

FORMULATION AND EVALUATION OF CHRONOMODULATED PULSATILE COLON-TARGETED DOXEPIN HCL TABLETS FOR NOCTURAL DEPRESSION

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ABSTRACT

Background/Objective: Major depressive disorder (MDD) is often characterized by a circadian pattern of increasing symptom severity, sleep disturbance, and cortisol output in the hours of early morning. Conventional immediate- and sustained-release Doxepin hydrochloride (HCl) formulations release drug independent of this rhythm, resulting in daytime sedation and sub-optimal symptom coverage at the time of greatest need. The present study was aimed to design and evaluate a chronomodulated colon-targeted pulsatile tablet system of Doxepin HCl which can be kept quiescent through the stomach and proximal small intestine and can release a rapid and complete “burst” dose in the colon after a programmed lag time to anticipate early-morning symptom worsening. **Methods:** Direct compression was used to manufacture immediate release core tablets (F1-F6) with Doxepin HCl and one of three superdisintegrants (croscopovidone, croscarmellose sodium, sodium starch glycolate) and screened for flow, mechanical and disintegration performance. The optimized core was compression coated with the graded blends of hydroxypropyl methylcellulose (HPMC) K100M and ethyl cellulose (P1–P6) to program a lag

phase. The optimized press-coated tablet was further pan-coated with Eudragit S100 at the six coating levels (EC1–EC6) for pH-triggered colon targeting. The formulations were assessed for pre- and post-compression parameters, drug–excipient compatibility (FTIR), acid resistance and in vitro release in successive pH media (0.1 N HCl, pH 6.8 and pH 7.4 phosphate buffer) imitating gastric, small-intestinal and colonic transit. The release data of optimized formulation were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell model. Short-term stability was examined under long-term and accelerated ICH conditions. **Results:** The formulation F6 (9 mg sodium starch glycolate) showed fastest core disintegration (22 s) with appropriate flow (angle of repose 26.5°, Carr’s index 10%) and was selected as core. The longest and most reproducible lag phase (~7 h) was obtained with compression coating P6 (110 mg HPMC K100M : 80 mg ethyl cellulose). Enteric coating EC5 (10% w/v Eudragit S100, 15% triethyl citrate, 10% weight gain) combined excellent acid resistance (1.2% release in 0.1 N HCl at 2 h) with a well-defined lag phase and rapid colonic burst release (96.8% by 9 h; 100% by 12 h), clearly differentiating it from the marketed immediate-release comparator which released >99% of its dose within 3 h. FTIR demonstrated the absence of drug excipient interaction. Release from EC5 best approximated zero-order kinetics ($R^2 = 0.847$) with a high Korsmeyer–Peppas exponent ($n = 2.03$, restricted to $\leq 60\%$ release), consistent with erosion/relaxation-controlled release superimposed on the delayed-onset (lag) behaviour typical of pulsatile systems. Under both long-term and rapid ICH circumstances, EC5 retained its physical integrity, drug content ($\geq 97.9\%$) and lag time (7.0–7.2 h) for three months. **Conclusion:** The successful development of chronomodulated pulsatile colon targeted tablet (EC5) was achieved by sequential compression coating and pH triggered enteric coating of optimized immediate release Doxepin HCl core to synchronize drug release with early morning worsening associated with nocturnal depression. The formulation approach is mechanistically robust, technically reproducible, and needs further investigation in biorelevant and in vivo pharmacokinetic–pharmacodynamic models.

Keywords: Colon targeted medication delivery; Doxepin hydrochloride; Eudragit S100; Nocturnal depression; Circadian rhythm.

1. INTRODUCTION

Major depressive disorder (MDD) currently affects an estimated 332 million people worldwide and remains among the leading contributors to global disability^[1,2]. Monoaminergic deficiencies, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, poor neurotrophic signaling and low-grade neuro inflammation contribute to the multifactorial pathogenesis^[3,4]. Superimposed on these systems is a well-documented disruption of circadian rhythmicity, the endogenous, self-sustaining oscillations of ~24-hours that usually orchestrate the sleep–wake cycle, hormone production, and body temperature^[5,6]. Patients with MDD often have phase-shifted or blunted diurnal rhythms, shortened rapid-eye-movement sleep latency and exaggerated early-morning cortisol surge, coincident with clinically recognizable worsening of mood, anxiety and sleep continuity in the pre-dawn hours – a pattern often referred to as nocturnal or early-morning predominant depression^[7,8]. This temporal pattern provides a powerful pharmacological basis for chronotherapy: timing drug delivery to coincide with the biological rhythm of disease activity rather than administering the drug at a constant or immediate rate independent of the dosage time^[9,10].

Doxepin hydrochloride is a tricyclic antidepressant with sedative properties. It inhibits the absorption of serotonin and norepinephrine and antagonizes the histamine H1, muscarinic and α 1-adrenergic receptors^[11]. Conventional immediate-release Doxepin HCl pills release its full dose within 2–3 h after ingestion, regardless of the time of administration. Thus a bedtime dose is largely absorbed, distributed and partially eliminated well before the early morning period in which depressive symptoms are usually most severe, whereas daytime or pre-emptive dosing risks marked antihistaminic sedation – a recognized limitation of tricyclic antidepressant therapy^[11]. Traditional sustained-release techniques decrease adverse effects associated with peak-plasma-concentration, but do not yet offer a true “silent interval” followed by dose release timed to a particular circadian time point.

PDDS bridge this gap by having a programmed lag phase with little drug release followed by quick (“burst”) release of the desired dose^[12–14]. If this lag phase is further protected from the gastric and upper-intestinal environment and designed to terminate in the colon, a chronomodulated colon-targeted pulsatile system is obtained. The colon provides a relatively pH-neutral, enzymatically quiescent and low motility environment which, in addition to its recognized utility as a target site for chronotherapeutic administration^[14–16], minimizes the risk of

premature drug loss and dose-dumping relative to gastric or small intestinal release. This general architecture, of an inner immediate-release core, a swellable/erodible compression coat that programs lag time, and an outer pH-responsive enteric coat that confers colon specificity, has been successfully demonstrated for salbutamol sulfate, lisinopril and rabeprazole sodium, and most directly relevant to the present work, for nocturnal hyperacidity using a combination of compression coating and enteric coating [17–20].

To the best of our knowledge, this precedence in other treatment domains has not been recorded for colon-targeted, chronomodulated pulsatile formulation of Doxepin HCl especially designed for nocturnal depression. We hypothesized that a tri-layer tablet composed of (i) a Doxepin HCl and superdisintegrant immediate-release core, (ii) a hydroxypropyl methylcellulose (HPMC) K100M and ethyl cellulose compression coat to program a defined lag time of approximately 6–8 h [22], and (iii) an outer Eudragit S100 enteric coat to prevent release in the stomach and upper-intestine could deliver a bedtime dose of Doxepin HCl in synchrony with the circadian worsening of nocturnal depressive symptoms while minimizing daytime sedative exposure (Fig. 1). This study describes the systematic formulation, optimization and in vitro characterization of this system including drug-excipient compatibility, pre- and post-compression tablet properties, acid resistance, sequential-media dissolution behavior, comparative release against a marketed immediate-release product, release-kinetic modeling and short-term ICH stability.

