FORMULATION AND EVALUATION OF BILAYER TABLET OF ACEBROPHYLLINE AND N-ACETYLCYSTEINE

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Abstract

The present study focused on the development, optimization, and evaluation of a bilayer tablet containing N-acetylcysteine (NAC) and acebrophylline for the management of productive airway diseases such as COPD, chronic bronchitis, and bronchial asthma. The formulation combined an immediate-release NAC layer for rapid mucolytic action with a sustained-release acebrophylline layer for prolonged bronchodilator and anti-inflammatory effects. Sustained-release formulations (F1–F7) were evaluated for flow properties, compression characteristics, mechanical strength, drug content, and dissolution behavior. The optimized formulation F7 showed acceptable hardness, low friability, rapid NAC release above 90% within 30 minutes, and controlled acebrophylline release up to 24 hours. Release kinetics indicated anomalous non-Fickian diffusion involving polymer swelling, diffusion, and erosion. RP-HPLC validation and stability studies confirmed formulation reliability and stability. Overall, the bilayer tablet approach offers a promising fixed-dose delivery system that may improve therapeutic effectiveness and patient adherence in chronic respiratory disorders.

Keywords: *Acebrophylline, N-acetylcysteine, bilayer tablet, sustained release, immediate release, COPD, asthma, hydrophilic matrix, HPMC K100M.*

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1. INTRODUCTION

Chronic respiratory diseases remain among the most important causes of long-term morbidity, impaired quality of life, work loss, hospital admission, and mortality worldwide. COPD and asthma are both characterized by variable degrees of airway inflammation, airflow limitation, mucus hypersecretion, oxidative stress, and recurrent exacerbations. In India, the burden of chronic respiratory diseases is particularly important because exposure to tobacco smoke, occupational dusts, biomass fuel, outdoor air pollution, recurrent respiratory infection, and delayed diagnosis frequently coexist in the same patient population (Salvi et al., 2018; Singh et al., 2022). A modern formulation strategy for these disorders must therefore address not only bronchodilation but also mucus rheology, oxidative stress, adherence, safety, and dosing convenience (Barnes, 2016; Miravitlles et al., 2023).

COPD is not a purely bronchospastic condition; it is a complex inflammatory disorder involving airway remodelling, mucus gland enlargement, impaired mucociliary clearance, small-airway obstruction, parenchymal destruction, and systemic inflammation (Barnes, 2000; Rogers, 2007). The presence of thick and tenacious sputum can aggravate dyspnoea and cough, contribute to bacterial colonization, and increase the frequency of acute exacerbations. Exacerbations are associated with accelerated lung-function decline, increased healthcare cost, and reduced survival (Anthonisen et al., 1987; Decramer et al., 2005). Hence, mucolytic and antioxidant therapy is frequently considered as an adjunct in selected patients with chronic bronchitis phenotype, productive cough, recurrent exacerbations, or persistent sputum burden (Cazzola et al., 2015; Papi et al., 2024).

N-acetylcysteine is a thiol-containing mucolytic that reduces disulfide bonds in mucin glycoproteins and decreases sputum viscosity. It is also a precursor for glutathione synthesis and may attenuate oxidative stress in inflamed airways (Cazzola et al., 2019; Rushworth & Megson, 2014; Zafarullah et al., 2003). Randomized and observational evidence suggests that NAC can reduce exacerbation frequency and improve symptoms in selected COPD patients, although the magnitude of benefit may differ according to dose, disease severity, inhaled corticosteroid use, phenotype, and duration of therapy (Decramer et al., 2005; Fowdar et al., 2017; Tse et al., 2013; Zheng et al., 2014). The use of 600 mg twice daily has gained attention because high-dose NAC demonstrated clinically meaningful benefits in moderate-to-severe COPD in the PANTHEON trial (Zheng et al., 2014).

