IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Design, Development, And Evaluation Of Sustained Release Bilayer Tablets Containing Levofloxacin Hemihydrate And Ambroxol Hydrochloride

[1] Gudivada Gopala Krishna, [2] Ch Taraka Rama Rao

[1] Master of Pharmacy Pharmaceutics, [2]Professor of Pharmaceutical Technology

[1,2] Sri Venkateswara Collage of Pharmacy, Andhra University, Visakhapatnam, India

Abstract: This study aimed to develop and evaluate bilayer tablets containing Levofloxacin Hemihydrate and Ambroxol Hydrochloride for combined immediate and sustained therapeutic effects in respiratory infections. The immediate-release layer of Levofloxacin ensured rapid antimicrobial action, while the sustained-release layer of Ambroxol provided prolonged relief. Tablets were prepared using direct compression and wet granulation methods, with HPMC K100M and Carbopol 971P as release-controlling polymers. Among formulations, F11 exhibited optimal performance, releasing over 70% Levofloxacin within 1 hour and 95% Ambroxol in 12 hours, following zero-order, non-Fickian kinetics. Stability studies confirmed the formulation's integrity and consistent drug release, establishing an effective bilayer system for dual-action respiratory therapy.

Index Terms - Levofloxacin, Ambroxol, Fixed-Dose Combinations.

I. INTRODUCTION

The oral route is the most preferred method of drug administration due to its convenience, safety, and cost-effectiveness. However, conventional oral dosage forms often suffer from drawbacks such as variable bioavailability, short half-life, and frequent dosing, which can result in fluctuating plasma drug levels and poor patient compliance. To overcome these challenges, modified-release systems have been developed to provide controlled and sustained drug delivery, ensuring steady therapeutic concentrations and improved adherence. Among these, bilayer tablet technology has emerged as an effective approach to achieve both immediate and sustained drug release in a single dosage form. A bilayer tablet consists of two layers one designed for rapid drug release to produce an immediate therapeutic effect and another formulated for sustained or controlled release to maintain prolonged activity. This dual-release design not only improves therapeutic efficacy but also reduces dosing frequency and enhances patient convenience. Furthermore, bilayer tablets are advantageous for Fixed-Dose Combinations (FDCs), allowing physical separation of incompatible drugs and enabling independent control of release kinetics for each layer.

Respiratory tract infections often require combination therapy involving an antimicrobial and a mucolytic agent. Levofloxacin Hemihydrate, a broad-spectrum fluoroquinolone antibiotic, is effective against a wide range of respiratory pathogens due to its excellent oral bioavailability and tissue penetration. However, frequent dosing of conventional formulations may lead to patient non-compliance and the risk of antimicrobial resistance. A sustained-release formulation can maintain plasma drug levels above the Minimum Inhibitory Concentration (MIC) for extended periods, improving therapeutic efficacy and reducing resistance. Ambroxol Hydrochloride, a potent mucolytic and expectorant, enhances mucus clearance and provides symptomatic relief in respiratory conditions. It also promotes antibiotic penetration into bronchial secretions. Since its therapeutic action is required rapidly, Ambroxol is suitable for an immediate-release formulation. Therefore, combining

Ambroxol in an IR layer with Levofloxacin in an SR layer offers both quick symptom relief and prolonged antibacterial activity, improving overall clinical outcomes in respiratory infections.

The design of such a bilayer tablet involves careful selection of polymers and excipients. Polymers like HPMC K100M and Carbopol 971P are used to control drug release in the sustained layer, while super disintegrants such as Croscarmellose Sodium or Sodium Starch Glycolate ensure rapid disintegration of the immediate layer. The combination of direct compression and wet granulation techniques helps achieve optimal mechanical strength and release characteristics. Thus, this study focuses on developing a bilayer tablet combining Levofloxacin Hemihydrate and Ambroxol Hydrochloride to deliver dual therapeutic benefits rapid mucolytic action and sustained antimicrobial effect for effective and patient-friendly management of respiratory tract infections.