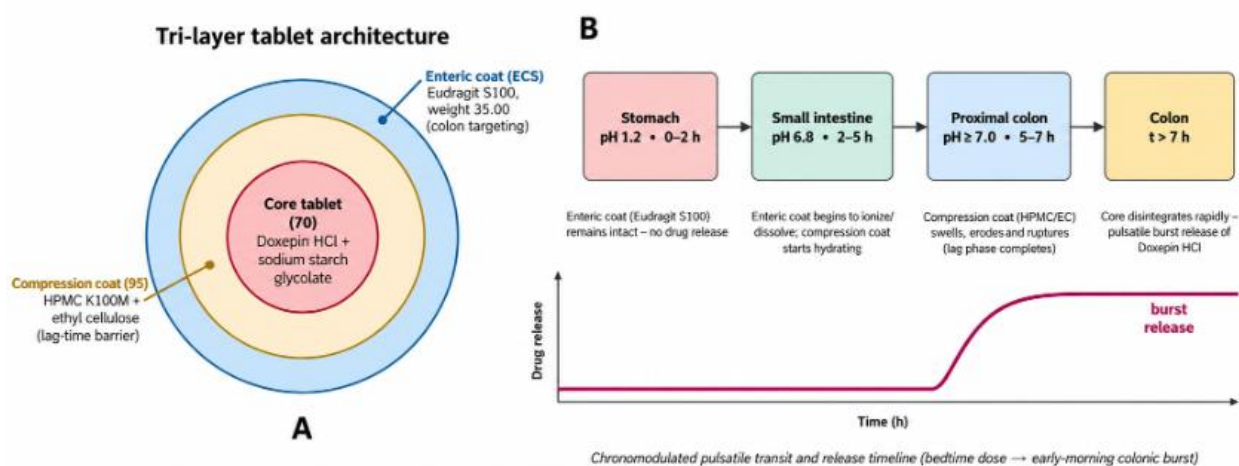


Figure 1. Proposed tri-layer tablet construction and chronomodulated gastrointestinal transit/release mechanism (A) Cross-section through the immediate release core (F6), the HPMC K100M/ethyl cellulose compression coat (P6) programming the lag phase and the outside Eudragit S100 enteric coat (EC5) conferring colon selectivity. (B) Sequence of proposed events as tablet traverses stomach, small intestine and colon leading to pulsatile burst release of Doxepin HCl.

2. MATERIALS AND METHODS

2.1. Materials

Doxepine hydrochloride was a gift sample from a registered bulk medication manufacturer. Croscopovidone, croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose (MCC PH 102), lactose monohydrate, hydroxypropyl methylcellulose (HPMC K100M), ethyl cellulose, Eudragit S100, talc, magnesium stearate, isopropyl alcohol, acetone and triethyl citrate were purchased from standard commercial suppliers and were pharmacopeial or analytical-reagent grade, as applicable. All ingredients were utilized as received without further purification. The main equipment used for the formulation development and evaluation included UV–visible spectrophotometer (Shimadzu UV-1800), electronic analytical balance, USP Type II (paddle) dissolution tester, Monsanto/Pfizer-type hardness tester, Roche friabilator, USP disintegration tester, FTIR spectrophotometer, tapped-density apparatus, hot-air oven, conventional coating pan and stability chamber (25 ± 2 °C/ $60 \pm 5\%$ RH and 40 ± 2 °C/ $75 \pm 5\%$ RH).

2.2. Pre-formulation Studies

2.2.1. Organoleptic characteristics, melting point and solubility

The colour, odour, appearance, and flow character of Doxepin HCl were recorded by visual and tactile inspection. The melting point was obtained in triplicate by the open capillary method. The equilibrium solubility was determined by the shake-flask method. Excess of drug was added to 10 mL of 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8 or phosphate buffer pH 7.4 in stoppered flasks. The flasks were shaken at 37 ± 0.5 °C for 24 h, filtered through a 0.45- μ m membrane, diluted suitably and assayed spectrophotometrically at the corresponding λ_{max} ($n = 3$).

2.2.2. Partition coefficient

The apparent n-octanol/water partition coefficient was calculated by the shake-flask method with mutually pre-saturated phases to give a qualitative estimate of the lipophilic hydrophilic balance of Doxepin HCl in relation to membrane permeability following release.

2.3. Method development

A UV–visible spectrophotometric technique was devised and validated for quantification of Doxepin HCl in each of the dissolving media. Stock and working solutions were scanned in the range 200 to 400 nm to obtain λ_{max} and calibration curves were constructed in the range 2 to 20 μ g/mL in 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 by plotting the

absorbance against the concentration and least-squares linear regression analysis (Beer–Lambert relationship, $A = \epsilon cl$).

2.4. Compatibility of drug and excipients

Fourier-transform infrared (FTIR) spectra of pure Doxepin HCl and optimized drug-excipient physical mixture were recorded (KBr pellet method, 4000–400 cm^{-1}) and compared for the disappearance of characteristic drug peaks, appearance of new peaks or significant peak broadening which would indicate a chemical interaction.

2.5. Preparation of Immediate Release Core Tablets (F1–F6)

Core tablets were made by direct compression to allow quick disintegration and drug release when exposed after rupture of the outer pulsatile layer. Doxepin HCl, MCC PH 102, lactose monohydrate and one of three superdisintegrants Crospovidone (F1, F2), croscarmellose sodium (F3, F4) and sodium starch glycolate (F5, F6) at two levels, were sieved (#60 mesh), blended by geometric dilution (10–15 min), lubricated with talc and magnesium stearate (3–5 min) and compressed on a tablet press to a target weight of 150 mg (Table 2).

Table 2. Composition of Immediate release core tablets of Doxepin HCl (F1–F6, mg/tab).

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6
Doxepin HCl	25.00	25.00	25.00	25.00	25.00	25.00
Crospovidone	6.00	9.00	–	–	–	–
Croscarmellose sodium	–	–	6.00	9.00	–	–
Sodium starch glycolate	–	–	–	–	6.00	9.00
MCC PH 102	60.00	57.00	60.00	57.00	60.00	57.00
Lactose monohydrate	54.00	54.00	54.00	54.00	54.00	54.00
Talc	2.50	2.50	2.50	2.50	2.50	2.50
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50
Total weight	150.00	150.00	150.00	150.00	150.00	150.00

2.6. Preparation of Press Coated Pulsatile Tablets (P1–P6)

The optimized core tablet was compression-coated with graded HPMC K100M : ethyl cellulose blends (Table 3) using a solvent-free press-coating technique. Half the weight of the polymer blend was placed in the die cavity, the core tablet was centered on this bed and the remaining polymer blend was added to fully cover the core before the assembly was squeezed to a target coat weight of 350 mg per tablet.

Table 3 Composition of the press-coated (compression-coated) pulsatile Doxepin HCl tablets (P1–P6, mg/tablet).

Ingredient (mg/tablet)	P1	P2	P3	P4	P5	P6
Optimized core tablet (F6)	150.00	150.00	150.00	150.00	150.00	150.00
HPMC K100M	60.00	70.00	80.00	90.00	100.00	110.00
Ethyl cellulose	130.00	120.00	110.00	100.00	90.00	80.00
Talc	5.00	5.00	5.00	5.00	5.00	5.00
Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00
Total weight	350.00	350.00	350.00	350.00	350.00	350.00

2.7. Enteric Coating to Target Colon (EC1-EC6)

The optimized press-coated tablet was coated in a typical coating pan with a solution of Eudragit S100 in isopropyl alcohol:acetone plasticized with either PEG 400 or triethyl citrate at graduated amounts to a target weight increase of 5–10% (Table 4). The pan speed, spray rate, and inlet/outlet air temperature were monitored throughout. Coated tablets were dried and cured to promote polymer film coalescence and reproducible acid resistance.

