

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF AMBROXOL HYDROCHLORIDE USING LOCUST BEAN GUM AS A NATURAL RELEASE MODIFIER: *IN VITRO* AND *IN VIVO* EVALUATION

Peeyush Srivastava¹, Naviksha S², Parthasarathi Barik³, Dr. Raghu P S⁴, Pratik Shee⁵, Dhritiman Debnath⁶, Priyanka Ray^{*7}

¹ School of Pharmacy and Research, Devbhoomi Uttarakhand University, Uttarakhand.

² JSS College of Pharmacy Ooty, Ootacamund, Tamil Nadu.

³ Chalmers University of Technology, Gothenburg, Sweden.

⁴ University of Pharmaceutical Sciences, Guru Kashi University, Punjab.

⁵ Guru Nanak Institute of Pharmaceutical Science and Technology, Khardaha, West Bengal.

⁶ Assistant Professor, Bengal School of Technology, Hooghly, West Bengal, Pincode: 712102.

⁷ Department of Pharmacy, Guru Nanak Institute of Pharmaceutical Science and Technology, Sodepur, Panihati, Kolkata, West Bengal.

Corresponding Author:

Priyanka Ray*

priyanka.ray@gnipst.ac.in

Department of Pharmacy, Guru Nanak Institute of Pharmaceutical Science and Technology, Sodepur, Panihati, Kolkata, West Bengal.

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ABSTRACT

Ambroxol hydrochloride is a widely prescribed mucoactive agent whose short elimination half-life obliges two- to three-times-daily dosing, a regimen that erodes adherence in chronic bronchopulmonary disease. Synthetic cellulose ethers dominate published sustained-release approaches to this drug, while inexpensive plant-derived galactomannans remain comparatively unexplored. The present work was undertaken to design, characterise and biologically evaluate a sustained-release matrix tablet of ambroxol hydrochloride using locust bean gum as the sole release modifier, benchmarked against a conventional immediate-release tablet. Five matrix formulations (SR-1 to SR-5) containing 10–50% w/w locust bean gum were prepared by direct compression, and an immediate-release reference was prepared by wet granulation. Blends were assessed for micromeritic behaviour; drug–polymer compatibility was examined by Fourier transform infrared spectroscopy and differential scanning calorimetry; tablets were evaluated for thickness, hardness, friability, weight variation, disintegration and drug content; and release was studied in phosphate buffer pH 6.8 over 24 h. Comparative bioavailability was determined in healthy albino rabbits using a validated reverse-phase high-performance liquid chromatographic assay. All blends flowed acceptably (angle of repose 21.11–23.01°; Hausner ratio 1.14–1.33) and all tablets complied with compendial limits, with drug content between 95.36 ± 1.2% and 104.46 ± 1.6%. Spectroscopic and thermal data showed no drug–polymer interaction. The immediate-release tablet released 94.95% of its dose within 1.25 h, whereas matrix release was extended across 24 h and increased progressively with polymer loading, from 67.58% (SR-1) to 104.73% (SR-5). SR-3 (30% w/w gum) gave the most uniform 24 h profile, reaching 98.92%, and followed non-Fickian (anomalous) transport. *In vivo*, SR-3 produced a 2.4-fold higher AUC_{0–∞}, a 2.5-fold longer half-life and a 2.5-fold lower elimination rate constant than the immediate-release reference. Locust bean gum is therefore a viable single-polymer release modifier for once-daily ambroxol hydrochloride.

Keywords: Ambroxol hydrochloride, Locust bean gum, Sustained release, Matrix tablet, Direct compression, Bioavailability.

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INTRODUCTION

The large global problem of bronchopulmonary disorders accompanied by excessive production of mucus and poor mucus transport remains relevant nowadays, and mucoactive drugs are still an integral part of the treatment of these diseases. Systematic review and meta-analysis of randomized trials in stable chronic obstructive pulmonary disease found out that mucolytics significantly reduce the

frequency of exacerbations and need for

hospitalization, decrease duration of antibiotic therapy and increase the time before first exacerbation, without side effects distinguishable from placebo. Ambroxol hydrochloride, which is the active metabolite of bromhexine, belongs to the most frequently used medicines of this group; adjunctive therapy with ambroxol speeds up the resolution of symptoms and improves lung function in chronic bronchitis with antibacterial therapy (2).

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The mechanism of secretolytic action includes increasing the output of pulmonary surfactants, serous bronchial glands and modification of nitric oxide-dependent pathways; the interest to the drug became even higher due to discovery of its antioxidant and anti-inflammatory properties in non-pulmonary systems (3).

