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Research

Development of a Sustained-Release Herbal Tablet using Natural Gums as Binding Agents: Formulation Optimization, Release Kinetics, Statistical Validation, and ICH Stability Assessment

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Abstract:
One of the ongoing pharmaceutical problems of herbal extracts is developing oral sustained-release (SR) preparations due to the complex phytochemical structure, low water solubility of bioactive markers, and uncontrolled gastrointestinal absorption. The current paper describes the development of the first systematic formulation and optimisation of SR matrix tablets of a standardised Boswellia serrata dry extract (BSE; 65% total boswellic acids) with binary blends of guar gum (GG) and xanthan gum (XG) as natural, biodegradable, hydrophilic matrix-forming binders - without any synthetic polymer adjunct. Wet granulation was utilized to prepare four formulations (F1-F4) with GG:XG mass ratios of 2:1, 3:1, 1:1, and 1:2 and a constant total gum content of 75mg and constant drug load of 200 mg/tablet. Extensive analysis included pre-compression granule characterisation (angle of repose, bulk and tapped density, Carrs index, Hausner ratio, particle size, moisture content), post-compression tablet testing (hardness, friability, thickness, weight uniformity, drug content, swelling index), in vitro drug release during Formulation F3 (GG:XG = 1:1) gave 91.2 ± 2.1% cumulative drug release in 8 hours with unusual non-Fickian release kinetics (Korsmeyer–Peppas $r^2 = 0.9931$; $n = 0.74$). ANOVA proved the statistically significant differences between formulations ($F = 18.74$; $df = 3, 20$; $p < 0.001$) with F3 being significantly better than F1 (Tukey HSD; $p < 0.05$). The FTIR and DSC analyses indicated the full compatibility of the physicochemical between BSE and the gum excipients. All important quality characteristics of F3 were within the pharmacopoeial specifications of six months of accelerated stability storage. The results confirm the binary GGXG system as a biodegradable, pharmacopoeially acceptable, and cost-effective system to develop SR herbal tablets.

Keywords: Boswellia serrata; Guar gum; Xanthan gum; Sustained-release tablet; Matrix tablet; Wet granulation; Korsmeyer–Peppas model; One-way ANOVA; Boswellic acids; Natural polysaccharide binder; ICH stability.

1. INTRODUCTION

The most popular form of drug administration is oral solid dosage form especially compressed tablets due to ease of production and manufacture, accurate dosage, stability of physicochemical data during storage and patient compliance. Sustained-release (SR) systems have taken a leading role in therapeutic applications due to their ability to sustain plasma drug concentrations within the

therapeutic window over a variable duration of time - usually 8-24 hours- and therefore decrease the frequency of dosing, minimise the peak-to-trough plasma changes and enhance the safety and efficacy profile of the delivered drugs [2]. SR tablets also decrease the amount of drug dose it takes to attain a therapeutic effect throughout a entire day which consequently decreases the chances of systemic adverse effects that may be caused by repeated exposure to peak plasma. In 2023, the sustained-release drug delivery market in the world was estimated to be USD 48.8 billion and is expected to increase by a compound annual growth rate (CAGR) of 7.4 % through 2030, indicating the tremendous demand that remains unmet in the need to have a better dosing convenience in the management of chronic diseases [3].

In line with this pattern in the pharmaceutical market, the increased worldwide tolerance towards phytomedicine and Ayurvedic-based therapeutic approaches based on evidence has encouraged researchers to employ the current SR formulation methods to herbal actives. Nevertheless, herbal extracts have unique formulation problems which differentiate them with single-entity synthetic medicines. They are the multi-constituent nature of botanical extract, dozens of pharmacologically-relevant compounds in batches, geographic, seasonal, and extraction variability in phytochemical profiles, low aqueous solubility of lipophilic bioactive markers, substantial pre-systemic hepatic metabolism, and complicated pharmacokinetic behaviour due to potential inter-constituent interactions [4] Nevertheless, SR formulation of herbal drugs is extremely desirable due to its increased pharmacological action extending the dosage to once- or twice-daily, decreased variability of drug absorption rate through independent control of release rate without dependence on gastrointestinal emptying, and reduced gastrointestinal adverse effects due to elevated local drug concentrations of the traditional immediate-release preparations.

Boswellia Roxb. serratum. The Indian frankincense or Shallaki (family Burseraceae), a branching, deciduous tree that is indigenous to the dry mountainous forests of the Indian subcontinent, and has some other populations in Northern Africa and the Middle East [5]. Its oleo-gum resin has a record of over three thousand years of use in Ayurvedic and Unani and traditional African medicines as a therapeutic agent mainly in the treatment of inflammatory musculoskeletal, inflammatory bowel, asthma and pain reliever. Its main active pharmacologically active ingredients are pentacyclic triterpenoid boswellic acids (BAs), which are tetracyclic and pentacyclic compounds with the most investigated ones being acetyl-11-keto-β-boswellic acid (AKBA), 11-keto-β-boswellic acid (KBA), β-boswellic acid, and acetyl-β-boswellic AKBA is known to be the strongest of the group with a selectivity to the 5-lipoxygenase (5-LOX) at nanomolar concentrations in vitro [5].

The anti-inflammatory process of boswellic acids is also mechanistically different and complementary to the classical NSAIDs. BAs inhibit the inflammatory cascade at many different points of control against its terminal enzyme targets (NF-κB transcription factor) and inflammasomes (NLRP3) instead of only one, as NSAIDs do [6]. This multi-target pharmacology renders BSE especially useful in diseases with chronic low-grade inflammation, like osteoarthritis, in which 5-LOX-mediated leukotriene cascades, which are not dealt with by COX-2 selective inhibitors, play an important role in the pathology of the synovium. There is good clinical evidence base, with several randomised controlled trials and a systematic meta-analysis by Bannuru et al. demonstrating statistically significant reductions in visual analogue pain scales (VAS) and WOMAC functional scales in patients with knee osteoarthritis undergoing standardised BSE [7]. A more recent multicentre placebo-controlled, double-blind trial also showed the reduction of the pain and stiffness with a clinically significant effect in the course of five days of the conventional use of BSE in form of supplementation [8].

Despite this clinical confirmation, the oral efficacy of traditional BSE preparations is greatly reduced by the extremely lipophilic nature of boswellic acids - their log P values are estimated to be greater than 5.0 - which leads to unpredictable and incomplete absorption in the gastrointestinal tract, enterohepatic recirculation, and a half-life that requires three to four daily doses to achieve pharmac Both doses are accompanied with a temporary elevated local gastric level of triterpenoid acids that may result in epigastric discomfort, especially in geriatric patients who make up the major osteoarthritis group. The following limitations would be overcome with a sustained-release matrix tablet preparation that releases 200 mg of standardised BSE (65% boswellic acids) over 8 hours: once-daily dosing would enhance adherence, slow release would decrease the exposure of the mucosal acids, and the gradual absorption levels would reduce the systemic effects of the peaks [9, 10].