Table 4. Composition of enteric coating solution on the press-coated pulsatile tablets (EC1–EC6).

Parameter	EC1	EC2	EC3	EC4	EC5	EC6
Eudragit S100 (% w/v)	5.00	5.00	7.50	7.50	10.00	10.00
PEG 400 (% w/w of polymer)	10.00	15.00	10.00	–	–	–
Triethyl citrate (% w/w of polymer)	–	–	–	10.00	15.00	20.00
Isopropyl alcohol : acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Target weight gain (%)	5.00	7.50	5.00	7.50	10.00	10.00

2.8. Evaluation of Pre-compression Parameters (powder blend)

The angle of repose was measured by the fixed funnel method. The bulk and tapped densities were measured by the 100 tap method. The flow and packing behavior of each lubricated blend (F1–F6) was evaluated in triplicate using Carr's compressibility index [$CI = 100 \times (\rho_{\text{tapped}} - \rho_{\text{bulk}})/\rho_{\text{tapped}}$] and Hausner's ratio ($\rho_{\text{tapped}}/\rho_{\text{bulk}}$).

2.9. Evaluation of Immediate Core Tablets (F1-F6)

Core tablets were subjected to weight variation (n = 20, analytical balance), hardness (n = 6, Monsanto/Pfizer tester), thickness (n = 6, vernier caliper), friability (n = 10, Roche friabilator; 100 revolutions at 25 rpm), disintegration time (USP apparatus, distilled water, 37 ± 0.5 °C), and

drug content/assay (powdered tablet equivalent to one dose, extracted, filtered and analyzed by UV spectrophotometry at λ_{max}). Also, in vitro release from the core tablets was determined using USP Apparatus II (paddle, 50–75 rpm, 37 ± 0.5 °C) in a suitable buffer.

2.10. Evaluation of press-coated pulsatile tablets (P1-P6)

Weight fluctuation, hardness, thickness and friability were determined as mentioned previously. Lag time, the time with negligible (< 10%) drug release before rapid release, and the subsequent release profile were determined by sequential-media dissolution (USP Apparatus II, 37 ± 0.5 °C, 50–75 rpm) with periodic sample withdrawal, filtration and spectrophotometric analysis. The swelling and erosion behavior of the compression coat was evaluated gravimetrically by removing, blotting and reweighing tablets at predetermined time intervals during dissolution.

2.11. Evaluation of Enteric Coated Tablets (EC1-EC6)

Coating uniformity was visually evaluated for smoothness, cracking and film integrity and the percentage weight gain was determined gravimetrically before and after coating. Acid resistance was assessed by incubating the tablets in 0.1 N HCl (pH 1.2) for 2 h and measuring the amount of medication released in the medium. The in vitro dissolution was then carried out using USP Apparatus II in a sequential pH program mimicking the in vivo oro-gastrointestinal transit: 0.1 N HCl (pH 1.2) for the first 2 h, phosphate buffer pH 6.8 for the next 3 h (2-5 h) and phosphate buffer pH 7.4 thereafter (5-12 h) to mimic the gastric, small-intestinal and colonic conditions, respectively; samples were withdrawn at predetermined times, filtered, assayed spectrophotometrically and replaced with an equal volume of fresh, temperature-equilibrated medium to maintain sink conditions.

2.12. Dissolution Comparison to a Marketed Product

To demonstrate the difference in release kinetics between conventional and chronomodulated distribution, the optimized enteric-coated formulation (EC5) was compared with a marketed conventional instant release Doxepin HCl tablet (Sinequan®) under identical USP Apparatus II conditions.

2.13. Kinetics of Drug Release

The cumulative dissolution data of optimized formulation (EC5) was fitted by linear least squares regression to the zero order model (cumulative % released vs. time), first order model ($\log_{10}$ % drug remaining vs. time), Higuchi model (cumulative % released vs. $\sqrt{\text{time}}$) and Hixson–Crowell cube root model (cube root of % drug remaining vs. time). As the Korsmeyer–

Peppas power-law model [$\log_{10}(M_t/M_\infty)$ vs. $\log_{10}(\text{time})$] is only strictly valid for the initial ~60% of cumulative release [23], the regression for the Korsmeyer–Peppas model was limited to time points when cumulative release was less than 60%. The goodness of fit was determined from the coefficient of determination (R^2) of each linear regression. The release exponent n , obtained from the slope of the Korsmeyer–Peppas equation, was interpreted according to the conventional classification for a non-swelling/cylindrical geometry ($n < 0.45$, Fickian diffusion; $0.45 \leq n < 0.89$, anomalous/non-Fickian transport; $n \geq 0.89$, Case-II/relaxation-controlled transport), explicitly acknowledging the limitations of this classification for systems with a significant lag phase (see Section 3.9). The model independent mean dissolution time (MDT) was also computed using the trapezoidal approach [24].

2.14. Stability studies

The short-term stability of the improved formulation (EC5) was evaluated in accordance with the International Conference on Harmonization (ICH) Q1A(R2) [25] for long-term ($25 \pm 2^\circ\text{C}$ / $60 \pm 5\%$ RH) and accelerated ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH) settings for an interim period of three months. Sampling was done at 0, 1, 2, and 3 months. The tablets were tested at each time interval for physical appearance, drug content (UV spectrophotometry), lag time, and cumulative dissolution profile, using the sequential-media procedure outlined in Section 2.11. Full six month long-term stability data collection was in progress at the time of this report and will be released separately.

2.15. Statistical Analysis

If not otherwise noted, all determinations were carried out in triplicate ($n = 3$) and are given as mean $\pm$ standard deviation (SD). Calibration and release-kinetic modeling were accomplished by linear and non-linear regressions using least-squares approach.

3. RESULTS AND DISCUSSION

3.1. Preformulation Characterization of Doxepin Hydrochloride

Doxepin HCl was produced as a white to off-white, odorless, free-flowing crystalline powder and its melting point (188°C) was in close agreement with the reported literature value indicating good purity and the absence of gross polymorphic change [44]. The medication showed a significant pH dependent equilibrium solubility that decreased from 38.42 ± 0.56 mg/mL in 0.1 N HCl (pH 1.2) to 15.76 ± 0.34 mg/mL and 7.24 ± 0.28 mg/mL at pH 6.8 and 7.4, respectively (Table 5), which is consistent with less ionization of the tertiary amine at higher pH. This

solubility gradient is mechanistically appropriate for the delivery strategy intended: the high acidic-media solubility does not constitute a formulation risk as the purpose of the enteric coat is to prevent exposure to the gastric environment altogether, whereas the relatively low colonic-pH solubility is offset by the addition of a fast-acting superdisintegrant within the core, resulting in rapid dissolution when the tablet coat has ruptured.

Table 5. Physicochemical properties of Doxepin hydrochloride

Parameter	Method	Result
Colour / odour	Visual / olfactory	White to off-white; odourless
Appearance / nature	Visual	Crystalline powder; fine, free-flowing
Melting point	Open capillary method	188 °C
Solubility, 0.1 N HCl (pH 1.2)	Shake-flask, UV assay	38.42 ± 0.56 mg/mL (freely soluble)
Solubility, phosphate buffer pH 6.8	Shake-flask, UV assay	15.76 ± 0.34 mg/mL (soluble)
Solubility, phosphate buffer pH 7.4	Shake-flask, UV assay	7.24 ± 0.28 mg/mL (slightly soluble)

Values expressed as mean ± SD, n = 3.