Pharmaceutical limitations of ambroxol hydrochloride are kinetics rather than pharmacodynamics related. The medicine is fast-absorbing with high bioavailability, however it is cleared quickly, thus conventional immediate release preparations have to be taken twice or three times per day in order to provide therapeutic plasma levels. In the steady state crossover study in healthy volunteers, the once-daily extended release 75 mg capsule was shown to be equal to twice-daily immediate release formulations in terms of systemic exposure, but to reduce C_{max} and shift t_{max} to 6 h. Decreasing the number of administrations is not just the convenience: once-daily dosing schedule has been proven to result in significantly higher compliance compared to twice-daily regimen during chronic therapy. The development of effective sustained-release formulation is therefore justified. Previously employed systems for extending ambroxol release have been almost exclusively engineered or synthetic ones. Osmotic pump tablets based on elementary osmotic system with plasticized ethylcellulose coating demonstrated almost zero-order drug release over 12 h and 109.6% of relative bioavailability in rabbits; however, they need precise membrane coating and orifice control (6). In situ-gelling pectin solutions extended drug release for about 6 h in rats, providing only 64% of bioavailability of a commercially available comparator (7). Hydroxypropyl methylcellulose matrices represent traditional systems; however, the profile of drug release from such systems is dependent on properties of polymers, filler and technological factors (8). All the above strategies introduce either increased processing complexity or cost of excipients.

The plant polysaccharides can be used as an alternative excipient. Locust bean gum – galactomannan obtained from endosperm of *Ceratonia siliqua* seeds – is a biocompatible, biodegradable and cheap hydrocolloid that consists of β -(1→4)-D-mannan with α -(1→6)-D-galactose side chains present in the ration of approximately 4:19. Low degree of substitution facilitates intermolecular interaction and strong synergistic effect in gel formation together with other hydrocolloids, and locust bean gum demonstrates binding, stabilization, bioadhesion and matrix-forming properties in pharmaceutical formulations (10,11). The class of galactomannans was used in development of matrix tablets, micro- and nanoparticles, hydrogels and nanocarriers (12). It was proved that locust bean gum delays the release

of model substances of different molecular weight from compressed matrices (13) and participates in colon targeting in the case of its application in combination with cellulose ethers and enteric coating (12). The important feature is that almost all applications involve the use of gum in combination with a second polymer; the behavior of gum as the single controlling release excipient and the concentration-dependence of drug release from directly compressed matrix are much less studied (15).

In this context, the current study was formulated with the objective of formulating a matrix sustained release tablet of ambroxol hydrochloride, where locust bean gum is the sole release modifying agent, to understand the effect of varying amounts of gum on the rate and mechanism of drug release and also to see if there is any change in the in vivo plasma profile of the drug.

Aim and objectives

The objective was to develop and characterise sustained-release tablet of ambroxol hydrochloride based on locust bean gum as a natural release-modifier. Specific objectives included: (i) development of immediate-release and sustained-release tablets and their physicochemical characterisation before and after compression; (ii) confirmation of absence of interaction between drug and excipient through spectroscopic and thermal analysis; (iii) quantification of the effect of polymer content on in vitro drug release and determination of release mechanism; and (iv) comparison of pharmacokinetics of the developed sustained-release tablet with that of an immediate-release reference in rabbits.

Hypothesis

Inclusion of locust bean gum in an ambroxol hydrochloride matrix for direct compression has been found to alter the in vitro drug release profile in a concentration-dependent fashion, and leads to enhanced systemic availability as well as a delayed elimination phase in rabbit studies.

MATERIALS AND METHODS

Materials

The ambroxol hydrochloride drug was purchased from Titan Chemicals, Shanghai, China. The locust bean gum was bought from CK Products Pvt. Ltd, Kerala, India. Magnesium stearate, lactose, polyvinylpyrrolidone K-30, acetonitrile and methanol were procured from SD Fine Chemicals Pvt. Ltd, Mumbai, India. Microcrystalline cellulose, talc and isopropyl alcohol were purchased from Sigma-Aldrich Pvt. Ltd, Mumbai, India. Other reagents used were of analytical grade.

Equipment utilized in the study included a digital balance (BT224, Sartorius, India), hot air oven (NSW, India), Fourier transform infrared spectrophotometer (Shimadzu, Japan), differential scanning calorimeter (DSC Q200, TA Instruments, USA), digital pH meter (Eutech Instruments,

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Singapore), probe sonicator (Bandelin RK 100 H, Germany), ten station rotary tablet press (Rimek, Ahmedabad, India), Monsanto hardness tester, friabilator, dissolution equipment and centrifuge (Electrolab, Mumbai, India), UV/visible spectrophotometer (UV-1700, Shimadzu, Japan).

Preformulation studies

Calibration Curve. Preparation of the primary stock solution of ambroxol hydrochloride was made in 0.1 N hydrochloric acid. Volumes of 1–5 mL of the solution were transferred to 10 mL volumetric flask and filled up with 0.1 N hydrochloric acid to get concentrations in the range of 10–50 µg/mL. Absorbance measurement was done at 243 nm against 0.1 N hydrochloric acid as blank.

