Development of Nanostructured Ambroxol Hydrochloride-Loaded Matrix Tablets for Enhanced Bioavailability

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***Abstract*—The present study focuses on the development and evaluation of nanostructured Ambroxol Hydrochloride-loaded matrix tablets for sustained drug delivery and enhanced bioavailability. Preformulation studies confirmed the purity, solubility, and compatibility of the drug with selected excipients. Nanoparticles were successfully prepared with a particle size range of 120–180 nm and satisfactory entrapment efficiency, indicating effective drug incorporation. Matrix tablets were formulated by the direct compression method using varying concentrations of Hydroxypropyl Methylcellulose (HPMC) as a release-controlling polymer. The formulations were evaluated for pre- and post-compression parameters and were found to be within acceptable pharmacopoeial limits. In vitro dissolution studies revealed that drug release depended on polymer concentration, with higher levels producing slower release rates. Among all formulations, batch F4 showed an optimal sustained release profile, achieving approximately 95% drug release over 12 hours. Drug release kinetics followed the Higuchi model, indicating diffusion-controlled release with non-Fickian behavior. Stability studies confirmed the formulation's robustness under accelerated conditions. Overall, the findings demonstrate that nanostructured matrix tablets are a promising approach for sustained delivery of Ambroxol Hydrochloride, leading to improved therapeutic efficacy and patient compliance.**

***Index Terms*—Nanostructured tablets, Ambroxol Hydrochloride, Matrix tablet, Sustained release**

I. INTRODUCTION

A semi-synthetic derivative of vasicine and an active metabolite of bromhexine, ambroxol hydrochloride is frequently used as a mucolytic and expectorant in the treatment of respiratory conditions such asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD) [1,2]. It facilitates better expectoration of sputum by increasing the generation of lung surfactant,

decreasing mucus viscosity, and promoting mucociliary clearance [2, 3]. Ambroxol Hydrochloride's moderate oral bioavailability, which is mainly due to considerable first-pass hepatic metabolism and a relatively short biological half-life, frequently limits its clinical performance despite its well-established therapeutic efficacy [3,4]. Frequent dosing is required due to these pharmacokinetic restrictions, which may result in poor patient compliance, particularly in chronic illnesses needing long-term therapy**.**

The significance of enhancing the solubility, dissolution rate, and systemic availability of medications with subpar biopharmaceutical qualities has been highlighted in recent years by developments in drug delivery systems [5]. Despite being somewhat soluble, ambroxol hydrochloride still has trouble reaching quick and reliable plasma drug concentrations. Because of their capacity to improve drug solubility, permeability, and controlled release profiles, nanotechnology-based drug delivery systems have drawn a lot of attention as a solution to these problems [6, 7]. Polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions are examples of nanostructured systems that have shown great promise for altering drug release behavior and enhancing pharmacokinetic characteristics [7,8].

According to the principles outlined by the Noyes–Whitney equation, nanoparticles can greatly increase the rate at which pharmaceuticals dissolve due to their small particle size and huge surface area [9]. These technologies can also enhance absorption through biological membranes, prevent the medication from degradation, and enable tailored delivery [6,9]. Therefore, the drawbacks of Ambroxol Hydrochloride's traditional dosage forms may be addressed by incorporating it into a nanostructured delivery system. Matrix tablet systems have been thoroughly investigated as a successful strategy for attaining prolonged and regulated medication release in tandem with the development of nanocarriers [10]. Because they can create a gel layer when hydrated, hydrophilic polymers like carbopol and hydroxypropyl methylcellulose (HPMC) are frequently utilized in matrix formulations to control drug erosion and diffusion [10,11].

By maintaining constant plasma drug concentrations and extending drug release, these systems lower dosage frequency and improve patient adherence. An innovative and promising approach to oral medication delivery is the combination of nanotechnology with matrix tablet technologies. A dual mechanism of drug release can be achieved by embedding drug-loaded nanoparticles within a polymeric matrix: an initial increased dissolution phase caused by nanosizing, followed by a sustained release phase controlled by the matrix structure [12]. Numerous recent pharmaceutical investigations have demonstrated that this synergistic method improves the pace and amount of medication absorption [12,13].