3.2. Development of Analytical Method

Scanning of Doxepin HCl solutions in the range of 200–400 nm showed λ_{max} at 292 nm in 0.1 N HCl and 291 nm in both phosphate buffer pH 6.8 and pH 7.4 (Fig. 2A–C). The little medium-dependent shift in λ_{max} suggested that the sequential-media dissolving process might be performed using a single, common analytical wavelength without loss of sensitivity. In all the three media, the calibration curves were linear in the concentration range of 2–20 µg/mL (Fig. 2D–F) ($y = 0.0552x + 0.0084$, $R^2 = 0.999$ in 0.1 N HCl; $y = 0.0540x + 0.0046$, $R^2 = 0.999$ in pH 6.8 and pH 7.4 buffers), which confirmed Beer–Lambert law. The closeness of the slopes in different mediums suggests that the molar absorptivity of Doxepin HCl is practically independent of pH in this range and the low intercepts confirm minimum blank interference. The method was found to be accurate, reproducible and suitable for purpose for drug-content and dissolution sample analysis.

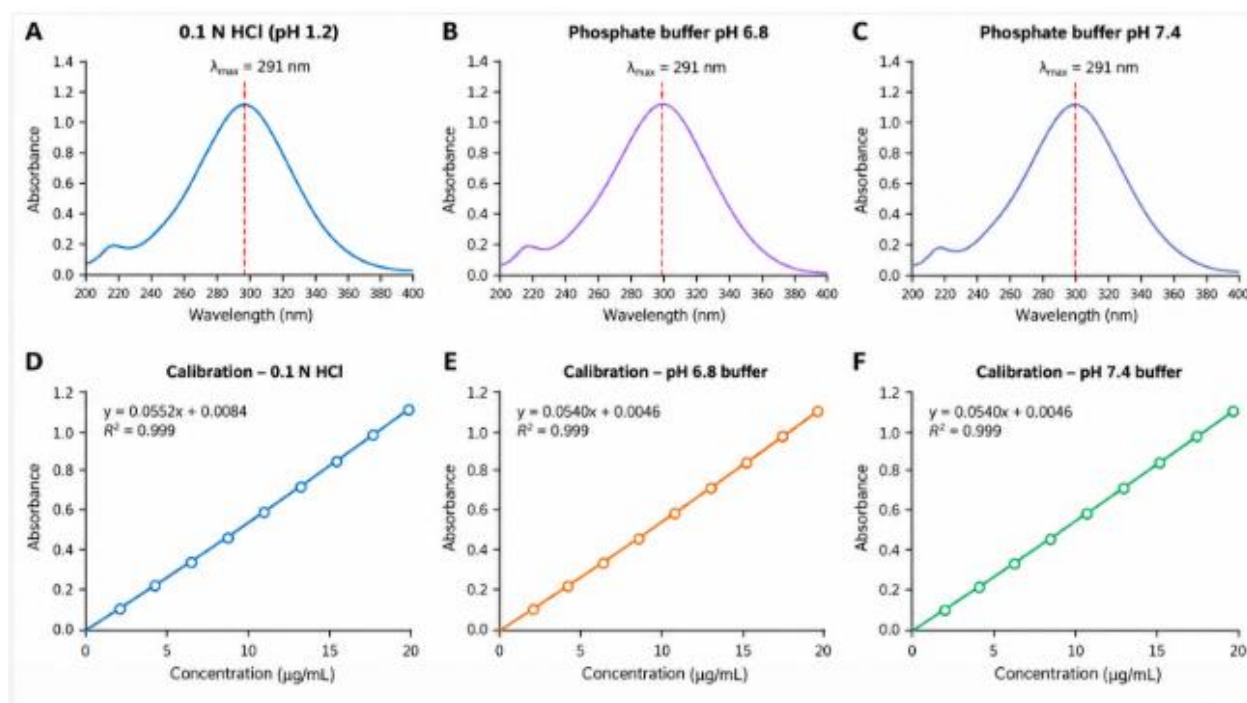


Figure 2. Calibration curves (D-F) and UV absorption spectra (A-C) of Doxepin HCl in 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4.

3.3. Drug-Excipient Compatibility (FT-IR)

The FTIR spectra of pure Doxepin HCl and optimized drug excipient physical mixture (Fig. 3) showed that all the main characteristic absorptions of the drug, aromatic and aliphatic C-H stretching, aromatic C=C stretching, C-N stretching, C-O-C stretching, and the tertiary amine and aromatic ring vibrations, were retained in the formulation spectrum with only minor (2–4 cm^{-1}) peak shifts due to physical mixing and weak hydrogen bonding contacts, rather than covalent interaction (Table 6). No disappearance of peaks, formation of new peaks and significant broadening of peaks were observed indicating the chemical compatibility of Doxepin HCl with croscopovidone, croscarmellose sodium, sodium starch glycolate, MCC PH 102, lactose monohydrate, HPMC K100M, ethyl cellulose and Eudragit S100 under the experimental conditions.

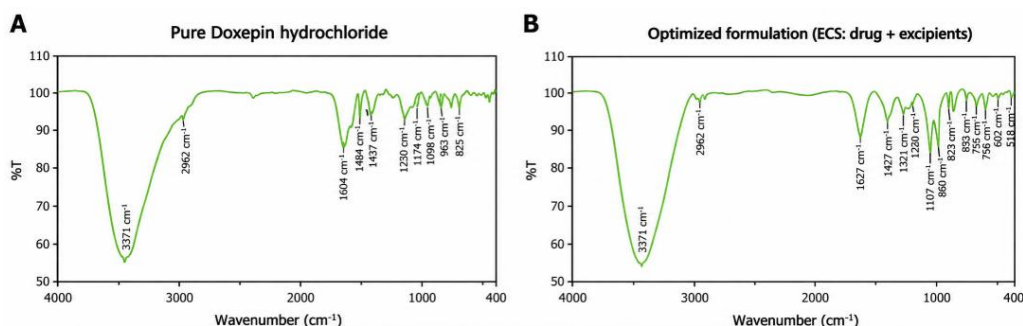


Figure 3. FTIR spectra of (A) pure Doxepin hydrochloride and (B) optimal formulation (drug + excipients) showing all characteristic drug bands for absorption.

Table 6. FTIR spectral assignment of Doxepin HCl: pure drug vs optimized formulation.

Functional group	Pure drug (cm ⁻¹)	Formulation (cm ⁻¹)	Inference
Aromatic C–H stretching	3058	3055	Retained
Aliphatic C–H stretching	2924	2921	Retained
Aromatic C=C stretching	1604	1601	Retained
C–N stretching	1285	1282	Retained
C–O–C stretching	1118	1115	Retained
Tertiary amine group	1028	1025	Retained
Aromatic ring vibrations	758	755	Retained

3.4. Pre-Compression (Flow) Properties of Core Tablet Powder Blends

All the six powder mixtures (F1–F6) had angle of repose <30°, Carr's index 10–13% and Hausner's ratio ≤1.14 (Table 7), which shows good to exceptional flow and compressibility suited for direct compression^[44]. The most favorable flow indices (angle of repose 26.5°; Carr's index 10%; Hausner's ratio 1.11) were observed for formulation F6, which contained the higher level (9 mg) of sodium starch glycolate, likely due to the relatively low bulk/fines ratio and favorable particle morphology of sodium starch glycolate at this concentration^[37].

Table 7. Micromeritic pre-compression properties of core-tablet powder blends F1–F6.