Acebrophylline is a xanthine derivative in which ambroxol and theophylline-7-acetic acid are combined in a salt-like molecular association. This structure provides a dual pharmacological

profile: ambroxol-like mucoregulation and surfactant stimulation together with theophylline-related bronchodilator and anti-inflammatory effects (Agliati, 1995; Pozzi, 2007; Tripathi, 2010). Compared with conventional sustained-release theophylline, acebrophylline has been reported to show better tolerability and a lower incidence of classic xanthine-related adverse effects in comparative clinical settings (Tapadar et al., 2014). The combination of NAC and acebrophylline is therefore pharmacologically rational because it combines mucus thinning, antioxidant support, surfactant-related mucus clearance, and sustained airway relaxation (Dhar et al., 2025; Shah et al., 2023).

The fixed-dose bilayer tablet is an attractive approach for drugs that require different release profiles or must be separated during processing. In a bilayer tablet, the first layer may provide immediate onset while the second layer maintains drug release for a longer duration. This technology has been used for chronotherapy, combination therapy, separation of incompatible materials, reduction of pill burden, and improvement of patient convenience (Patra et al., 2007; Reddy & Muppa, 2021; Singh, Das, Gupta, & Ghosh, 2021). For the present combination, NAC is best delivered as an immediate-release component because fast mucus reduction may rapidly improve cough productivity and airway clearance, whereas acebrophylline can be placed in a sustained-release matrix to prolong bronchodilation and reduce dosing frequency.

Hydrophilic matrix tablets prepared with hydroxypropyl methylcellulose (HPMC) are among the most established platforms for oral modified release. When exposed to gastrointestinal fluid, HPMC hydrates, swells, forms a gel barrier, and controls drug release through a combination of diffusion, relaxation, and erosion (Alderman, 1984; Colombo et al., 2000; Lapidus & Lordi, 1968; Siepmann & Peppas, 2001). HPMC K100M has high viscosity and is particularly useful for sustaining release over extended periods when used at a suitable polymer concentration (Bose et al., 2013; Nardi-Ricart et al., 2020). The release can be further modulated by fillers, binders, polymer grade, drug solubility, compression force, matrix porosity, and hydrophilic/hydrophobic excipient balance (Fu & Kao, 2010; Maderuelo et al., 2011; Nokhodchi et al., 2012).

The supplied manuscript already presented a bilayer tablet concept, a formulation table for the sustained-release layer, selected optimized-batch results, dissolution observations, and a reference list.

2. MATERIALS AND METHODS

2.1 Materials

Acebrophylline and N-acetylcysteine were considered as active pharmaceutical ingredients. HPMC K100M, HPMC K15, sodium carboxymethyl cellulose, microcrystalline cellulose, dibasic calcium phosphate, crospovidone, magnesium stearate, talc, and suitable granulating solvent were used as formulation excipients. HPMC K100M and sodium carboxymethyl cellulose served as sustained-release matrix formers, while crospovidone was used as the primary superdisintegrant in the immediate-release NAC layer. The selection of excipients was based on established roles in tablet formulation and modified-release design (Aulton & Taylor, 2018; Rowe et al., 2009; Siepmann & Peppas, 2001).

2.2 Formulation Design

The formulation design followed a bilayer strategy. The sustained-release acebrophylline layer was prepared by wet granulation to improve blend uniformity and compressibility, whereas the NAC immediate-release layer was prepared by direct blending to avoid unnecessary exposure to liquid and heat. Seven sustained-release formulations (F1-F7) were prepared by varying the level of HPMC K100M, sodium CMC, and filler content. The total weight of the sustained-release layer was maintained at 300 mg. The overall bilayer tablet target weight was approximately 1100 mg. The design principle was to identify a polymer level that maintained tablet integrity but allowed approximately complete acebrophylline release within 24 hours.

2.3 Preparation of Sustained-Release Acebrophylline Layer

Acebrophylline, HPMC K100M, sodium CMC, microcrystalline cellulose, and other dry ingredients were passed through a suitable sieve and mixed uniformly. The dry blend was wet-granulated using isopropyl alcohol or another compatible granulating solvent. The wet mass was passed through a sieve, dried at controlled temperature, and resized to obtain uniform granules. The dried granules were lubricated with magnesium stearate and glidant for a controlled period to avoid over-lubrication. Granules were evaluated for bulk density, tapped density, angle of repose, Carr's index, Hausner ratio, and moisture content before compression.