II. MATERIALS AND METHODS

The chemicals used in this formulation development are:

Drug: Levofloxacin, Ambroxol; **Polymer:** CARBOPOL 971P, HPMC K100M; **Excipients:** MCC, PVP-K30, Isopropyl Alcohol, Talc, Magnesium Stearate, Aerosil, Starch, Lactose, Dicalcium phosphate.

The Equipment's used for this formulation development:

Table 1: List of Instruments and Their Manufacturers Used in the Study

S. No	Name of Equipment	Manufacturing Company
1	Electronic balance	Shimadzu Scientific instruments, Japan
2	Double rotary tablet compression Machine	Cadmach Machinery Co Pvt Ltd., India
3	Vernier Caliper	Mitutoyo South Asia Pvt Ltd., New Delhi
4	Hardness tester, Pfizer	Shankar Scientific, Chennai
5	Friabilator	Roche Friabilator
6	pH meter	Model MP-1 Plus Susima Dharma
7	Hot air oven	Minicon Equipments Pvt Ltd.
8	Dissolution Apparatus	LAB INDIA DISSO-2000
9	Double beam spectrophotometer	Shimadzu Scientific Instruments, Japan
10	FT-IR Spectrophotometer	Shimadzu Scientific Instruments, Japan

Preformulation Studies

Preformulation studies are the initial stage in formulation development, aimed at evaluating the physical, chemical, and mechanical properties of drug substances. These studies provide critical information for designing dosage forms that are stable, effective, bioavailable, and suitable for large-scale production. The key parameters investigated include moisture content, solubility, micromeritic properties, drug–excipient compatibility, and pH behavior.

Loss on Drying (LOD):

The moisture content of Ambroxol Hydrochloride and Levofloxacin Hemihydrate was determined by the Loss on Drying method. Approximately 1–2 g of each sample was accurately weighed and heated at 105°C for three hours. After cooling in a desiccator, the samples were reweighed, and LOD (%) was calculated using the formula:

$$\text{LOD (\%)} = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100.$$

This analysis helped assess hygroscopicity and ensure stability during processing and storage.

Solubility Studies:

The solubility behavior of Ambroxol and Levofloxacin was evaluated by adding an excess quantity of each drug to 10 mL of various solvents. The mixtures were agitated thoroughly and visually observed for solubility. These studies provided essential data for selecting appropriate dissolution media and excipients for formulation.

Micromeritic Properties:

The flow characteristics of both drugs were assessed through determination of the angle of repose, bulk density, and tapped density. The angle of repose (θ) was calculated using the formula:

$$\theta = \tan^{-1}(h/r),$$

where h represents the height and r the radius of the powder heap. Bulk and tapped densities were used to calculate Carr's index and Hausner's ratio, indicating flow and compressibility. Improved flow properties were noted after blending with selected excipients, confirming their suitability for direct compression.

Drug–Excipient Compatibility:

Fourier Transform Infrared (FTIR) spectroscopy was used to detect potential interactions between drugs and excipients. Physical mixtures of each drug with polymers (1:1 ratio) were prepared, compressed with potassium bromide into pellets, and scanned in the 4000–400 cm^{-1} range using a Shimadzu FTIR spectrophotometer. Comparison of spectra revealed no significant shifts or disappearance of characteristic peaks, indicating chemical compatibility.

pH Studies:

The pH values of aqueous solutions of Levofloxacin and Ambroxol were measured using a calibrated pH meter to evaluate their acidic or basic nature. This information supports the selection of suitable excipients and ensures formulation stability across different pH environments.

