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Development and Evaluation of Dapagliflozin-Loaded Sodium Alginate Nanoparticles Incorporated into a capsule Dosage Form for Cardio-Renal Therapy

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ABSTRACT

Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor with established cardio-renal benefits, is limited in conventional oral dosage forms by pH-dependent solubility, extensive first-pass metabolism and a short elimination half-life that necessitates daily dosing. The present work aimed to develop dapagliflozin-loaded sodium alginate nanoparticles by ionic gelation and to convert the optimized batch into a hard gelatin capsule for sustained, oncedaily cardio-renal therapy. Nine nanoparticle batches (F1–F9) were prepared by varying sodium alginate concentration, calcium chloride (cross-linker) concentration and stirring speed, and were evaluated for percentage yield, mean particle size, polydispersity index (PDI), zeta potential and entrapment efficiency. Batch F5 (100 mg sodium alginate, 36 mg calcium chloride, 750 rpm) was selected as the optimized formulation, showing a mean particle size of 176.8 nm, PDI of 0.241, zeta potential of −28.6 mV, entrapment efficiency of 91.5% and practical yield of 89.8%. Scanning electron microscopy confirmed discrete, near-spherical nanoparticles with smooth surfaces, and FTIR analysis indicated retention of characteristic functional groups with only minor peak shifts, consistent with drug–polymer compatibility. The dried F5 nanoparticles were blended with microcrystalline cellulose and filled into size '0' hard gelatin capsules, giving an average fill weight of 250.4 ± 3.1 mg, weight variation within ±6.8%, drug content of 99.2% of label claim and a disintegration time of 18 min 40 s. In vitro dissolution testing showed an extended release profile, with 99.2% of dapagliflozin released by 12.9 h, slower than a marketed immediate-release tablet used for comparison. Release data fitted best to the Korsmeyer–Peppas (R^2 = 0.9941, n = 0.615) and Higuchi (R^2 = 0.9893) models, indicating diffusion-controlled, anomalous (non-Fickian) transport. These findings demonstrate the technical feasibility of an alginate nanoparticle-in-capsule platform for sustained oral delivery of dapagliflozin; confirmation of the anticipated bioavailability and cardio-renal benefit will require further in vivo pharmacokinetic and pharmacodynamic evaluation.

Introduction

Type 2 diabetes mellitus (T2DM) has grown from a manageable metabolic disorder into a systemic disease with major cardiovascular and renal consequences. Chronic hyperglycaemia, oxidative stress, inflammation and endothelial dysfunction interact to accelerate damage to target organs, and the resulting overlap between diabetes, cardiovascular disease and chronic kidney disease is now recognised as "cardio-renal syndrome" — a condition in which dysfunction of one organ system worsens pathology in the other [1–4]. Global prevalence data illustrate the scale of the problem: the International Diabetes Federation estimated approximately 537 million adults living with diabetes worldwide, projected to rise to 783 million by 2045, with India alone accounting for more than 77 million cases [1,2].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a therapeutic class capable of providing cardiorenal protection independent of their glucose-lowering action. Among them, dapagliflozin has shown consistent benefit across major outcome trials in heart failure and chronic kidney disease [4,7,8]. However, its clinical utility in conventional oral formulations is constrained by pH-dependent aqueous solubility, extensive first-pass hepatic metabolism and a relatively short plasma half-life, all of which necessitate once-daily dosing and can compromise patient adherence [1,3].

Nanoparticulate drug delivery systems offer a means of addressing these limitations by improving apparent solubility, protecting the drug from degradation, and enabling sustained or site-modulated release [9]. Sodium alginate, a naturally occurring anionic polysaccharide, is a widely used polymer for such systems because its guluronic acid residues cross-link electrostatically with

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divalent cations (typically Ca^{2+}) in a mild, aqueous, solventfree process known as ionic gelation, avoiding the heat and organic solvents that can degrade sensitive drugs [9,10]. Converting an optimized nanoparticle batch into a hard gelatin capsule further offers a practical, patient-acceptable, once-daily solid oral dosage form.

The present study was therefore designed to develop dapagliflozin-loaded sodium alginate nanoparticles by ionic gelation, to identify an optimized formulation through comparative evaluation of particle size, polydispersity index, zeta potential and entrapment efficiency, and to convert this formulation into a hard gelatin capsule suitable for sustained, once-daily cardio-renal therapy.