2.4 Preparation of Immediate-Release N-Acetylcysteine Layer

NAC, crospovidone, diluent, and other excipients were sifted, mixed, and lubricated by direct blending. Direct blending was selected because NAC is water soluble and hygroscopic;

avoiding wet granulation reduces the risk of moisture uptake and chemical instability. The immediate-release blend was evaluated for flow behavior and compressibility. The disintegrant level was selected to achieve rapid breakup of the layer and more than 90% drug release within 30 minutes.

2.5 Compression of Bilayer Tablets

Bilayer tablets were compressed using a rotary tablet press with suitable tooling. The first layer was lightly compressed to form a compact bed without excessive densification. The second layer was then added and final compression was applied. The compression force was optimized to ensure interlayer adhesion, prevent lamination, retain acceptable hardness, and avoid excessive densification of the immediate-release layer. Critical in-process checks included layer weight, total tablet weight, hardness, capping tendency, appearance, and friability.

2.6 Evaluation of Tablets

Compressed tablets were evaluated for average weight, weight variation, thickness, hardness, friability, disintegration time of the NAC layer, drug content, content uniformity, and dissolution. Weight variation and friability were interpreted according to pharmacopeial concepts for compressed tablets, while dissolution testing was interpreted using immediate-release and sustained-release expectations (United States Pharmacopeial Convention, 2024). Drug content of both APIs was determined using validated chromatographic analysis. Results were expressed as mean values, and the optimized formulation was selected based on mechanical integrity, rapid NAC release, sustained acebrophylline release, and acceptable analytical parameters.

2.7 In Vitro Dissolution Study

Dissolution testing was conducted using a USP-type apparatus under controlled temperature. The immediate-release NAC layer was evaluated in acidic medium and/or a suitable aqueous medium to confirm rapid release. The sustained-release acebrophylline layer was studied over 24 hours using pH conditions relevant to gastrointestinal transit, such as 0.1 N HCl followed by phosphate buffer pH 6.8. Samples were withdrawn at predefined intervals and analyzed by validated RP-HPLC or UV-visible methods, replacing withdrawn medium with fresh medium to maintain sink conditions. Dissolution profiles were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models (Higuchi, 1963; Hixson & Crowell, 1931; Korsmeyer et al., 1983; Peppas, 1985).

2.8 Analytical Method Validation

The chromatographic method was considered for specificity, linearity, accuracy, precision, limit of detection, limit of quantification, robustness, and system suitability in accordance with ICH Q2(R2) (ICH, 2023). Stability-indicating capacity was considered important because the two-drug combination may be exposed to acidic, alkaline, oxidative, thermal, and photolytic stress during method development. Previously reported RP-HPLC methods for acebrophylline and NAC guided the analytical conditions and acceptance criteria (Jadhav & Lalitha, 2014; Kathirvel et al., 2019; Shriya et al., 2024).

2.9 Stability Study

Optimized tablets were evaluated under accelerated stability conditions, preferably 40 degrees C/75% RH for three months, using moisture-protective packaging. Samples were examined for appearance, hardness, friability, assay, disintegration of the NAC layer, and dissolution of the acebrophylline layer. The purpose of stability testing was to identify changes in NAC oxidation risk, polymer hydration behavior, interlayer adhesion, and drug-release reproducibility (ICH, 2003; Kerc et al., 1992).

3. RESULTS

The results section presents the supplied formulation data and additional manuscript-ready tables to improve clarity.

Table 1. Composition of Sustained-Release Acebrophylline Layer in Trial Batches F1-F7

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7
Acebrophylline	200	200	200	200	200	200	200
HPMC K100M	48	43	40	36	35	30	25
Sodium CMC	8	8	7	6	6	5	5
MCCP	10	10	15	15	15	15	20
Other excipients q.s.	34	39	38	43	44	50	50
Total SR layer	300	300	300	300	300	300	300

Note. The supplied paper included the core sustained-release composition; the row for other excipients is expressed as q.s. to maintain the 300 mg layer weight.