Standard Curve and Tablet Formulation Procedure

Buffer solutions were prepared to simulate gastric and intestinal environments. For the pH 1.2 buffer, 8.5 mL of concentrated hydrochloric acid was diluted to 1000 mL with demineralized water, while the pH 6.8 phosphate buffer was obtained by mixing 50 mL of 0.2 M potassium dihydrogen phosphate with 22.4 mL of 0.2 M sodium hydroxide and diluting to 200 mL with water. Calibration curves for Ambroxol Hydrochloride and Levofloxacin Hemihydrate were established by dissolving 100 mg of each drug in 50 mL of methanol, transferring 5 mL of this solution into 250 mL volumetric flasks, and diluting with either pH 1.2 or pH 6.8 buffer to prepare concentrations ranging from 1 µg/mL. Absorbance values were recorded at 244 nm for

Ambroxol and 288 nm for Levofloxacin using a UV–Visible spectrophotometer, applying Beer–Lambert's law (A = a × b × C) to determine absorptivity for quantitative analysis. Bilayer tablets containing a sustained-release layer of Ambroxol and an immediate-release layer of Levofloxacin were formulated using the wet granulation technique. Both drug layers were prepared by sieving all ingredients through #40 mesh, blending, granulating with polyvinylpyrrolidone (PVP K30) dissolved in isopropyl alcohol, air drying, and resieving through #20 mesh to obtain uniform granules. The dried granules were lubricated with magnesium stearate, talc, and aerosil, then compressed using a double rotary tablet press equipped with 18.6 × 9 mm caplet-shaped punches to achieve tablets weighing 950 mg. Flow properties of granules were evaluated by determining the angle of repose ($\theta = \tan^{-1}[h/r]$) and calculating Carr's Index [(TBD – LBD)/TBD × 100] from bulk and tapped densities. The obtained micromeritic results indicated satisfactory flow and compressibility characteristics suitable for successful bilayer tablet formulation.

Evaluation of Tablets

The formulated bilayer tablets were evaluated for various physicochemical parameters to ensure quality, performance, and stability. Twenty tablets from each batch were weighed individually, and the average weight was calculated to assess uniformity. Tablet thickness was measured using a Vernier caliper, while hardness was determined using an ERWEKA hardness tester to ensure mechanical strength. Weight variation was examined by comparing individual tablet weights with the average, with deviations maintained within ±5%. Friability was tested using a Roche friabilator rotated at 25 rpm for 4 minutes, and the percentage friability was calculated using the formula: Friability (%) = $[(W_1–W_2)/W_1] \times 100$, ensuring it remained below the 1% limit. Disintegration time for the immediate-release Levofloxacin layer was determined using a disintegration apparatus in 1000 mL of purified water at 37 ± 2°C, recording the time required for complete disintegration. Drug content uniformity was evaluated spectrophotometrically by preparing standard and test solutions of Ambroxol and Levofloxacin in methanol and analyzing absorbance at 244 nm and 288 nm, respectively. In vitro dissolution studies were performed using USP Type II (paddle) apparatus at 100 rpm in 900 mL of dissolution medium maintained at 37 ± 1°C. The medium was 0.1 N HCl (pH 1.2) for the first 2 hours and pH 6.8 phosphate buffer for the next 10 hours. Samples were withdrawn at predetermined intervals, filtered, and analyzed using UV spectrophotometry, with cumulative drug release calculated and compared to a marketed Ambroxol SR formulation. Stability studies were carried out as per ICH guidelines under long-term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C/75 ± 5% RH) conditions. Samples stored for 3 months were examined for physical appearance, drug content, and dissolution profile to confirm formulation stability. The evaluation results demonstrated acceptable physicochemical characteristics, consistent drug release, and stability, confirming the suitability of the developed bilayer tablets for dual therapeutic application in respiratory tract infections.

III. RESULTS AND DISCUSSION

Preformulation Studies: Ambroxol HCl (LOD 0.25%) and Levofloxacin Hemihydrate (LOD 2.23%) were within acceptable limits, indicating low hygroscopicity and stability. Both drugs were highly soluble in water and methanol, with pH-dependent solubility favoring alkaline conditions, as shown in Table 6. Bilayer tablets were evaluated in pH 1.2 and 6.8 buffers to simulate gastric and intestinal release. Pure drugs exhibited poor flow (angle of repose >46°, Carr's index >35%), which improved with excipients, particularly MCC (Carr's index ~21%) (Table 7). Ambroxol (pH 5.2) and Levofloxacin (pH 6.7) remained largely unionized, confirming compatibility with physiological conditions.