The most commercially available oral SR platform is the hydrophilic polymer matrix which has been widely

investigated with synthetic drugs. When in contact with gastrointestinal fluid, the hydrophilic polymer hydrates to create a gelatinous viscous barrier, through which the drug can be released by a balance of molecular diffusion and matrix erosion - the relative activity of each of which is determined by the type of polymer, polymer concentration and molecular weight [11]. The marketplace of SR tablets is dominated by hydroxypropyl methylcellulose (HPMC K4M and K100M) but its application in herbal SR formulations is associated with a number of practical issues: HPMC is a semi-synthetic, petrochemical or wood-pulp cellulose ether that is inconsistent with natural or clean-label labelling imperatives increasingly [12, 13].

A pharmacopoeially established, biodegradable and cost-effective alternative class of SR excipients is natural polysaccharide gums in plant exudates, seed endosperms or microbial fermentation. Guar gum (GG) is a high-molecular-weight galactomannan that has been purified by isolating it out of the seed endosperm of Cyamopsis tetragonoloba (L.). Taub., is composed of a backbone of (1 4)-linked 2, β-D-mannopyranose units, and single (1 6)-linked 2, α-D-galactopyranose side chains in a mannose: galactose ratio of about 2:1. The property of this non-ionic cold-water-dispersible polymer is that it is able to hydrate quickly and make coherent, high-viscosity gels that can be used in SR matrix tablets [14]. Xanthan gum (XG), synthesised by the bacterium Xanthomonas campestris NRRL B-1459, is a high-molecular-weight anionic hetero-polysaccharide, which has a (1→4)-β-D-glucopyranose backbone - structurally related to cellulose - with alternating trisaccharide side chains of Its polyanionic nature together with an ordered helical structure that is stabilised by acidic conditions and low temperatures (40 C) allows XG to be highly resistant to pH and acid-tolerant than both GG and HPMC [15].

A well-documented synergistic interaction with GG especially makes binary blends of GG and XG quite appealing to SR matrix tablet development: when mixed in aqueous media, GG mannose backbone chains will align with and adsorb onto the ordered XG helix, enhancing the density of the junction zone of the interpenetrated polysaccharide network. This molecular complementarity forms a three-dimensional gel with a much higher viscosity and elastic modulus than either of the gum in the same overall concentrations and no chemical cross-linking is required [14, 15]. Published experiments have shown that individual GG or XG matrixes have the potential of being used as synthetic drugs such as metformin, diclofenac sodium, famotidine, and flurbiprofen; although none of the previously conducted studies have characterised binary GGXG blends as the primary matrixforming and binding excipient in compressed SR tablets with a specific aim of using a standardised herbal extract [19,27] Moreover, the optimum GG:XG mass ratio of synergistic gels, the effect of this ratio on the kinetics of boswellic acid release and the mechanistic paradigm of the release of a compound of this type have not been published in the peer-reviewed literature. The current study seals these gaps, giving the first statistically validated, characterised kinetically, FTIR/DSC-proven, and ICH stability-tested SR tablet system of standardised BSE with a completely natural, biodegradable excipient base.

2. MATERIALS AND METHODS

2.1 Materials

Standardised dry extract of Boswellia serrata (BSE; ≥65% total boswellic acids; ≥7.0% AKBA by RP-HPLC; Lot No. BSE-2024-1104; Certificate of Analysis checked) was purchased at Sabinsa Corporation, Piscataway, NJ, USA. Pharmaceutical-grade guar gum (viscosity 3,500–5,000 mPa·s at 1% w/v; 25 °C; Lot No. GG-TCI-2024) and food-grade xanthan gum (viscosity 1,200–1,600 mPa·s at 1% w/v; 25 °C; Lot No. XG-TCI-2024) were sourced from TCI Chemicals (India) Pvt. Ltd., Mumbai. Microcrystalline cellulose (MCC; Avicel 201 PH-101) and dicalcium phosphate (DCP; anhydrous), magnesium stearate and colloidal silicon dioxide (Aerosil 200) were purchased at SD Fine Chemicals Ltd., Mumbai. The AKBA reference standard (purity 98.0% and above) was bought in Chromadex Inc., USA. All the organic solvents (acetone, HPLC grade; methanol, AR grade) were of Merck Life Sciences, India. All aqueous preparations and analysis procedures were done using purified water with a conductivity of 1.3 µS/cm, which is within the range of Indian Pharmacopoeia 2018.

2.2 Phytochemical Standardisation of BSE

The concentration of total boswellic acid and AKBA were determined using a validated reverse-phase HPLC system with a Waters Alliance e2695 separation column that has a photodiode array (PDA) detector at 210 nm (Waters 2998). Chromatographic separation was performed on an Inertsil ODS-3 C18 column (250 mm × 4.6 mm, 5 0 m particle size; GL Sciences, Japan) that was at 30 °C. A 72:28, v/v acetonitrile and 0.1% v/v orthophosphoric acid in water (isocratic mobile phase) was injected at a rate of 1.0 mL/min; the injection volume was 20 µL. The method was validated per ICH Q2(R1) for specificity, linearity

(10–200 µg/mL; $r^2 \geq 0.9995$ for both analytes), precision (intra-day and inter-day CV < 2%), accuracy (98.2–101.4% recovery), LOD (AKBA: 0.18 µg/mL; total BAs: 0.52 µg/mL), and LOQ (AKBA: 0.55 µg/mL; total BAs: 1.58 µg/mL). Also, Folin-Ciocalteu colorimetric was used to determine total phenolic content (TPC) (expressed as mg gallic acid equivalents/g, mg GAE/g) whereas the aluminium chloride method was used to determine total flavonoid content (TFC) (mg quercetin equivalents/g, mg QE/g). Quality control of the herbal materials was done by determining loss on drying, total ash, acid-insoluble ash and water-soluble extractive according to the WHO guidelines on the same (WHO/TRS/1010, 2018) [16].

2.3 Physicochemical Characterisation of Gums

Guar gum and xanthan gum were individually evaluated for the following parameters: pH of 1% w/v aqueous dispersions (digital pH metre, Mettler-Toledo SevenEasy S20); viscosity at 25 ± 0.5°C and 20 rpm using a Brookfield DV-II+ Pro rotational viscometer with spindle S-64; swelling capacity (gravimetric water absorption at 1, 2, and 4 hours at 37 °C); gelation temperature by differential scanning calorimetry (Mettler-Toledo DSC 3+); moisture content by Karl Fischer titration (Metrohm 870 KF Titrino Plus); and loss on drying at 105°C for 2 hours (digital moisture analyser, Ohaus, Switzerland). To characterise the functional groups and ensure no chemical moieties were unexpectedly present in the sample, Fourier-transform infrared (FTIR) spectra were recorded on a Shimadzu IRAffinity-1S spectrometer (4004,000 cm^{-1}; application of KBr pellet; 4 cm^{-1} resolution).