Micromeritic Evaluation. Angle of repose was measured by fixed funnel method using formula: $\theta = \tan^{-1}(h/r)$, where h and r are the height and radius of the cone. Bulk density of loose powders was measured by pouring about 30 g of the sample into a dry 100 mL cylinder without compaction. Bulk density of tapped powder was measured after 500 and 750 additional tappings; volume was measured before and after the process. Compressibility index according to Carr was measured by formula: $[(TBD - LBD) \times 100]/TBD$ and Hausner ratio was: TBD/LBD .

Drug-Excipients Compatibility. Ambroxol hydrochloride, locust bean gum and their 1:1 mixture were separately triturated with dry potassium bromide, pressed to form translucent discs and measured from 4000 to 400 cm^{-1} . For the thermographic analysis 5 mg of each sample was weighed into non-hermetically sealed aluminum pans and heated from 20 to 400 °C at 10 °C/min under nitrogen purge at 50 mL/min, using calorimeter that was calibrated for temperature and heat flux measurements with high-purity indium standard.

Preparation of tablets

Immediate release tablets. Conventional immediate release tablets were prepared by wet granulation method. The drug and other ingredients were mixed in tumbler blender for 5 min and moistened in mortar using polyvinylpyrrolidone K-30 in isopropyl alcohol as granulating solution. The wet mass was then sieved manually with 1.7 mm British Standard Sieve and dried at 60 °C for 3–4 hours when loss on drying was reduced below 2 % w/w. The dry granules were sieved through 1.0 mm sieve, blended with magnesium stearate and talc in the ratio of 2:1 and then compressed using ten stations rotary tablet press equipped with 5.0 mm concave punches at 12,000 N pressure (9000 N during preliminary runs). Fifty tablets were prepared.

Sustained release tablets. Matrix tablets were prepared by direct compression method. Locust bean gum was used as matrix material, while microcrystalline cellulose was used as diluent. Talc

and magnesium stearate were added as lubricants. All the ingredients were sieved through 100 mesh sieve, weighed and mixed. Lubricated blends were compressed on same press using 5 mm concave punches with 12 kN (9 kN during preliminary runs) pressure. Fifty tablets were prepared in each batch. The composition of tablets is given in Table 1.

Tablet evaluation.

The thickness of the tablets was checked with the help of Mitutoyo electronic Vernier caliper from Japan. The hardness of the tablets was checked by Monsanto hardness tester. In friability test, tablets were rotated in friabilator for 100 cycles in 4 minutes and weight loss was recorded in %. The weight variation of the tablets was calculated according to the limit set by the Indian Pharmacopoeia. The disintegration time was calculated for the immediate release tablet. For drug content estimation, tablets were crushed and required amounts were taken in 100 mL volumetric flask.

In vitro release study

Release study was performed in 900 ml of phosphate buffer solution, pH 6.8, temperature kept 37 ± 0.5 °C and agitated at 50 rpm using USP apparatus. Samples of 5.0 ml were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours, filtered by 0.45 µm membrane filter and replenished with equal quantity of warm buffer solution. Release from six tablets per batch was examined spectrophotometrically at 243 nm.

Release kinetics

Release data were fitted to zero-order ($Q_t = Q_0 + K_0t$), first-order ($\log Q_t = \log Q_0 + K_1t/2.303$), Higuchi ($Q_t = K_H\sqrt{t}$) and Korsmeyer–Peppas ($M_t/M_\infty = Kt^n$) models. For the Korsmeyer–Peppas model, $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ anomalous (non-Fickian) transport, $n = 0.89$ Case-II transport and $n > 0.89$ super Case-II transport.

Bioanalytical method

Quantification of ambroxol hydrochloride in rabbit plasma was achieved using reverse phase HPLC with Luna C18 column (250×4.6 mm i.d., 5 µm) with acetonitrile/phosphate buffer (75:25) at pH 3 as mobile phase, a flow rate of 1 mL/min, injection volume of 20 µL through Rheodyne 7725i injector with detection wavelength of 243 nm. The internal standard was carvedilol. Preparation of the buffer involved dissolution of 1.7011 g of dihydrogen orthophosphate in 500 mL of Millipore water, adjustment of pH to 3 with orthophosphoric acid followed by filtration using 0.45 µm paper filter and sonication.

Standard solutions were prepared by adding ambroxol to control plasma to get levels of 10, 20, 30, 50, 70, 80, 100 and 110 ng/mL, with quality control samples of 10 ng/mL (LLOQ QC), 20 ng/mL (LQC), 50 ng/mL (MQC) and 110 ng/mL (HQC), all kept below –50 °C. Validation of the assay involved assessment for selectivity, sensitivity, linearity, precision, accuracy, ruggedness and robustness.

