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REVIEW ON METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF DICYCLOMINE HYDROCHLORIDE IN PHARMACEUTICAL DOSAGE FORM

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ABSTRACT
This study presents the development and validation of a simple, accurate, precise, and stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) method for the quantitative determination of Dicyclomine Hydrochloride in pharmaceutical dosage forms. Unlike previous studies, which did not explore on Dicyclomine Hydrochloride Capsule, chromatographic separation was achieved using an HPLC system (Waters with Empower2 software) with a Phenomex C18 (250 x 4.6 mm, 5 µm) column. The mobile phase consisted of a 60:40 v/v mixture of Acetonitrile And Triethylamine, adjusted to pH 3.0 with ortho phosphoric acid. The method operated at a flow rate of 0.9 mL/min, with the column maintained at ambient temperature, and detection occurred at 218 nm using a UV-Visible Detector. Dicyclomine Hydrochloride were effectively resolved with retention times of 4.4 minutes, respectively. The method demonstrated linearity within the concentration range of 2-12 µg/mL, with a correlation coefficient (r^2) of 0.999. The method was validated for stability under forced degradation conditions, confirming its suitability for routine pharmaceutical analysis.

KEYWORDS: Dicyclomine HCL, RP-HPLC, HPLC, UV-Spectroscopy.

INTRODUCTION[1,2]

Dicyclomine hydrochloride (DIC) is 2-(diethylamino) ethyl-1-cyclohexylcyclohexane-1-carboxylate hydrochloride chemically is used as a parasympatholytic and antispasmodic agent. This drug blocks effect of acetylcholine on parasympathetic receptors in the smooth muscle along with direct relaxing effect on smooth muscle.

It has one-eighth the neurotropic activity of atropine and approximately twice the Musculo tropic activity of papaverine. It is used for its spasmolytic effect on various smooth muscle spasms, particularly those associated with the gastrointestinal tract. It is also useful in dysmenorrhoeal, pyloric spam and biliary dysfunction. It is used to treat a certain type of intestinal problem called irritable bowel syndrome. It helps to reduce the symptoms of stomach and intestinal cramping. This medication works by slowing the natural movements of the gut and by relaxing the muscles in the stomach and intestines.

Dicycloverine was approved for medical use in the United States in 1950. It is available as a generic medication. In 2022, it was the 176th most commonly prescribed medication in the United States, with more than 2 million prescriptions Dicyclomine is an anticholinergic agent that is used to manage smooth muscle spasm in the gastrointestinal, biliary, and urinary tracts. Dicyclomine also has antimuscarinic activity and is prescribed before meals to reduce postprandial cramping.

Pharmacodynamics[3,30]

Dicycloverine is a selective muscarinic acetylcholine M_1 receptor antagonist. It blocks the action of acetylcholine on muscarinic receptors on smooth muscles in the gastrointestinal tract, relaxing the smooth muscle. This medicine should not be used for people who have an obstructive GI or urinary condition, severe ulcerative colitis, reflux, any unstable cardiac condition, glaucoma, myasthenia gravis, and anyone who is acutely bleeding.

It should not be given to children or infants with colic due to the risks of convulsions, difficult breathing,

irritability, and restlessness, and there is little evidence to support the efficacy in such use in any case.

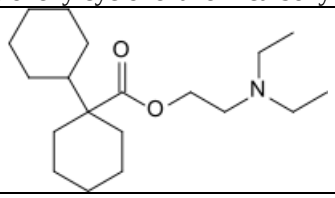
History[4,31,32]

Dicycloverine was first synthesized chemically in the United States circa 1945 by scientists at William S. Merrell company. It was first marketed in 1952 for gastrointestinal disorders, including colic in infants. The INN name "Dicycloverine" was recommended in 1959. It was included in the combination drug for morning sickness called Bendectin, along with doxylamine and vitamin B_6 which was launched in the US in 1956; dicycloverine was removed from the formulation in 1976 after Merrell determined that it added no value. Bendectin became the subject of many lawsuits due to allegations that it had caused birth defects similar to Thalidomide, which Merrell had also marketed in the US and Canada.

In the 1980s, several governments restricted its use in infants due to reports of convulsions, difficult breathing, irritability, and restlessness in infants given the drug.

In 1994, the US Federal trade commission ordered Marion Merrell Dow, which had acquired Rugby Darby the only generic manufacturer of Dicycloverine in the US to promise to grant licenses to its intellectual property on the drug to any company that wanted it, based on antitrust concerns. The US market for the medication at that time was around $8 million; Dow had 60% of it and Rugby had 40%. The next year, Hoechst Marion Roussell, which by that time had acquired the business, granted a license to Endo Pharmaceuticals. By 2000 several other generic competitors had started selling the medication. The case was part of the reshaping of the US pharmaceutical market that occurred in the 1990s, to favour generic entry.