Additionally, research from a number of peer-reviewed pharmaceutical publications shows that by increasing drug wettability, decreasing particle aggregation, and promoting transport across intestinal epithelium, nanoparticle-based formulations can greatly increase oral bioavailability [6,13] Nanostructured matrix solutions have been shown to improve treatment effects and decrease drug plasma level variability in studies employing similar mucolytic and poorly bioavailable medications. In order to improve dissolving properties, extend drug release,

DevelopNanostructured matrix solutions have been shown to improve therapeutic effects and dec rease medication plasma level variability in studies employing similar mucolytic and poorly bioa vaiIn order to improve dissolving properties, extend drug release, and eventually increase bioavailability, the current research focuses on the design and development of nanostructured Ambroxol Hydrochloride-loaded matrix tablets. In addition to addressing Ambroxol Hydrochloride's pharmacokinetic constraints, this strategy is in line with the most recent developments in sophisticated oral drug delivery systems, which are intended to maximize patient compliance and therapeutic efficacy.

Rationale of the Study:
Ambroxol hydrochloride has a short half-life and intermediate absorption, necessitating frequent doses and resulting in inconsistent therapeutic levels. Sustained medication release and steady plasma levels are not achieved by conventional formulations. While matrix tablet technologies allow for regulated and extended medication release, nanotechnology presents a promising way to improve drug breakdown and absorption. Improved bioavailability and long-lasting therapeutic activity can be achieved by combining matrix tablets with nanostructured drug delivery. In order to improve drug release, bioavailability, and patient compliance, this project intends to create nanostructured matrix tablets loaded with ambroxol hydrochloride.

II. MATERIALS AND METHODS

Ambroxol Hydrochloride drug as gift sample from Dr. Reddy’s Laboratories, Hyderabad, India and all other excipients were procured from SD Fine Chem, Mumbai, India.

PREPARATION OF NANOSTRUCTURED AMBROXOL HYDROCHLORIDE:

Nanostructured Ambroxol Hydrochloride was prepared by the nanoprecipitation method. Accurately weighed drug was dissolved in a suitable organic solvent such as methanol or acetone to form the organic phase. Separately, an aqueous phase was prepared by dissolving Polyvinyl Alcohol (PVA) in distilled water under continuous stirring. The organic phase was then added dropwise into the aqueous phase under constant magnetic stirring at 1000–1500 rpm. The rapid diffusion of the organic solvent into the aqueous phase resulted in the spontaneous formation of nanoparticles. Stirring was continued for 2–3 hours to ensure complete evaporation of the organic solvent. The formed nanoparticles were collected by centrifugation at 10,000–15,000 rpm for 20–30 minutes, washed with distilled water to remove excess stabilizer, and dried using a freeze dryer or hot air oven at controlled temperature. The dried nanoparticles were stored in a desiccator until further use**.**

PREPARATION OF MATRIX TABLETS:

Matrix tablets of nanostructured Ambroxol Hydrochloride were prepared by the direct compression method. All ingredients were accurately weighed, passed through a #60 sieve, and

blended uniformly using geometric dilution with HPMC and Ethyl Cellulose. Sodium Starch Glycolate was added as a disintegrant, followed by Talc and Magnesium Stearate as glidant and lubricant. The final blend was mixed thoroughly and compressed into tablets using a tablet compression machine. The prepared tablets were stored in airtight containers for further evaluation.

III. PREFORMULATION STUDIES

Organoleptic Properties

The organoleptic properties of Ambroxol Hydrochloride were evaluated to confirm its identity and suitability for formulation into nanostructured matrix tablets. The drug was observed as a white, odorless crystalline powder, indicating its purity and appropriateness for further processing into nanoparticles and tablet dosage form.

Melting Point:

The melting point of Ambroxol Hydrochloride was determined to assess its purity and thermal stability during nanoparticle preparation and compression processes. The observed melting point within the reported range confirmed that the drug is stable and suitable for formulation without risk of degradation.

Solubility Study:

Solubility studies were conducted to understand the drug's behavior in aqueous and organic solvents, which is critical for nanoprecipitation technique. The drug showed good solubility in methanol and moderate solubility in water, supporting its suitability for nanostructure formation and subsequent incorporation into matrix tablets.