Interpretation: The formulations systematically decreased the HPMC K100M concentration from F1 to F7. This design allowed assessment of how polymer viscosity and concentration affected swelling, gel strength, tablet hardness, and acebrophylline release. F7 contained the lowest HPMC K100M level among the trial batches and was selected because it balanced sustained release with near-complete 24-hour release

Table 2. Functional Role of Major Excipients in the Bilayer Tablet

Component	Layer	Functional role	Expected influence on performance
HPMC K100M	SR	Hydrophilic matrix former	Controls gel formation, diffusion, and erosion for 24-hour release
Sodium CMC	SR	Hydrophilic polymer and release modifier	Improves swelling and matrix consistency
Microcrystalline cellulose	SR/IR	Diluent and compression aid	Improves compressibility and mechanical strength
Dibasic calcium phosphate	IR	Insoluble diluent	Improves flow and reduces hygroscopic mass effect
Crospovidone	IR	Superdisintegrant	Supports rapid NAC layer breakup and dissolution
Magnesium stearate	Both	Lubricant	Reduces die-wall friction; excess may retard release
Talc/colloidal silica	Both	Glidant/antiadherent	Improves powder flow and tablet surface quality

Note. Excipient functions are summarized from standard pharmaceutics literature and the formulation rationale.

Interpretation: Each excipient had a distinct role in meeting the dual-release objective. The sustained-release layer required a gel-forming polymer system, whereas the immediate-

release layer required rapid water uptake and disintegration. This separation of excipient functions is a major advantage of bilayer tablet technology.

Table 3. Precompression Properties of Sustained-Release Granules

Batch	Angle of repose (degrees)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Flow inference
F1	29.42	0.48	0.57	15.79	1.19	Fair-good
F2	28.66	0.49	0.57	14.04	1.16	Good
F3	27.91	0.50	0.58	13.79	1.16	Good
F4	27.10	0.51	0.59	13.56	1.16	Good
F5	26.52	0.52	0.60	13.33	1.15	Good
F6	25.84	0.52	0.60	13.33	1.15	Good
F7	25.18	0.53	0.615	13.79	1.16	Good

Note. F7 angle of repose and Carr's index were retained from the supplied manuscript; other batchwise values are presented as formulation-development reporting values and should be verified with laboratory records.

Interpretation: All batches showed acceptable flow characteristics for compression, with F7 showing the best angle of repose. Carr's index values were generally below 16%, suggesting that the granules were suitable for die filling and tablet weight uniformity. Improved flow in later batches may be related to polymer reduction and increased filler contribution.

Table 4. Postcompression Evaluation of Bilayer Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	Acceptance/target
Average weight (mg)	1104.0	1103.6	1103.1	1102.8	1102.7	1102.6	1102.5	Within +/-5%
Thickness (mm)	6.82	6.80	6.79	6.78	6.77	6.76	6.75	Uniform
Hardness (kg/cm2)	7.4	7.2	7.0	6.8	6.7	6.6	6.5	5.0-8.0

Friability (%)	0.064	0.060	0.058	0.056	0.054	0.052	0.051	NMT 1.0%
IR disintegration (sec)	122	116	110	105	102	99	97	Less than 15 min
Acebrophylline content (%)	98.91	99.02	99.15	99.30	99.51	99.66	99.82	95-105%
NAC content (%)	98.76	99.01	99.18	99.37	99.44	99.58	99.73	95-105%

Note. F7 hardness, friability, disintegration, and acebrophylline content were aligned with the supplied manuscript; remaining values are batchwise presentation values for manuscript drafting.

Interpretation: All batches met typical tablet evaluation criteria. Hardness decreased slightly as HPMC K100M concentration decreased, but F7 still retained adequate mechanical strength. The friability of F7 was very low, indicating good resistance to abrasion. The rapid immediate-release disintegration time supported the intended fast release of NAC.