MATERIALS AND METHODS

Materials

Dapagliflozin was obtained as a gift sample (Pharmafabrikon, Madurai). Sodium alginate (Loba Chemie Pvt. Ltd.) served as the polymer, and calcium chloride (Fisher Scientific) as the ionic cross-linking agent. Microcrystalline cellulose (Sigma-Aldrich) was used as diluent/adsorbent for the capsule blend, and size '0' hard gelatin capsule shells were procured from Capsugel India Pvt. Ltd. Ethanol (Merck) and distilled water served as solvents/vehicles. All other reagents were of analytical grade.

Instrumentation

Formulation and evaluation employed a digital analytical balance, digital melting point apparatus, UV-Visible double-beam spectrophotometer, Fourier-Transform Infrared (FTIR) spectrophotometer, hot-air oven, orbital shaking incubator, digital pH meter, cooling centrifuge, particle size/zeta potential analyzer (dynamic and electrophoretic light scattering), scanning electron microscope, magnetic stirrer with hot plate, and standard volumetric glassware.

Preformulation Studies

The procured drug was characterized prior to formulation to confirm identity and establish suitable analytical protocols, following standard pharmaceutical preformulation practice [13]. Organoleptic properties (colour, odour, taste, appearance) were noted visually. Solubility was assessed qualitatively in water, methanol, ethanol, phosphate buffer pH 6.8, 0.1 N HCl and acetone. Melting point was determined using a digital melting-point apparatus. The apparent partition coefficient (n-octanol/water) and log P were determined by the shake-flask method [13]. UV scanning (200–400 nm) established λmax, and a calibration curve (1–5 µg/mL) was constructed in the selected medium and fitted by linear regression. FTIR spectroscopy was used to identify characteristic functional-group absorptions of the pure drug and to assess drug–excipient compatibility [24].

Preparation of Dapagliflozin-Loaded Sodium Alginate Nanoparticles

Nanoparticles were prepared by ionic gelation, which exploits the electrostatic cross-linking of the anionic guluronate blocks of sodium alginate with divalent Ca^{2+} ions to form a three-dimensional "egg-box" network, avoiding organic solvents and high shear or heat that could degrade the drug [10,15,16]. Sodium alginate was dissolved in distilled water under continuous stirring; dapagliflozin was then dispersed uniformly into this solution. A calcium chloride solution of defined concentration was added dropwise under continuous stirring, inducing instantaneous cross-linking and spontaneous nanoparticle formation. Stirring was continued for a fixed period to ensure complete gelation, after which the dispersion was centrifuged to separate the nanoparticles from the supernatant. Nine batches (F1–F9, Table 1) were prepared by systematically varying sodium alginate concentration (75, 100 or 125 mg), calcium chloride concentration (27, 36 or 45 mg) and stirring speed (500, 750 or 1000 rpm), with the drug content fixed at 10 mg per batch, in accordance with a full formulation-variable screening design [17].

Table 1. Composition of dapagliflozin-loaded sodium alginate nanoparticle batches F1–F9 (F5 was ultimately selected as optimized

Batch	Dapagliflozin (mg)	Sodium alginate (mg)	$CaCl_2$ (mg)	Stirring speed (rpm)
F1	10	75	27	500
F2	10	75	36	750
F3	10	75	45	1000
F4	10	100	27	500
F5	10	100	36	750
F6	10	100	45	1000
F7	10	125	27	500
F8	10	125	36	750
F9	10	125	45	1000

Nanoparticle Evaluation

Each batch was evaluated for percentage practical yield (ratio of practical to theoretical dried nanoparticle weight × 100) [21], mean particle size and polydispersity index by dynamic light scattering (DLS) [18,19], and zeta potential by electrophoretic light scattering [18,19]. Entrapment efficiency was determined indirectly: nanoparticles were separated by centrifugation, and the free drug remaining in the clear supernatant was quantified by UV spectrophotometry at the previously determined λmax; entrapment efficiency was calculated as [(total drug − free drug)/total drug] × 100 [20]. The formulation showing the most favourable combined profile — smaller particle size, lower PDI, more negative zeta potential, and higher entrapment efficiency and yield

— was selected as optimized [18–21]. The optimized batch was additionally examined by scanning electron microscopy (SEM), after mounting on a metallic stub and sputter-coating, to assess surface morphology [21], and by FTIR to confirm drug–polymer compatibility after nanoparticle formation [24].