Drug profile[5,6]

Product name	**Dicyclomine**
Chemical Name	2-(Diethyl amino) ethyl 1-cyclohexylcyclohexane-1-carboxylate
Molecular Structure	
Molecular formula	$C_{19}H_{35}NO_2$
Molecular weight	345.95 g/mol
CAS Registry Number	67-92-5
Drug category	Dicyclomine is an anticholinergic agent that is used to manage smooth muscle spasm in the gastrointestinal, biliary, and urinary tracts.
Colour	Blue colour
State	White crystalline powder
Solubility	Highly Soluble in Acetonitrile, soluble in methanol, practically soluble in water.
Melting point	169°C to 174°C
Strength	10mg
PH	5 to 5.5
Boiling point	Not available
Half life	1.8 Hours
Pak	8.96
Log P	4.93
Log S	-5
λ max	213 nm
Drug classes	Anticholinergic, antispasmodic
Route of elimination	Dicyclomine is 79.5% eliminated in the urine and 8.4% in the faeces.

Mechanism of action[3,7,30]

- Dicyclomine is used to treat a certain type of intestinal problem called irritable bowel syndrome. It helps to reduce the symptoms of stomach and intestinal cramping.
- This medication works by slowing the natural movements of the gut and by relaxing the muscles in the stomach and intestines.

- Dicyclomine must not be used in children younger than 6 months old because of the risk of serious side effects. Dicyclomine is available under the following different brand names: Bently. Dicycloverine blocks the action of acetylcholine on cholinergic receptors on smooth muscles in the GI tract, relaxing the smooth muscle.
- Dicyclomine is a muscarinic M1, M3, and M2 receptor antagonist as well as a non- competitive inhibitor of histamine and bradykinin used to treat spasms of the intestines seen in functional bowel disorder and irritable bowel syndrome.

Uses[8,9,10]

- Management of Irritable Bowel Syndrome.
- Relief of Gastrointestinal Muscle Spasms.
- Treatment of Functional Bowel Disorders.
- Alleviation of Abdominal Cramping.
- Reduction of Bloating and Flatulence.
- Management of Dyspepsia (Indigestion).
- Support in Diagnostic Procedures.

Literature review

SI. No.	Title/ Method	Descriptions	Ref. No
1.	Development and validation of new analytical methods for the simultaneous estimation of paracetamol and dicyclomine hydrochloride in bulk and pharmaceutical dosage forms by using rp hplc and uv methods	Column: Agilent CN (250mm x 4.6mm, 5 µm) Mobile phase: Buffer (1ml of Triethyl amine is dissolved into 1lt Water and Adjust the pH-6.0 with Ortho Phosphoric acid: MEOH (60:40) v/v. Retention time: Paracetamol is about 2.0 – 3.0 min, Dicyclomine is about 4.5 - 5.5 min. Linearity: 0-487µg/ml and 0-150µg/ml. Wavelength: 220 nm Flow Rate:1.5 ml/min	[11]
2.	Development and Validation of a Liquid Chromatographic Method for Estimation of Dicyclomine Hydrochloride, Mefenamic Acid and Paracetamol in Tablets	Column: C18 (250mm x 4.6mm, 5 µm) Mobile phase:70% Acetonitrile: 30% Potassium dihydrogen phosphate PH:4.0 Flow rate: 1.0 mL/min Wavelength: 220 nm Retention time: 10–100 µg/ml for dicyclomine hydrochloride, 0.05-10 µg/ml for mefenamic acid and 0.1−20 µg/ml for paracetamol.	[12]
3.	A novel rp-hplc method for simultaneous determination of dicyclomine and ethyl morphine in bulk and pharmaceutical formulation	Column: C18 (250 x 4.6 mm, 5 µm) Mobile phase: water (pH 5.4 adjusted with orthophosphoric acid): acetonitrile (40:60 v/v) Flow rate: 1.0 ml/min Wavelength: 215 nm Retention time: dicyclomine(3.166 ± 0.02) and ethyl morphine (4.204 ± 0.19 min) LOD : 0.05 µg/ml, and 0.20 µg/ml LOQ : 0.17 µg/ml and 0.62 µg/ml Accuracy : 98.61 % and 99.24 %	[13]
4.	A new stability-indicating RP- HPLC method for the determination of dicyclomine hydrochloride and dimethicone combination in tablet dosage form	Column: Xterra C18 (250 x 4.6 mm, 5□m) Mobile phase: 0.1M K2HPO4 : acetonitrile (55:45, v/v) Flow rate: 0.8 mL/min Retention time: 2.134 and 2.865 min Accuracy: 99.453 to 100.417% and 99.703 to 100.303% Linearity : 5–15 µg/mL for DEH and 20– 60 µg/mL for DEC	[14]
5.	Development and Validation of RP-HPLC Method for Simultaneous Determination of Tramadol hydro chloride, Paracetamol and Dicyclomine hydro chloride by using Design of Experiment Software (DOE)	Column: Kromasil C18 (250mm x4.6 mm and 4.5 µm) Mobile phase: MEOH: water containing 0.1 %trifluoro acetic acid and10 % tetrahydrofuran (90:10 % v/v) Flow rate: 0.5mL/min Wavelength: 281 nm PH : 3.0	[15]
6.	Development and validation of rp - hplc method for simultaneous determination of dicyclomine and mefenamic acid	Column: Lichrocart C18 column (250 x 4.60 x 5 µm) Mobile phase: 50 mM KH2 P04 : Acetonitrile in the ratio of (75:25 v/v) Wavelength: 256nm Flow rate: 1 mL/min Retention time: 7.213± 0.3 min and 11.102± 0.3 min	[16]

