85 %v/v). **Flow rate:** 0.8 mL/min **Injection volume:** 20 µL **Detection wavelength:** 270 nm.	**41**
28	HPLC Determination and Validation of Tramadol Hydrochloride in Capsules	**Stationary phase:** LiChrospher 100 CN. **Mobile phase:** Acetonitrile: Ion pair solution (25:75) % v/v. **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 275 nm.	**42**
29	RP-HPLC Method for Estimation of Tramadol hydrochloride and Paracetamol in Pharmaceutical formulation	**Stationary phase:** C18G column (250 x 4.6 mm, 5 µm) **Mobile phase:**1 % Glacial acetic acid: Acetonitrile (50:50 %v/v). **Flow rate:** 1 mL/min **Injection volume:** 20 µL	**43**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

		Detection wavelength: 272 nm.	
30	RP -HPLC method development and validation of Tramadol hydrochloride in bulk form by ion-pair liquid chromatography	**Stationary phase:** Phenomenex luna C-18 (250x4.6 mm,5µ) **Mobile phase:** 20 mM Potassium dihydrogen phosphate:1.75mM 1-Octane sulfonic acid sodium salt: 2% Isopropanol: Methanol (25:75 %v/v) pH 4.0 adjusted with Orthophosphoric acid **Flow rate:** 1 mL/min **Detection wavelength:** 272 nm	**44**
31	Development and Validation of RP-HPLC Method for Simultaneous Estimation of Paracetamol and Tramadol Hydrochloride	**Stationary phase:** C18 column (250×4.6 mm i.d., 5µm) **Mobile phase:** 60:40 (%v/v) mixture of 10 mM potassium dihydrogen orthophosphate buffer (pH3): Acetonitrile **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 272 nm.	**45**
32	Application of HPLC for the Simultaneous Determination of Aceclofenac, Paracetamol and Tramadol Hydrochloride in Pharmaceutical Dosage Form	**Stationary phase:** C18 column (250×4.6 mm i.d., 5 µm particle size). **Mobile phase:** 40: 60 (%v/v); Phosphate buffer (pH 6.0): Methanol. **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 270 nm	**46**
33	Development and validation of RP- HPLC method for the Simultaneous Estimation of Tramadol hydrochloride and Dicyclomine in bulk and pharmaceutical formulation	**Stationary phase:** Phenomex Gemini C18 column (4.6 x 250 mm, 5µ particle size). **Mobile phase:** Methanol: Acetonitrile: 0.1% Triethylamine (TEA) pH 3.0 (adjusted with Orthophosphoric acid) 35:5:60 (%v/v/v). **Flow rate:** 1 mL/min **Injection volume: 2**0 µL **Detection wavelength:** 275 nm.	**47**
34	RP-HPLC-method development and validation for the Simultaneous Estimation of Dexketoprofen Trometamol and Tramadol Hydrochloride in pharmaceutical dosage form	**Stationary phase:** Inertsil-ODS C18 (250 x 4.6 mm, 5). **Mobile phase:** Methanol: Buffer (75:25) % v/v. **Flow rate:** 1 mL/min **Injection volume: 2**0 µL **Detection wavelength:** 240 nm.	**48**
35	Simultaneous Estimation of Diclofenac Sodium and Tramadol Hydrochloride Using First Derivative Spectroscopy and RP-HPLC Method.	**Stationary phase:** Phenomenex Luna ODS C18 (150mm X 4.6 mm i.d., 5µm; particle size). **Mobile phase:** Acetonitrile: Methanol: Phosphate buffer (pH 3) (30:30:40) %v/v. **Flow rate:** 1 mL/min **Injection volume:** 20 µL	**49**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1048-1059 www.ijprajournal.com ISSN: 2249-7781

		Detection wavelength: 274 nm	
36	Stability-Indicating RP-HPLC Method for Analysis of Paracetamol and Tramadol in a Pharmaceutical Dosage Form	**Stationary phase:** Inertsil C18 (250 mm x 4.6 mm, 5µm). **Mobile phase:** Orthophosphoric acid: Methanol (60:40, %v/v). **Flow rate:** 1 mL/min **Injection volume:** 20 µL **Detection wavelength:** 228 nm	**50**
37	Development and Validation of HPTLC Method for Estimation of Tramadol HCl in Bulk and in Capsule Dosage Form	**Stationary phase:** Silica gel 60 F_{254} **Mobile phase:**Ethyl acetate: Methanol: Ammonia(25%) [9.0 : 1.0 :0.5 ml)(%v/v/v)] **Detection wavelength:** 271nm **R_f Value :** 0.76 ± 0.011	**51**
38	Development and validation of HPTLC method for simultaneous analysis of Tramadol HCl and paracetamol in fixed-dose combination tablets	**Stationary phase:** Silica gel 60 F_{254} **Mobile phase:** Chloroform: Methanol: Ethyl acetate (7.5 : 1.5 : 0.5)%v /v **Detection wavelength:** 254 nm **R_f Value :** Tramadol: 0.2 ± 0.03 Paracetamol: 0.4 ±0.04	**52**
39	Stability Indicating High Performance Thin Layer Chromatographic Method for the Determination of Tramadol Hydrochloride in Pharmaceutical Formulation	**Stationary phase:** Silica gel 60 F_{254} **Mobile phase:** Ethyl acetate: Methanol: Ammonia (9:0.8:0.5 %v/v/v). **Detection wavelength:** 271 nm **R_f Value :** 0.64± 0.02	**53**

Sr. no	Ingredient	Quantity(mg)	Role
1	Sildenafil Citrate	50	API
2	Tramadol Hydrochloride	100	API
3	Microcrystalline cellulose	20	Disintegrate
4	Hydroxypropyl methyl cellulose	15	Binder

Table no.4 Formulation of synthetic mixture

II. CONCLUSION

This review describes the reported Spectroscopic and Chromatographic methods developedSildenafil citrate and Tramadol hydrochloride. As per this review, it was concluded that for sildenafil citrate and tramadol hydrochloride, different Spectroscopic and chromatographic methods are available for single-single drugs. It was observed that still, any combination method of sildenafil citrate and tramadol hydrochloride is not available.Thus, all methods were simple, accurate, economical, precise, and reproducible. Nearly all Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time, and sensitivity.

International Journal of Pharmaceutical Research and Applications
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