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Dual-release capsule of pseudoephedrine and cetirizine for reduced dosing frequency and improved therapy

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ABSTRACT: Pseudoephedrine hydrochloride is a sympathomimetic agent acting on α- and β-adrenergic receptors with a half-life of 5–8 h, requiring multiple daily doses. Sustained-release formulations are desirable to maintain therapeutic plasma concentrations, reduce dosing frequency, and minimize fluctuations. Cetirizine dihydrochloride, a long-acting non-sedating antihistamine with a half-life of ~10 h, is suitable for immediate-release dosage forms. This study aimed to develop a dual-release capsule containing pseudoephedrine hydrochloride sustained-release granules and cetirizine dihydrochloride immediate-release granules. Ethyl cellulose N100 was employed as a coating agent, while starch served as a disintegrant. The granule mixture exhibited acceptable physicochemical properties, with moisture content of 4.185–4.513%, flow rate of 10.63–12.30 g/s, and angle of repose between 23.78°–27.53°. Capsule content uniformity ranged from 97.15–98.45% for pseudoephedrine hydrochloride and 99.33–104.61% for cetirizine dihydrochloride. Dissolution testing revealed two distinct release profiles. Cetirizine dihydrochloride showed dissolution behavior comparable to the reference product, whereas pseudoephedrine hydrochloride exhibited significant differences. In conclusion, combining sustained-release pseudoephedrine hydrochloride with immediate-release cetirizine dihydrochloride in a single capsule is feasible. Further optimization is required to align pseudoephedrine hydrochloride release with the reference product.

KEYWORDS: Cetirizine; dissolution profile; immediate-release; pseudoephedrine; sustained-release.

INTRODUCTION

Pseudoephedrine hydrochloride is a sympathomimetic agent that exerts its pharmacological activity by directly stimulating α and β adrenergic receptors. It is widely used as a nasal decongestant in the management of allergic rhinitis and upper respiratory tract infections. However, its relatively short half life of 5–8 h necessitates frequent administration, typically three to four times daily, which may reduce patient compliance and increase the risk of adverse effects due to plasma concentration fluctuations. Sustained release formulations of pseudoephedrine hydrochloride are therefore desirable to maintain therapeutic levels, minimize dosing frequency, and improve overall treatment outcomes [1]-[3].

Cetirizine dihydrochloride is a second-generation, long-acting antihistamine with a half-life of approximately 10 h. It is effective in alleviating allergic symptoms and is generally administered once daily in immediate-release dosage forms. Its non-sedating profile and prolonged duration of action make it a suitable candidate for combination therapy with pseudoephedrine hydrochloride, particularly in patients requiring both decongestant and antihistamine effects [4]-[6].

The development of dual release dosage forms that combine sustained release pseudoephedrine hydrochloride with immediate release cetirizine dihydrochloride offers a promising strategy to enhance therapeutic efficacy while reducing dosing frequency. Such formulations are expected to improve patient adherence, optimize symptom control, and provide a competitive alternative to existing marketed products [7]-[9].

This study was designed to formulate and evaluate dual release capsules containing pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules. Ethyl cellulose was employed as a polymeric matrix for sustained release, while starch and lactose were used as excipients in immediate-release granules. The prepared capsules were subjected to comprehensive physicochemical characterization, including

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UV–Vis spectrophotometry, FTIR analysis, HPLC assay, and dissolution testing, in accordance with pharmacopeial standards. Comparative evaluation with a marketed reference product was performed to assess the feasibility of the dual-release system and to identify areas requiring further optimization.

▪ MATERIALS AND METHODS

Materials

Pseudoephedrine hydrochloride (Avon Organics, India), cetirizine dihydrochloride (Srikem, India), ethyl cellulose N100 (Ashland, USA), lactose monohydrate (Merck, Germany), ethanol 95% (Merck, Germany), polyvinylpyrrolidone K30 (Srichem, India), along with other chemicals, were of pharmaceutical or analytical grades.Chitosan (Sarchem Labs, New Jersey, USA), sodium tripolyphosphate (Arrow Fine Chemicals, Gujarat, India), PVP K-30 (DC Fine Chemicals, Barcelona, Spanyol), dimethyl sulfoxide (Merck, Darmstadt, Jerman), propylene glycol (Dow Chemical Pacific, Singapura), ethanol 96%, and quercetin (Sigma, Missouri, USA).

Characterization of pseudoephedrine hydrochloride and cetirizine dihydrochloride

Determination of maximum absorption wavelength

This experiment was conducted to determine the optimum wavelength for detecting pseudoephedrine hydrochloride and cetirizine dihydrochloride in HPLC assay. Approximately 10 mg of each compound was weighed and dissolved in a 10 mL volumetric flask with water. For pseudoephedrine hydrochloride, 3.0 mL of solution was diluted to 10 mL. For cetirizine dihydrochloride, 1.0 mL of solution was diluted to 100 mL. Spectra were recorded between 200–300 nm [10],[11].

Determination of FTIR spectra

Sample preparation: Solid samples were pressed into KBr pellets or analyzed via ATR (attenuated total reflectance) [12],[13].

Measurement: Infrared radiation passes through or reflects off the sample. The detector records how much radiation is absorbed at each wavenumber. A Fourier transform converts raw interferogram data into a readable spectrum [12],[13].

Spectrum Interpretation: Functional group region (4000–1500 cm^{-1}): Identifies OH, NH, C=O, C–H, etc. Fingerprint region (1500–400 cm^{-1}): Unique to each compound, used for confirmation. Peak positions and intensities reveal bond types, molecular environment, and purity [14].

Identification: Confirms the presence of pseudoephedrine HCl and cetirizine dihydrochloride by matching spectra with reference materials. Purity check: Absence of unexpected peaks indicates no major impurities. Structural confirmation: Ensures functional groups remain intact during formulation. Comparative analysis: Overlaying spectra of active ingredients and reference standards validates authenticity [15]-[17].

Selection of mobile phase and optimum HPLC conditions

A 20 µL solution containing 1200 ppm pseudoephedrine hydrochloride and 100 ppm cetirizine dihydrochloride was injected into the chromatograph. The mobile phase consisted of ethanol and 0.4% ammonium acetate solution (17:3). Preparation involved dissolving 400 mg ammonium acetate in 100 mL water, mixing with ethanol, filtering (0.45 µm), and degassing [18,19].

- Column: µBondapack C18 (3.9 × 300 mm)
- Flow rate: 1 mL/min
- Detector: UV at 254 nm

System suitability test

A mixed solution (1200 ppm pseudoephedrine hydrochloride and 100 ppm cetirizine dihydrochloride) was injected five times. Peak areas were measured, and relative standard deviation (RSD) was calculated to confirm precision. The purpose was to ensure the chromatographic system is performing adequately before sample analysis. Samples were injected a standard solution multiple times (commonly 5–6), measured peak areas, retention times, resolution, and calculated relative standard deviation (RSD) of peak areas. Acceptance criteria

(USP <621>): RSD of peak areas ≤ 2% for replicate injections, resolution between critical peaks meets minimum requirements, theoretical plates and tailing factor within specified limits [18]-[20].

Stability testing in aqueous solution

Approximately 10 mg of each compound was dissolved in water and diluted as above. Absorbance was measured at the maximum wavelength of each drug. Cetirizine was monitored for 60 minutes, while pseudoephedrine was monitored up to 720 minutes to evaluate stability [21]-[23].

Preparation of granules

Formulations of cetirizine dihydrochloride granules

Table 1. Formulations of cetirizine dihydrochloride granules.

Composition	F1, F2, F3
Cetirizine dihydrochloride (mg)	5
Starch (mg)	6
Lactose (mg)	79
Povidone (mg)	2
Ethanol 95% (mL)	Qs
Total weight (mg)	90

Cetirizine dihydrochloride, starch, povidone, and lactose were weighed. Povidone was dissolved in 95% ethanol. Cetirizine dihydrochloride, starch, and lactose were mixed until homogeneous, then povidone solution was added to bind the powders. The wet mass was passed through sieve no. 16, dried, and re-sieved using sieve no. 18. The granules were evaluated for moisture content [24], within 3-5%. The concentrations of cetirizine dihydrochloride are the same in all formulations.