2.4 Formulation of Sustained-Release Tablets by Wet Granulation

Four formulations (F1-F4) were developed by adjusting the GG:XG mass ratio - 2:1 (F1), 3:1 major GG (F2), 1:1 equimolar (F3) and 1:2 major XG (F4) and keeping total gum content in each formulation at 75 mg per tablet and BSE load at 200 mg per tablet Table 1 gives full composition of the excipients. Prior to granulation, sieving BSE, GG and XG through a #40 mesh (425 µm aperture) was done to eliminate agglomerates and create uniform powder. A stainless-steel planetary mixer (LM-8, Shakti Engineering, Ahmedabad) was used to co-blend BSE, MCC (Avicel PH-101) and DCP at 60 rpm and 15 minutes. The properly mixed GG:XG mixture (in the required mass proportion) was then added and mixed further after 5 minutes. Each formulation was prepared by making a fresh granulating binder solution, i.e., dissolving the identical GG:XG mixture in purified water at 70 °C with constant stirring to produce a 5% w/v total gum mucilage, cooled down to room temperature and used. This mucilage was introduced drop-by-drop to the powder mixture to be continually mixed at 30 rpm until the required consistency of coherent and pliable non-sticky damp mass was obtained. To obtain cylindrical granules, the wet mass was extruded using stainless-steel mesh screen (#16; 1.18 mm aperture). A single layer of granules was placed on the aluminium trays and dried in forced-air convection oven at 55 ± 2 °C at a time of 2 hours, with a desired residual moisture content of the granules of 2.5% w/w. A 40-m mesh (425 µm) was used to resieve dried granules. The lubrication process was carried out in the following way: 1. Aerosil 200 (2.17% w/w of final blend) was added followed by magnesium stearate (1.09% w/w), with tumbling of the planetary mixer taking place in between, after each addition. The lubricated granules blends were pressed under 13 mm diameter flat-faced bevelled-edge tooling on a single-punch tablet press (Cadmach C-10, Ahmedabad) to a target hardness of the tablet of 7.0 ± 0.5 kg/cm 2 and a target mean tablet weight of 460 ± 5 % mg [17].

2.5 Pre-compression Granule Evaluation

Many complementary indices were used to describe granule flow characteristics. The angle of repose was measured using the fixed-funnel technique (height of funnel tip was 10 cm above the base; height of the cone was kept at < 6 cm). The bulk density (rb) and tapped density (rt) were determined by pouring 50 g of the granules in a graduated cylinder with 100 mL volume and determining the initial volume and final volume after 1,250 standardised taps (Electrolab ETD-1020 tap density tester). These values formed the compressibility index (CI = [(rho t - rho b)/rho t]/100) and ratio of Hausner (HR = rho t/rho b) determined by Carr. Mechanical sieve analysis with a standard USP stack (600, 425, 250, 180 µm apertures) vibrated 10 minutes at 1 mm amplitude was used to characterise particle size distribution. Final lubricated granules moisture content was determined in 30 minutes at 105 °C [18].

2.6 Post-compression Tablet Evaluation

A Monsanto hardness tester was used to test the hardness of ten randomly selected tablet per formulation. The friability was measured by a Roche friabilator (25 rpm; 4 minutes; 100 rotations) on 10 pre-weighed tablets; the percentage friabilator was determined as the loss of mass as a percentage of the original mass. Five tablets were measured with digital vernier callipers (Mitutoyo, Japan) with regards to their thickness. An analytical balance (Ohaus Pioneer) was used to test the uniformity of the

weight of 20 tablets. The content of drugs was measured: a single tablet was dissolved in 50 mL of PBS pH 6.8 with probe sonication (20 kHz; 30 minutes); the solution was filtered through a 0.45 µm PVDF syringe filter and spectrophotometers at 250 nm using a validated BSE calibration curve (r^2 = 0.999 Swelling index (SI): a gravimetric measurement was performed: tablets were weighted separately (W 0), placed in PBS pH 6.8, 50 mL in a closed container at 37 °C, 0 2, 0 4, 0 6 and 0 8 hours, blotted on towels to remove surface water, and weighted again (W t). SI (%) = [(Wt − W_0) / W_0] × 100 [19].

2.7 In Vitro Drug Release Study

A USP Apparatus II (paddle) dissolution system (Electrolab TDT-08L) was used to test dissolution at 50 rpm and 37 + 0.5 C. To mimic the gastrointestinal transit in vivo, a two-step sequential dissolution procedure was chosen: Stage 1 was performed with 900 mL of 0.1 M HCl (pH 1.2) over the first 2 hours to simulate gastrointestinal conditions in the stomach; Stage 2 was performed with 900 mL of PBS (pH 6.8) At 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours, sample aliquots of 5.0 mL were withdrawn, and immediately filtered through a 0.45 µm PVDF membrane, and equal volumes of fresh medium were added to keep sink conditions constant. A Shimadzu UV-1900i UV-Vis spectrophotometer was used to measure absorbance of filtered samples at 250 nm. Each of the formulations was subjected to six replicates (n = 6). The validated calibration equation was used to calculate percent cumulative drug release (CDR). The sink conditions were verified by making sure that concentration of the drug in dissolution medium was not more than 20 % of the saturation concentration at any given time-point [20].

2.8 Drug Release Kinetics Modelling

Cumulative drug release-time data were fitted to five mathematical kinetic models using DDSolver 2013 (an Excel add-in for pharmacokinetic modelling): zero-order ($Q_t = Q_0 + K_0 t$, where Qt is the amount of drug released at time t and K_0 is the zero-order release constant); first-order ($\ln[100 - Q_t] = \ln 100 - K_1 t$, where K_1 is the first-order rate constant); Higuchi matrix diffusion model ($Q_t = KH\sqrt{t}$, where KH is the Higuchi diffusion rate constant); Hixson–Crowell cube-root model ($Q_0^{(1/3)} - Q_t^{(1/3)} = K_s \cdot t$, where Ks is the Hixson–Crowell erosion rate constant); and Korsmeyer–Peppas power-law model ($M_t/M_\infty = K_{KP} \cdot t^n$, where M_t/M_∞ is the fractional drug release, KKP is the kinetic constant, and n is the release exponent). Pearson's correlation coefficient (r^2) and Akaike information criterion (AIC) were used as model selection criteria. The Korsmeyer–Peppas exponent n was interpreted as: $n \leq 0.45$ (Fickian diffusion, Case-I transport); $0.45 < n < 0.89$ (anomalous non-Fickian transport, mixed diffusion and erosion); $n = 0.89$ (Case-II transport, zero-order erosion-dominated); and $n > 0.89$ (super-Case-II transport) [21].

2.9 Statistical Analysis

Any numerical data will be in terms of mean, standard deviation (SD). GraphPad Prism v10.2 was used to conduct one-way analysis of variance (ANOVA) to compare 8-hour cumulative drug release values and swelling index values with four formulations (F1-F4) (GraphPad Software, San Diego, CA, USA). Significant differences that ANOVA determined to be statistically significant ($p < 0.05$) were tested using post-hoc, honestly significant difference (HSD) pairwise comparison test. Student paired t-test was used to compare within-formulation stability data (t = 0 vs each subsequent month) at $p < 0.05$. The similarity factor (f_2) was not calculated since all formulations were investigational comparators and not test versus reference dissolution profiles as per ICH guidelines [22].