Drying and Capsule Formulation

The optimized nanoparticles, recovered by centrifugation, were dried in a hot-air oven to give a free-flowing powder suitable for downstream processing [25,26], which was blended with microcrystalline cellulose as diluent and filled manually into size '0' hard gelatin capsules [22,27]. The capsule blend was evaluated for micromeritic properties (angle of repose, bulk and tapped density, Carr's index, Hausner's ratio, moisture content) to confirm suitability for uniform capsule filling. Filled capsules were evaluated for physical appearance, average fill weight and weight variation (20 units), drug content (assay), and disintegration time, following standard pharmacopoeial approaches for hard gelatin capsules [27].

In Vitro Drug Release and Release-Kinetics Modelling

In vitro dissolution of the optimized capsule formulation was carried out under simulated gastrointestinal conditions (successive media representative of gastric and intestinal pH) and compared against a marketed immediate-release dapagliflozin tablet [23]. Cumulative drug release was determined spectrophotometrically at defined time points up to approximately 13 h. The release data were fitted to zero-order and first-order kinetic models [31], the Higuchi diffusion model [29], and the Korsmeyer–Peppas model [30]; the model giving the highest coefficient of determination (R^2) was taken to best describe the release mechanism, and the Korsmeyer–Peppas release exponent
(n) was used to characterize the release/transport mechanism as Fickian or non-Fickian (anomalous) [32].

RESULTS AND DISCUSSION

Preformulation Characterization

Dapagliflozin was obtained as a white, crystalline, odourless, slightly bitter fine powder, consistent with standard pharmacopoeial description and confirming physical stability of the procured sample. The drug was slightly soluble in water, 0.1 N HCl and phosphate buffer pH 6.8, freely soluble in methanol, soluble in ethanol, and sparingly soluble in acetone — a solubility pattern that supported the rationale for a nanoparticulate approach. The observed melting point (74.8 °C) fell within the reported range (74–76 °C), confirming purity and crystallinity. The apparent partition coefficient was 1.42 (log P = 0.15), indicating mild lipophilicity consistent with adequate interaction with, and retention within, the polymer matrix during formulation.

UV scanning identified λmax at 237 nm (Fig. 1), which was used for all subsequent spectrophotometric estimations. A calibration curve over 1–5 µg/mL was linear (y = 0.2812x + 0.0056; R^2 = 0.9994), confirming compliance with the Beer–Lambert law and suitability of the method for entrapment-efficiency and dissolution studies. FTIR spectra of the pure drug showed characteristic absorptions (broad O–H stretch near 3300 cm^{-1}; COO^- asymmetric stretch at 1614 cm^{-1}; C–O/C–O–C bands at 1245 and 1003 cm^{-1}), consistent with its reported functional groups.

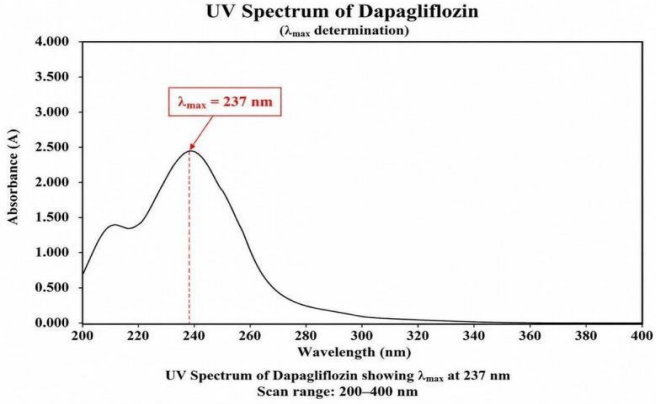

Figure 1. UV absorption spectrum of dapagliflozin showing λmax at 237 nm.

Nanoparticle Batch Optimization (F1–F9)

Across the nine batches, percentage practical yield ranged from 79.8% (F7) to 89.8% (F5); mean particle size ranged from 176.8 nm (F5) to 214.6 nm (F7); PDI ranged from 0.241 (F5) to 0.356 (F7); zeta potential ranged from −20.6 mV (F7) to −28.6 mV (F5); and entrapment efficiency ranged from 82.4% (F7) to 91.5% (F5) (Table 2, Figs. 2–4). Batch F5 (100 mg sodium alginate, 36 mg $CaCl_2$, 750 rpm) consistently returned the most favourable values across all five parameters and was therefore selected as the optimized formulation for subsequent capsule development.