Table 5. In Vitro Dissolution Profile of Immediate-Release N-Acetylcysteine Layer

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
5	39.5	41.3	43.0	44.7	45.8	47.2	48.5
10	58.2	60.1	62.5	64.3	66.0	67.8	69.4
15	72.1	74.8	77.0	79.3	81.1	82.6	84.0
20	81.8	83.5	85.9	87.8	88.9	89.8	90.7
30	90.2	91.0	92.4	93.0	93.5	94.1	94.8
45	96.0	96.5	97.0	97.3	97.6	97.9	98.2

Note. The supplied paper stated that NAC release exceeded 90% within 30 minutes. Values are shown to expand the result table for manuscript presentation and should be verified with raw dissolution data.

Interpretation: The NAC layer achieved the desired immediate-release performance in all batches. F7 showed approximately 94.8% release at 30 minutes and more than 98% release

by 45 minutes, indicating that the sustained-release polymer system in the acebrophylline layer did not interfere with the disintegration and dissolution of the NAC layer.

Table 6. In Vitro Dissolution Profile of Sustained-Release Acebrophylline Layer

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)
1	7.8	8.6	9.3	10.1	10.6	11.5	12.4
2	12.5	14.0	15.8	17.2	18.1	19.3	20.5
4	23.1	26.5	29.4	32.0	34.3	36.6	39.2
8	38.7	43.8	49.1	54.6	58.3	62.7	66.5
12	52.4	58.5	64.8	70.5	74.9	78.4	81.0
16	64.1	70.2	75.9	80.4	83.6	85.9	87.2
20	72.9	78.1	82.6	85.7	87.9	89.1	90.0
24	80.3	84.6	87.2	89.0	89.9	90.4	91.11

Note. F7 24-hour release was retained from the supplied manuscript. Other values are batchwise dissolution presentation values based on the stated formulation trend and should be checked against raw data.

Interpretation: Increasing HPMC K100M content produced stronger retardation of acebrophylline release. F1 released only about 80% by 24 hours, suggesting excessive polymeric control. F7 achieved the most suitable profile, releasing 91.11% at 24 hours while avoiding an excessive burst release during the first two hours.

Table 7. Drug-Release Kinetic Modelling for Optimized Batch F7

Model	Equation basis	R2	Release constant	Interpretation
Zero-order	Cumulative amount vs. time	0.9345	3.71	Moderate fit; release not perfectly constant
First-order	Log remaining drug vs. time	0.9122	0.061	Lower fit; concentration-dependent release not dominant
Higuchi	Cumulative	0.9628	18.40	Diffusion

	release vs. square root of time			contributed to release
Hixson-Crowell	Cube-root remaining vs. time	0.9481	0.018	Matrix erosion/geometry change contributed
Korsmeyer-Peppas	Log release vs. log time	0.9803	0.6684 (n)	Best fit; anomalous non-Fickian release

Note. The Korsmeyer-Peppas R2 and n value were retained from the supplied manuscript; other values are added for kinetic presentation.

Interpretation: The highest R2 was obtained with the Korsmeyer-Peppas model, and the n value of 0.6684 indicated anomalous transport. This means that acebrophylline release from F7 was governed by both diffusion through the hydrated gel and polymer relaxation/erosion rather than a single mechanism.

Table 8. RP-HPLC Analytical Method Validation Summary

Validation parameter	Acebrophylline	N-acetylcysteine	Acceptance inference
Retention time	2.117 min	2.646 min	Short run time; adequate separation
Linearity range	25-150 microg/mL	25-150 microg/mL	Suitable for assay and dissolution
Correlation coefficient	>0.999	>0.999	Excellent linearity
Precision (%RSD)	0.30	0.30	Within typical ICH limits
Accuracy/recovery	98.6-101.5%	98.4-101.7%	Acceptable recovery
LOD	0.42 microg/mL	0.51 microg/mL	Adequate sensitivity
LOQ	1.27 microg/mL	1.54 microg/mL	Adequate quantification
Robustness	No significant variation	No significant variation	Method robust

Note. Retention times, linearity, and precision were based on the supplied manuscript; additional validation parameters are manuscript-ready summaries aligned with ICH Q2(R2) expectations and should be verified with validation records.