2.10 FTIR and DSC Physicochemical Compatibility

FTIR spectra of five samples (pure BSE, pure GG, pure XG, a ternary physical mixture (BSE + GG + XG in F3 proportions, without other excipients) and a ground F3 compressed tablet were obtained. The data were recorded on the Shimadzu IRAffinity-1S spectrometer (400–4,000 cm^{-1}; KBr disc; 4 cm^{-1} resolution; 32 co-added scans). Peak shifts more than 10 cm^{-1} or the development of new absorption bands in the physical mixture or tablet spectrum were considered as an indication of possible molecular interaction. Each of the same five samples was analyzed by DSC in a Mettler-Toledo DSC 3+ calorimeter at a constant load under a 10 kN load cell with STAR® SW 16 software. Evidence of physicochemical incompatibility was evaluated by samples of 5 ± 0.3 mg sealed under a nitrogen purge of 50 mL/min at heating rates of 10 °C/min. with 30 °C to 300 °C scans, changes in onset temperature, peak temperature or enthalpy of melting or dehydration endotherms, and the emergence of new exothermic.

2.11 ICH Accelerated Stability Study

Optimised formulation F3 pills were packed in aluminium-foil blisters (250 µm PVC bottom / 20 µm hard temper aluminium lidding foil, heat-sealed at 160 °C)Programmable stability chambers (Memmert HPP 260, Germany) were loaded with blister strips at two ICH Q1A(R2) conditions: (i) accelerated storage - 40 ± 2 °C and 75 ± 5 relative humidity (RH); and (ii) intermediate

storage - 30 ± 2 °C and 65 ± 5 RH, with a total Calibrated dataloggers (readings at 1-hour intervals) were used to continuouslymonitor temperature and humidity in each chamber. At baseline (t = 0), 1 month, 3 months and 6 months, sample sets were withdrawn. Tablets were observed at each time-point regarding visual appearance, hardness, friability, drug content, and cumulative drug release in 8 hours in in vitro as outlined in Section 2.6 and 2.7 [24].

3. RESULTS AND DISCUSSION

3.1 Phytochemical Standardisation of BSE

The RP-HPLC technique validated the BSE lot had 65.3 +-1.2% total boswellic acids (as the sum of all identified BA peaks/reference standard) and 7.8 +-0.3% AKBA, as per the specifications of the Sabinsa Certificate of Analysis (total BAs ≥ 65% AKBA ≥ 7%). Adequate analytical precision was verified by three independent HPLC solutions of the same lot of BSE that had intra- and inter-day CV of 0.8% and 1.4% of total BA content, respectively. In spiked matrix solutions AKBA had a recovery accuracy of 99.2 ± 0.8%. The phenolic content was 128.4 + 4.6 mg GAE/g and flavonoid content was 42.7 + 2.1 mg QE/g - both agree with published values of commercially-standardised BSE. Loss on drying was 3.2 ± 0.4%; total ash was 4.6 ± 0.3%; acid-insoluble ash was 0.8 ± 0.1%; and the water-soluble extractive value was 38.6 ± 1.4%. All values were met within WHO specifications on quality control of botanical dry extracts to ensure that the material was not excessively contaminated with inorganic impurities, was adequately dried and could be used as a starting material to prepare compressed tablets [16, 25]. The comprehensive phytochemical characterisation before formulation is the most important in SR herbal tablets as the variation in active markers content would in turn affect the dose consistency and the ability of drug to release consistently across batches.

3.2 Physicochemical Characterisation of Gums

Guar gum (1% w/v aqueous dispersion) exhibited a pH of 6.2 ± 0.1, a Brookfield viscosity of 4,120 ± 180 mPa·s at 20 rpm, 25 °C, and a swelling capacity of 285 ± 18% at 4 hours. The analysis of GG by FTIR revealed the following typical absorption bands: a broad OH stretching at 3,302 cm^{-1} (the OH groups of the galactomannan backbone and side chains); an aliphatic CH stretching at 2,920 cm^{-1}; acarbonyl C=O at 1,640 cm^{-1}(the water of hydration); the typical DSC reported an endothermic dehydration reaction at 82 °C and a thermal reaction at temperatures higher than 240 °C which validates sufficient thermal stability to be used in wet granulation (drying at 55 °C) and tablet compression.

Xanthan gum (1% w/v) exhibited a pH of 7.1 ± 0.1, a Brookfield viscosity of 1,380 ± 95 mPa·s, and a swelling capacity of 348 ± 22% at 4 hours. XG has a better swelling capacity as compared to GG due to its polyanionic nature (pyruvate and glucuronate carboxylate groups) that produce electrostatic repulsion between chains and augmented hydration enthalpy at the neutral pH. XG was identified as having typical pyruvate carboxylate asymmetric and symmetric bands of 1,598 and 1,402 cm^{-1},minus the OH, respectively, using FTIR; C–H aliphatic band of 2,927 cm^{-1} minus the OH; and glycosidic C–O–C band of 1,031 cm^{-1} minus the OH. DSC exhibited a hydration/dehydration endotherm at 96 °C and the beginning of decomposition at above 265 °C The fact that XG dehydrates at approximately 25 °C higher than GG, is an indication of the stronger hydration shell of the anionic XG, which holds onto the water more strongly [14, 15]. Both gums did not exhibit any thermal events during the processing temperature (2555 °C) which is within the range of parameters of the wet granulation process utilized in this experiment.

3.3 Pre-compression Granule Properties

Table 2. Pre-compression Granule Flow Properties of All Four Formulations (Mean ± SD; n = 3 batches)

Parameter	F1	F2	F3	F4	Limit	Flow
Angle of repose (°)	27.8 ± 1.4	26.4 ± 1.1	24.3 ± 1.1*	25.6 ± 1.3	< 30	Good
Bulk density (g/mL)	0.41 ± 0.02	0.43 ± 0.01	0.45 ± 0.02	0.44 ± 0.02	—	—
Tapped density (g/mL)	0.49 ± 0.02	0.50 ± 0.02	0.51 ± 0.01	0.51 ± 0.02	—	—
Carr's index (%)	16.2 ± 0.8	14.0 ± 0.7	11.8 ± 0.6*	13.7 ± 0.7	≤ 15	Good
Hausner ratio	1.19 ± 0.01	1.16 ± 0.01	1.13 ± 0.01*	1.16 ± 0.01	< 1.25	Good

Parameter	F1	F2	F3	F4	Limit	Flow
Moisture content (% w/w)	2.4 ± 0.1	2.1 ± 0.1	1.8 ± 0.1*	2.0 ± 0.1	≤ 3.0	Pass
D90 particle size (µm)	476 ± 22	461 ± 18	432 ± 16	448 ± 20	—	—

*Best value among formulations. — = no pharmacopoeial specification. Flow classification per USP General Chapter <1174>. Acc. = accelerated; Int. = intermediate.

Each of the four formulations resulted in the creation of granules that had good flow characteristics that were satisfactory to pharmacopoeial standards (Table 2). Angles of repose ranged from 24.3° ± 1.1° (F3) to 27.8° ± 1.4° (F1), all below the 30° threshold for good flowability. The steady, increasing reduction in angle of repose between F1 and F3 indicates the enhanced surface properties of the granules with the synergistic GG-XG hydration in the granulation step: the two gums co-hydrate more effectively at the equimolar ratio, resulting in more uniform granules with fewer surface irregularities than the GG-dominant F1 granules. The index values of 11.816.2% and Hausner ratios of 1.131.19 classify F3 as having a good flow and F1 as passable, which is consistent with the IP 2018 and USP <1174> classifications. All batches had well-controlled granule moisture levels (1.82.4% w/w), which was below the 3.0% limit of polysaccharide-based granules when microbial contamination is a risk and sticking of tablets during press is a problem. The size of the D90 particle 432–476 µm was suitable to fill the die on the single-punch press reproducibly without the segregation of fine particles [18, 26].