Table 2. Comparative evaluation of dapagliflozin–sodium alginate nanoparticle batches F1–F9 (F5, highlighted, was selected as the optimized formulation)

Batch	Yield (%)	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)
F1	82.6	198.6	0.312	−22.4	85.2
F2	85.3	187.4	0.286	−24.1	87.6
F3	80.9	205.2	0.328	−21.8	83.8
F4	87.4	182.3	0.263	−25.6	89.6
F5	89.8	176.8	0.241	−28.6	91.5
F6	84.7	190.7	0.298	−23.5	86.9
F7	79.8	214.6	0.356	−20.6	82.4
F8	83.5	196.3	0.307	−22.9	85.7
F9	81.7	208.9	0.339	−21.4	84.3

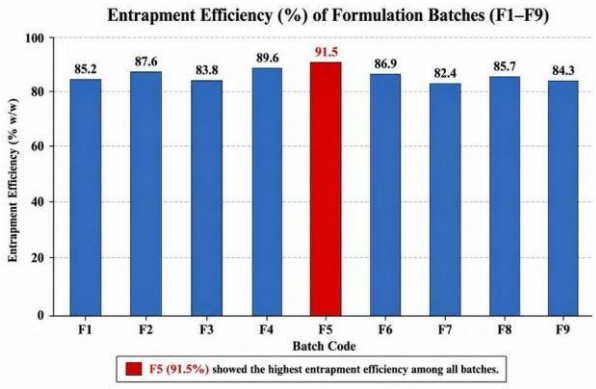

Figure 2. Percentage practical yield of formulation batches F1–F9.

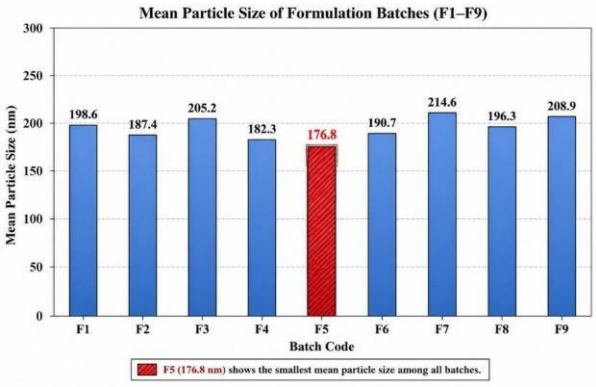

Figure 3. Mean particle size of formulation batches F1–F9.

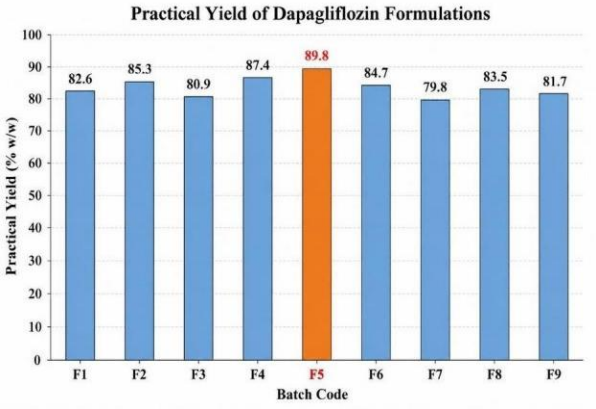

Figure 4. Percentage entrapment efficiency of formulation batches F1–F9.

The trend across batches suggested that increasing sodium alginate concentration up to 100 mg improved drug entrapment, most likely by providing an adequate gel-forming matrix, while a further increase to 125 mg (F7–F9) was associated with reduced yield and entrapment, potentially reflecting increased dispersion viscosity that hindered efficient cross-linking and drug capture. The comparatively higher zeta-potential magnitude and lower PDI of F5 point to reduced aggregation tendency and a more uniform particle population, consistent with its favourable particle-size and entrapment results.

Characterization of the Optimized Formulation (F5)

The optimized batch F5 showed a mean particle size of 176.8 nm, PDI of 0.241, zeta potential of −28.6 mV (Fig. 5) and entrapment efficiency of 91.5% (Table 3). The sub-300 nm size together with the low PDI indicates a reasonably uniform nanoparticulate dispersion, while the negative zeta potential — arising from the free carboxylate groups of the alginate backbone — is consistent with electrostatic stabilization against aggregation.

Table 3. Characterization summary of the optimized nanoparticle formulation (F5).