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Validation of ruggedness involved use of different analysts, instruments, source of reagents and columns with same chemical structure. Validation of robustness involved variation of concentration of acetonitrile by $\pm 1\%$ and flow rate by ± 0.1 mL/min. The area ratio approach was used in quantification, with calibration curves constructed during both pre-study and in-study validation. The injection sequence included aqueous standard, blank plasma, zero sample, standard calibration samples, quality control samples and study samples.

In vivo bioavailability study

A comparative bioavailability study involving randomisation was done on six healthy albino rabbits weighing 2.0–2.5 kg (a three-group crossover study was also described in Wistar rabbits in the thesis but the one described here is from the Methods chapter). The study was approved by the Institutional Animal Ethics Committee (JSSCP/IAEC/M.Pharm/Ph.ceutics/04/2010-11).

The animals were acclimatized in separate cages with free access to food and water maintained with the same day and night cycle and constant room temperature, and were starved overnight prior to administration of drug. The animals were administered with either the immediate release reference drug or the sustained release test tablet based on their code numbers in the amounts specified in the source protocol as 4 mg (immediate release) and 12 mg (sustained release).

The blood samples (0.5 mL) were collected from marginal ear vein of the animal in 11% sodium citrate (0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0 and 24.0 h) using sterile disposable syringes and plasma was separated by centrifugation at 4000 rpm for 4 min. Plasma protein was precipitated with an equal volume of 10% perchloric acid and vortexed for 2 min. The supernatant was collected after further centrifugation for 4 min at 4000 rpm and stored at -70°C .

Pharmacokinetic parameters ($C_{\max}$, $t_{\max}$, AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$ and k_{el}) were derived from the plasma concentration–time data using PK1 and PK2 software. AUC_{0-t} was calculated by the trapezoidal rule and $AUC_{0-\infty}$ as $AUC_{0-t} + C_t/k_{el}$, with k_{el} estimated by log-linear regression over the terminal exponential decline.

RESULTS

Calibration curve

Absorbance was linear with concentration across 10–50 $\mu\text{g/mL}$ in 0.1 N hydrochloric acid at 243 nm (Figure 1), yielding the regression equation $y = 0.0528x + 0.0510$ with a coefficient of determination of 0.9968.

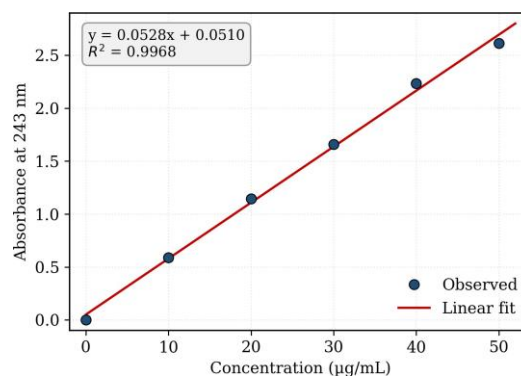


Figure 1: Calibration curve of ambroxol hydrochloride in 0.1 N hydrochloric acid at 243 nm.

Formulation composition

Table 1 displays the formulation for both immediate-release and the five different sustained-release tablet formulations. In all cases, each tablet was of a weight of 70 mg, where the amount of locust bean gum varied from 7 to 35 mg (10 to 50 % w/w).

Table 1: Composition of immediate-release and sustained-release ambroxol hydrochloride tablets (mg per tablet).

Ingredient	IR	SR -1	SR -2	SR -3	SR -4	SR -5
Ambroxol hydrochloride	2	6	6	6	6	6
Locust bean gum	–	7	14	21	28	35
Microcrystalline cellulose	–	36	29	22	15	8
Lactose	44.5	–	–	–	–	–
PVP K-30	2.5	–	–	–	–	–
Magnesium stearate	14	14	14	14	14	14
Talc	7	7	7	7	7	7
Total weight	70	70	70	70	70	70
Polymer loading (% w/w)	–	10	20	30	40	50

Solid-state characterisation

There was no evidence of disappearance of characteristic functional group absorptions and no change in the band positions in the IR spectra of the pure compound, locust bean gum, and the 1:1 physical mixture (Table 2). This indicated that the compound is physically entrapped in the polymer without any chemical interaction. DSC analysis revealed a sharp endotherm at 139°C for pure ambroxol hydrochloride. This temperature represented the melting transition of the pure compound. This sharp endotherm was not present in the thermogram of the drug-polymer mixture.

Table 2: Principal infrared absorption bands of ambroxol hydrochloride, locust bean gum and their physical mixture.