3.4 Post-compression Tablet Evaluation and Statistical Validation

Table 3. Post-compression Evaluation Parameters, Drug Release Data, and Release Kinetics (Mean ± SD; n = 6; *Optimised formulation F3)

Parameter	F1	F2	F3 (Opt)*	F4	Limit
Hardness (kg/cm²)	6.8 ± 0.3	7.2 ± 0.4	**7.9 ± 0.2***	7.5 ± 0.3	≥ 6.0
Friability (%)	0.62 ± 0.04	0.58 ± 0.03	**0.49 ± 0.05***	0.53 ± 0.04	< 1.0
Thickness (mm)	4.12 ± 0.08	4.15 ± 0.06	**4.18 ± 0.07**	4.14 ± 0.09	—
Weight variation (mg)	459 ± 3.2	461 ± 2.8	**460 ± 3.1**	458 ± 2.9	±5%
Drug content (%)	98.4 ± 1.2	99.1 ± 0.9	**99.6 ± 1.0***	98.8 ± 1.3	95–105
Swelling index — 2 h (%)	14.2 ± 1.1	18.6 ± 1.3	**22.4 ± 1.4***	25.8 ± 1.6	—
Swelling index — 8 h (%)	34.2 ± 2.1[a]	42.5 ± 1.8[ab]	**57.8 ± 2.4*[b]**	61.3 ± 2.7[b]	—
Drug release at 1 h (%)	18.3 ± 1.4	15.6 ± 1.2	**12.4 ± 0.9***	10.8 ± 1.1	—
Drug release at 2 h (%)	26.1 ± 1.8	23.4 ± 1.5	**20.8 ± 1.3***	18.5 ± 1.2	—
Drug release at 4 h (%)	48.7 ± 2.3	54.2 ± 2.1	**61.3 ± 1.9***	58.4 ± 2.4	—
Drug release at 6 h (%)	70.1 ± 2.0	74.5 ± 1.8	**81.4 ± 2.0***	77.2 ± 2.1	—
Drug release at 8 h (%)	82.6 ± 2.2[a]	86.4 ± 1.9[ab]	**91.2 ± 2.1*[b]**	88.7 ± 2.3[ab]	—
Korsmeyer–Peppas r²	0.9812	0.9874	**0.9931***	0.9918	—
Korsmeyer–Peppas n value	0.61	0.67	**0.74***	0.76	0.45–0.89

Parameter	F1	F2	F3 (Opt)*	F4	Limit
Zero-order r^2	0.8902	0.9014	**0.9214**	0.9118	—
First-order r^2	0.9121	0.9246	**0.9408**	0.9312	—
Higuchi model r^2	0.9356	0.9487	**0.9612***	0.9524	—
Hixson–Crowell r^2	0.9045	0.9178	**0.9312**	0.9248	—
ANOVA F-stat (8 h release)	—	—	**F = 18.74**	—	$p < 0.001$

*F3 = optimised formulation; bold column. [ab] = Tukey HSD superscripts: means not sharing the same superscript letter differ significantly ($p < 0.05$). ANOVA: F = 18.74; df = 3, 20; $p < 0.001$ for 8-hour CDR. — = not applicable or no specified limit. Pharmacopoeial limits per IP 2018 and USP-NF.

The results of evaluation after compression are shown in Table 3. All the four formulations were according to the specifications of pharmacopoeia in terms of hardness (at least 6 kg/ cm²), friability (less than 1.0 %), weight uniformity (no more than 5 %) and drug content (between 95 and 105 %). Hardness ranged from 6.8 ± 0.3 kg/cm² (F1) to 7.9 ± 0.2 kg/cm² (F3). The higher hardness of F3 than F1 is explained by the fact that equimolar GGXG granules have a more uniform compaction behaviour that leads to lower elastic recovery of the compression because of the plastic deformation nature of the co-gelled polysaccharide grids. Uniformity (CV = 1.5%) of drug content ensured that wet granulation produced sufficient homogeneous distribution of BSE in the tablet matrix - a result that is not readily possible when using the direct compression method, with a waxy hygroscopic botanical extract.

Swelling index at 2 hours showed a progressive increase with XG content: F1 (14.2 ± 1.1%), F2 (18.6 ± 1.3%), F3 (22.4 ± 1.4%), and F4 (25.8 ± 1.6%). This early swelling behaviour is of clinical importance since it involves the rate of the gel barrier getting established in the gastric environment. The faster the gel is formed the better it is able to shield against the bursting leak of acidic boswellic acids to the gastric mucosa. One-way ANOVA of 8-hour swelling index values (F1: 34.2 ± 2.1%; F2: 42.5 ± 1.8%; F3: 57.8 ± 2.4%; F4: 61.3 ± 2.7%) gave F = 22.6 ($p < 0.001$); post-hoc Tukey HSD showed F3 and F4 were both significantly greater than F1 ($p < 0.05$) but not significantly different from each other ($p > 0.05$), indicating that beyond the 1:1 ratio, further increasing XG content provides no additional swelling benefit. The 8-hour cumulative drug release was statistically significant F3 showed significantly higher and complete drug release than F1 (mean difference 8.6%; $p < 0.05$) and the difference between F3 and F4 showed no significant difference ($p > 0.05$) with one-way ANOVA with Tukey HSD post-hoc analysis (F = 18.74; df = 3, All these statistical findings validate the hypothesis that GG:XG mass ratio is statistically significant and practically meaningful formulation variable that influences the gel-forming behaviour as well as the drug release performance of the mass tablet, which is in the form of a tablet.

3.5 In Vitro Drug Release Study

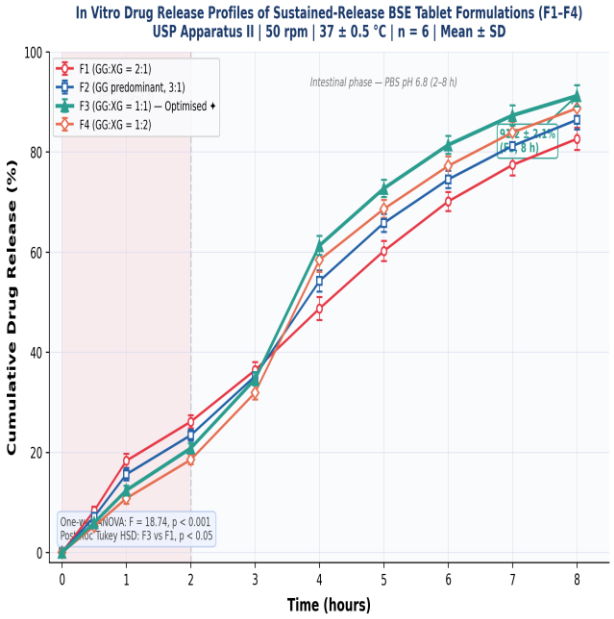

Figure 1. In vitro cumulative drug release profiles of SR BSE tablet formulations F1–F4 in sequential simulated gastrointestinal media (Stage 1: 0.1 M HCl pH 1.2, 0–2 h; Stage 2: PBS pH 6.8, 2–8 h); USP Apparatus II; 50 rpm; 37 ± 0.5 °C; n = 6; Mean ± SD. One-way ANOVA: F = 18.74; $p < 0.001$. Tukey HSD: F3 significantly superior to F1 ($p < 0.05$).