Parameter	Result (F5)
Percentage yield	89.8%
Mean particle size	176.8 nm
Polydispersity index (PDI)	0.241
Zeta potential	−28.6 mV
Entrapment efficiency	91.5%

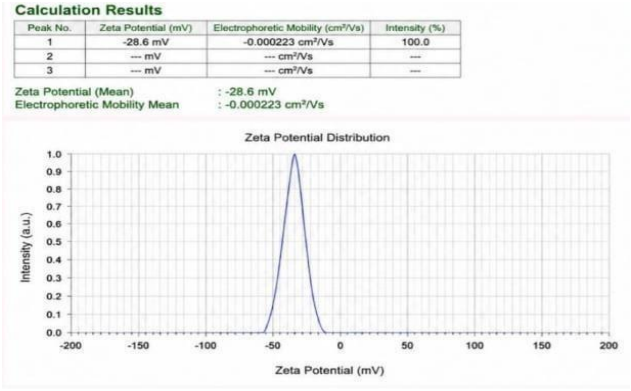

Figure 5. Zeta potential distribution of the optimized nanoparticle formulation (F5), mean = −28.6 mV.

Scanning electron microscopy of F5 (Fig. 6) revealed discrete, near-spherical particles with smooth surfaces and no significant aggregation, in general agreement with the dynamic-light-scattering size data. FTIR analysis of the optimized nanoparticles retained the principal functional-group absorptions of both dapagliflozin and sodium alginate (O–H stretch ~3432 cm^{-1}, aliphatic C–H ~2923 cm^{-1}, C=O ~1748 cm^{-1}, COO^- asymmetric stretch ~1649 cm^{-1}, C–O/C–O–C ~1032 cm^{-1}), with only minor peak shifts — consistent with physical drug–polymer interaction without significant chemical alteration.

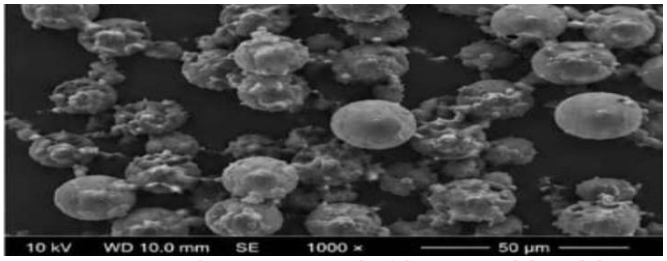

Figure 6. Scanning electron micrograph of the optimized dapagliflozin–sodium alginate nanoparticles (F5), showing discrete, near-spherical particles.

Drying and Capsule Evaluation

Drying of the optimized nanoparticles yielded a fine, free-flowing, off-white powder with 91.8% powder recovery, 89.4% post-drying yield and 3.2% moisture content, indicating minimal material loss and adequate handling properties. The dried nanoparticles were blended with microcrystalline cellulose (nanoparticle:MCC ≈ 1:0.72) and filled into size '0' hard gelatin capsules. Micromeritic evaluation of the blend (angle of repose, Carr's index, Hausner's ratio) fell within ranges conventionally regarded as indicating good powder flow, supporting consistent capsule filling.

Filled capsules (Fig. 7) were intact and uniform with no visible defects, an average fill weight of 250.4 ± 3.1 mg, weight variation within ±6.8% (within the ±7.5% pharmacopoeial limit for capsules of this fill weight), drug content of 99.2% of the labelled claim, and a disintegration time of 18 min 40 s — well within the 30-minute pharmacopoeial limit for hard gelatin capsules (Table 4). These results indicate that the optimized nanoparticles could be converted into a reproducible solid oral dosage form with acceptable pharmaceutical properties.

Figure 7. Final dapagliflozin-loaded sodium alginate nanoparticle capsules (optimized batch F5).

Table 4. Evaluation of final filled capsules (optimized batch F5).

Parameter	Result
Average fill weight	250.4 ± 3.1 mg
Weight variation	Within ±6.8%
Drug content (assay)	99.2% of label claim
Disintegration time	18 min 40 s

In Vitro Drug Release and Release Kinetics

The optimized nanoparticle capsule showed a gradual, extended release profile: 24% at 1 h, 41% at 2 h, 63% at 4 h, 79% at 6 h, 91% at 8 h, 96% at 10 h and 99.2% at 12.9 h, distinctly slower than the marketed immediate-release tablet used as comparator (Fig. 8). The comparatively limited release in the early hours suggests an initial retardation effect from the cross-linked alginate matrix, attributable to the compact network formed at the optimized alginate–calcium chloride ratio, followed by more extensive release as the matrix hydrated, swelled and eroded.