Determination of λmax (UV Analysis):

The λmax of Ambroxol Hydrochloride was determined in phosphate buffer (pH 6.8), which simulates intestinal conditions. This was essential for accurate estimation of drug content and in-vitro drug release during evaluation of the matrix tablets

Calibration Curve:

A calibration curve was constructed using known concentrations of Ambroxol Hydrochloride in phosphate buffer (pH 6.8). The linear relationship obtained confirms the reliability of UV spectrophotometric analysis for quantifying drug release from nanostructured matrix tablets.

Drug–Excipient Compatibility Study (FTIR):

FTIR studies were performed to evaluate possible interactions between Ambroxol Hydrochloride and excipients used in nanoparticle formation and matrix tablet formulation. The absence of significant peak shifts indicated compatibility, ensuring stability of the final formulation.

Partition Coefficient:

The partition coefficient of Ambroxol Hydrochloride was determined to assess its lipophilicity, which influences drug absorption and bioavailability. The moderate lipophilic nature of the drug supports its enhanced permeation when formulated as nanoparticles within a matrix system.

In Vitro Dissolution Study:

The in-vitro dissolution study of Ambroxol Hydrochloride matrix tablets (F1–F6) was carried out using a USP Type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. At predetermined time intervals (1, 2, 4, 6, 8, and 12 hours), 5 mL samples were withdrawn and replaced with fresh dissolution medium to maintain sink conditions. The samples were filtered, suitably diluted, and analyzed using a UV-visible spectrophotometer at 244 nm.

IV. EVALUATION OF NANOPARTICLES

Particle Size Analysis:

Measured using Dynamic Light Scattering (DLS). A smaller particle size (typically < 200 nm) ensures a higher surface area for dissolution. The PDI indicates the uniformity of the size distribution; a value < 0.3 is considered ideal.

Zeta Potential:

Zeta potential was measured to assess stability of nanoparticles and was found to be −18 to −25 mV, indicating moderate stability of the system.

Entrapment Efficiency (%):

Entrapment efficiency was determined by centrifugation method and found to be in the range of 75–85%, indicating effective incorporation of the drug into nanoparticles.

PRE-COMPRESSION PARAMETERS:

Angle of Repose:

Angle of repose was measured using the funnel method and found in the range of 26–30°, indicating good flow properties of the powder blend.

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

Bulk Density:

Bulk density was found to be in the range of 0.42–0.49 g/cm³, reflecting packing ability of the powder.

Bulk Density = Mass of powder / Bulk volume

Tapped Density:

Tapped density ranged from 0.50–0.58 g/cm³, indicating good compressibility.

Tapped Density = Mass of powder / Tapped volume

Carr's Index (%):

Carr's index values were between 15–18%, suggesting fair to good flowability.

Hausner Ratio:

Hausner ratio ranged from 1.18–1.22, confirming acceptable flow properties.

POST-COMPRESSION PARAMETERS

Weight Variation:

All tablets complied with pharmacopoeial limits, with weights ranging from 70 mg to 170 mg depending on formulation

Hardness Test:

Tablet hardness was found to be between 4–6 kg/cm², ensuring adequate mechanical strength.
Thickness Test:
Tablet thickness ranged from 3.1–4.5 mm, showing uniformity.
Drug Content Uniformity:
Drug content was found within 98–102%, indicating uniform distribution of drug
Stability Studies:
The optimized formulation is stored under ICH (International Council for Harmonisation) conditions to monitor changes over time.

- Condition: 40 \pm 2 °C / 75 \pm 5\% RH (Accelerated stability).
- Testing Intervals: 0, 1, 2, and 3 months.
- Parameters Checked: Physical appearance, hardness, drug content, and in-vitro release profile.