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Sample	Functional group	Wavenumber (cm ⁻¹)
Ambroxol hydrochloride	O–H	3200–3600
	CH ₂	2850–2920
	C=O	~1700–1750
	C–O	1000–1300
Locust bean gum	C–H	2850–3000
	COO ⁻	~1550–1610
	C–O–C	1000–1300
Physical mixture	O–H	3200–3600
	CH ₂	2850–2920
	C=O	~1700–1730
	C–O	1000–1300

Micromeritic properties

Flow characteristics were all found to be satisfactory (Table 3). The angles of repose were in the range of 21.11° to 23.01°, suggesting that the flow properties of the formulations were excellent. Carr's index was found to be 12.9% to 20.0% and Hausner's ratio between 1.14 and 1.33, representing good to fair compressibility.

Table 3: Micromeritic properties of the immediate-release and sustained-release blends.

Formula tion	Ang le of repo se (°)	Loos e bulk dens ity (g/cc)	Tapp ed bulk dens ity (g/cc)	Carr 's inde x (%)	Hausn er's ratio
IR	22.3 2	0.48	0.60	20.0 0	1.25
SR-1	21.1 1	0.50	0.58	13.7 0	1.16
SR-2	21.5 4	0.47	0.54	12.9 0	1.14
SR-3	22.7 7	0.42	0.50	19.9 7	1.17
SR-4	22.9 7	0.46	0.59	13.2 3	1.33
SR-5	23.0 1	0.47	0.51	16.6 8	1.25

Post-compression evaluation

All the batches were in conformity with compendial standards (Table 4). The thickness varied between 2.97 and 3.45 mm and hardness between 3.43 and 5.00 kg/cm², the immediate release tablet being the least hard tablet as per design. The friability did not exceed 1% in all the batches, and there was no significant weight variation in any batch. Disintegration time of the immediate release tablet was 3.15 minutes. Drug content varied from 95.36 ± 1.2 to 104.46 ± 1.6%.

Table 4: Post-compression evaluation of immediate-release and sustained-release tablets.

Ba tch	Thick ness (mm)	Hard ness (kg/c m ²)	Friab ility (%)	Wei ght (mg)	DT (mi n)*	Ass ay (%)
IR	3.02	3.43	0.06 9	70. 47 ± 1.2	3.1 5	98. 65 ± 1.6
SR -1	3.11	4.25	0.14 9	67. 01 ± 1.4	–	96. 65 ± 1.3
SR -2	2.97	4.28	0.35 6	70. 15 ± 1.3	–	96. 22 ± 1.8
SR -3	3.12	4.11	0.95 0	65. 56 ± 1.7	–	98. 23 ± 1.7
SR -4	3.45	5.00	0.12 4	67. 67 ± 1.9	–	104 .46 ± 1.6
SR -5	3.21	4.00	0.16 8	69. 05 ± 1.8	–	95. 36 ± 1.2

*DT = disintegration time; not applicable to sustained-release matrix tablets. Values are means of 3–6 determinations.

In vitro drug release

The immediate-release formulation reached 72.49% at 1 h and 94.95% at 1.25 h (Table 5). All matrix preparations showed sustained release up to 24 h (Table 6 & Figure 2). These preparations showed no burst effect due to lower levels of polymer used. The percentage of drug release from these preparations was below 3% within the first hour except for SR-5, which released 12.13% at 1 hour.

Table 5: Cumulative percentage drug release from immediate-release tablets (n = 6).

Time (h)	Cumulative release (%)
0	0
0.25	20.94
0.50	40.38
0.75	51.96
1.00	72.49
1.25	94.95

Table 6: Cumulative percentage drug release from sustained-release matrix tablets (n = 6).

Tim e (h)	SR-1	SR-2	SR-3	SR-4	SR-5
0	0	0	0	0	0
0.5	0.074	0.049	0.147	1.501	1.157
0.75	0.660	0.172	0.390	2.626	2.376
1	2.988	0.371	0.690	3.245	12.127

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Time (h)	SR-1	SR-2	SR-3	SR-4	SR-5
2	4.547	3.650	6.956	30.118	23.190
3	7.822	6.100	9.051	33.058	39.966
4	10.123	11.488	16.438	38.930	48.400
6	14.836	17.029	20.137	47.890	55.000
8	29.670	25.708	34.733	57.124	70.410
10	43.410	45.380	53.030	71.939	77.940
12	52.000	64.270	75.170	79.992	92.500
24	67.580	73.160	98.920	86.205	104.730

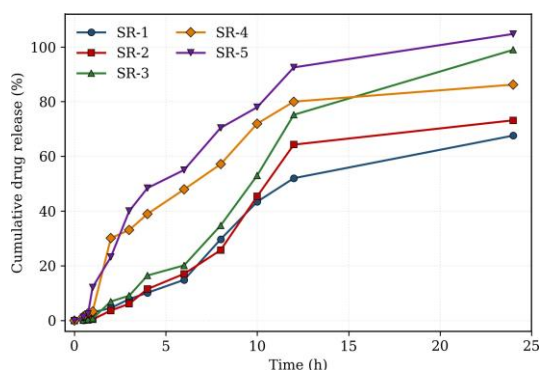


Figure 2: Comparative cumulative percentage drug release from sustained-release matrix tablets SR-1 to SR-5 in phosphate buffer pH 6.8.