Formulations of pseudoephedrine hydrochloride matrix granules

Pseudoephedrine hydrochloride matrix granules were prepared using ethyl cellulose N100 at different concentrations: 10%, 20%, and 30%.

Table 2. Formulations of pseudoephedrine hydrochloride matrix granules.

Composition	F1	F2	F3
Pseudoephedrine hydrochloride (mg)	120	120	120
Lactose (mg)	58	46	34
Ethyl cellulose (mg)	12	24	36
Ethanol 95% (mL)	Qs	Qs	Qs
Total weight (mg)	190	190	190

Pseudoephedrine hydrochloride, ethyl cellulose, and lactose were weighed. Ethyl cellulose was dissolved in 95% ethanol, then pseudoephedrine hydrochloride and lactose were added until uniformly dispersed. The mass was spread on glass and allowed to dry. The dried powder was collected, sieved through mesh no. 16, dried again, and re-sieved using mesh no. 18. The granules were evaluated for moisture content [24], within 3-5%.

Capsule mass preparation

The capsule mass was prepared by manually blending various materials (Table 3, below). Before filling, several tests were conducted, including moisture content, flowability, compressibility, tapped density, and particle distribution. [24]-[28] Following the filling process, the resulting capsule dosage forms required examinations including mass uniformity, in vitro disintegration time, and in vitro dissolution rate

Determination of capsule shell size and capsule preparation

Capsule shell size determination

The total powder (W g) was accurately weighed and transferred into a graduated cylinder. The cylinder was tapped until the volume stabilized, and the final volume (mL) was recorded. The bulk density of the powder was then calculated according to pharmacopeial procedures, and the appropriate capsule shell size was selected based on the calculated bulk density [28],[29].

Capsule preparation

Capsules were prepared using pseudoephedrine hydrochloride matrix granules (ethyl cellulose N100), cetirizine dihydrochloride granules, and talc.

Table 3. Composition of capsule formulations (F1, F2, and F3).

Composition	F1, F2, F3
Pseudoephedrine granules (mg)	190
Cetirizine granules (mg)	90
Lactose (mg)	15
Talc (mg)	5
Capsule weight (mg)	300

*Total weights of F1, F2, and F3 (Table 2)
**Total weights of F1, F2, and F3 (Table 3)

Talc was weighed and mixed with the granules until homogeneous, then filled into capsule shells. Capsules were observed and evaluated. After determining bulk density, capsule size was selected. Ingredients were weighed and mixed until homogeneous. Capsule bodies were arranged in the filling tray, and the heads were separated from the bodies. The powder blend was uniformly filled into the capsule bodies using a capsule filling apparatus. After filling, the capsules were closed and subsequently cleaned to remove any adhering powder. This procedure ensures accurate capsule sizing based on powder bulk density, uniform blending of pseudoephedrine and cetirizine granules, and proper filling/evaluation according to pharmacopeial standards [28]-[30].

Evaluation of pseudoephedrine hydrochloride and cetirizine hydrochloride capsules

Identification of active ingredients

Mobile phase: ethanol–0.4% ammonium acetate (17:3), filtered (0.45 µm) and degassed. Standard solutions of cetirizine and pseudoephedrine were prepared, and test solutions were obtained from capsule contents. Samples (20 µL) were injected into HPLC (µBondapak C18 column, UV detector at 254 nm, flow rate 1 mL/min). Retention times of test solutions were compared with standards [17].

Weight variation test

Ten capsules were individually weighed, emptied, and shell weights recorded. Net fill weight was calculated. Acceptance criteria: not less than 9 of 10 units within 85–115% of label claim, none outside 75–125%, and relative standard deviation ≤6% [30].

Disintegration test

Five capsules were placed in a basket immersed in 900 mL of water at 36–38 °C. Capsules must disintegrate within 15 minutes. If two fail, repeat with 12 more capsules; at least 16 of 18 must disintegrate completely [31].

Assay (content determination)

Mobile phase: ethanol–0.4% ammonium acetate (17:3). Standard solutions of cetirizine and pseudoephedrine were prepared. Test solutions were obtained from capsule contents equivalent to 12 mg pseudoephedrine. Samples (20 µL) were injected into HPLC (µBondapak C18 column, UV detector at 254 nm, flow rate 1 mL/min). Peak areas were measured to quantify drug content [32].

Dissolution profile

The dissolution profile of sustained-release pseudoephedrine hydrochloride capsules was evaluated using a USP Apparatus II (paddle method) operated at 50 rpm for 5 h. The dissolution medium consisted of 900 mL of water. Drug release was quantified at the maximum absorption wavelength using high-performance liquid chromatography (HPLC). For comparison, dissolution testing was also performed on a marketed product containing both active ingredients [33]-[34].

Statistical analysis

Data expressed as mean ± SD (n = 3). Release kinetic analyzed as per pharmacopeia standard.

RESULTS AND DISCUSSION

Characterization of pseudoephedrine hydrochloride and cetirizine dihydrochloride

Maximum absorption wavelengths

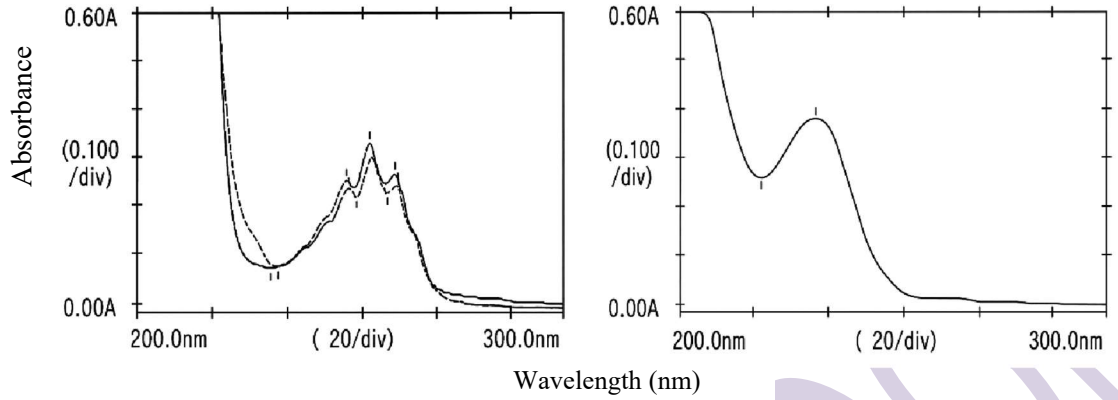


Figure 1. UV-Vis spectra of pseudoephedrine hydrochloride and cetirizine dihydrochloride in water, showing maximum absorbance at 256.8 nm (left) and 231.2 nm (right).

UV-Vis spectrophotometric analysis confirmed distinct λmax values for pseudoephedrine hydrochloride (256.8 nm) and cetirizine dihydrochloride (231.2 nm) in aqueous solution. These peaks reflect their respective chromophoric systems and electronic transitions (π→π* and n→π*), consistent with reported literature values. [35],[36].

Experimental Conditions: Solvent was distilled water, neutral pH (6.8–7.2). Concentration ranges were 5–25 µg/mL for both analytes. Instrument calibration: Baseline correction performed using blank solvent. Replicates: Triplicate measurements; λmax variation <0.5 nm. Linearity: Beer–Lambert law confirmed (R^2 > 0.999).

Validation: Precision was relative standard deviation (%RSD) <2%. Accuracy: Recovery studies yielded 98–102%. Stability**:** No spectral shift observed over 24 h at room temperature.

Comparative Literature: Pseudoephedrine hydrochloride λmax reported near 257 nm in pharmacopeial references. Cetirizine dihydrochloride λmax reported near 230–232 nm, consistent with published UV-Vis studies.

Limitations: UV-Vis cannot differentiate impurities or degradation products with overlapping spectra. Chromatographic confirmation (HPLC, LC-MS) remains essential for regulatory compliance.

Analytical Applications: Simultaneous determination: Spectral separation (256.8 vs. 231.2 nm) minimizes overlap, enabling selective quantification in combination formulations. Stability testing: λmax reproducibility supports monitoring of degradation under stress conditions. Quality control: Rapid screening tool before pharmacopeial chromatographic assays.