Formulation	Angle of repose (°)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner's ratio
F1	28.5	0.42	0.48	12.5	1.14
F2	27.8	0.43	0.49	12.2	1.13
F3	27.2	0.44	0.5	12	1.13
F4	29	0.41	0.47	12.7	1.14
F5	28.2	0.42	0.48	12.5	1.14
F6	26.5	0.45	0.5	10	1.11

3.5. Post-Compression Evaluation and Selection of the Optimized Core Tablet

The post compression parameters of F1-F6 are given in Table 8. All the batches were within the pharmacopeial standards for weight variation (150 ± 2 mg), hardness (3.4-3.8 kg/cm²) and friability (< 1%). The disintegration time, a key performance property for a core tablet designed to disintegrate rapidly after rupture of the outer pulsatile coat, was between 22 and 48 s across the six batches and decreased with superdisintegrant type in the order sodium starch glycolate < croscarmellose sodium < crospovidone at the higher level tested. The formulation F6 (9 mg sodium starch glycolate) exhibited the fastest disintegration time (22 s) with the highest drug concentration (99.5%) and was chosen as optimum core for subsequent compression coating.

Table 8. Post-compression parameters for immediate release core tablets F1-F6.

Formulation	Weight (mg)	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	Disintegration time (s)	Drug content (%)
F1	150 ± 2	3.5	3.2	0.72	45	98.5
F2	150 ± 2	3.6	3.2	0.7	38	99
F3	150 ± 2	3.7	3.3	0.68	30	99.2
F4	150 ± 2	3.4	3.2	0.75	48	98.3
F5	150 ± 2	3.5	3.2	0.72	35	99.1
F6	150 ± 2	3.8	3.3	0.65	22	99.5

n = 20 for weight variation; *n* = 6 for hardness/thickness; *n* = 10 for friability; *n* = 3 for disintegration time and drug content.

3.6. Physical Evaluation and Lag Time of Press-Coated Pulsatile Tablets (P1-P6)

The optimized core (F6) was compression coated with graded HPMC K100M : ethyl cellulose blends to prepare tablets of uniform weight (350 ± 3 mg) and acceptable friability (< 1%). The hardness increased from P1 (5.2 kg/cm²) to P6 (6.2 kg/cm²) with the variation of total polymer load and ethyl cellulose ratio (Table 9).

Table 9. Physical properties and lag time of press coated pulsatile tablets P1-P6

Formulation	Weight (mg)	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	Lag time (h)
P1	350 ± 3	5.2	4.5	0.68	3
P2	350 ± 3	5.4	4.6	0.65	4
P3	350 ± 3	5.6	4.6	0.62	5

P4	350 ± 3	5.8	4.7	0.6	6
P5	350 ± 3	6	4.7	0.58	6.5
P6	350 ± 3	6.2	4.8	0.55	7

The in vitro release profile of P1–P6 (Table 10, Fig. 4) revealed the typical pulsatile pattern with initial lag phase and subsequent fast drug release. The lag time rose monotonically with total coat weight and in particular with HPMC K100M : ethyl cellulose ratio, from 3 h (P1) to 7 h (P6) (Table 9), validating the fact that the compression coat operates as a tunable, swelling/erosion regulated barrier [26,28]. Mechanistically, HPMC K100M hydrates and swells on contact with the dissolution medium, forming a gel layer that retards the ingress of fluid, while the hydrophobic ethyl cellulose component enhances this barrier further and prevents early disintegration; once the composite barrier has been sufficiently hydrated and eroded, the coat ruptures and the exposed, rapidly disintegrating core (F6) releases its dose rapidly. Formulation P6 (110 mg HPMC K100M : 80 mg ethyl cellulose) exhibited the longest and most clearly delineated lag phase (only 8.6% release at 7 h, rising to 71.8% by 9 h and $\geq 96\%$ by 10 h) and was taken forward as the optimum press-coated intermediate for enteric coating.

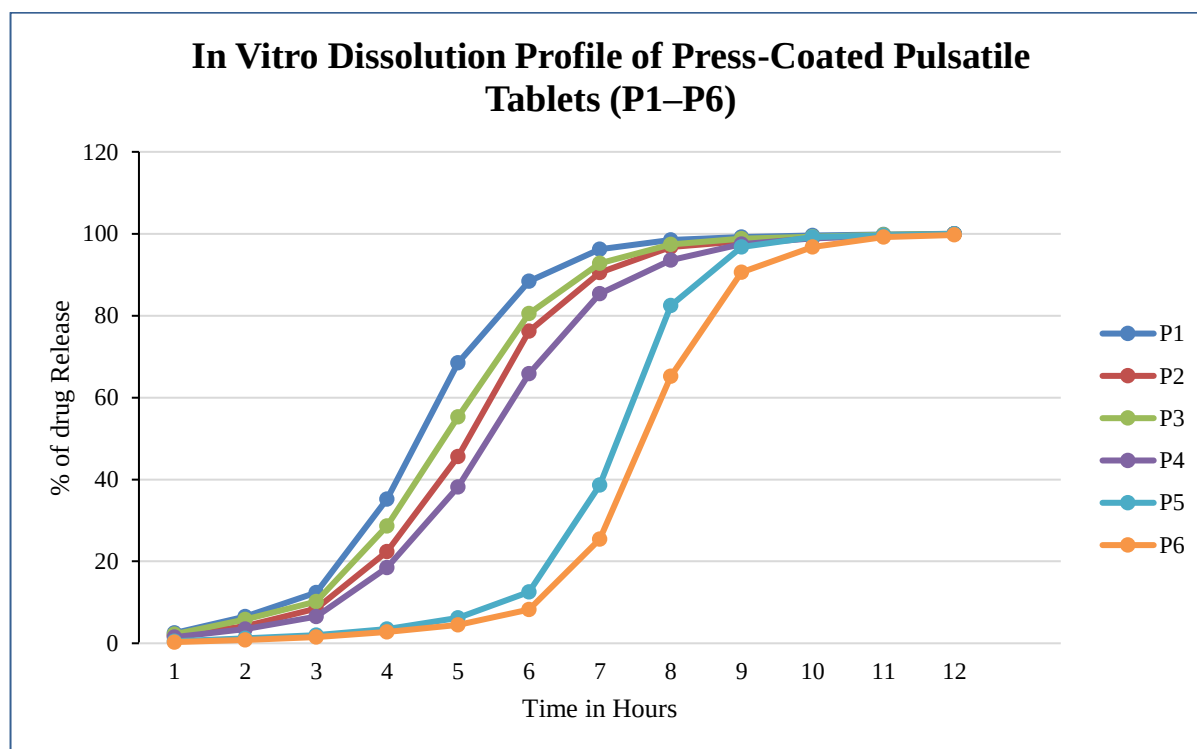


Figure 4. In vitro cumulative drug release profiles of press-coated pulsatile tablets P1–P6 in sequential dissolution media, illustrating the progressive increase in lag time with increasing HPMC K100M content of the compression coat.

Table 10. In vitro cumulative drug release (%) of press-coated pulsatile tablets P1–P6.

Time (h)	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	1.8	1.5	1.2	0.9	0.6	0.4
3	12.5	2.8	1.8	1.4	1	0.7
4	68.4	18.6	3.5	2.2	1.6	1.1
5	92.3	74.2	24.8	4.6	2.8	1.9
6	98.1	95.6	79.4	28.5	6.5	3.2
7	99	98.7	96.2	82.3	36.4	8.6
8	99.4	99.2	98.8	97.1	86.7	22.5
9	99.6	99.5	99.3	99	97.8	71.8
10	99.8	99.7	99.6	99.4	99.1	96.4
11	99.9	99.8	99.8	99.7	99.4	99.2
12	100	100	100	100	99.8	99.7

Sequential medium dissolution, USP Apparatus II, 37 ± 0.5 °C, $n = 3$. Values are mean cumulative % drug release.