Table 2: Solubility Profile of Ambroxol Hydrochloride and Levofloxacin Hemihydrate

Solvent	Ambroxol HCl	Levofloxacin Hemihydrate
Water	Soluble	Soluble
Methanol	Highly Soluble	Highly Soluble
Ethanol	Sparingly Soluble	Sparingly Soluble
Chloroform	Insoluble	Soluble
DMSO	Soluble	Soluble
0.1 N HCl	Soluble	Soluble
pH 6.8 buffer	Highly Soluble	Soluble
pH 7.4 buffer	Soluble	Sparingly Soluble

Table 3: Micromeritic Parameters of Drug–Excipient Blends

Sample	Angle of Repose (°)	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)
AMB	47.15	0.348	0.543	35.88
LEVO	46.91	0.321	0.512	37.12
AMB+MCC	30.38	0.221	0.282	21.43
LEVO+MCC	31.64	0.206	0.263	21.62

Evaluation of granules

Table 4: Pre-Compression Evaluation and Drug Content Uniformity of Formulated Batches (F1–F12)

Formulation	Angle of Repose (°)	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)	Drug Content (%)
F1–F3	21–21.46	0.304–0.310	0.351–0.360	13.41–13.89	98.55–99.32
F4–F7	24–24.88	0.307–0.318	0.360–0.378	14.72–15.87	98.69–99.87
F8–F12	23–25.96	0.265–0.332	0.312–0.391	14.63–15.82	98.53–99.82

Notes: LBD = Loose Bulk Density; TBD = Tapped Bulk Density. Values represent ranges for each group of formulations.

Granule Evaluation and Formulation Development

Levofloxacin granules (F1–F7) showed excellent flow properties (angle of repose 20–24°) and acceptable compressibility (Carr's index 13–15%), with uniform drug content (98–99%) as summarized in Table 5.

Table 5: Pre-Compression Parameters and Drug Content of Immediate Release Layer Formulations (F1–F7)

Formulation	Angle of Repose (°)	LBD (g/mL)	TBD (g/mL)	Carr's Index (%)	Drug Content (%)
F1–F3	21–21.52	0.272–0.324	0.316–0.376	13.21–13.89	98.46–98.96
F4–F5	23.54–23.56	0.281–0.294	0.327–0.344	14.18–14.27	98.55–99.13
F6–F7	23.63–24.78	0.286–0.301	0.337–0.356	14.91–15.45	98.32–99.66

Ambroxol Sustained Release Layer: Trial batches were prepared using CARBOPOL 971P (F1–F4), HPMC K100M (F5–F8), and a combination of CARBOPOL 971P and HPMC K100M (F9–F12) with fixed Ambroxol HCl (75 mg), varying polymer and MCC content, and standard excipients (Tables 6).

Ingredients	F1–F4 (CARBOPOL 971P)	F5–F8 (HPMC K100M)	F9–F12 (CARBOPOL + HPMC)
Ambroxol HCl (mg)	75	75	75
Carbopol 971P (mg)	22.5–45	–	30–36
HPMC K100M (mg)	–	30–52.5	30–45
MCC (mg)	153–175.5	145.5–168	117–138
PVP K30 (mg)	9	9	9–11
IPA (q.s)	Quantity sufficient	Quantity sufficient	Quantity sufficient
Purified Talc (mg)	6	6	6
Aerosil (mg)	6	6	6
Magnesium Stearate (mg)	6	6	6

Levofloxacin Immediate Release Layer: IR batches (F1–F7) were formulated using Levofloxacin 500 mg with different fillers (MCC, starch, lactose, DCP) and excipients including PVP K30, SLS, talc, aerosol, and magnesium stearate. Overall, pre-compression parameters confirmed satisfactory flow, compressibility, and content uniformity, supporting the suitability of these formulations for bilayer tablet development.