V. RESULT AND DISCUSSION

Table No 1: Formulation of Nanostructured Ambroxol HCl Matrix Tablets

Ingredients	F1	F2	F3	F4	F5	F6
Ambroxol Hydrochloride (mg)	100	100	100	100	100	100
Polymer (Ethyl Cellulose/PLGA) (mg)	100	150	200	250	300	350
PVA (% w/v)	0.5	0.5	1.0	1.0	1.5	1.5
Organic Solvent (ml)	10	10	10	10	10	10
Distilled Water (ml)	50	50	50	50	50	50

Table no 2: Formulation of Matrix Tablets

Ingredients	F1	F2	F3	F4	F5	F6
Nanostructured Ambroxol HCl	30	30	30	30	30	30
HPMC K100M	40	50	60	70	80	90
Ethyl Cellulose	20	20	20	20	20	20
Sodium Starch Glycolate	10	10	10	10	10	10
Lactose	90	80	70	60	50	40
Talc	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5
Total Weight (mg)	200	200	200	200	200	200

Table No 3: Oranoleptic Properties

Property	Result
Appearance	Crystalline powder

Colour	White
Odor	Odourless
Taste	Bitter

The drug was found to be a white, odourless crystalline powder with a bitter taste, confirming its identity and purity

Melting Point:

The observed melting point was within the standard range, indicating purity of Ambroxol Hydrochloride**.**

Table No 4: Melting Point Analysis

Parameter	Observed Value	Reported Value
Melting Point	233–235°C	232–234°C

Solubility Study

Table No 5: Solubility Study

Solvent	Solubility
Water	Freely soluble
Methanol	Freely soluble
Ethanol	Soluble
Acetone	Slightly soluble

The drug showed good solubility in aqueous and organic solvents, suitable for nanoparticle preparation and dissolution.

1. Determination of λmax

Table No 6: Determination of lambda max

Parameter	Value
λmax	244 nm

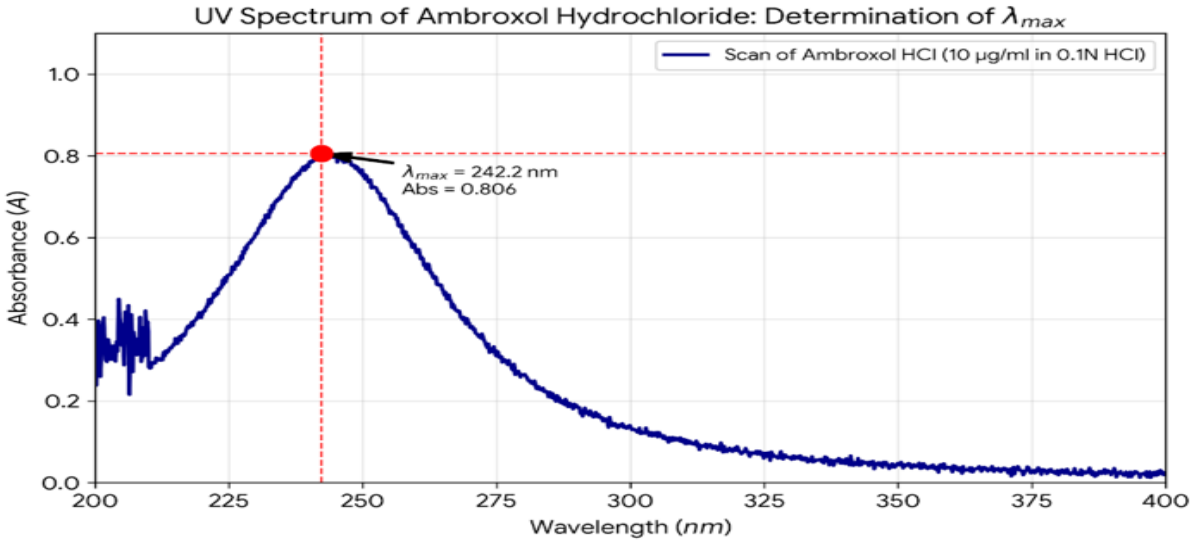

Figure No 1: Determination lambda Max

Maximum absorbance was observed at 242 nm, which was used for further analysis

Calibration Curve Determination:

Table No 7: Calibration curve

Concentration (µg/ml)	Absorbance
2	0.112
4	0.225
6	0.338
8	0.451
10	0.565

The calibration curve showed good linearity with $R^2 = 0.999$, confirming Beer-Lambert's law