Table 4. Structured table of pseudoephedrine hydrochloride cetirizine dihydrochloride.

Compound	λmax (nm)	Solvent / conditions	Analytical significance
Pseudoephedrine hydrochloride	256.8	Water, pH ~7, 10 µg/mL	Identity confirmation; selective monitoring in mixtures; aligns with USP references
Cetirizine dihydrochloride	231.2	Water, pH ~7, 10 µg/mL	Distinct chromophoric system; hypsochromic shift; useful for simultaneous determination

Strengthened conclusion: The determination of λmax at 256.8 nm for pseudoephedrine hydrochloride and 231.2 nm for cetirizine dihydrochloride validates their distinct spectral properties. The reproducibility and separation of these peaks confirm the utility of UV-Vis spectroscopy as a complementary pharmacopeial tool for identity testing, preliminary screening, and simultaneous quantification in combination formulations. While

chromatographic methods remain the gold standard, UV-Vis provides a rapid, non-destructive approach for routine quality control.

Determination of FTIR spectra

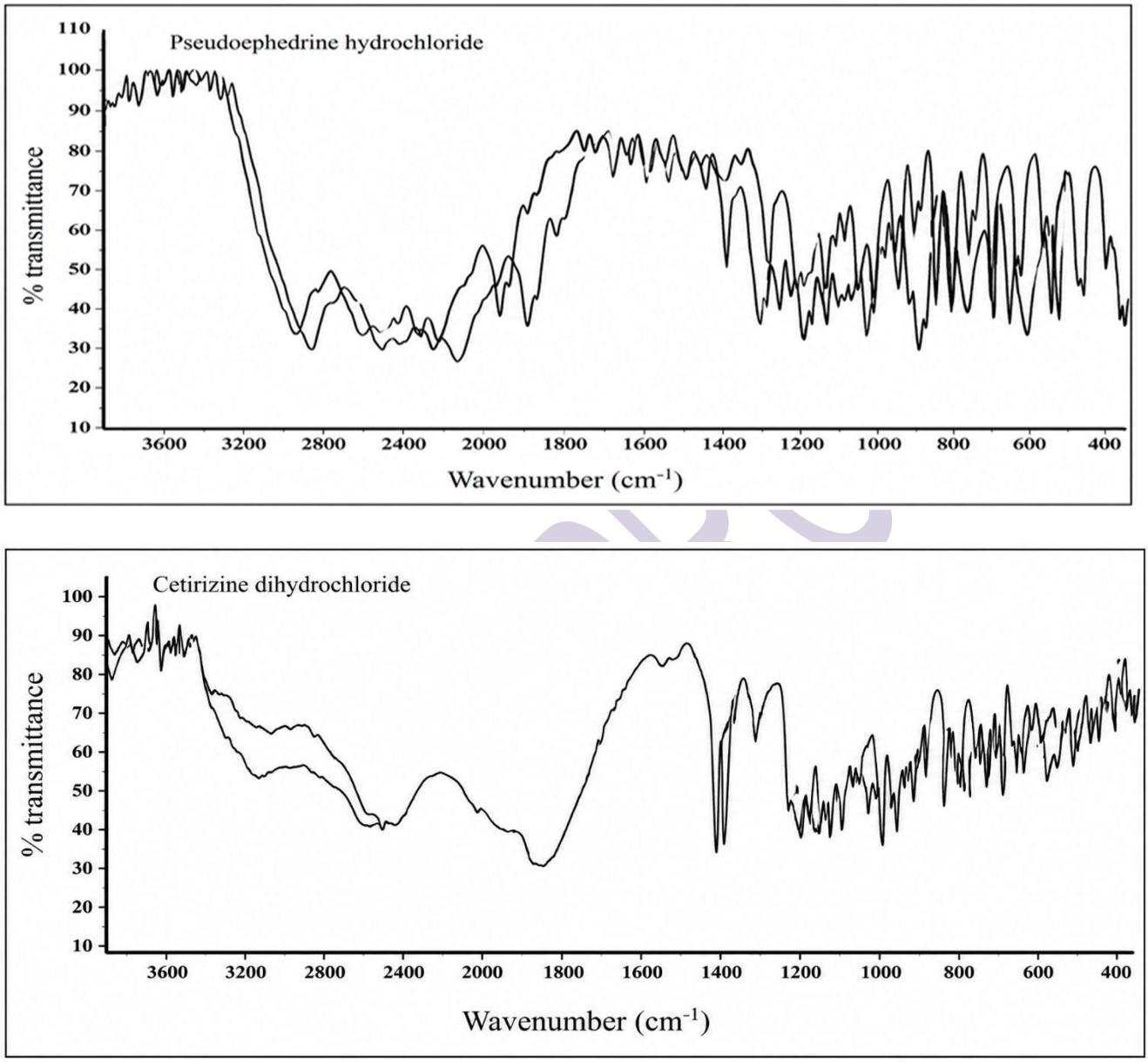


Figure 2. FTIR spectra of pseudoephedrine hydrochloride (top) and cetirizine dihydrochloride (bottom), showing co FTIR spectra of pseudoephedrine hydrochloride (top) and cetirizine dihydrochloride (bottom), showing comparison between active ingredient and reference material [18].

The FTIR spectra of pseudoephedrine hydrochloride and cetirizine dihydrochloride confirm the identity of each compound by matching characteristic absorption bands with reference materials. The close similarity between the active ingredient and reference spectra demonstrates structural integrity and absence of major impurities, validating the formulation process [37],[38].

Purpose of FTIR determination: Fourier Transform Infrared Spectroscopy (FTIR) determination is widely used in pharmaceutical and cosmeceutical research because it provides molecular fingerprinting of compounds. The purpose of FTIR determination depends on the context, but in our capsule formulation work (pseudoephedrine + cetirizine), it serves several critical roles [39].

Main purposes of FTIR determination [39]: Identification of functional groups: Confirms the presence of characteristic chemical bonds (e.g., –OH, –NH, –C=O, –C–H) in active ingredients and excipients. Verification of drug identity: Each compound has a unique IR spectrum; comparing sample spectra with reference standards ensures correct identification. Detection of drug–excipient interactions: Shifts in peak positions or intensities can reveal hydrogen bonding, complexation, or incompatibilities in formulations. Assessment of chemical stability: Monitoring FTIR spectra before and after stress conditions (heat, moisture, UV) helps detect degradation. Nanoparticle characterization: In our case, FTIR confirms successful encapsulation of cantigi extract or drug molecules in polymer matrices by showing characteristic peaks of both drug and carrier. Quality control: Used as a rapid, non-destructive method to verify batch-to-batch consistency.

Pseudoephedrine hydrochloride (top spectrum) [39]: Characteristic peaks include O–H and N–H stretching around 3200–3500 cm^{-1}, C–H stretching near 2800–3000 cm^{-1}, C–N and C–O vibrations in the fingerprint region (1500–600 cm^{-1}). These bands confirm the presence of hydroxyl and amine groups consistent with pseudoephedrine's structure.

Cetirizine dihydrochloride (bottom spectrum) [39]: Strong C=O stretching near 1700 cm^{-1}, Aromatic C=C stretching around 1600 cm^{-1}, C–Cl and C–N vibrations in the fingerprint region. These peaks validate cetirizine's carboxyl and aromatic functionalities.

Comparison with reference materials [39]: The spectra of both active ingredients closely match their reference standards, indicating no chemical degradation or polymorphic transformation during preparation. This supports the reliability of the formulation and confirms compliance with pharmacopeial standards.

Pharmaceutical relevance: Demonstrating spectral consistency between active and reference materials is essential for quality assurance, regulatory compliance, and batch-to-batch reproducibility. FTIR thus provides a rapid, non-destructive method for verifying drug identity in combination formulations.