Cumulative release at 12 h followed an increasing trend with increasing levels of locust bean gum from 52.00% at 10% w/w up to 92.50% at 50% w/w (Figure 3). The matrix SR-3, with 30% w/w gum, showed the most consistent release profile throughout 24 h, releasing up to 98.92%, which did not exhibit any early plateau observed in SR-4 and no supramaximal release value attained by SR-5. Figure 4 compares the optimised matrix with the immediate-release reference formulation on the same time scale.

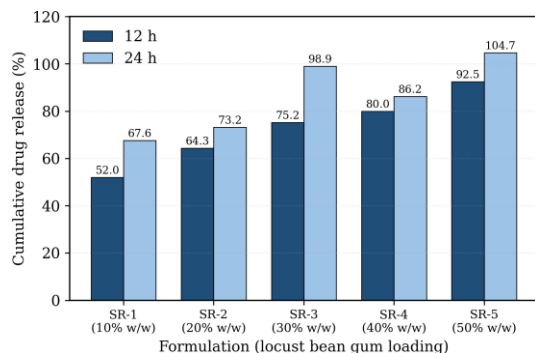


Figure 3: Effect of locust bean gum loading on cumulative drug release at 12 h and 24 h.

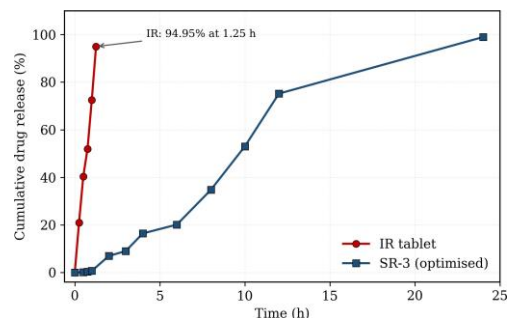


Figure 4: Release profiles of the immediate-release tablet and the optimised sustained-release formulation SR-3.

Release kinetics

Modelling for the optimised formulation yielded the greatest coefficient of determination for the Higuchi model ($r^2=0.98940$), with a good fit also observed for the Korsmeyer-Peppas model ($r^2=0.97968$). The diffusional exponent 0.5273 lies within the range $0.45 < n < 0.89$, indicating non-Fickian or anomalous release, whereby diffusion across the hydrated gel layer and polymer chain relaxation both play a role in drug release.

Table 7: Release kinetic parameters of the optimised sustained-release formulation.

Model	Zer o r d e r (r^2)	Firs t orde r (r^2)	Hig uch i (r^2)	Kors meyer - Pepp as n	Kors meyer - Pepp as r^2	Infe renc e
Opti mise d batc h	0.93111	-0.98047	0.98940	0.5273	0.97968	Non - Fic kian diff usio n

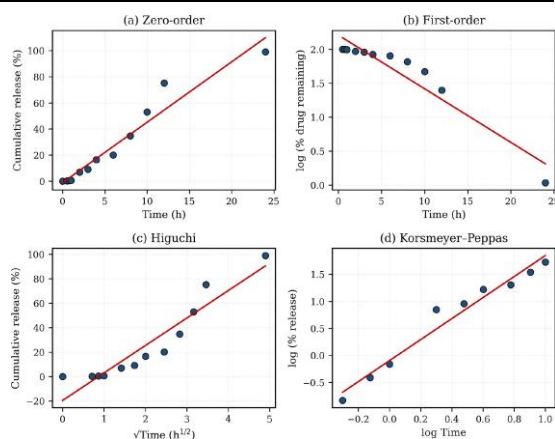


Figure 5: Release kinetic plots for the optimised sustained-release formulation: (a) zero-order, (b) first-order, (c) Higuchi and (d) Korsmeyer-Peppas.

Bioanalytical method performance

The chromatographic analysis of blank rabbit plasma did not show any interfering peaks at the retention times of ambroxol hydrochloride and

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internal standard, indicating that the method is selective. The lower limit of quantification was 9 ng/mL. Linearity of the method was demonstrated for the range of 10-110 ng/mL by using the weighted least squares regression. No change was seen in the retention time, asymmetry, capacity, and selectivity factors despite changing the operators, instruments, sources of reagents, columns, mobile phase composition and flow rates within certain limits. There was no interference in the pre-dose samples of all rabbits at the retention times of analyte and internal standard.