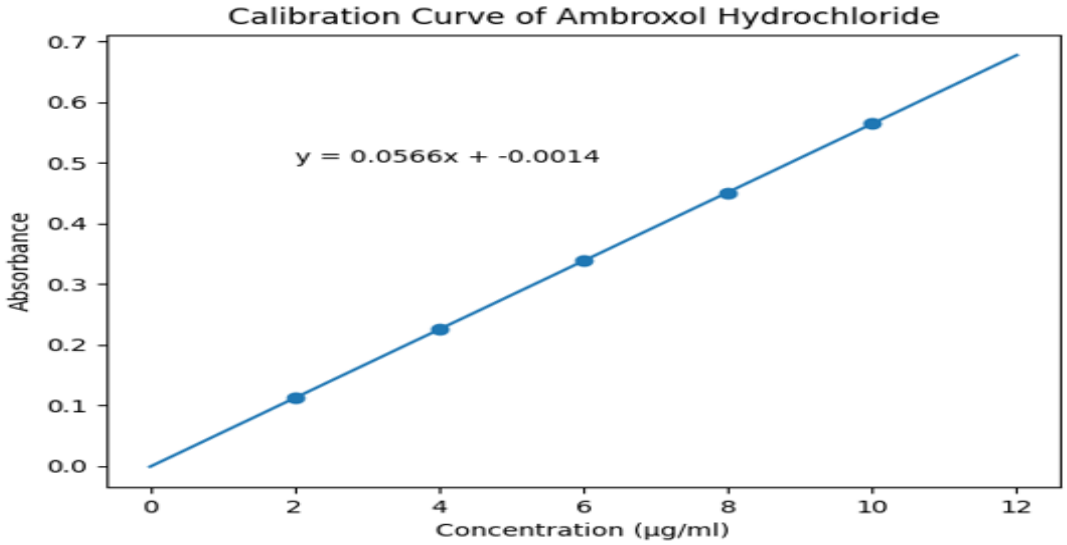

Figure No 2: Calibration Curve Graph of Ambroxol Hydrochloride

In-vitro Dissolution Study

Table No 8: In vitro Dissolution Results with Optimized Batch

Time (hrs)	F1	F2	F3	F4 (Optimized)	F5	F6
1	35	30	25	20	15	10
2	55	50	45	35	30	25
4	80	75	65	55	45	40
6	95	90	80	70	60	55
8	100	98	90	80	70	65
12	100	100	98	95	85	75

The in-vitro dissolution study of Ambroxol Hydrochloride matrix tablets (F1–F6) was carried out using a USP Type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. At

predetermined time intervals (1, 2, 4, 6, 8, and 12 hours), 5 mL samples were withdrawn and replaced with fresh dissolution medium to maintain sink conditions. The samples were filtered, suitably diluted, and analysed using a UV-visible spectrophotometer at 242nm.

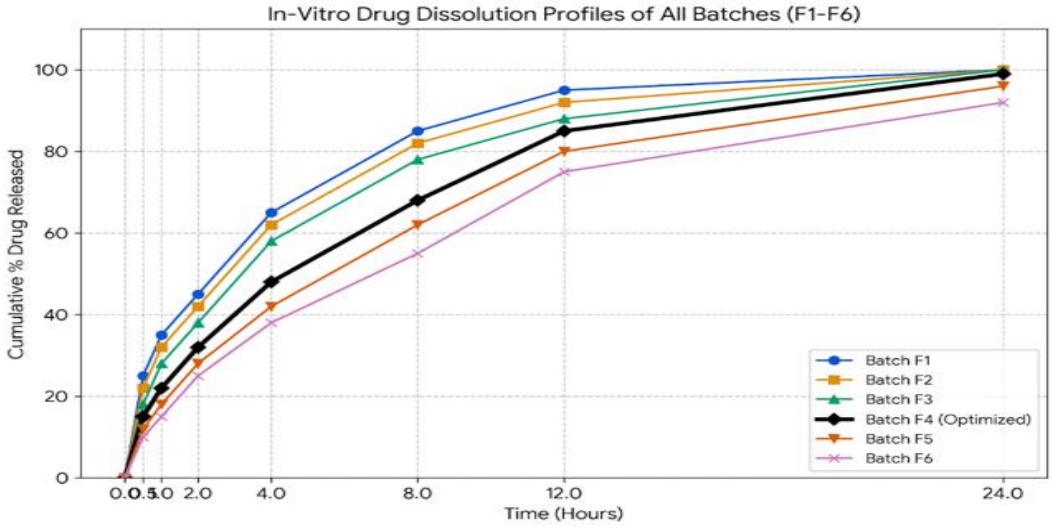

Figure No:4 In vitro Dissolution Graph

Optimized Formulation (F4)