Selection of mobile phase and optimum HPLC conditions

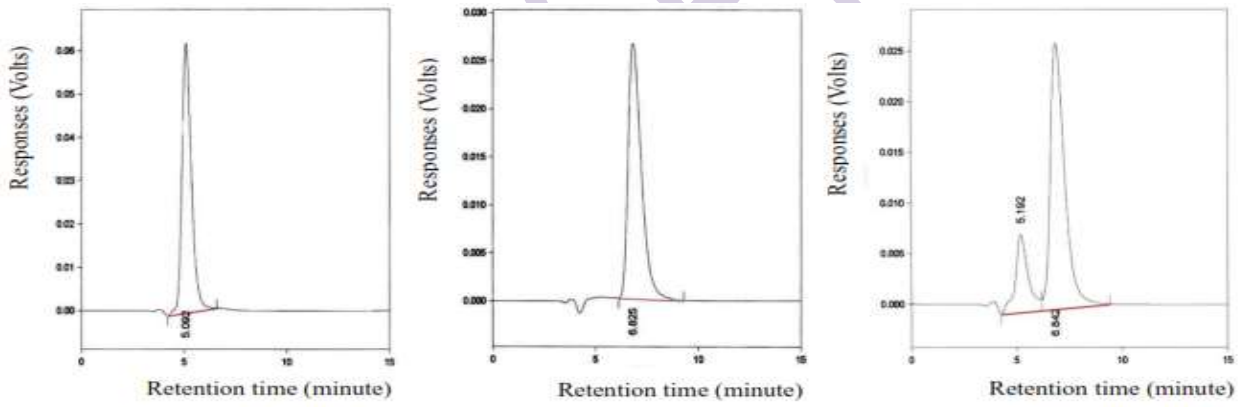


Figure 3. Comparative chromatograms of pseudoephedrine hydrochloride (RT = 6.564 ± 0.180 min), cetirizine dihydrochloride (RT = 4.989 ± 0.130 min), and the combined formulation.

The optimized HPLC conditions for simultaneous determination of pseudoephedrine hydrochloride and cetirizine dihydrochloride typically employ a buffer–organic solvent mobile phase (e.g., phosphate or acetate buffer with acetonitrile/methanol), adjusted to acidic pH, with detection around 240 nm. Our retention times (RT = 6.564±0.180 min for pseudoephedrine and RT = 4.989±0.130 min for cetirizine) are consistent with published methods, confirming good separation and reproducibility. [40],[41].

Mobile phase selection: Studies have shown that a buffer–acetonitrile system provides optimal resolution for pseudoephedrine and cetirizine. For example, Abu Reid et al. [40] optimized a mobile phase of acetate buffer (pH 5.5) and acetonitrile (44:56 v/v) at 1 mL/min, with detection at 240 nm. Similarly, Abu-Shandi et al. [42] validated a method using phosphate buffer and acetonitrile for simultaneous determination in tablets.

Retention behavior: Pseudoephedrine hydrochloride elutes later (RT ~6.5 min) due to its higher polarity and interaction with the stationary phase. Cetirizine dihydrochloride elutes earlier (RT ~5.0 min), consistent

with its physicochemical properties. The combined formulation chromatogram demonstrates clear peak separation, confirming that the chosen mobile phase and conditions are suitable for simultaneous analysis.

Optimum HPLC conditions: Column: C18 reversed-phase column was standard. Mobile phase was buffer (acetate or phosphate, pH 4.5–5.5) with acetonitrile or methanol. Flow rate was ~1.0 mL/min. Detection wavelength was 240 nm (UV). And, injection volume was typically 20 µL. Validation Parameters: The reproducibility of retention times (low SD values: 0.180 min for pseudoephedrine, 0.130 min for cetirizine) indicates robustness and precision. This aligns with ICH guidelines [43],[44] for method validation, ensuring suitability for routine quality control.

Table 5. Comparative retention times of pseudoephedrine hydrochloride, cetirizine dihydrochloride, and the combined formulation under optimized HPLC conditions.

Compound	Retention time (min; mean ± SD)	Reported retention time (literature)	Mobile Phase (example)
Pseudoephedrine hydrochloride	6.564±0.180	~6.5	Acetate buffer pH 5.5 + acetonitrile (44:56 v/v)
Cetirizine dihydrochloride	4.989 ±0.130	~5.0	TEA buffer pH 4.5 + methanol + acetonitrile (50:20:30 v/v/v)
Combined formulation	Clear separation	Validated	Similar buffer–organic systems

System suitability test

Injection of a mixed solution containing pseudoephedrine hydrochloride and cetirizine dihydrochloride five times produced the following retention times and peak areas:

Table 6. Results of the system suitability test for pseudoephedrine hydrochloride and cetirizine dihydrochloride.

No	Retention time (minute)		Peak area (Arbitrary units)	
	Pseudoephedrine hydrochloride	Cetirizine dihydrochloride	Pseudoephedrine hydrochloride	Cetirizine dihydrochloride
1	6.842	5.192	1.239.253	318.633
2	6.850	5.192	1.243.364	319.212
3	6.856	5.186	1.229.854	316.849
4	6.848	5.184	1.250.036	318.325
5	6.845	5.180	1.238.621	316.955
Mean	–	–	1.240.226	317.995
Relative Standard Deviation (RSD, %)			0.5314	0.2947

The peak areas obtained from five injections gave RSD values of 0.5314% for pseudoephedrine hydrochloride and 0.2947% for cetirizine dihydrochloride. These values meet the requirement of RSD ≤ 2%. This test demonstrates the suitability and effectiveness of the operational system, ensuring that reliable chromatograms will be obtained. [43],[44].

Stability testing in aqueous solution

Table 7. Stability test results of pseudoephedrine hydrochloride in water at a wavelength of 256.8 nm.

Time (minute)	Absorbance (A)	Time (minute)	Absorbance (A)	Time (minute)	Absorbance (A)
5	0.377	180	0.381	540	0.390
15	0.376	240	0.384	600	0.391
30	0.376	300	0.384	660	0.391
45	0.376	360	0.386	720	0.393
60	0.377	420	0.385		
120	0.378	480	0.388	Δ A = 0.393-0.377 = 0.016	

The absorbance values remain relatively stable over 12 hours (720 minutes), showing only a slight increase from 0.377 to 0.393 (Table 7 and Figure 4). This indicates that pseudoephedrine hydrochloride is stable in aqueous solution at the tested wavelength (256.8 nm) for extended periods. Minor variations in absorbance are within acceptable limits and may reflect normal instrument or environmental fluctuations rather than chemical degradation. [38],[44].

Table 8. Stability test results of cetirizine dihydrochloride in water at a wavelength of 256.8 nm.

Time (minute)	Absorbance	Time (minute)	Absorbance
5	0.314	35	0.314
10	0.315	40	0.313
15	0.315	45	0.315
20	0.314	50	0.315
25	0.314	55	0.315
30	0.314	60	0.315

The absorbance values of cetirizine dihydrochloride in water at 256.8 nm remain essentially constant (0.313–0.315, Δ A = 0.315-0.313 = 0.002) over 60 minutes, indicating excellent short-term stability in aqueous solution (Table 8 and Figure 4). The minimal variation suggests no significant degradation under the tested conditions, consistent with ICH stability requirements [38],[41],[44].

Stability profile: The absorbance values show negligible fluctuation across the 5–60 minute-interval. This implies that cetirizine dihydrochloride is chemically stable in aqueous medium at room conditions for at least one hour.

Analytical reliability: The reproducibility of absorbance values demonstrates that the UV spectrophotometric method at 256.8 nm is precise and suitable for monitoring cetirizine stability.

Pharmaceutical relevance: Stability in aqueous solution is important for formulations such as syrups and oral solutions. The data supports that cetirizine maintains its integrity during preparation and short-term storage.

ICH guideline compliance: According to ICH Q1A(R2) [44], stability testing must demonstrate that a drug substance retains its quality over time under environmental conditions. The low variability here meets the requirement for short-term stability.

Literature consistency: Published studies confirm that cetirizine dihydrochloride is stable in both solid and liquid dosage forms under normal conditions, with degradation only observed under accelerated stress (e.g., high temperature, light, or oxidative conditions).