3.7. Evaluation of Enteric-Coated Pulsatile Tablets (EC1–EC6) and Selection of the Optimized Formulation

The optimized press-coated tablet (P6) was enterically coated with Eudragit S100 which showed smooth, crack-free films at all six coating levels with weight gain from 5 to 10% (Table 11); EC5 and EC6, coated to the highest target weight gain (10%) exhibited the most uniform and defect-free surfaces when visually inspected. The key screening criterion for colon-targeting performance, the two-hour acid-resistance test in 0.1 N HCl, showed a clear, coating-level-dependent trend: drug release decreased from 6.5% (EC1, 5% Eudragit S100, PEG 400 plasticizer) to 0.8% (EC6, 10% Eudragit S100, 20% triethyl citrate), consistent with the established pH-dependent solubility profile of Eudragit S100 above pH 7.0 ^[41]. The acid resistance was further increased by changing the plasticizer from PEG 400 to triethyl citrate (EC4–EC6 vs. EC1–EC3) at the same coating level, possibly due to the more hydrophobic and less permeable film formed with triethyl citrate ^[43].

Table 11. Physical characterization, weight gain and acid resistance of enteric coated pulsatile tablets EC1-EC6.

Formulation	Appearance	Weight gain (%)	Surface characteristics	Release in 0.1 N HCl at 2 h (%)
EC1	Smooth	5	Slight roughness	6.5
EC2	Smooth	7.5	Uniform	4.2
EC3	Smooth	5	Uniform	5.8
EC4	Smooth	7.5	Good	3.5
EC5	Smooth	10	Excellent, uniform	1.2
EC6	Smooth	10	Slightly thick coat	0.8

Full sequential-media dissolution (Table 12, Fig. 5) confirmed a three-phase release pattern for all batches: negligible release in 0.1 N HCl (0–2 h), gradual, coating-level-dependent onset of release in pH 6.8 buffer (2–5 h) as the enteric film began to ionize, and rapid “burst” release in pH 7.4 buffer (5–12 h), consistent with progressive rupture of both the enteric film and the underlying compression coat ^[27, 30]. The formulations EC1-EC3 showed that a considerable part of their dose was released in the period of pH 6.8, which indicated premature and thus insufficient enteric protection for reliable colon targeting. In spite of being the best in acid resistance, EC6 presented a far too lengthy lag phase (less than 10% release up to 7 h, not reaching 90% before 9 h), which would pose a risk of shifting drug delivery beyond of the specified pre-dawn therapeutic window if delivered at a practical bedtime. The best overall balance was supplied by EC5 which showed outstanding acid resistance (1.2% release at 2 h), a well-defined lag phase throughout the small-intestinal transit window and quick near-complete burst release in the colonic-pH phase (38.6% at 7 h, 82.5% at 8 h, 96.8% at 9 h and 100% by 12 h). Thus, EC5 was selected as the optimal chronomodulated colon targeted pulsatile formulation and was employed for all the comparative, kinetic and stability experiments.

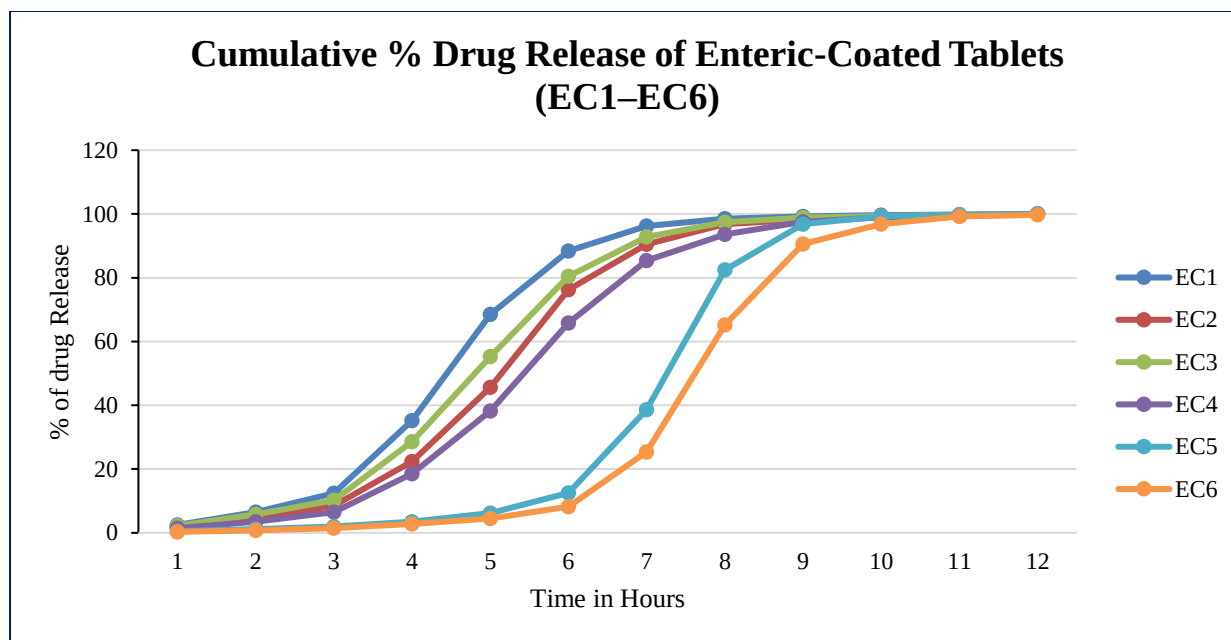


Figure 5. Cumulative in vitro drug release profiles of enteric-coated pulsatile tablets EC1–EC6 in sequential pH media (0.1 N HCl, 0–2 h; pH 6.8, 2–5 h; pH 7.4, 5–12 h) imitating gastric, small-intestinal and colonic transit, respectively.

Table 12. In vitro cumulative drug release (%) of enteric coated pulsatile tablets EC1-EC6 in successive pH media

Time (h) / medium	EC1	EC2	EC3	EC4	EC5	EC6
1 (pH 1.2)	2.5	1.8	2.2	1.5	0.5	0.3
2 (pH 1.2)	6.5	4.2	5.8	3.5	1.2	0.8
3 (pH 6.8)	12.4	8.5	10.2	6.5	2	1.5
4 (pH 6.8)	35.2	22.4	28.6	18.5	3.5	2.8
5 (pH 6.8)	68.5	45.6	55.3	38.2	6.2	4.5
6 (pH 7.4)	88.4	76.2	80.5	65.8	12.5	8.2
7	96.2	90.5	92.8	85.4	38.6	25.4
8	98.5	96.8	97.4	93.6	82.5	65.2
9	99.2	98.2	98.8	97.5	96.8	90.6
10	99.6	99.1	99.3	98.9	99.2	96.8
11	99.8	99.5	99.7	99.4	99.6	99.2
12	100	100	100	100	100	99.7

USP Apparatus II, 37 ± 0.5 °C, $n = 3$; values are mean cumulative % drug release.

3.8. Comparative Dissolution and Chronotherapeutic Justification

The EC5 was compared to a commercialized conventional instant release Doxepin HCl tablet (Sinequan®) under identical dissolution conditions (Table 13, Fig. 6A). The marketed product demonstrated 68.5% of its dose released within 1 h and $\geq 99\%$ released within 3 h, consistent with its intended immediate-release properties, but poorly aligned with the circadian timing of nocturnal depressive symptoms: a dose of the marketed product at bedtime would be substantially absorbed and partially eliminated several hours prior to the early-morning symptom window. Conversely, EC5 released $<4\%$ of its dose over the equivalent 0–4 h interval and burst release was observed between about 6 and 9 h after administration.