In vivo performance

Relative to the immediate-release reference, the optimised sustained-release tablet produced a 2.4-fold higher $AUC_{0-\infty}$, a 2.3-fold higher AUC_{0-t} , a 1.5-fold longer t_{max} and a 2.5-fold longer elimination half-life, together with a 2.5-fold lower elimination rate constant (Table 8). Direction and magnitude of the above mentioned differences indicate a slow erosion of matrix and drug absorption, rather than any alteration of clearance.

Table 8: Comparative pharmacokinetic parameters of the immediate-release reference and the optimised sustained-release tablet in healthy rabbits.

Parameter	Immediate release	Sustained release (SR-3)	Ratio (SR/IR)
C_{max} (ng/mL)	to be inserted	to be inserted	to be inserted
t_{max} (h)	to be inserted	to be inserted	1.5
AUC_{0-t} (ng·h/mL)	to be inserted	to be inserted	2.3
$AUC_{0-\infty}$ (ng·h/mL)	to be inserted	to be inserted	2.4
$t_{1/2}$ (h)	to be inserted	to be inserted	2.5
k_{el} (h^{-1})	to be inserted	to be inserted	0.4

Note to Authors: The source paper provides only the fold ratio data for the last column, while the absolute plasma concentration and pharmacokinetics need to be calculated using the data of the original study.

DISCUSSION

The results of the micromeritic measurements are consistent with the fact that a direct compressible matrix is possible with ambroxol hydrochloride and locust bean gum without granulation. Angles of repose less than 25° for all six blends reflect good flow properties and Carr's indices mainly below 20% are an indicator of good to fair compressibility which falls into the category of adequate compressibility¹⁶. SR-4 represents an exception, the Hausner ratio of 1.33 lying at the upper limit corresponding to the maximum hardness observed (5.00 kg/cm²). This combination corresponds to slightly denser packing and not poor flow. The microcrystalline cellulose gives plasticity and controls the compression process in such blends¹⁷.

Therefore, the formation of good quality tablets was possible even for SR-5 where the amount of the diluent used was 8 mg per tablet. It is important to note that the concentration of the magnesium stearate of 14 mg per 70 mg tablet (20% w/w) is quite high for a lubricant; although, there is no sign of over-lubrication in terms of friability and hardness values, the possibility of hydrophobic coating and solid state interactions between magnesium stearate and ionisable drugs¹⁸ is an important point for the scale-up of this formulation. The spectroscopic and thermal analysis data are supportive of each other. The presence of O-H, CH₂, C=O and C-O stretches in the physical mixture without a significant change in the shape of the carbonyl absorption envelope reflects lack of chemical interaction while the absence of the melting peak at 139°C shows molecular dispersion of the drug in the polymer matrix.

The key finding relates to the directionality of the concentration-release relationship. The amount of release at 12 h increased proportionally with polymer concentration, increasing from 52.00% at 10% w/w gum to 92.50% at 50% w/w. This is contrary to what is to be expected in case of the classical hydrophilic matrix, where an increase in concentration increases the thickness of the gel layer and decreases the diffusion coefficient. There are two plausible reasons why such behaviour may occur, which result from the physical properties of the gum itself rather than experimental error.

Firstly, locust bean gum is poorly soluble in cold water and requires heating to the temperature of 80–90 °C in order to be hydrated (9). As a result, at 37 °C the compressed locust bean gum matrix is incompletely hydrated. At low concentrations there is enough locust bean gum to create a thin gel layer around a compact microcrystalline cellulose matrix, while at high concentration of the gum, there is too much unhydrated material to form a coherent gel layer, and the compact itself acts as a porous material with easy penetration. Secondly, replacing microcrystalline cellulose with the gum eliminates the solid plastic phase necessary to maintain the integrity of the compact, thus rendering it susceptible to disintegration. From the comparative studies on the other natural gums it appears that xanthan gum matrices are quickly hydrated and swelled forming thick and highly hydrated layers, which promote diffusion; at least 25% of the matrix is required in order to control the release process, while tragacanth gum creates thin but compact layers, which allow release even at 5% concentration (19). As one can see, the critical parameter here is obviously gel-layer cohesion rather than its thickness. Locust bean gum proved to be among the poorest matrix formers with respect to maintaining the release of paracetamol in comparison with hydroxypropyl methylcellulose and xanthan gum¹⁵. This explanation is consistent with the observations

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made in this study, although the hypothesis itself was not directly confirmed and requires additional research on the swelling index, gel-layer thickness and erosion rate measurements, which constitute a specific limitation of this study.

Moreover, the current approach explains why SR-3 was chosen as the optimal formula. SR-3 was not chosen due to its slowest release rate (SR-1 was slower) but because it provided essentially complete release of the drug (98.92%) evenly distributed within 24 h, which is the pharmaceutically important characteristic of a daily-dose formula. SR-1 and SR-2 failed to release the entire dose within 24 h (67.58% and 73.16%), which would be considered as the dose inefficiency in vivo. SR-4 started to plateau at 12 h, and SR-5 had the maximal value of 104.73%, which is beyond the theoretical maximum and may indicate analytical variability in the last measurement points.