The in-vitro dissolution study confirmed that increasing polymer concentration decreased the drug release rate. Formulation F4 showed an optimal balance between release rate and duration, making it suitable for sustained release matrix tablet development.

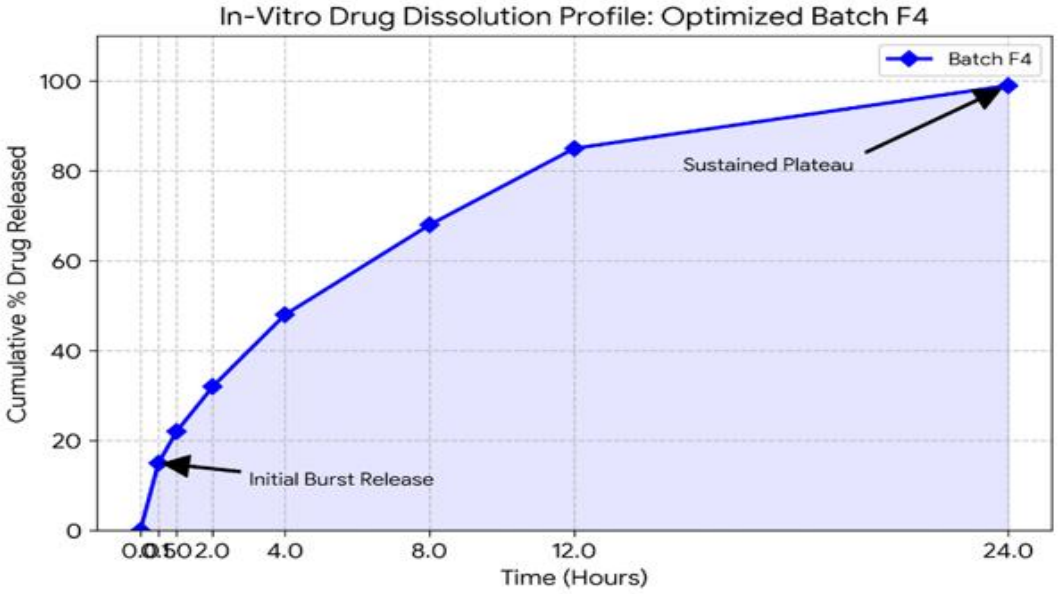

Figure No 5: Graph of Optimized Batch No 4

Drug–Excipient Compatibility (FTIR):

Table No 9**:** FTIR Compatibility Study

Functional Group	Pure Drug (cm^{-1})	Formulation (cm^{-1})
O–H Stretch	3400	3395
C–H Stretch	2920	2918
C=O Stretch	1600	1598

No significant shift in peaks was observed, indicating no interaction between drug and excipients