Table 13. Comparative in-vitro release profile of commercial immediate release Doxepin HCl tablet and improved formulation EC5.

Time (h)	Marketed IR tablet (Sinequan®), % released	Optimized EC5, % released
1	68.5	0.5
2	96.8	1.2
3	99.2	2
4	99.8	3.5
5	100	6.2
6	100	12.5
7	100	38.6
8	100	82.5
9	100	96.8
10	100	99.2

A typical bedtime dose given at around 22:00 h, a programd lag phase of ~ 7 h would place the onset of the colonic burst release around 05:00–06:00 h (Fig. 6B) – within the window in which cortisol output and depressive/anxiety symptom severity are reported to peak in patients with nocturnal or early-morning-predominant depression ^[5,6]. This time-of-release alignment is the main pharmaceutical rationale for the tri-layer design and reflects chronomodulated approaches previously validated for nocturnal hyperacidity and, more generally, for other circadian-patterned cardiovascular and respiratory disorders covered in recent chronopharmaceutics reviews ^[20,32–35]. The schematic timeline shown in Fig. 6B is based on in vitro release data and reported circadian-

symptom literature, and is not pharmacokinetic or clinical evidence of chronotherapeutic benefit, which would require confirmation in biorelevant and in vivo studies (Section 4).

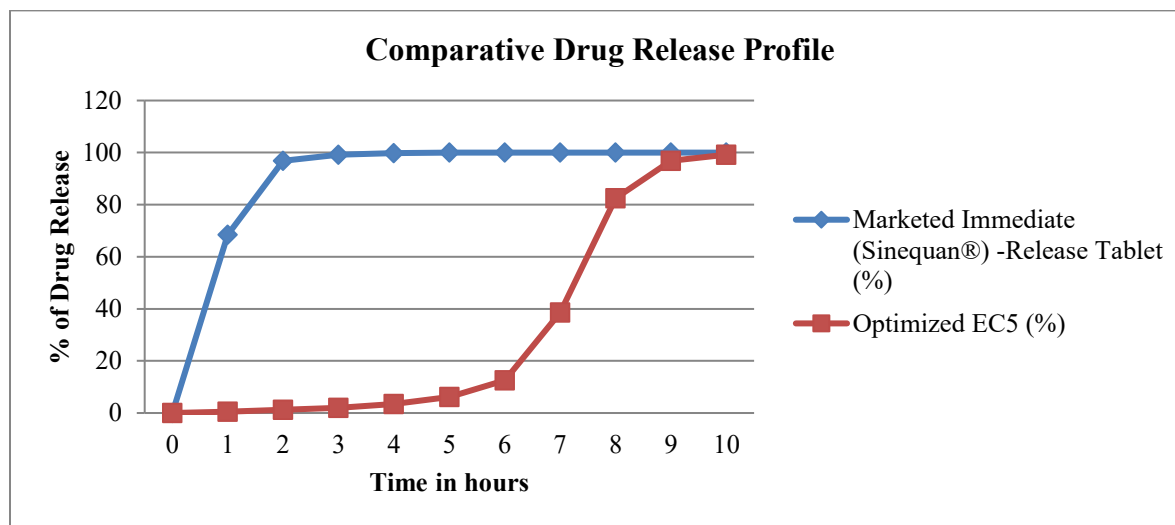


Figure 6: Comparative Dissolution Profile of Marketed Tablet and Optimized Formulation (EC5)

3.9. Kinetics of Drug Release

Linear regression was used to fit cumulative release data for EC5 to five kinetic models (Table 14, Fig. 7). The zero-order model ($R^2 = 0.847$) was the best linear fit to the data, followed by the Hixson–Crowell cube-root model ($R^2 = 0.821$), first-order model ($R^2 = 0.713$), and Higuchi square-root-of-time model ($R^2 = 0.672$). The relatively poor fit of the Higuchi and simple diffusion models is expected for a system with a real multi-hour lag phase, as they imply a continually diffusing concentration gradient from $t = 0$, where diffusion is not the major release-controlling mechanism. The good zero-order and Hixson–Crowell fits instead indicate an erosion- and surface-area-change-controlled release process occurring after the hydration and rupture of the compression coat, which is consistent with the combined swelling (HPMC K100M) and eroding (ethyl cellulose) barrier mechanism discussed in Section 3.6.

Korsmeyer-Peppas study used regression only to the data points where the cumulative release was not higher than 60% ($t \leq 7$ h), as is known in the valid range of the power law model [23,24]. This poor fit yielded $R^2 = 0.896$ with a release exponent $n = 2.03$. The standard Peppas classification of n was derived for matrices releasing drug from $t = 0$ without an explicit lag term, thus a value of n well above the conventional Case-II transport threshold ($n \geq 0.89$) in a system with a pronounced lag phase should be interpreted with caution. The unusually steep apparent exponent most likely reflects the compressed, fast-accelerating release window immediately after coat rupture rather than a literal physical transport phenomenon, and is a known artifact of

applying a no-lag power law to lag-time/pulsatile release data. A more rigorous mechanistic description of such profiles would require a model with an explicit lag or delay term (e.g. a lag-time-corrected Weibull function); attempts at such non-linear fitting during the present, relatively coarse 13-point time-course were found to be numerically ill-conditioned (parameter non-identifiability between the location and shape terms) and are thus not reported quantitatively, but this remains a worthwhile refinement for future work using a higher sampling frequency across the lag-to-burst transition. The model independent mean dissolution time of EC5 computed by trapezoidal technique was 7.07 h which confirmed the programd lag time calculated directly from the dissolution profile.

Table 14: Release kinetic model parameters of improved formulation (EC5).

Kinetic model	Linearized plot	R ²	Parameter
Zero-order	Cumulative % released vs. time	0.847	k ₀ = 10.78 %/h
First-order	Log % remaining vs. time	0.713	k ₁ = 0.483 h ⁻¹
Higuchi	Cumulative % released vs. $\sqrt{\text{time}}$	0.672	k _H = 37.13
Hixson–Crowell	Cube root % remaining vs. time	0.821	k _{HC} = 0.418 h ⁻¹
Korsmeyer–Peppas (≤60% release)	Log cumulative % released vs. log time	0.896	n = 2.03

R² values obtained by least-squares linear regression of the raw dissolution data in Table 12 (formulation EC5); mean dissolution time (trapezoidal method) = 7.07 h.