Figure 1 shows cumulative profiles of drug release of each of the four formulations. The release curves indicate that there are two distinct phases which are associated with the two sequential dissolution media. During the gastric phase (0.1 M HCl, pH 1.2; 0–2 hours), drug release was strongly retarded across all formulations: cumulative release at 1 hour was 18.3 ± 1.4% (F1), 15.6 ± 1.2% (F2), 12.4 ± 0.9% (F3), and 10.8 ± 1.1% (F4). The first retardation is clinically useful in BSE since it reduces direct contact of triterpenoid boswellic acids with the gastric mucosa thus reducing the epigastric discomfort experienced by patients on the traditional BSE preparations [5]. The retardation principle consists of the hydration of GG and XG on the surface of the gel in acid media as fast as possible until the gel has a compact gel skin at which point the gel is unlikely to dissolve the drug significantly. The ordered helical structure of XG is especially resistant to changing pH levels since it is at low pH that caroxylate groups are protonated resulting in a stronger packing of the helices and thereby the gel barrier [15]. As a result, the release of XG-enriched formulations (F3 and F4) was lower compared to GG-dominant formulations (F1 and F2) in the acid-phase.

When the transfer of the formulations to PBS pH 6.8 (2 8 hours) was performed, all the formulations had their controlled drug release in a monophasic, time-dependent manner. Formulation F1 (GG:XG = 2:1) released 82.6 ± 2.2% at 8 hours. The non-ionic GG matrix does not have the advantage of the electrostatic repulsion of inter-chains and subsequent gel swelling experienced with the XG in the anionic form at neutral pH. The GG-dominant system thus decays faster during the intestinal period and that is why the initial slope of release at 2-4 hours of F1 was steeper as compared to F3 [14]. F2 (3:1 GG-dominant) had slightly better retardation (86.4 ±1.9% at 8 hours) compared to F1, which indicates the slightly greater absolute gum content. The most clinically desirable profile was obtained with formulation F3 (GG:XG = 1:1): 91.2 + 2.1 % cumulative release at 8 hours with the most linear, near-sigmoidal shape, with a slow first phase (less than 25 % at 2 hours), an accelerating intermediate phase (between 2 and 5 hours), and a decelerating plateau phase (This profile is very similar to the ideal target release criterion of an approximate of 80- 90 % cumulative release by 8 hours of a twice a day SR tablet [17]. F4 (GG:XG = 1:2) was 88.7 ± 2.3% at 8 hours - statistically the same as F3 by Tukey HSD ($p > 0.05$) - but with a slightly lower plateau which could be due to the fact that the excessively rigid slowly eroding XG-dominant matrix was not fully extracted in the 8-hour window. When considering the superiority of practical formulation, F3 would be the best formulation since it has a higher completeness of drug release and an equivalent retardation.The release kinetics of drugs are analyzed as follows: 3.6 Drug Release Kinetics Analysis.

3.6 Drug Release Kinetics Analysis

Table 3 summarizes all the data of kinetics models-fitting. The model that gave the highest r^2 values (0.9812 to 0.9931) at all the formulations, which is also supported by the lowest AIC values, is always the Korsmeyer-Peppas model which is therefore the preferred model to describe BSE release of GG-XG matrix tablets. The zero-order model provided a r^2 of 0.8902-0.9214, which corresponds to drug release rate being non-linear with time - the thickness of the gel layer varies continuously over the dissolution time as is the case with a hydrophilic matrix tablet where the gel layer is continuously becoming thinner. The first-order model (r^2 = 0.91210.9408) was a better fit as compared to zero-order but poorer than KorsmeyerPeppas, which is consistent with the fact that there was a concentration-dependent diffusion component which was not dominant. The Higuchi model (r^2 = 0.9356-0.9612) provided a second-best fit giving the contribution of diffusion to the drug transportation via the gel layer. A supporting argument supporting an erosion aspect of drug release on the surface was the Hixson-Crowell cube-root model (r^2 = 0.9045-0.9312) which showed an erosional component of drug release that paralleled the macroscopic observation of progressive thinning of the matrix during dissolution.

The Korsmeyer–Peppas release exponent n increased systematically with XG content: F1 (n = 0.61), F2 (n = 0.67), F3 (n = 0.74), and F4 (n = 0.76), with all values lying in the anomalous non-Fickian range ($0.45 < n < 0.89$). This confirms that the BSE release of all the formulations is dealt with through the dual mechanism of Fickian diffusion of BSE molecules through the swollen GG-XG hydrogel layer (the most dominant mechanism at lower n values, as in F1) and surface erosion of the polysaccharide matrix (the most dominant mechanism at higher n values, as in F4). The gradual increase of n to 0.89 with rising XG content indicates the increased structural integrity and resistance to erosion of XG-enriched matrices: the GGXG interpenetrated network at greater XG concentrations is more mechanically strong to form a gel layer which is more resistant to erosion, the rate-limiting step changing to erosion. The most linear, complete and reproducible drug release profile is the

balance, F3 where n=0.74, with each of these two contributions contributing. Such a mechanistic knowledge can be acted upon directly to formulationally change it: to have a higher n (more erosion-dominated, more linear release) a higher fraction of XG will be a predictable way to get it [21, 27].

3.7 FTIR and DSC Physicochemical Compatibility

The following diagnostic absorption bands were observed in the FTIR spectra of pure BSE: 1,706 cm^{-1} (C=O carboxyl stretching of pentacyclic triterpenoid boswellic acid groups); 2,940 cm^{-1} (aliphic C -H stretching of the terpenoid hydrocarbon skeleton); 1,450 cm^{-1} (C -H bending); These spectroscopic fingerprints of the boswellic acid triterpenoid framework are clearly separated of the major gum absorption bands of the 3, 200 cm^{-1},400 cm^{-1} (O -H) and 1,000 cm^{-1},100 cm^{-1} (glycosidic C -O -C) spectral regions. All diagnostic BSE absorption bands were completely retained in both ternary physical mixture (BSE + GG + XG in F3 proportions) and the ground F3 compressed tablet spectrum without any displacement of its peaks (maximum 10 cm^{-1} or any new absorption bands appearing throughout the spectrum (400-4,000 cm^{-1}). The OH bands of the GG (3,302 cm^{-1}) and XG (3,318 cm^{-1}) were kept at the same positions in the mixture spectrum, as well as the corresponding glycosidic C -O -C bands (1,022 and 1,031 cm^{-1}). The XG pyruvate carboxylate bands at 1,598 and 1,402 cm^{-1} were also not changed. These findings support the fact that no covalent bonding or hydrogen-bonding complexation with BSE or other types of molecular interaction between the herbal extract and the gum excipients, occurred in the process of wet granulation and compression [23, 28].