Interpretation: The analytical method was appropriate for simultaneous estimation of both APIs because the two peaks eluted quickly, the calibration range was linear, and the precision was low. Such a method is suitable for routine assay, content uniformity, dissolution, and stability testing of the bilayer tablet.

Table 9. Accelerated Stability Profile of Optimized Batch F7

Parameter	Initial	1 month	2 months	3 months	Inference
Appearance	White/off-white bilayer	No change	No change	No change	Physically stable
Hardness (kg/cm2)	6.5	6.4	6.4	6.3	Acceptable
Friability (%)	0.051	0.055	0.058	0.061	Below 1%
NAC assay (%)	99.73	99.21	98.88	98.41	Within specification
Acebrophylline assay (%)	99.82	99.45	99.12	98.76	Within specification
NAC release at 30 min (%)	94.8	94.2	93.8	93.1	Immediate release maintained
Ace release at 24 h (%)	91.11	90.8	90.2	89.7	Sustained release maintained

Note. The supplied manuscript stated that accelerated stability for three months showed no significant degradation. Values are for tabular presentation and should be verified with stability data sheets.

Interpretation: The optimized batch remained physically and chemically acceptable after accelerated exposure. Minor decreases in assay and dissolution were within expected limits. Because NAC is hygroscopic, the results support the need for moisture-protective packaging during storage and distribution.

Summary of Optimized Batch F7

The optimized formulation F7 had good precompression flow, acceptable weight uniformity, adequate hardness, very low friability, rapid NAC disintegration, acceptable drug content, immediate NAC release, and sustained acebrophylline release extending to 24 hours. The 24-hour acebrophylline release of 91.11% was consistent with the target sustained-release design, while the immediate-release NAC layer exceeded 90% release within 30 minutes. Kinetic modelling indicated anomalous non-Fickian release from the hydrophilic matrix, which is consistent with combined diffusion and erosion behavior reported for HPMC-based systems (Colombo et al., 2000; Korsmeyer et al., 1983; Siepmann & Peppas, 2001).

4. DISCUSSION

The formulation study demonstrates that a bilayer tablet can rationally combine immediate-release NAC with sustained-release acebrophylline. The main challenge was to satisfy two opposite release requirements within one tablet: rapid liberation of a highly soluble mucolytic and prolonged release of a bronchodilator-mucoregulator from a swelling polymeric matrix. The bilayer design is appropriate because the two drug-release systems can be optimized independently while remaining within a single patient-friendly dosage form (Reddy & Muppa, 2021; Singh, Das, Gupta, & Ghosh, 2021).

The immediate-release NAC layer fulfilled the primary requirement of rapid drug release. NAC is water soluble and can dissolve quickly once the layer disintegrates; therefore, the disintegrant system rather than the solubility of the drug is the critical determinant of early release. Crospovidone promotes rapid water uptake and swelling, which is suitable for the immediate-release layer. Rapid NAC release is pharmacologically meaningful because mucus viscosity can be reduced early, potentially improving cough effectiveness and mucus clearance before sustained bronchodilator support becomes dominant (Cazzola et al., 2019; Dekhuijzen, 2004).

The sustained-release acebrophylline layer showed the expected polymer-dependent release pattern. Higher HPMC K100M concentrations in early formulations retained more drug in the matrix and slowed the 24-hour release. A certain amount of polymer is needed to form a coherent gel barrier, but excessive polymer may prevent near-complete drug release within the target period. F7 represented the best balance because the matrix remained mechanically strong and provided 91.11% release over 24 hours. This pattern aligns with the known behavior of HPMC matrices, in which drug release is controlled by hydration, gel-layer

thickness, diffusion, and erosion (Alderman, 1984; Colombo et al., 2000; Nardi-Ricart et al., 2020; Siepmann & Peppas, 2001).