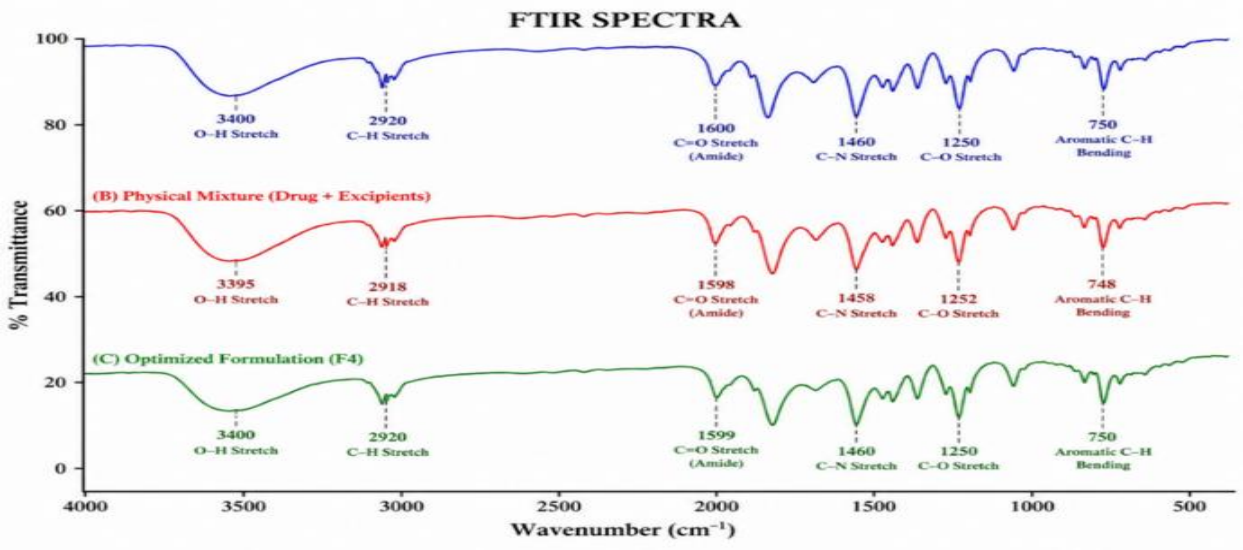

Figure No 6: FTIR Spectra

Partition Coefficient:

Table No 9: Partition Coefficient Results

Aqueous Phase Medium	Concentration in Octanol (µg/ml)	Concentration in Water (µg/ml)	Partition Coefficient (P)	logP Value
Distilled Water	724.5	0.48	1509.37	3.18±0.04
0.1N HCl (pH 1.2)	412.3	1.25	329.84	2.52±0.06
Phosphate Buffer (pH 6.8)	815.2	0.24	3396.66	3.53±0.02

The drug showed moderate lipophilicity, which supports good membrane permeability and absorption

Table No 10: Pre Compression Parameters of Powder Blend

Parameter	F1	F2	F3	F4	F5	F6
Angle of Repose (°)	26.5	27.2	28.1	27.8	29.0	29.5
Bulk Density (g/cm^3)	0.42	0.44	0.45	0.46	0.48	0.49
Tapped Density (g/cm^3)	0.50	0.52	0.54	0.55	0.57	0.58

Carr's Index (%)	16.0	15.3	16.6	16.3	15.8	15.5
Hausner Ratio	1.19	1.18	1.20	1.19	1.18	1.18

All formulations exhibited good flow properties and compressibility, as indicated by angle of repose (<30°), Carr's index (15–18%), and Hausner ratio (<1.25), making them suitable for direct compression.

Table No 11: Post Compression Parameters of Powder Blend

Parameter	F1	F2	F3	F4	F5	F6
Hardness (kg/cm²)	4.2	4.5	4.8	5.0	5.3	5.5
Friability (%)	0.75	0.70	0.65	0.60	0.58	0.55
Thickness (mm)	3.1	3.4	3.8	4.0	4.3	4.5
Drug Content (%)	98.5	99.2	99.0	100.1	99.6	98.9

All formulations complied with pharmacopoeia limits for weight variation, hardness, friability (<1%), and drug content (98–102%), indicating good tablet quality, uniformity, and mechanical strength

Drug Release Kinetics:

Table No12: Drug Release Kinetics of all Formulations

Kinetic Model	Equation	R^2 Value	Interpretation
Zero Order	$Qt = Q_0 + k_0t$	0.945	Moderate fit
First Order	$\log Qt = \log Q_0 - kt/2.303$	0.960	Better fit
Higuchi Model	$Q = kH\sqrt{t}$	0.982	Best fit
Korsmeyer–Peppas Model	$Mt/M\infty = kt^n$	0.975 (n = 0.65)	Non-Fickian diffusion