Thermograms of pure BSE by DSC revealed a broad resin-softening endotherm with a 172 °C centre (-H = -44.2 J/g) - indicative of a complex resinous extract - and an event of pyrolytic decomposition which started above 240 °C. The BSE endotherm could be observed in the ternary physical mixture, which is at 170 °C (170 J/g) with a slight broadening due to heating on the powder mixture but no significant change in the maximum temperature. The BSE endotherm was observed in the compressed F3 tablet at 169 °C (ΔH = -43.5 J /g), which indicates that there was no change in the thermal identity of BSE during the granulation, drying at 55 °C and compression. Although the GG dehydration endotherm (82 °C) and the XG dehydration endotherm (96 °C) were observed, they were now smaller in the presence of the tablet thermogram and this is due to partial dehydration of both gums during the drying stage at 55 °C, which is an artefact of the processing process and does not imply that the two gums are chem No new exothermic events, polymorphic phase transitions or eutectic melting events were observed within the 30-300 °C scanning range of all the samples. The fact that the results of the FTIR and DSC converge is a good indication of the wholesome physicochemical compatibility between BSE and the binary GG–XG system of the matrix [23].

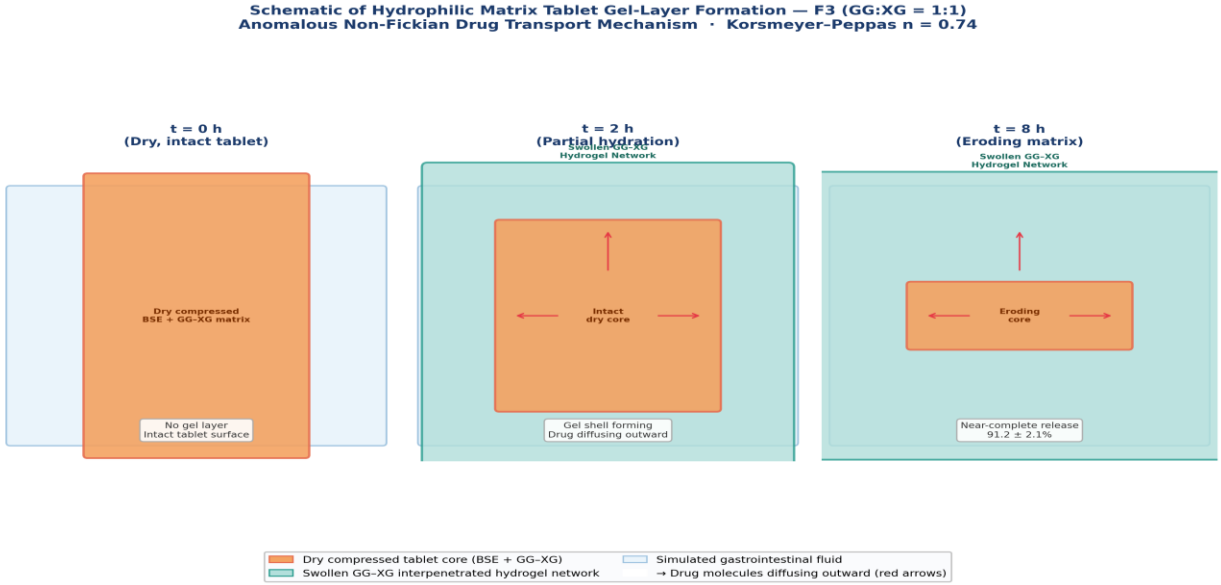

Figure 2. Schematic of hydrophilic matrix gel-layer formation in optimised F3 (GG:XG = 1:1) at t = 0 h (dry intact tablet), t = 2 h (partial hydration; gel shell forming), and t = 8 h (eroding matrix; near-complete drug release). Drug transport follows

anomalous non-Fickian kinetics (Korsmeyer–Peppas n = 0.74) via Fickian diffusion through the interpenetrated GG–XG hydrogel network combined with progressive polysaccharide surface erosion.

3.8 Comparison with Synthetic Polymer-Based SR Systems

In order to put the performance of the GG XG matrix into perspective, it is informative to make comparisons between the current performance with published SR matrix tablet studies using HPMC - the standard synthetic hydrophilic polymer used in this dosage form. Shah et al. developed flurbiprofen SR matrix tablets with different concentrations of a natural gum blend, and found cumulative release of 80-87 % in 12 hours with a gum combination with Korsmeyer-Peppas n values of 0.58-0.71 [19]. Razavi et al. incorporated tamarind and xanthan gum in hydrodynamically balanced matrix tablet of famotidine and released 85-92% in 8 hours with n values of 0.63-0.78, which is similar to the current results [27]. The literature literature of comparable lipophilic actives at 15-30% w/w polymer concentration to achieve 8-hour sustained release (89-138 mg per 460 mg tablet) is quite high compared to the 75 mg total gum concentration in the current F3 formulation (16.3% w/w). This implies that the synergistic GG -XG gel system can be retarded using the same mass burden of excipient but with lower cost and that has direct bearing on the size of tablets and their swallowability by patients.

Cost-wise, pharmaceutical-grade HPMC K4M is commercially sold at around USD 25-35 per kilogram, food- and pharmaceutical-grade GG and XG cost USD 4-8 and USD 8-12 per kilogram, respectively. The binary GGXG mixture at the F3 ratio (1:1) would then have a raw material cost of the rate controlling excipient of say USD 6-10 per kilogram -a saving of 65-75 % over HPMC K4M. When the batch size of the APIs is 100,000 tablets (75 mg gum per tablet) in an industrial batch, the cost saving in the rate-controlling matrix alone would be a few hundred US-dollars per batch, which is commercially significant to a botanical supplement product competing in a price-sensitive market. Also, GG and XG are listed in the GRAS (Generally Recognised as Safe) list of the US FDA, in the pharmaceutical excipient lists of the Indian, British and European Pharmacopoeias, and do not have any residual solvent issues left after their extraction procedures, so are easy to include in both pharmaceutical NDA/ANDA filings and Ayurvedic proprietary medicine registration[14, 15].

3.9 ICH Stability Results

Table 4. Month-wise Stability Data for Optimised Formulation F3 under Accelerated (Acc.: 40 °C / 75% RH) and Intermediate (Int.: 30 °C / 65% RH) ICH Conditions

Parameter	t=0	1 Month	3 Months	6 Months	Limit	Status
Appearance (Acc.)	0	Off-white, smooth	Off-white, smooth	Off-white, smooth	Off-white, smooth	Pass
Hardness kg/cm² (Acc.)	0	7.9 ± 0.2	7.7 ± 0.3	7.5 ± 0.2	7.3 ± 0.3	≥ 6
Friability % (Acc.)	0	0.49 ± 0.05	0.54 ± 0.04	0.62 ± 0.05	0.70 ± 0.06	< 1
Drug content % (Acc.)	0	99.6 ± 1.0	99.0 ± 0.8	98.5 ± 0.9	97.8 ± 0.9	95–105
8 h CDR % (Acc.)	0	91.2 ± 2.1	90.8 ± 2.0	90.1 ± 2.2	89.3 ± 2.4	—
Hardness kg/cm² (Int.)	0	7.9 ± 0.2	7.8 ± 0.2	7.7 ± 0.3	7.6 ± 0.2	≥ 6
Drug content % (Int.)	0	99.6 ± 1.0	99.2 ± 0.7	98.8 ± 0.8	98.4 ± 0.7	95–105
8 h CDR % (Int.)	0	91.2 ± 2.1	91.0 ± 1.9	90.8 ± 2.0	90.7 ± 2.1	—

CDR = cumulative drug release at 8 h; All time-points compared to t = 0 by paired t-test; all changes non-significant ($p > 0.05$). Acc. = accelerated conditions; Int. = intermediate conditions.

