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Formulation and In-Vitro Evaluation of Gliclazide Microspheres Using Chitosan and Sodium Alginate by Ionic Gelation Method

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Abstract: Gliclazide-loaded chitosan–sodium alginate microspheres were developed by ionic gelation to obtain sustained oral drug release. Six formulations (F1–F6) were prepared by varying polymer concentrations while maintaining gliclazide, sodium tripolyphosphate and Tween 80 levels constant. The microspheres were characterized for micromeritic properties, percentage yield, entrapment efficiency, drug loading, swelling, particle size, surface morphology, drug content and in-vitro drug release. Drug–polymer compatibility was assessed by Fourier transform infrared spectroscopy and differential scanning calorimetry. F4 showed the most favourable overall characteristics, with 92.4% yield, 90.3% entrapment efficiency, 10.86% drug loading and 106% swelling at 8 h. The optimized formulation showed a cumulated diameter of 662.1 nm, PDI 0.402 and zeta potential of -26.77 ± 0.25 mV. Drug release from F4 was 9.0% at 1 h and 94.2% at 24 h. The Korsmeyer–Peppas model provided the best fit ($R^2 = 0.9994$; $n = 0.769$), indicating anomalous/non-Fickian release. Compared with the marketed modified-release product, F4 showed 24-h release of 94.2% versus 93.5%, with $f_1 = 1.38$ and $f_2 = 95.28$. Short-term stability over 45 days showed only minor changes in the evaluated characteristics. The findings indicate that the optimized chitosan–sodium alginate microspheres can provide prolonged gliclazide release over 24 h.

Keywords: Gliclazide; Microspheres; Chitosan; Sodium alginate; Ionic gelation; Sodium tripolyphosphate; Sustained drug release; Drug entrapment efficiency.

INTRODUCTION

Gliclazide is a second-generation sulfonylurea widely used in the management of type 2 diabetes mellitus. Modified-release gliclazide formulations are designed to provide progressive drug release over an extended period and support once-daily administration.¹ Conventional dosage forms may nevertheless be associated with fluctuations in drug exposure, creating a rationale for polymeric systems capable of controlling the release rate.

Natural polysaccharides such as chitosan and sodium alginate have attracted considerable interest in oral drug delivery because of their biocompatibility, biodegradability and ability to form particulate matrices. Chitosan is a cationic polysaccharide, whereas alginate is an anionic polymer; their complementary ionic characteristics can produce polyelectrolyte networks with useful encapsulation and release-controlling properties.^{2, 3, 7, 8, 12, 16}

Ionotropic or ionic gelation is a mild formulation approach that can produce drug-loaded particulate systems without severe processing conditions. Chitosan can undergo ionic cross-linking with multivalent anions such as sodium tripolyphosphate (STPP), while interactions between chitosan and alginate can further influence matrix density, swelling and drug diffusion.^{4,10,16}

Previous studies have demonstrated the potential of chitosan-based and alginate-based particulate systems for sustained oral delivery of gliclazide. Barakat and Almurshedi reported gliclazide-loaded chitosan microparticles prepared by tripolyphosphate ionic cross-linking with sustained drug release and prolonged hypoglycaemic activity in an animal model.⁵ Similarly, gliclazide-loaded alginate-based microspheres have shown prolonged in-vitro release and favourable drug entrapment.⁶ These findings support the use of natural polymeric matrices for controlling gliclazide release.

However, the release behaviour of polymeric microspheres depends strongly on polymer concentration, cross-linking and matrix structure. Excessive polymer concentration may retard drug release excessively, whereas insufficient polymer may lead to comparatively rapid release.^{3,4} Therefore, optimization of the chitosan–alginate composition is important for obtaining a balance between entrapment, particle characteristics, swelling and sustained drug release.^{3,8,13,14,20}

In the present study, gliclazide-loaded chitosan–sodium alginate microspheres were prepared by ionic gelation using STPP as the ionic cross-linking agent. Six formulations (F1–F6) were developed by varying the concentrations of chitosan and sodium alginate while maintaining the drug, STPP and Tween 80 levels constant. The formulations were evaluated for physicochemical characteristics, drug entrapment, particle size, morphology, swelling, drug content and in-vitro drug release. The optimized formulation was further evaluated for release kinetics, dissolution similarity with a marketed modified-release gliclazide product and short-term stability.^{8,12,13,14,18,20}

MATERIALS

Gliclazide was used as the drug. Chitosan and sodium alginate were selected as matrix-forming polymers, while sodium tripolyphosphate (STPP) was used as the ionic cross-linking agent. Tween 80 was incorporated as a surfactant. Acetic acid, distilled water, hydrochloric acid and other analytical-grade reagents were used as required for preparation and evaluation.

METHODS

1. Preformulation Studies

Preformulation studies were performed to characterize gliclazide and assess its compatibility with chitosan and sodium alginate. The studies included determination of melting point, solubility, drug–excipient compatibility by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC), and preparation of a standard calibration curve of gliclazide.