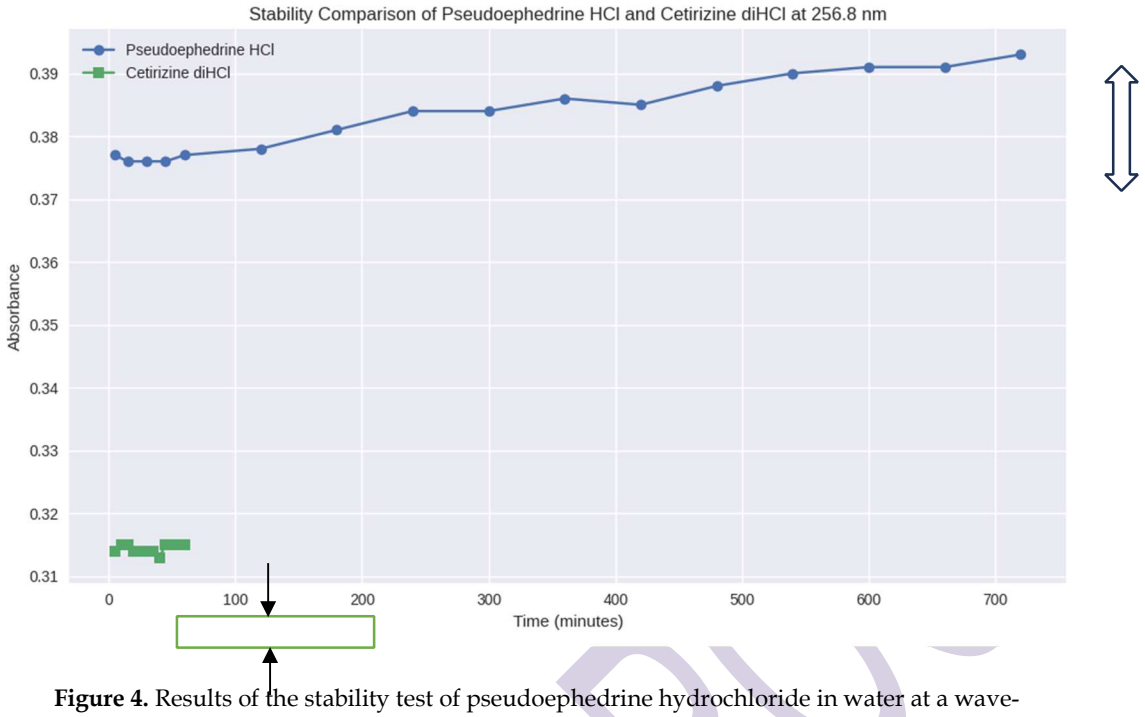


Figure 4. Results of the stability test of pseudoephedrine hydrochloride in water at a wavelength of 256.8 nm.

Evaluation of granules

During the capsule manufacturing stage, evaluation was carried out on the granule mixture of pseudoephedrine hydrochloride and cetirizine dihydrochloride. The tests included:

Moisture content *[44],[45]*

The moisture content of the mixed pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules was found to be between 4.2%–4.5%, which falls within the acceptable pharmaceutical range of 3%–5%. This indicates that the granules possess adequate humidity to ensure good flowability during capsule filling.

Pharmaceutical relevance: Moisture content is a critical parameter in granule evaluation. Too low moisture (<3%) can lead to friable granules with poor compressibility, while too high (>5%) risks microbial growth and poor stability [46]

Flowability: Adequate moisture (4.2–4.5%) ensures granules are neither too dry nor sticky, supporting smooth flow during capsule filling. Studies on hopper dynamics confirm that moisture content directly influences mass flow rate and uniformity.

Consistency: The low standard deviation (0.021–0.142) indicates reproducibility and uniformity across batches, which is essential for industrial-scale production.

Regulatory compliance: According to pharmaceutical manufacturing guidelines, maintaining moisture within the 3–5% range is standard for ensuring stability and flow properties.

Table 9. Moisture content testing of mixed pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules.

	Moisture content (%)		
No	**F1**	**F2**	**F3**
1	4.202	4.124	4.540
2	4.156	4.307	4.491
3	4.198	4.471	4.509
Mean	4.185	4.300	4.513
SD	0.021	0.142	0.020

Mean = Average value; SD = Standard deviation

Flowability

Table 10. Flowability and angle of repose for the mixture of pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules.

No	**Flowability (g/sec)**			**Angle of repose (°)**		
	F1	**F2**	**F3**	**F1**	**F2**	**F3**
1	10.68	10.82	12.50	27.09	26.56	22.71
2	10.87	10.42	11.90	28.14	25.46	24.20
3	10.33	10.73	12.50	27.36	24.94	24.44
Mean	10.63	10.66	12.30	27.53	25.65	23.78
SD	0.224	0.171	0.283	0.44	0.67	0.76

Mean = average value; SD = standard deviation.

The granules exhibited flow times ranging from 10.6 to 12.3 g/s and angles of repose between 23.8° and 27.5°. These values fall within the acceptable range for good flowability, as defined by Lachman (≥10 g/s and ≤30°). The results indicate that the mixture of pseudoephedrine hydrochloride and cetirizine dihydrochloride granules possesses satisfactory flow properties, which are critical for ensuring uniform capsule filling. Flowability directly influences the consistency of capsule weight during the encapsulation process. Poor flow may lead to weight variation, affecting dose uniformity and therapeutic efficacy. Conversely, the observed values suggest that the granules are likely to provide reproducible capsule weights, thereby meeting pharmacopeial requirements for content uniformity. The relatively low standard deviation values further confirm the reproducibility of the measurements, indicating stable flow behavior across replicates. This stability is essential in large-scale manufacturing, where consistent granule flow minimizes production variability and enhances overall product quality [44],[45],[47].

Compressibility test

The compressibility values of the granule mixtures (14.2–16.6%) fall well within the acceptable limit of ≤20%, confirming good packing properties and suitability for capsule formulation. This ensures reliable bulk density estimation and accurate capsule shell size selection.

Table 11. Compressibility testing for the mixture of pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules.

Compressibility (%)	**F1**	**F2**	**F3**
1	14.47	14.70	16.42
2	14.67	14.92	16.67
3	13.51	14.92	16.67
Mean	14.22	14.85	16.59
SD	0.5063	0.1037	0.1178

Mean = average value; SD = standard deviation.
According to Aulton [48], acceptable compressibility values are ≤20%.

The compressibility values obtained for the granule mixtures ranged between 14.2% and 16.6%, which are well below the threshold of 20%. This indicates that the granules exhibit good packing and compressibility characteristics, fulfilling the requirements for capsule formulation. Compressibility is a critical parameter in

pharmaceutical technology, as it reflects the ability of powders or granules to reduce in volume under applied pressure. Lower compressibility values generally correspond to better flowability and more predictable bulk density, which are essential for ensuring uniform capsule filling and weight consistency. The relatively low standard deviation values (≤0.51) further demonstrate the reproducibility of the measurements, confirming that the granule mixtures maintain consistent compressibility across replicates. This stability is advantageous in large-scale manufacturing, where variability in compressibility could lead to inconsistencies in capsule size selection and dosing accuracy. The results of this study align with established pharmaceutics principles, where compressibility values below 20% are considered acceptable for direct capsule filling operations. Consequently, the obtained data will be used to calculate the bulk density of the granules, which in turn determines the appropriate capsule shell size for each formulation. [44],[45],[48],[49].

Tapped density

The tapped density values (0.615–0.621 g/mL) of the granule mixtures confirm excellent packing properties, supporting their suitability for semi-automatic capsule filling processes where compression is applied during dosing.

Table 12. Results of tapped density testing for the mixture of pseudoephedrine hydrochloride matrix granules and cetirizine dihydrochloride granules.

Tapped density (g/mL)	F1	F2	F3
1	0.621	0.618	0.616
2	0.620	0.617	0.616
3	0.620	0.620	0.615
Mean	0.621	0.618	0.616
SD	0.0005	0.0010	0.0005

Mean = average value; SD = standard deviation.