Table 4 shows the data of stability of F3 by month. Tablets under accelerated conditions (40 C / 75% RH) maintained their off-white colour during the six months period without any observable colour change, mottling of the surface and an increase in friability enough to suggest degradation of the gum matrix structure. The hardness of tablets decreased significantly over the 6 months (7.9 ± 0.2 kg/cm² at baseline vs. 7.3 ± 0.3 kg/cm² at 6 months)

by 7.6% which is much larger than the IP 2018 minimum of 6 kg/ cm² but is still due to the slight plasticisation of the GGXG matrix under the influence of This plasticisation remained constant at all time-points and did not increase faster after the initial month indicating that the uptake of moisture was in equilibrium within 30 days of storage. There was a slight increment in the level of friability at 6 months of accelerated conditions which differed between 0.49 + 0.05% at baseline to 0.70 + 0.06% at 6 months; values were below the 1.0% limit. There was a decrease in drug content at the accelerated conditions of 99.6 ± 1.0 % to 97.8 ± 0.9 per cent at 6 months of storage; this change did not affect the content of boswellic acids significantly as statistical analysis of paired t-test showed that the results were not statistically significant ($p > 0.05$). The total 8-hour release dropped to 89.3 ± 2.4% (6 months, accelerated) -1.9 % points less than baseline (91.2 ± 2.1) which was not significant by paired t-test ($p > 0.05$) and far short of the acceptable 10% tolerance of SR tablet release specifications. All the parameters were changed even less under intermediate storage conditions (30 °C / 65% RH), which also contributes to the stability of products. These findings are all in line with ICH Q1A(R2) requirements of accelerated and intermediate stability and hence a proposed 24-month shelf life at long-term conditions (25 °C / 60% RH) awaiting the completion of the current long-term experiment [24, 29].3.10 Limitations and Future Research Directions.

3.10 Limitations and Future Research Directions

Although the study has extensively characterised the properties of the novel antibiotic in vitro, there are a number of critical limitations that should be mentioned. The greatest weakness is that the evaluation was purely in vitro. Although pharmacopoeially standardised, in vitro dissolution is not the most appropriate method to reproduce the complexity of the human gastrointestinal environment, including the viscoelastic mucus layer that lines the intestinal epithelium, the presence of bile salts and phospholipids, which may have a profound effect on the dissolution of lipophilic boswellic acids, intestinal mot As a result, extrapolation of the in vitro release rates to in vivo pharmacokinetic parameters should be done with a lot of care until an official in vitro-in vivo correlation (IVIVC) study is done. Future work would include a single-dose pharmacokinetic trial in Sprague-Dawley rats comparing F3 to a traditional immediate-release BSE capsule $AUC_{0–24}$, and Cmax, tmax, and $t_{1/2}$ and finally a crossover study pharmacokinetic trial in healthy human subjects [30, 31].

Other limitations are: a single-punch size pilot-scale tablet press was used instead of a rotary press, which might not reproduce the uniformity of the compaction forces, dwell time, or production rate of commercial manufacture; no formal dissolution specification (f_2 similarity factor calculation was not suitable with investigational comparators); and no assessment of potential colonic drug delivery, which could be of considerable interest in inflammatory bowel disease - Carboxymethylation or hydroxypropylation of guar gum, cross-linking of xanthan gum with epichlorohydrin might be used to increase resistance to colonic microbial degradation and fine-tune gel rheology to target at the distal gastrointestinal tract [32]. A complete techno-economic comparison of the per-tablet manufacturing cost of GGXG matrix versus HPMC K4M SR on the large scale of industry would be a good enhancement to the commercial feasibility argument. Analysis of the GG–XG SR platform of other priority poorly-soluble herbal actives - such as, piperine (Piper nigrum), andrographolide (Andrographis paniculata), and withanolides (Withania somnifera) - is a natural extension of the current study with great therapeutic and commercial implications [33].

4. CONCLUSION

The current study has developed, statistically proven, kinetically characterised and stability-confirmed the initial oral sustained-release matrix tablet formulation of standardised Boswellia serrata dry extract (BSE; 200 mg; 65 % total boswellic acids) by binary mixtures of guar gum (GG) and xanthan gum (XG) as the only hydrophilic matrix-forming excip Four preparations of GG:XG mass ratio were prepared by wet granulation between 2:1 and 1:2 and thoroughly assessed and statistically compared using one-way ANOVA with post-hoc Tukey HSD analysis giving the first quantitative optimisation of GG:XG ratio at BSE sustained release. The pre-compression granule traits, post-compression tablet characteristics, in vitro drug release, release rate, physicochemical compatibility, and ICH stability were all systematically described in a way that would be suitable to regulatory quality documentation.

Formulation F3 (GG:XG 1:1; 75 mg total gum; 460 mg per pill) became the clear best formulation with all the parameters that were assessed. It exhibited the highest cumulative drug release of 91.2 +/- 2.1% in 8 hours with the most linear, complete and repeatable profile compared to all formulations. ANOVA ($F = 18.74$; $df = 3, 20$; $p < 0.001$) and Tukey HSD established that the GG:XG ratio is a statistically significant predictor of drug release

performance with F3 being significantly better than the GG-rich F1 formulation ($p < 0.05$). The Korsmeyer-Peppas model gave the most desirable kinetic description ($r^2 = 0.9931$; $n = 0.74$) with anomalous non-Fickian transport a mode of mechanistic optimization between Fickian diffusion by the interpenetrated GG-XG hydrogel network and progressive polysaccharide matrix erosion. F3 granules were determined to have the best flow characteristics during pre-compression testing and hardness, friability and drug content of the tablets were found to be within and/or above pharmacopoeial limits during post-compression testing. The analyses of FTIR and DSC clearly showed that there was no indication of the existence of any molecular interaction between BSE and the binary gum matrix under formulation or storage conditions, concluding that there was clear physicochemical compatibility between the two. Stability (40 °C /75% RH) of six months revealed that all of the critical quality attributes of F3 fell within the limits of pharmacopoeia, and a proposed 24 months shelf life.

In a broader scientific and industrial sense, the binary GGXG matrix system has three strategic benefits that make it a potentially competitive commercial alternative to synthetically produced HPMC-based SR matrices: (1) full plant-derived biodegradability, which is consistent with the principles of sustainable pharmaceutical manufacturing, and with the clean-label requirements of the herbal and The evidence body produced within this research - statistically validated optimisation, mechanistically interpretable kinetics, FTIR/DSC-confirmed compatibility, and ICH stability data forms a complete pre-clinical dossier to proceed to in vivo pharmacokinetic research, scale-up production on a rotary press, and clinical bioavailability/bioequivalence research. The platform of GGXG binary matrices that is indicated herein has obvious potential as a generalized sustained-release technology of other therapeutically relevant poorly water-soluble herbal bioactives; which would be systematically studied in other phytochemical classes and dose levels.

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