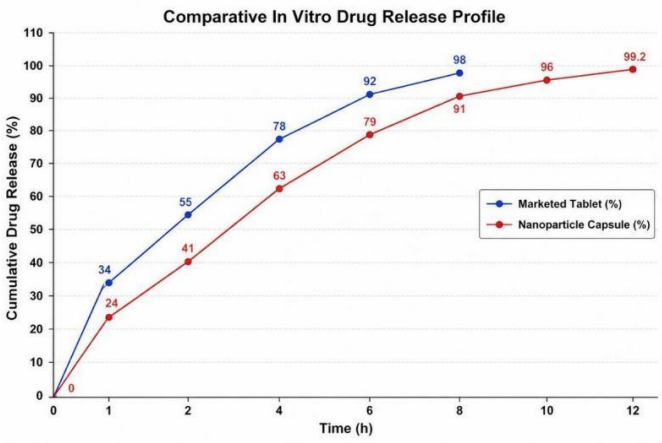

Figure 8. Comparative in vitro drug release of the optimized nanoparticle capsule versus a marketed dapagliflozin tablet.

Regression analysis of the release data (Table 5) showed the strongest fit with the Higuchi (R^2 = 0.9893) and Korsmeyer–Peppas (R^2 = 0.9941) models, followed by zero-order (R^2 = 0.9622) and first-order (R^2 = 0.9184) kinetics. The Korsmeyer–Peppas release exponent (n = 0.615) falls between 0.45 and 0.89, indicating anomalous (nonFickian) transport — a combination of drug diffusion through, and relaxation/swelling of, the alginate matrix — rather than simple diffusion or pure matrix erosion alone.

Table 5. Release-kinetics model fitting for the optimized dapagliflozin nanoparticle capsule (F5).

Kinetic model	Regression equation	R^2	Interpretation
Zero-order	y = 8.210x + 9.802	0.9622	Constant, concentration-independent release
First-order	y = −0.1392x + 2.0511	0.9184	Some concentration dependence
Higuchi	y = 28.58√t + 3.15	0.9893	Diffusion-controlled release
Korsmeyer–Peppas	y = 0.615x + 1.370	0.9941	n = 0.615; anomalous (non-Fickian) transport

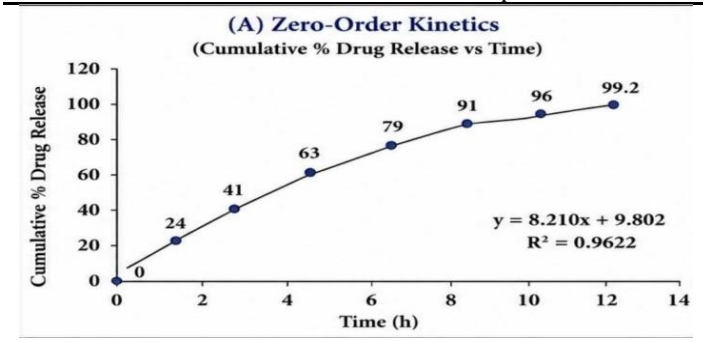

Figure 9. Zero-order release kinetics plot for the optimized formulation (F5).

Collectively, the kinetic analysis indicates that encapsulation within the alginate nanoparticle matrix shifted drug release away from the rapid, near first-order behaviour typical of an immediate-release tablet towards a more sustained, diffusion-influenced delivery pattern, consistent with the intended once-daily, extended-release objective of the formulation.

Conclusion

Dapagliflozin-loaded sodium alginate nanoparticles were successfully prepared by ionic gelation and converted into a hard gelatin capsule dosage form. Comparative evaluation of nine batches identified F5 (100 mg sodium alginate, 36 mg calcium chloride) as optimal, with a mean particle size of 176.8 nm, PDI of 0.241, zeta potential of −28.6 mV, entrapment efficiency of 91.5% and yield of 89.8%. SEM confirmed discrete, near-spherical, non-aggregated nanoparticles, and FTIR indicated drug–polymer compatibility. The resulting capsules met pharmacopoeial expectations for fill-weight uniformity, drug content and disintegration time, and in vitro dissolution demonstrated an extended-release profile best described by the Korsmeyer–Peppas and Higuchi models, indicating diffusioninfluenced, non-Fickian drug transport. These findings establish the formulation feasibility and favourable in vitro performance of an alginate nanoparticle-in-capsule platform for sustained dapagliflozin delivery; translation of this feasibility into demonstrated bioavailability, pharmacokinetic advantage and cardio-renal clinical benefit will require further in vivo pharmacokinetic, pharmacodynamic and stability studies.

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