2. Drug–Excipient Compatibility Studies

The compatibility of gliclazide with chitosan and sodium alginate was evaluated by FTIR and DSC. FTIR spectra of pure gliclazide, chitosan, sodium alginate and their physical mixture were obtained after KBr pellet preparation over 4000–400 cm⁻¹. DSC analysis was performed using approximately 2–5 mg of each sample, heated from 30 to 300°C at 10°C/min under nitrogen at 40 mL/min. The spectra and thermograms were compared for significant changes in characteristic drug or polymer features.^{4,5,9,10,16}

3. Solubility and Standard Calibration Curve

The solubility of gliclazide was investigated in distilled water, 0.1 N hydrochloric acid, phosphate buffer pH 7.4, methanol and ethanol. Excess drug was added to each solvent and shaken for 24 h at room temperature. The samples were filtered through Whatman No. 1 filter paper, suitably diluted and analyzed by UV–Visible spectrophotometry. Gliclazide was quantitatively estimated at 226 nm. A stock solution of 1000 µg/mL was prepared, and working solutions covering 4–40 µg/mL were analyzed using 0.1 N HCl as the blank.

4. Preparation of Gliclazide-Loaded Microspheres

Gliclazide-loaded chitosan–sodium alginate microspheres were prepared by ionic gelation. Chitosan was dissolved in 1% v/v acetic acid and sodium alginate was separately dissolved in distilled water; the polymer solutions were then mixed under continuous stirring. Gliclazide (100 mg) was dispersed uniformly in the polymeric solution, followed by addition of Tween 80 (2.5%). A 0.5% w/v STPP solution

was prepared separately. The drug-polymer dispersion was transferred into a syringe fitted with a 22-gauge needle and added dropwise into the STPP solution from approximately 5–10 cm under continuous stirring. The formed microspheres were cured for 1–2 h, collected by filtration, washed three times with distilled water, dried at 40–45°C for 12–24 h or until constant weight, and stored in airtight containers. Ionic gelation is widely used for chitosan-based particulate drug delivery because it permits cross-linking under relatively mild conditions.^{4,8,10,13,16}

5. Evaluation of Microspheres

The prepared microspheres were evaluated for micromeritic properties, percentage yield, entrapment efficiency, drug loading, particle size, polydispersity index (PDI), zeta potential, surface morphology, swelling behaviour, drug content and in-vitro drug release. Surface morphology was examined by scanning electron microscopy. Drug-release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. The optimized formulation was compared with a marketed modified-release gliclazide product using f_1 and f_2 dissolution-comparison factors and was subjected to short-term stability assessment.^{8,9,14,15,17,19,20}

Table 1. Composition of gliclazide–chitosan/sodium alginate microsphere formulations (F1–F6).

Formulation	Gliclazide (mg)	Sodium alginate (mg)	Chitosan (mg)
F1	100	100	100
F2	100	200	200
F3	100	300	300
F4	100	400	400
F5	100	500	500
F6	100	600	600

STPP (0.5% w/v) and Tween 80 (2.5%) were maintained constant across all formulations.

RESULTS

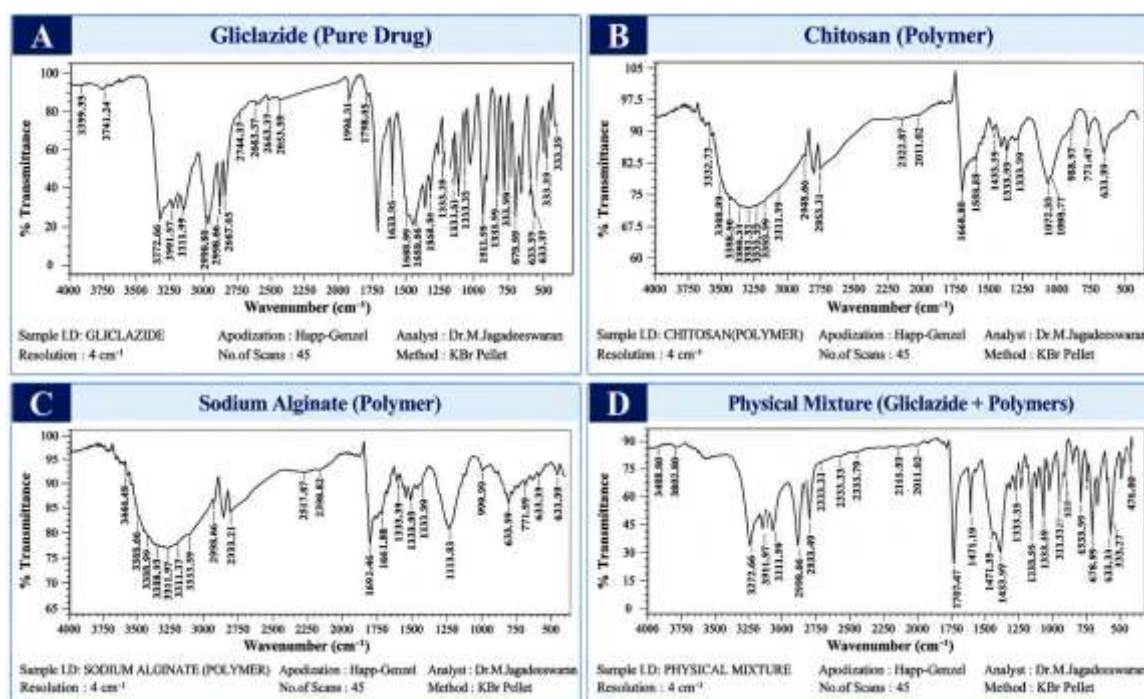


Fig 1: FTIR spectra of (A) gliclazide, (B) chitosan, (C) sodium alginate, and (D) physical mixture.