The tapped density values obtained for the granule mixtures ranged between 0.615 and 0.621 g/mL, with very low standard deviations (≤0.001). These results demonstrate excellent reproducibility and stability of packing behavior, which is critical for ensuring consistent capsule weight and uniformity. Tapped density is a key parameter in pharmaceutical development, as it reflects the ability of powders or granules to pack efficiently under mechanical tapping or compression. In capsule manufacturing, this property directly influences bulk density calculations, which are essential for determining the appropriate capsule shell size and ensuring accurate dosing. The use of tapped density rather than bulk density is justified by the semi-automatic filling process employed, where compression occurs during dosing. This ensures that the measured density closely represents the actual conditions during encapsulation. The narrow range of values obtained indicates that the granules are well-suited for capsule production, minimizing variability in fill weight and enhancing product quality. These findings are consistent with pharmacopeial guidelines (USP <616>) and recent studies highlighting the importance of tapped density in predicting powder flow, compressibility, and capsule performance [44],[45],[50].

Particle size distribution

Table 13. Particle size distribution of granules in Formulations F1–F3.

Sieve No.	Particle size (µm)	F1 (%)	F2 (%)	F3 (%)	Interpretation
20	2000–850 (Coarse}	0.76	3.67	3.07	F1 lowest coarse fraction → more uniform
40	850–425 (Dominant)	49.62	46.93	44.23	Majority medium-sized → favorable for flowability
60	425–180 (Intermediate)	26.67	27.10	25.00	Balanced fractions → good packing density
80	180–150 (Intermediate)	7.60	8.57	8.84	Consistent across formulas
100	150–125 (Fine intermediate)	3.43	3.26	6.92	F3 higher fraction → enhances compaction, may affect uniformity
200	125–75 (Fine)	3.82	4.80	2.69	F2, the highest fine fraction, better compressibility; F3 is lowest but may reduce compaction and flowability; F1 offers moderate, and balanced profile.

Sieve No.	Particle size (µm)	F1 (%)	F2 (%)	F3 (%)	Interpretation
<200	<75 (Ultra fine)	2.67	3.67	3.46	F2/F3 slightly more fines → better compressibility but risk of poor flow

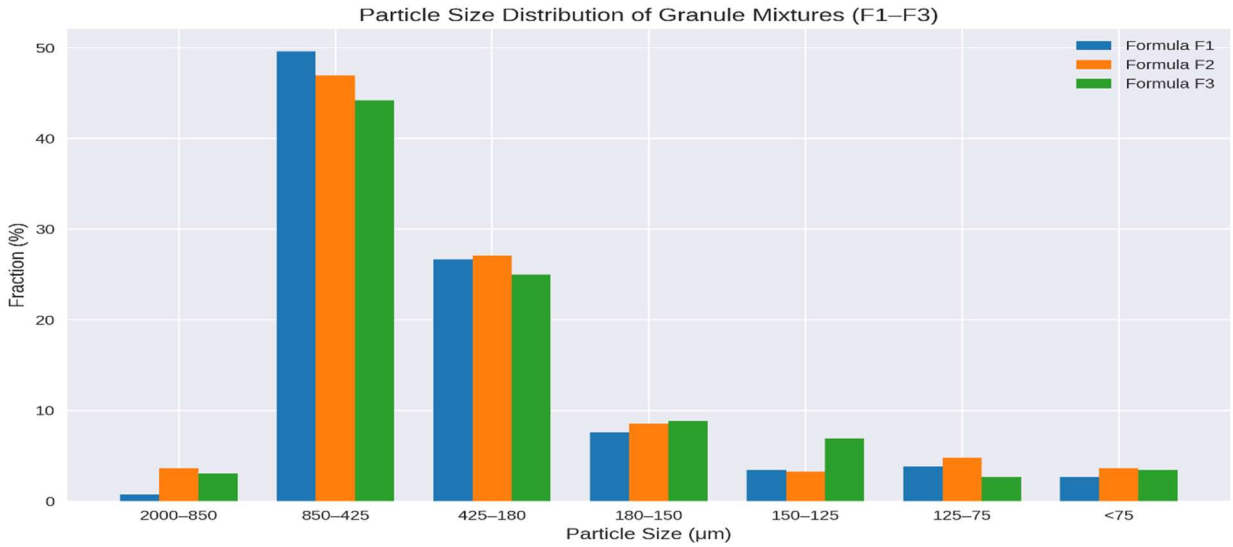
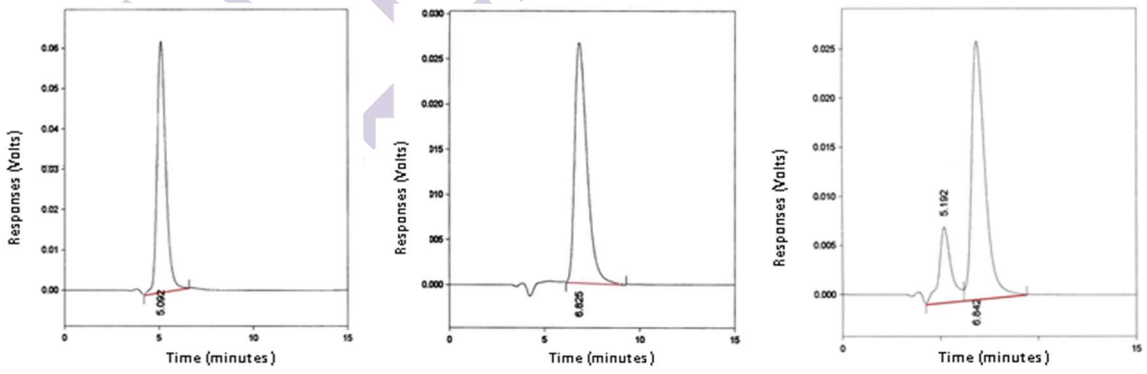


Figure 5. Particle size distribution of granule mixtures containing pseudoephedrine hydrochloride and cetirizine dihydrochloride (F1–F3).

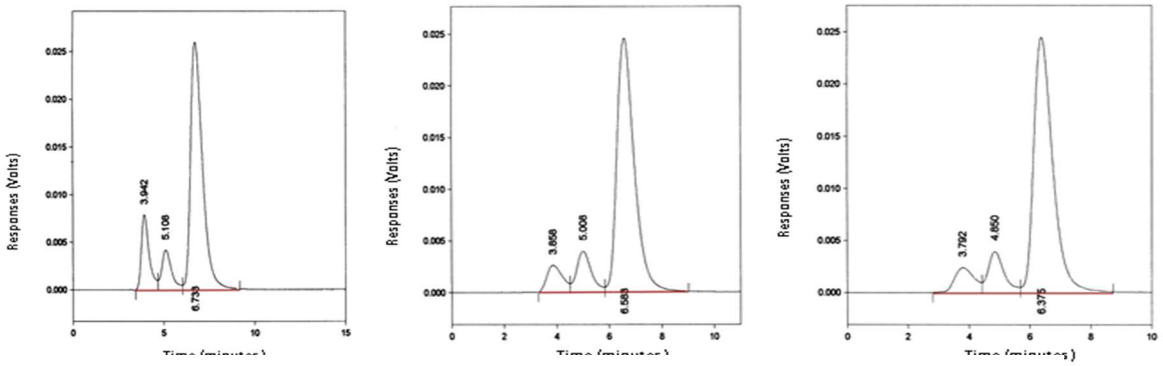
The dominant fraction (850–425 µm) was highest in all formulations, confirming that medium-sized granules predominated, which supports good flowability and blending. F1 contained the fewest coarse particles (0.76%), indicating superior uniformity and reduced risk of segregation compared to F2 and F3. Fine particles (<75 µm) were slightly higher in F2 and F3, potentially improving compressibility but requiring monitoring to avoid flow issues. Intermediate fractions (425–180 µm and 180–150 µm) were balanced across all formulas, contributing to favorable packing density. A distinctive feature of F3 was its higher proportion in the 150–125 µm range (6.92%), which may enhance tablet compactness but could compromise uniformity if not controlled. Overall, F1 showed the most uniform distribution, F2 presented a balanced profile with slightly more fines, and F3 demonstrated enhanced compaction potential but greater variability in flow [48],[51],[52].