		for DCL and MFA Concentration: 5-25 ìg/ml, 50-250 ìg/ml for DCL and MFA	
7.	Development and Validation of Mefenamic Acid, Dicyclomine HCl and Pamabrom in Marketed Formulation by HPLC	Column: C18 (250 mm× 4.6 mm, 5 µm) Mobile phase: 70%acetonitrile :30% Potassium dihydrogen orthophosphate Flow rate:1.0 ml/min Wavelength: 285, 218 and 278 nm for MEF, DCL and PABr Calibration graphs : 2-24 µg/mL Retention time: 5.789, 2.522 and 4.284 min for MEF, DCL and PABr	[17]
8.	Validated HPTLC method for Nimesulide and Dicyclomine Hydrochloride in formulation	Stationary phase : aluminium plates precoated with silica gel 60 F254 Mobile phase: toluene: acetone: methanol: ammonia 7: 1.2: 1: 0.05 (v/v/v/v) (RF) values : 0.53 ± 0.02 and 0.65 ± 0.02 for Nimesulide and Dicyclomine hydrochloride Wavelength: 345 nm Accuracy : (100.10 ± 1.16 % for Nimesulide and 99.19 ± 0.50 % for Dicyclomine hydrochloride	[18]
9.	Potentiometric flow injection analysis of dicyclomine hydrochloride in serum, urine and milk	concentration range : 4.0×10 6 to 1.0×10 2 M average recoveries : 96.1–102.7% standard deviation : 0.055–1.994% K_{SP} : 1.78 µg/mL Volume : 1.0 – 5.0 ml PH : 4-5 Linearity : 4.0 x 10^{-6} 1.0 x 10^{-2} M LOD : 4.0 x 10^{-6} 1.0 x 10^{-2} Time : 3-10 S	[19]
10.	Simple UV Spectrophotometric Method for Estimation of Dicyclomine Hydrochloride in Bulk and Tablet Formulation	Wavelength: 213 nm Concentration range : 100 – 500 µg/mL UV- Range : 200-400 nm Linearity : 100-500 mcg/ml LOD : 9.24 mcg/ml LOQ : 28 mcg/ml Correlation coefficient : 0.999 Regression equation : 0.0006+0.004	[20]
11.	Validated uv-spectrophotometric absorbance correction method for simultaneous estimation of paracetamol, pamabrom and dicyclomine hydrochloride in bulk and pharmaceutical dosage form.	Wavelength: 295nm, 230 nm and 217nm for Paracetamol, Pamabrom, Dicyclomine Hydrochloride Calibration curve : 6.5-39 μg/mL for Paracetamol, 0.5-3 μg/mL for Pamabrom and 100-600 μg/mL for Dicyclomine Hydrochloride percentage recovery : 99.05 100.38%, 99.09-99.50% and 98.00-99.79% Concentration : 13 μg/mL, 1 μg/mL, 200 μg/mL LOD =3.3σ/ s LOQ = 10σ/ s Detector: Photo diode array detector	[21]
12.	Development and Validation of Absorption Correction UV Spectrophotometry Method for Simultaneous Estimation of Ranitidine HCL and Dicyclomine Hydrochloride in Their Marketed Formulation	Wavelength: 311.4 nm and at 217 nm for RANTD and DICY Linearity: 7.5-37.5 µg/ml and 1-5 µg/ml for RANTD and DICY LOD : 3.3 x (SD / Slope) LOQ : 10 x (SD / Slope) Accuracy : 15 µg/ml of PCM & 2 µg/ml of DICY Concentration : 7.5-37.5µg/ml (for RANTD) and 1 5µg/ml (for DICY) Solvent : Methanol	[22]
13.	Validated RP-HPLC method for simultaneous estimation of paracetamol, pamabrom and dicyclomine, hydrochloride in bulk and pharmaceutical dosage form	Column: Qualisil Gold-C18 (250 x 4.6 mm, 5 mm) Mobile phase: 83% Methanol : 17% Water wavelength: 221nm Flow rate:1 ml/min Detector: Photo diode array detector recovery value :	[23]