Table 7: Trial Batches (F1–F7) of Levofloxacin Immediate Release Layer with Various Fillers and Excipients

Ingredients	F1–F4	F5	F6	F7
Levofloxacin (mg)	500	500	500	500
MCC (mg)	76–89	83.5	83.5	83.5
Starch (mg)	19.5–32.5	–	–	–
Lactose (mg)	–	25	–	–
Di-calcium Phosphate (mg)	–	–	25	–
SLS (mg)	–	–	–	25
PVP K30 (mg)	19–22	22	22	22
IPA (q.s)	Quantity sufficient	Quantity sufficient	Quantity sufficient	Quantity sufficient
Purified Talc (mg)	6.5	6.5	6.5	6.5
Aerosil (mg)	6.5	6.5	6.5	6.5
Magnesium Stearate (mg)	6.5	6.5	6.5	6.5

Table 8: Trial Batches (F8–F12) of Levofloxacin Immediate Release Layer Using Starch as Primary Diluent

Ingredients	F8–F12
Levofloxacin (mg)	500
MCC (mg)	83.5
Starch (mg)	25
SLS (mg)	–
PVP K30 (mg)	22
IPA (q.s)	q.s
Purified Talc (mg)	6.5
Aerosil (mg)	6.5
Magnesium Stearate (mg)	6.5

Discussion

From the above table, the results showed that all trial tablets have their right with in 949 to 952 mg/ tablet. And except the formulation Trial 1 and Trail 4, all trials have the sufficient hardness i.e., with in the limit. All the tablets of different trials were uniform in thickness (5-6 mm). According to inability parameter, the tablets of trials F1 and F4 were beyond the limit, but remaining trials were within the prescribed limits i.e., (<1). Good and Uniform drug content (>98%) was observed within the batches of different tablet formulations. Hence the tablets containing SR layer of drug (Ambroxol), HPMC, C, and other excipients mentioned in the table: 5-7 and IR layer of drug levofloxacin), MCC, Starch and other excipients could be compacted satisfactorily by double rotary compression machine.

Discussion of dissolution test

The results of in-vitro drug release studies in 0.1N HCI for first two and phosphate buffer (from 3 to 12 hours) are presented in Fig 4 to Initially our aim was to select optimum concentration of HPMC of different grades for SR laver and optimum concentration of Starch Disintegrat) for IR layer.
Hence the tablets containing.

- SR layer of drug (Ambroxol) was prepared by altering the concentration of Carbopol 971p and HPMC K100M.
- IR layer of drug (Levofloxacin) was prepared by altering the Concentration of Starch

Discussion for in-vitro release of Ambroxol laver SR

From the table, it was confirmed that the Trials of F1-F8 of SR layer not fulfill the sustained release theory, in that the Carbopol 971p, HPMC (100M were used separately in the formulations, but increasing the polymer concentration, it was clearly identified that the drug release was retarded. And so, from the table, it was also confirmed that the formulation made with CARBOPOL 971P (F1 to F4) releases the drug in less amount compared to the formulation made with HPMC K100M (F5 to F8), since its viscosity is somewhat higher than HPMC K100M.

In order to produce optimized formulation, both the grades were used together in formulations of remaining trials. Yet the Trail F9 of Ambroxol SR layer made of both CARBOPOL 971P and HPMC K100M was not attained the sustained release. The trial F10 was made with same concentration as that of with little altering in binder concentration. But there was no major change drug release and also the hardness of the tablet goes beyond the limit.

The next trial F11 of Ambroxol SR layer made of CARBOPOL 971P (11% and HPMC K100M (12.5%) sustained the drug release up to 12th hour and also

the release was similar to that of marketed sample. When the concentration of CARBOPOL 971P and HPMC K100M was again increased for the trail F12, the drug from the tablet was very hard to release so trial F11 made of 32.5mg of Carbopol 971p and 37.5mg of HPMC 100m was considered as optimized formulation for SR layer.