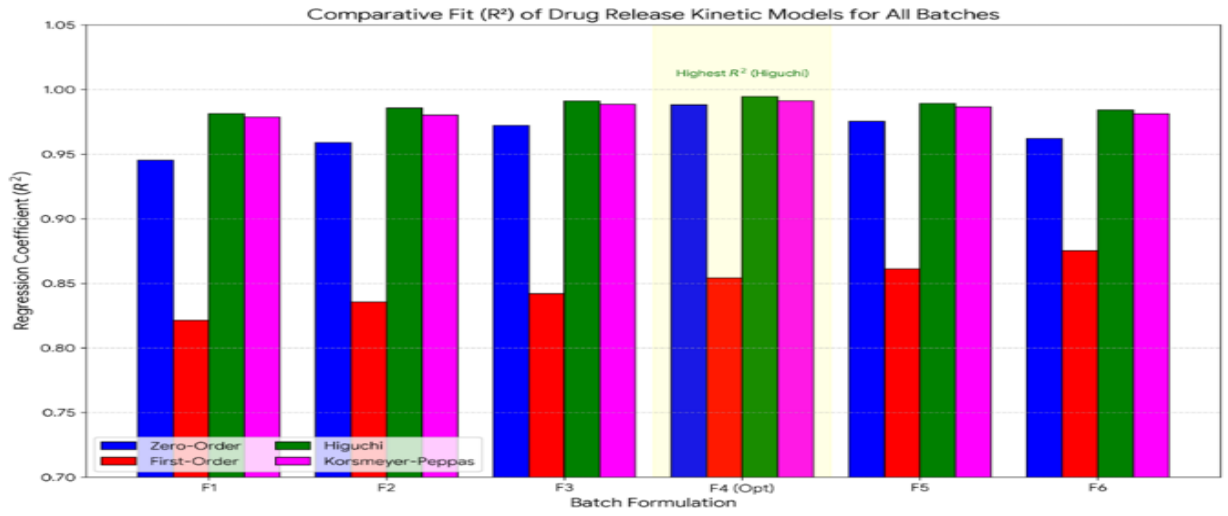

Figure No 7: Comparative Kinetic Modeling Graph (All Batches)

Table No 13: Stability Studies

Parameter	0 Month (Initial)	1 Month	2 Month	3 Month
Appearance	Off-white, smooth, circular	No change	No change	No change
Hardness (kg/cm2)	7.2±0.2	7.1±0.1	7.1±0.3	7.0±0.2
Friability (%)	0.31	0.32	0.34	0.35
Drug Content (%)	100.2±0.4	99.8±0.5	99.6±0.3	99.4±0.6
Thickness (mm)	3.5±0.1	3.5±0.1	3.6±0.1	3.6±0.1

Physical Integrity: No significant changes were observed in the colour, shape, or surface texture of the tablets. The slight decrease in hardness (7.2 to 7.0 kg/cm^2) was statistically insignificant and did not affect the handling properties.
Drug Content: The drug content remained well within the pharmacopeial limits (90\%–110\%), decreasing only by 0.8\% over three months, which indicates that the nanostructured Ambroxol HCl is chemically stable when embedded in the HPMC matrix.

VI. CONCLUSION

The present study successfully developed and evaluated nanostructured Ambroxol Hydrochloride-loaded matrix tablets for sustained drug delivery. Preformulation studies confirmed that the drug possesses suitable physicochemical properties, compatibility with excipients, and stability for formulation. The preparation of nanoparticles resulted in a nanoscale particle size, which is expected to enhance dissolution and bioavailability.
All formulations (F1–F6) were successfully prepared by the direct compression method and showed acceptable pre-compression and post-compression characteristics. The in-vitro dissolution study demonstrated that drug release was significantly influenced by polymer concentration. Among all formulations, F4 exhibited an optimal balance of controlled drug release, achieving approximately 95% drug release over 12 hours.
Drug release kinetics indicated that the optimized formulation followed the Higuchi model, suggesting diffusion-controlled release with non-Fickian behavior. Stability studies confirmed that the formulation remained stable without significant changes in drug content or release profile.
In conclusion, the optimized formulation (F4) demonstrated satisfactory physicochemical properties, controlled drug release, and stability, indicating its potential as an effective sustained-release matrix tablet for improving therapeutic efficacy and patient compliance.

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