		98-102% PH : 3-5.5 Volume : 20 µl	
14.	Development and Validation of Stability Indicating Rp-Hplc Method for Simultaneous Estimation of Mefenamic Acid and Dicyclomine Hydrochloride in Bulk and in Pharmaceutical Solid Dosage Form	Column: GLS-ODS C18 (250 x 4.6mm ,5µm) Mobile phase methanol Flow rate:1 ml/min wavelength: 263nm linearity : MEF and DCL were in the range of 25-125µg/ml and 100-500µg/ml retention times : MEF and DCL were found to be 2.27min and 7.41min percentage recoveries : 99.999% and 99.993% of MEF and DCL	[24]
15.	RP-HPLC method for simultaneous estimation of ciprofloxacin, tinidazole and dicyclomine in bulk and tablet dosage form	Column: C18 (250 x 4.6 mm, 5 µm) particle size : 5 µm. Mobile phase: 95% Tetra butyl ammonium hydrogen sulphate buffer:5% methanol wavelength: - 218 nm Flow rate:1 mL/min Retention time: 6,64 min order of elution : TNZ (5.42 min), DIC (6.96 min) and CPX (8.04 min) linearity : 5-30 ~g/ml (CPX and TNZ) and 250-650 ~g/ml (DIC).	[25]
16.	Method development and validation of rp-hplc method for simultaneous estimation of clidinium bromide, chlordiazepoxide and dicyclomine hydrochloride in bulk and combined tablet dosage forms	Column: Kromasil C18 (250 mm × 4.6 mm id, 5µm) Mobile phase : (40:30:30) Methanol: Acetonitrile: Potassium di hydrogen phosphate buffer Flow rate: 1 mL/min Wavelength: 270 nm Retention time: 7.457 min, 4.400 min and 3.397 min	[26]
17.	Development and validation of a reversed-phase hplc method for the simultaneous estimation of dicyclomine hydrochloride and famotidine in bulk and tablets	Column: Gemini C18 column (4.6 x 250 mm, 5µ particle size) Mobile phase: methanol and 0.1% triethylamine (TEA) pH 3.0 (adjusted with orthophosphoric acid) in the ratio of 40:60 (v/v) Flow rate: 1 mL/min PH : 3.0 Wavelength: 270 nm Retention time: 10.72 and 2.72 min	[27]
18.	Development and Validation of Stability Indicating Rp-Hplc Method for Simultaneous Estimation of Mefenamic Acid and Dicyclomine Hydrochloride in Bulk and in Pharmaceutical Solid Dosage Form	Column: GLS-ODS C18 (250 x 4.6mm i.d. 5µm) Mobile phase: methanol Flow rate: 1 mL/min Wavelength: 263 nm Linearity; MEF and DCL were in the range of 25-125µg/ml and 100-500µg/ml Retention time: MEF and DCL were found to be 2.27min and 7.41min percentage recoveries : 99.999% and 99.993% of MEF and DCL	[28]
19.	A new stability-indicating RP- HPLC method for the determination of dicyclomine hydrochloride and dimethicone combination in tablet dosage forms	Column: XTerra C18 column (250 mm × 4.6 mm, 5 µm) Mobile phase: 0.1M K2HPO4-acetonitrile (55:45, v/v) Flow rate:1 mL/min Retention time: 2.134 and 2.865 min Accuracy : (99.453 to 100.417% and 99.703 to 100.303% recovery values for DEH and DEC Precision : (RSV value 0.135% for DEC and 0.171% for DEH) linearity ; (5–15 µg/mL for DEH and 20–60 µg/mL for DEC)	[29]

CONCLUSION

The comprehensive review of the study emphasizes the various analytical techniques employed for determining Dicyclomine Hydrochloride, and their combination in bulk drugs, pharmaceutical formulations, and biological samples. Among these,

High-Performance Liquid Chromatography (HPLC) and Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) emerged as the most commonly utilized methods. HPLC, in particular, is preferred due to its superior sensitivity, specificity, and enhanced separation capabilities for both qualitative and quantitative analysis. The mobile phase of 60:40 v/v mixture of Acetonitrile And Triethylamine ratio, despite the fact that these drugs are freely soluble in water. To date, no studies have been conducted On Dicyclomine Hydrochloride Capsule for this drug. Therefore, we preferred this method for our analysis.

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