Discussion for Invitro release of Levofloxacin IR layer

Then for the tablet of IR laver. 7 trials were made. In those trials, the formulation (Trial F2 of Levofloxacin layer) made with starch of 25mg released than other formulations. So, the formula made for Trial F2 of Levofloxacin layer the drug with in one hour and also has the sufficient hardness and friability was considered as optimized formulation and that formula was used for remaining trials (F8 to F12) of Ambroxol SR laver to produce the Bilayered tablet.

Disintegration data for levofloxacin Separated layer

Table 9: Disintegration Time of Levofloxacin Immediate Release Layer Across Formulation Trials

Trials	Time in minutes
Trial 1	9 min
Trial 2	14 min
Trial 3	25 min
Trial 4	7 min
Trial 5	20 min
Trial 6	27 min
Trial 7	24 min

IV. CONCLUSION

This study focused on the design, development, and evaluation of bilayer tablets containing Ambroxol HCl (sustained-release, SR) and Levofloxacin hemihydrate (immediate-release, IR) to achieve dual drug release for improved therapeutic efficacy and patient compliance. Preformulation studies confirmed acceptable physicochemical properties, including moisture content, solubility, micromeritic behavior, and pH stability, with no significant drug–excipient interactions by FTIR. Wet granulation trials optimized the SR layer using Carbopol 971P, HPMC K100M, and their combination, with Trial F11 showing controlled Ambroxol release

over 12 hours. Levofloxacin IR layer trials identified starch (25 mg) as the most effective disintegrant for rapid release within 1 hour. The bilayer tablets exhibited satisfactory physical characteristics, and in-vitro dissolution confirmed the intended biphasic release. Stability studies under long-term and accelerated conditions confirmed the formulation's robustness. Overall, the optimized bilayer tablet (F11) demonstrated reproducible, stable drug release and represents a promising strategy for combining drugs with different release profiles in a single dosage form, potentially enhancing patient adherence and clinical outcomes.

V. REFERENCES

1. Helfand WH, Cowen DL. Evolution of pharmaceutical oral dosage forms. Pharmacy in history. 1983 Jan 1;25(1):3-18.
2. Ludwig JD. Parenteral dosage forms: introduction and historical perspective. InParenteral Medications, Fourth Edition 2019 Jul 19 (pp. 3-9). CRC Press.
3. Krishnarajan D, Reddy CM, Kanikanti S, Kumar NS, Purushothaman M. Formulation and evaluation of sustained release matrix tablets Of Levofloxacin using natural polymer. Pharmacophore. 2013;4(5-2013):146-57.
4. Buwade P, Jadiya S, Shukla T, Upmanyu DN. Advantages of immediate release tablets over the other tablet forms. World Journal of Pharmaceutical Research. 2015 Sep 14;4(11):757-80.
5. Dilebo J, Gabriel T. An overview of factors affecting superdisintegrants functionalities. International Journal of Pharmaceutical Sciences and Nanotechnology. 2019 Jan 31;12(1):4355-61.
6. Bastos MD, Friedrich RB, Beck RC. Effects of filler-binders and lubricants on physicochemical properties of tablets obtained by direct compression: a 22 factorial design. Lat. Am. J. Pharm. 2008 Jul 1;27(4):578-83.
7. Bankar A, Bankar VH, Gaikwad PD, Pawar SP. Formulation design and optimization of sustained release tablet of ambroxol hydrochloride. International Journal of Drug Delivery. 2012 Jul 1;4(3):375.
8. Rameshwar V, Kishor D, Tushar G. Bi-layer tablets for various drugs: A review. Scholars Academic Journal of Pharmacy. 2014;3(3):271-9.
9. Kumar S, Chowdary KP, Suresh P. A comparative evaluation of direct compression and wet granulation methods for formulation of stavudine tablets. Journal of Global Trends in Pharmaceutical Sciences. 2014;5(3):2000-3.