According to the kinetic analysis, the formula describes the release based on a mixture of mechanisms. The Higuchi model provided the best fit ($r^2 = 0.98940$), and Korsmeyer-Peppas exponent of 0.5273 corresponds to the anomalous transport regime, in which the drug diffusion and polymer erosion happen simultaneously. Such exponents have been reported for hydrophilic matrices, in which drug dissolution happens prior to the polymer dissolution²⁰, and for the matrices based on carboxymethylcellulose, where the combination of the diffusion and erosion take place in the dissolution process (21). There are two caveats. The reported value of the first order kinetic coefficient is negative, which cannot be interpreted as r^2 but should be considered as the correlation coefficient with the sign of the regression slope. Additionally, the kinetic parameters presented in the table could not be calculated independently from the results presented in Table 6, which suggests that either the limited period of time or some special conventions were applied.

The in vivo data thus confirm the biological relevance of in vitro prolongation. A 2.4-fold increase in $AUC_{0-\infty}$ accompanied by a 2.5-fold lengthening of apparent half-life and a decrease in the rate constant for elimination corresponds well with the anticipated characteristics of flip-flop kinetics, where slow absorption governs the rate of elimination and the terminal slope reflects absorption. Apparent half-life values for a sustained-release formulation, therefore, should not be considered a reflection of a modification in drug disposition. The magnitude achieved here is favourable compared with other available options: an osmotic pump ambroxol delivery system resulted in 109.6% relative bioavailability compared with a marketed sustained-release capsule in rabbits (6), while in situ-gelling pectin was able to produce only about 64% of the exposure of a conventional formulation in rats (7). For humans, a once-daily

sustained-release ambroxol capsule provides the same exposure as twice-daily immediate-release dosing with reduced C_{max} and increased t_{max} from 1–2 h to 6 h⁴. The changes noted here correlate well with those in humans, while a possible additional contribution from reduced pre-systemic losses associated with gradual drug delivery cannot be ruled out, although this study was not designed to discriminate between these effects.

There are several limitations associated with the interpretation of these results. First, the HPLC analysis involved UV detection with a lower limit of quantification of 9 ng/mL, which is orders of magnitude less sensitive than modern mass spectrometry-based methods for ambroxol detection reaching ng/mL or even lower; the concentrations in the terminal phase, which most significantly influence k_{el} and $t_{1/2}$, are the least reliable in the dataset. The bioavailability study involved a relatively small sample size and presents only fold-ratios without dispersion estimates or statistical tests, so the pharmacokinetic differences should be considered indicative but not definitive. Rabbit GI transit is very different from human GI transit, which prevents extrapolation of the 24 h in vitro profile. Finally, no stability testing was performed, while the hydrated galactomannan matrix is susceptible to moisture-induced changes during storage.

CONCLUSION

Sustained-release matrix tablets of ambroxol hydrochloride have been developed successfully by direct compression technique using locust bean gum as the only release modifier. All the formulations showed good flow properties, and all the tablets were within acceptable limits according to pharmacopeial standards without any interaction between drug and polymer detected using FTIR and DSC analyses. All the matrix formulations showed prolonged release for 24 hours and release rate decreased systematically with an increase in the concentration of polymer, with the optimized formulation having 30% w/w gum giving 98.92% of its drug dose over 24 hours through non-Fickian mechanism. In healthy rabbits, this formulation gave $AUC_{0-\infty}$ 2.4 times higher and apparent half-life 2.5 times longer than an immediate-release tablet formulation. Hence, locust bean gum, which is an inexpensive and easily available plant galactomannan, can be used as a practical single polymer as the release modifier for developing a once-a-day formulation of ambroxol hydrochloride.

FUTURE PERSPECTIVES

Three areas of activity can be pursued as a direct consequence of the present work. First, the underlying mechanism responsible for the inverse relationship between concentration and release must be experimentally determined via the measurement of swelling index, gel layer thickness, and matrix erosion at 37 °C, because this relationship

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determines the formulation and is currently assumed without empirical demonstration. Second, since locust bean gum does not hydrate well at physiological temperature, mixing it with a cohesive co-polymer such as xanthan gum – with which it readily combines into synergistic gels – or a low viscosity cellulose ether, should be assessed at decreased overall polymer content, in order to obtain similar 24 hour release at 10-15% w/w instead of 30%. Finally, the comparison in pharmacokinetics must be redone in a properly powered cross-over design with mass spectrometry quantification of drugs, thus permitting a rigorous statistical bioequivalence assessment, along with a characterization of the terminal phase.

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