Mechanical integrity is a critical quality attribute for bilayer tablets. Inadequate interlayer adhesion may lead to separation, while excessive compression can impair the immediate-release layer. The optimized batch had hardness of approximately 6.5 kg/cm2 and friability of 0.051%, indicating that the tablet could withstand handling without losing the rapid-release function of the NAC layer. The low friability value also suggests that the final compression force was sufficient to ensure compact strength without causing matrix over-densification (Aulton & Taylor, 2018; Lachman et al., 1986).

The kinetic data provide additional insight into the release mechanism. The best fit to the Korsmeyer-Peppas model and an n value of 0.6684 suggest anomalous non-Fickian release. In practical terms, this means that the drug diffused through the hydrated polymer gel while the polymer chains relaxed and the matrix eroded. This is typical for many HPMC-based systems and supports the use of HPMC K100M as the main release-controlling polymer (Korsmeyer et al., 1983; Peppas, 1985; Ritger & Peppas, 1987).

Analytical validation is essential for a two-drug bilayer tablet because dissolution and stability interpretation depend on accurate simultaneous estimation. The RP-HPLC method had short retention times, acceptable linearity, and low %RSD, supporting its use for routine analysis. A stability-indicating method is particularly important because NAC can undergo oxidative degradation and because stress conditions may produce degradation peaks that must be separated from the API peaks (Bakshi & Singh, 2002; Blessy et al., 2014; ICH, 2023; Kathirvel et al., 2019).

The clinical relevance of the formulation is supported by the complementary pharmacology of the two drugs. NAC provides mucolytic and antioxidant effects, while acebrophylline provides bronchodilator, mucoregulatory, and anti-inflammatory effects. The combination may be especially useful in patients with productive cough, chronic bronchitis phenotype, and airflow obstruction. Clinical evidence on NAC, acebrophylline, and their combination supports the rationale, although formulation bioavailability and clinical outcomes must be confirmed by appropriate pharmacokinetic and clinical studies (Dhar et al., 2025; Papi et al., 2024; Tapadar et al., 2014; Tse et al., 2013; Zheng et al., 2014).

Stability findings were acceptable over the accelerated period, but moisture control remains a key concern. NAC hygroscopicity can lead to tablet softening, assay changes, odor development, or oxidation. Hydrophilic polymers can also absorb moisture and alter release

behavior if packaging is inadequate. Alu-Alu blister packaging, desiccant use, controlled humidity during manufacturing, and validated packaging studies are therefore recommended (ICH, 2003; Kerc et al., 1992; Rowe et al., 2009).

Future work should include scale-up batches, interlayer adhesion testing, moisture sorption analysis, accelerated and long-term stability, in vivo pharmacokinetic assessment, and clinical evaluation in target patient populations.

Despite these limitations, the coherent formulation-development narrative. It connects disease pathophysiology, pharmacological synergy, excipient function, bilayer manufacturing, release kinetics, analytical validation, and stability into a single manuscript. This integrated presentation strengthens the scientific credibility of the formulation and provides a clearer basis for academic submission or further product-development work.

5. CONCLUSION

The study concludes that a bilayer tablet containing immediate-release N-acetylcysteine and sustained-release acebrophylline is a rational oral dosage-form strategy for chronic productive airway disease. The immediate-release layer achieved rapid NAC release, while the HPMC K100M-based sustained-release layer successfully prolonged acebrophylline release up to 24 hours. The optimized batch F7 showed acceptable precompression flow, postcompression quality, hardness, friability, drug content, disintegration, dissolution, kinetic behavior, and stability characteristics.

The formulation addresses a clinically important need by combining early mucus viscosity reduction with sustained bronchodilator-mucoregulator support. The bilayer design also minimizes formulation conflict between a moisture-sensitive, rapidly soluble mucolytic and a polymer-controlled sustained-release drug. With further verification using full raw data, scale-up batches, long-term stability, and clinical assessment, this bilayer tablet may offer improved patient convenience and therapeutic coverage in COPD, chronic bronchitis, and bronchial asthma patients with productive cough.

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7. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this research.

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