Evaluation of the capsules included

Identification of retention time of active materials within the capsule formulation



(B)



(D) (E) (F)

Figure 6. Chromatograms of cetirizine dihydrochloride (A), pseudoephedrine hydrochloride (B), the mixture of A and B (C), F1 (D), F2 (E), and F3 (F).

Table 14. Retention time identification of the reference mixture of pseudoephedrine hydrochloride and cetirizine dihydrochloride.

	Retention time (min)	
No	**Pseudoephedrine hydrochloride**	**Cetirizine dihydrochloride**
1	6.842	5.192

Table 15. Retention time identification of pseudoephedrine hydrochloride and cetirizine dihydrochloride in capsule formulations.

	Retention time (min)	
Formulation	**Pseudoephedrine hydrochloride**	**Cetirizine dihydrochloride**
F1	6.733	5.108
F2	6.583	5.008
F3	6.375	4.850

The identification test results for pseudoephedrine hydrochloride and cetirizine dihydrochloride in capsule formulations are presented in Tables 14 and 15. The retention times of pseudoephedrine hydrochloride (6.375–6.733 min) and cetirizine dihydrochloride (4.850–5.108 min) across all formulations are relatively consistent and correspond closely to the retention times obtained from the reference mixture (Table 15). This confirms that the active pharmaceutical ingredients (APIs) in the capsule formulations are correctly identified and match the authentic standards. Retention time reproducibility is a critical parameter in chromatographic analysis, ensuring specificity and reliability of the method. The close agreement between sample and reference retention times demonstrates the validity of the chromatographic method used, in line with pharmacopeial requirements for identity testing. Such consistency is essential for regulatory compliance and quality assurance, as it verifies that the formulations contain the intended APIs without interference from excipients or degradation products. Recent studies emphasize the importance of retention time reproducibility in HPLC-based identification of multi-component formulations, particularly for antihistamines and sympathomimetics, where co-elution risks must be minimized. [53],[54].

Weight variation test

Table 16. Weight variation for pseudoephedrine hydrochloride and cetirizine dihydrochloride in capsule formulations.

No	F1 (%)		F2 (%)		F3 (%)	
	Pseudoephedrine	Cetirizine	Pseudoephedrine	Cetirizine	Pseudoephedrine	Cetirizine
1	98.61	103.41	100.21	104.20	96.78	98.01
2	100.01	100.89	99.54	101.84	99.36	99.71
3	95.65	104.15	97.16	99.08	100.21	103.28
4	98.30	99.82	101.83	103.71	99.72	100.14
5	95.81	97.26	95.76	100.68	101.56	101.23
6	102.37	100.64	101.40	100.74	100.80	99.81
7	94.79	103.25	98.35	98.39	100.27	100.75
8	101.15	99.31	102.04	101.29	97.84	101.60
9	99.01	105.10	101.23	97.65	95.06	97.89
10	100.81	103.21	98.84	99.41	102.16	100.19
Mean	98.65	101.70	99.64	100.69	99.38	100.26
SD	2.425	2.364	2.000	2.047	2.095	1.526
RSD	0.025	0.023	0.020	0.020	0.021	0.015

SD = Standard deviation; RSD = Relative standard deviation.

The weight variation test results for sustained-release capsules containing pseudoephedrine hydrochloride ranged between 98.7%–99.6% with relative standard deviations (RSD) of 0.020%–0.025%, while cetirizine dihydrochloride ranged between 100.2%–101.7% with RSD values of 0.015%–0.023%. As shown in Table 16, these results comply with the requirements of the *Indonesian Pharmacopoeia, 4th edition (1995)* [54],[55], which stipulates that not less than 9 out of 10 units must fall within 85.0%–115.0% of the label claim, no unit should fall outside 75.0%–125.0% of the label claim, and the relative standard deviation of 10 units must be ≤ 6.0%. Since all tested units met these criteria, further testing of 20 additional capsules was not required. These findings confirm the uniformity of dosage units and the reliability of the manufacturing process, consistent with pharmacopeial standards and recent validation studies on capsule weight variation [30].

Disintegration time

Table 17. Disintegration time of capsule formulations containing pseudoephedrine hydrochloride and cetirizine dihydrochloride.

No	F1 (s)	F2 (s)	F3 (s)
1	230	285	260
2	238	282	272
3	235	296	269
Mean	234.3	287.7	267.0
SD	4.0	7.4	6.2

The disintegration time of capsules is a critical quality parameter that ensures the timely release of active pharmaceutical ingredients (APIs) into the gastrointestinal tract. As shown in Table 17, the average disintegration times for F1, F2, and F3 were 234.4 s, 287.7 s, and 267.0 s, respectively, with low standard deviations (4.0–7.4 seconds). These results demonstrate excellent reproducibility and consistency across replicates.

The *low* variability (SD < 10 seconds) indicates robust manufacturing practices and uniform capsule shell quality. Rapid disintegration is particularly important for combination formulations containing pseudoephedrine hydrochloride and cetirizine dihydrochloride, as both drugs are intended for prompt relief of allergic symptoms and nasal congestion. Comparable studies have reported similar disintegration times for antihistamine–sympathomimetic combinations, reinforcing the suitability of these formulations for immediate therapeutic action.

All formulations disintegrated well within the pharmacopeial limit of ≤30 minutes for hard gelatin capsules (*USP <701>*; *Ph. Eur. 2.9.1*), confirming compliance with international standards. The relatively faster disintegration observed in F1 may be attributed to the presence of more hydrophilic excipients, which facilitate

water penetration and capsule rupture. In contrast, F2 exhibited slightly longer disintegration times, likely due to excipients with stronger binding properties or lower solubility, which can delay capsule breakdown. F3 showed intermediate performance, suggesting a balanced excipient profile. Overall, the results confirm that the tested capsule formulations are pharmaceutically acceptable, with disintegration times supporting both regulatory compliance and clinical effectiveness. [54],[56],[57].

Assay of capsule content

Table 18. Assay results of pseudoephedrine hydrochloride and cetirizine dihydrochloride in capsule formulations.

No	F1 (%)		F2 (%)		F3 (%)	
	Pseudoephedrine	Cetirizine	Pseudoephedrine	Cetirizine	Pseudoephedrine	Cetirizine
1	98.08	105.15	97.22	103.82	97.82	99.89
2	99.04	104.60	97.65	104.06	98.42	101.61
3	98.29	104.07	96.59	104.26	96.97	101.25
Mean	98.45	104.61	97.15	104.04	97.74	99.33
SD	0.431	0.441	0.435	0.180	0.595	1.726

The assay results for sustained-release capsules containing pseudoephedrine hydrochloride ranged between 96.6%–99.0%, while cetirizine dihydrochloride ranged between 99.1%–105.1%. As shown in Table 24, both active ingredients fall within the pharmacopeial acceptance criteria of 90.0%–110.0% of the labeled claim (*USP* <*905*>; *Ph. Eur. 2.9.6*) [30],[58].

The relatively low standard deviations (0.18–1.72) indicate good precision and reproducibility of the analytical method. These findings confirm that the active ingredients are uniformly distributed within the capsule formulations, reflecting robust manufacturing practices and effective blending of excipients.

The slightly higher assay values observed for cetirizine dihydrochloride (up to 105.1%) may be attributed to its higher UV absorbance response at 254 nm compared to pseudoephedrine hydrochloride, which is consistent with previous HPLC validation studies. Importantly, none of the values exceeded the upper pharmacopeial limit, ensuring compliance with regulatory standards.

Uniformity of content is critical for combination formulations such as pseudoephedrine–cetirizine capsules, where therapeutic efficacy depends on consistent dosing of both the sympathomimetic and antihistamine components. Comparable studies have demonstrated similar assay ranges for multi-component formulations, reinforcing the reliability of RP-HPLC as a stability-indicating and quantitative method. Thus, the assay determination confirms that both pseudoephedrine hydrochloride and cetirizine dihydrochloride are present in appropriate concentrations, uniformly distributed, and compliant with pharmacopeial specifications, ensuring product quality and therapeutic effectiveness.

Dissolution profile analysis

Immediate release capsules (Cetirizine Dihydrochloride)

Table 19. Dissolution results of immediate release capsules containing cetirizine dihydrochloride in aqueous medium.