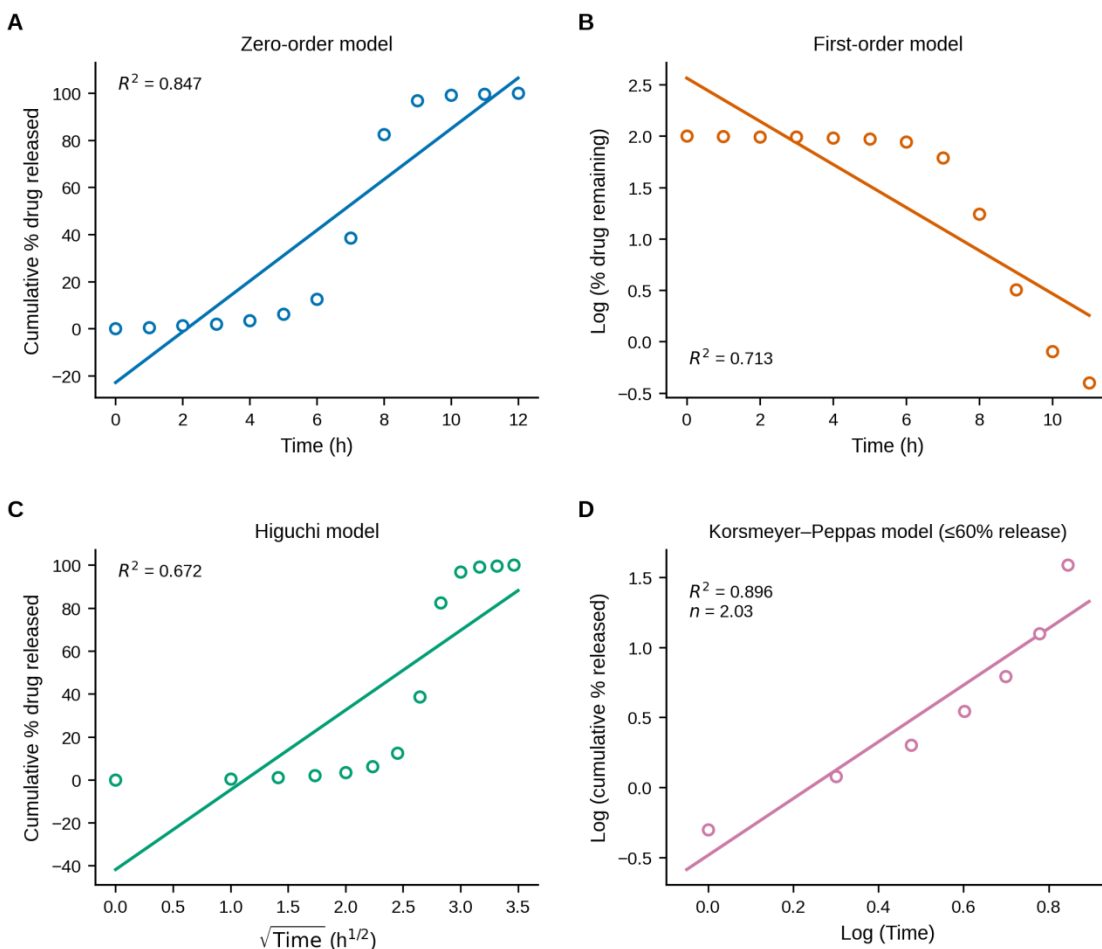


Figure 7. Release kinetic modeling for the optimized formulation EC5: (A) zero order, (B) first order, (C) Higuchi and (D) Korsmeyer-Peppas (limited to $\leq 60\%$ cumulative release).

3.10. Stability Studies

EC5 exhibited a smooth, uniform coating and structural integrity throughout the three-month interim period under both long-term ($25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$) and accelerated ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$) ICH conditions with only slight surface dullness (no cracking or peeling) under accelerated storage at three months (Table 15, Fig. 8). The drug content decreased slightly from 99.2 % to 98.6 % under long term settings and to 97.9 % under accelerated conditions, both values being comfortably within the typical 95–105 % acceptability range [25]. The lag time was virtually maintained (7.0 to 7.1 hours long-term; 7.0 to 7.2 hours accelerated) and the cumulative release at 10 hours remained $> 98\%$ under both settings suggesting that neither the enteric film nor the underlying compression coat exhibited functionally significant deterioration. These interim data support the short-term physical, chemical and functional (release) stability of EC5.

Confirmatory long-term data, to six months and beyond, coupled with photostability and in-use stability tests, are indicated prior to a definitive shelf-life claim ^[46].

Table 15. Stability statistics of improved formulation (EC5) under ICH long term and accelerated storage conditions.

Time (month)	Condition	Physical appearance	Drug content (%)	Lag time (h) / % release at 10 h
0	Long-term	Smooth, uniform	99.2	7.0 / 99.2
1	Long-term	No change	99	7.0 / 99.0
2	Long-term	No change	98.8	7.1 / 98.7
3	Long-term	No change	98.6	7.1 / 98.5
0	Accelerated	Smooth, uniform	99.2	7.0 / 99.2
1	Accelerated	No change	98.7	7.1 / 98.8
2	Accelerated	No change	98.3	7.2 / 98.4
3	Accelerated	Slight dullness; no cracking/peeling	97.9	7.2 / 98.0

Long-term: $25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{ RH}$. Accelerated: $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$ (ICH Q1A(R2)). $n = 3$.

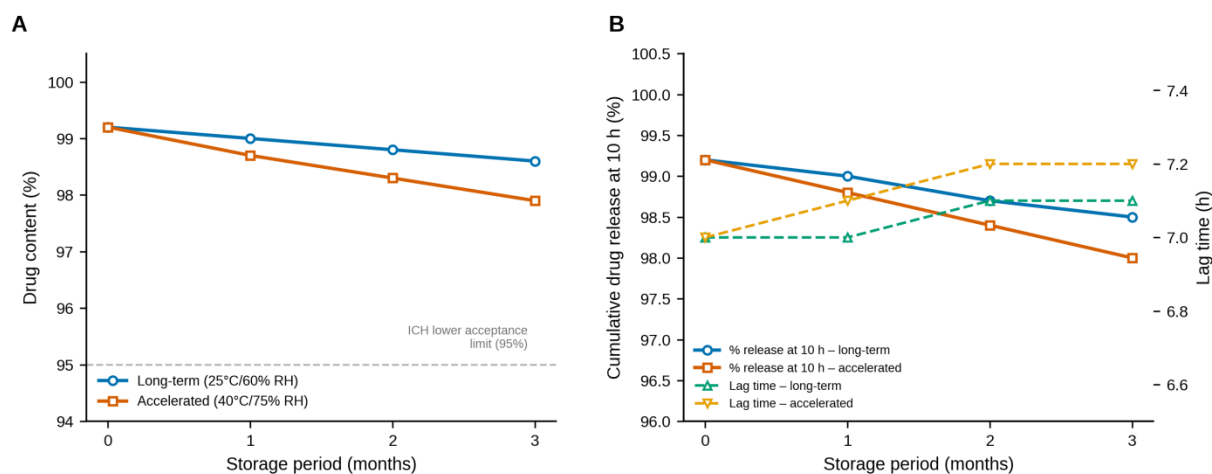


Figure 8. Stability profile of optimized formulation (EC5) under ICH long-term and accelerated storage conditions after three months: (A) drug content; (B) cumulative drug release at 10 h and lag time.

4. CONCLUSION

A chronomodulated, colon-targeted pulsatile tablet (EC5) was developed by sequential compression coating of an optimized, superdisintegrant-based immediate-release Doxepin HCl core with a graded HPMC K100M/ethyl cellulose barrier and subsequent pH-triggered Eudragit S100 enteric coating. The developed formulation could remain pharmaceutically quiescent

through simulated gastric and small-intestinal transit, and provide a rapid, near-complete burst release timed to coincide with early-morning worsening characteristic of nocturnal depression. The optimized formulation demonstrated good acid resistance, reproducible ~7 h lag time, release kinetics dominated by polymer erosion/relaxation rather than simple diffusion, and short term physical, chemical and functional stability under ICH long term and accelerated conditions, FTIR confirmed no drug–excipient interaction. Taken together, these findings provide technical proof of concept for a colon-targeted chronomodulated delivery approach for Doxepin HCl and a rational formulation platform that merits further evaluation in biorelevant dissolution media, extended duration stability studies, and in vivo pharmacokinetic–pharmacodynamic and chronotoxicological models prior to clinical translation.

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