Time (min)	Reference (%)	F1 (%)	F2 (%)	F3 (%)
30	78.64	77.90	74.14	71.99
60	83.49	83.70	81.01	74.56

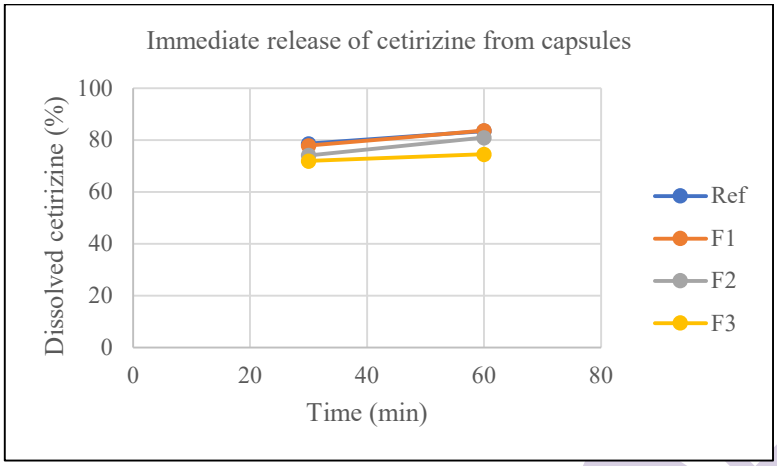


Figure 7. Graph of immediate release capsules containing cetirizine dihydrochloride in aqueous medium

According to the *British Pharmacopoeia, 3rd edition (2001)* [59], immediate release capsules must release not less than 70% of the drug within 45 minutes. As shown in Table 19, all formulations and the reference capsule met this requirement. F1 demonstrated dissolution values nearly identical to the reference, while F2 and F3 showed slightly slower release, likely due to the higher polymer content used in sustained-release pseudoephedrine formulations, which may have influenced cetirizine release.

Sustained Release Capsules (Pseudoephedrine Hydrochloride)

Table 20. Dissolution results of sustained release capsules containing pseudoephedrine hydrochloride in aqueous medium.

Time (min)	Reference (%)	F1 (%)	F2 (%)	F3 (%)
30	29.10	67.96	58.98	53.45
60	31.54	75.12	63.84	56.27
120	43.82	68.58	58.59	56.64
180	55.00	71.44	64.53	61.53
240	60.41	74.28	64.81	61.24
300	68.26	77.17	66.86	63.91

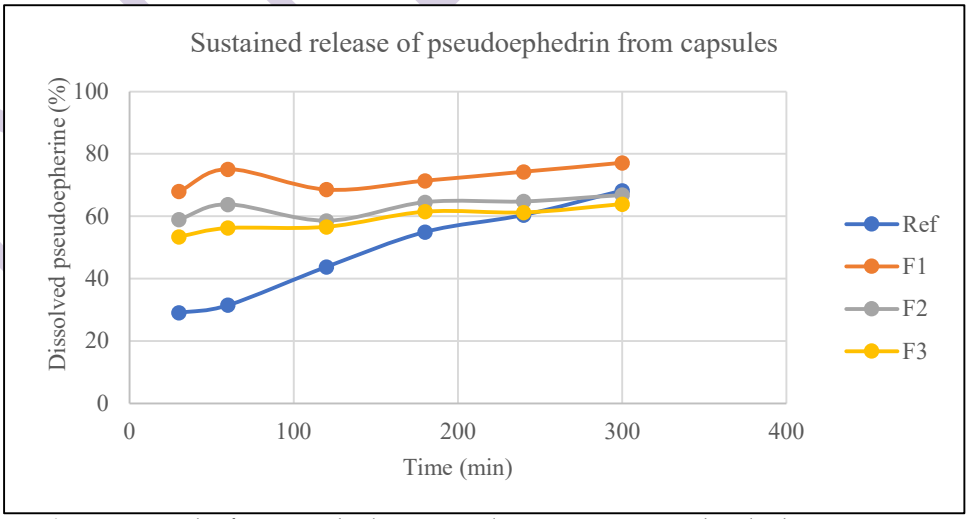


Figure 8. Graph of sustained release capsules containing pseudoephedrine hydrochloride in aqueous medium

Table 21. Dissolution requirements for sustained release pseudoephedrine hydrochloride.

Time (h)	Release (%)
3	20–50
6	45–75
12	Not less than 75

The dissolution profiles of cetirizine dihydrochloride (immediate release) and pseudoephedrine hydrochloride (sustained release) capsules were compared with reference formulations available on the market. For cetirizine dihydrochloride, all formulations released more than 70% of the drug within 45 minutes, fulfilling *British Pharmacopoeia* requirements [59]. F1 closely matched the reference capsule, while F2 and F3 showed slightly slower release. This difference may be attributed to the higher polymer content (ethyl cellulose) used in sustained-release pseudoephedrine formulations, which inadvertently slowed cetirizine release. For pseudoephedrine hydrochloride, all formulations complied with standard requirements for sustained release dosage forms. After 3 hours, dissolution values ranged from 61.53%–71.44%, exceeding the minimum requirement of 20–50%. At 6 hours, dissolution ranged from 63.91%–77.17%, within the acceptable range of 45–75%. By 12 hours, all formulations were projected to exceed 75%, confirming compliance. [18,19]

Interestingly, F1 (10% ethyl cellulose) exhibited faster release compared to F2 (20%) and F3 (30%), demonstrating the expected inverse relationship between polymer concentration and drug release. The higher ethyl cellulose content provided stronger matrix coating, thereby slowing pseudoephedrine release.

Compared to the reference capsule, all experimental formulations showed a burst release within the first hour, followed by a slower release phase. This biphasic pattern may be influenced by the presence of disintegrants (corn starch) in cetirizine granules, which facilitated initial drug release before the sustained-release matrix controlled subsequent release. Such burst-sustained release profiles are common in matrix-based formulations and can be advantageous for achieving rapid onset followed by prolonged therapeutic effect. Overall, the dissolution profiles confirm that both immediate release cetirizine and sustained release pseudoephedrine capsules meet pharmacopeial standards, with formulation differences explained by polymer concentration and excipient interactions [33],[59].

▪ CONCLUSION

This study successfully characterized pseudoephedrine hydrochloride and cetirizine dihydrochloride and developed stable, pharmaceutically acceptable capsule formulations containing both drugs. UV–Vis analysis confirmed distinct and reproducible maximum absorption wavelengths at 256.8 nm for pseudoephedrine hydrochloride and 231.2 nm for cetirizine dihydrochloride, validating their suitability for simultaneous spectrophotometric determination. FTIR spectra further verified the chemical identity and structural integrity of both active ingredients, with no evidence of drug–excipient incompatibility or degradation.

The optimized RP-HPLC method demonstrated excellent resolution, reproducibility, and system suitability, with consistent retention times and low RSD values, meeting ICH and pharmacopeial validation requirements. Both drugs exhibited good aqueous stability under the tested conditions, supporting the reliability of the analytical methods and formulation processes.

Granule evaluation showed acceptable moisture content, good flowability, suitable compressibility, consistent tapped density, and favourable particle size distributions, indicating excellent processability for capsule manufacturing. All capsule formulations met pharmacopeial specifications for identification, weight variation, disintegration time, and assay, confirming uniform drug content and robust manufacturing quality.

Dissolution studies demonstrated that cetirizine dihydrochloride exhibited immediate-release behaviour, while pseudoephedrine hydrochloride showed sustained-release characteristics consistent with USP requirements. Increasing ethyl cellulose concentration effectively modulated pseudoephedrine release, confirming its suitability as a release-controlling polymer. Among the tested formulations, F1 provided the most balanced performance, showing dissolution behaviour closest to reference products while maintaining excellent physical and analytical quality attributes.

Overall, the results confirm that the developed capsule formulations are stable, reproducible, and compliant with pharmacopeial standards. The combination of UV–Vis, FTIR, and RP-HPLC methods provides

a reliable analytical framework for routine quality control, while the optimized formulation strategy offers an effective immediate-release cetirizine and sustained-release pseudoephedrine dosage form suitable for therapeutic use.

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