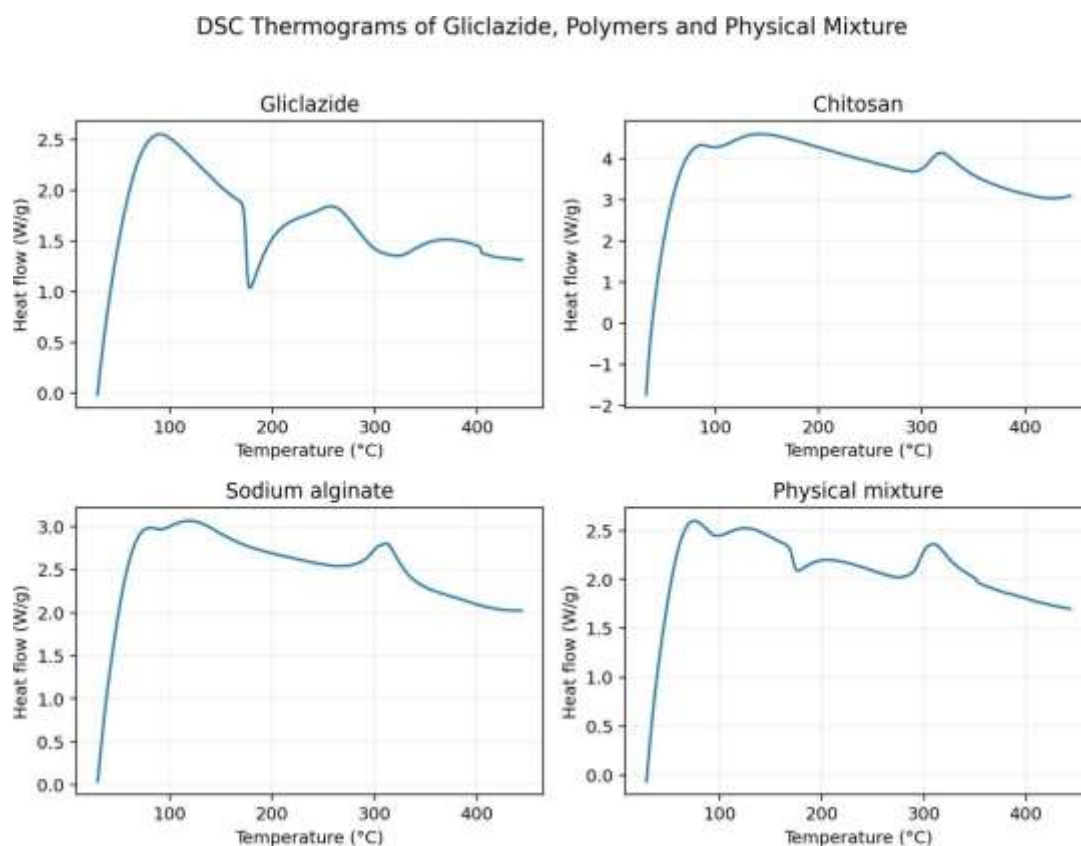


Fig 2: DSC thermograms of gliclazide, chitosan, sodium alginate, and their physical mixture.

Preformulation and Compatibility Studies

Gliclazide exhibited a melting point of 179–181°C and limited aqueous solubility. The UV calibration curve showed linearity over 4–40 µg/mL at 226 nm with $R^2 = 0.9999$. FTIR spectra of gliclazide, chitosan, sodium alginate and their physical mixture retained the characteristic absorption bands without evidence of major new peaks. DSC thermograms similarly retained the characteristic thermal transition of gliclazide with only a minor shift, indicating no major drug–polymer incompatibility. The corresponding FTIR and DSC profiles are presented in Figures 1 and 2, respectively.

Formulation Characteristics

Among the six formulations, F4 was selected as the optimized formulation based on its overall balance of yield, entrapment, swelling and release characteristics. F4 showed 92.4% yield, 90.3% entrapment efficiency, 10.86% drug loading and $99.13 \pm 0.15\%$ drug content. The swelling index reached 106% at 8 h.

Particle Size, PDI and Zeta Potential

The optimized F4 formulation showed a cumulant particle diameter of 662.1 nm with a PDI of 0.402. The zeta potential was -26.77 ± 0.25 mV. These values indicate a nanoscale hydrodynamic size with a moderately broad particle-size distribution.

Surface Morphology

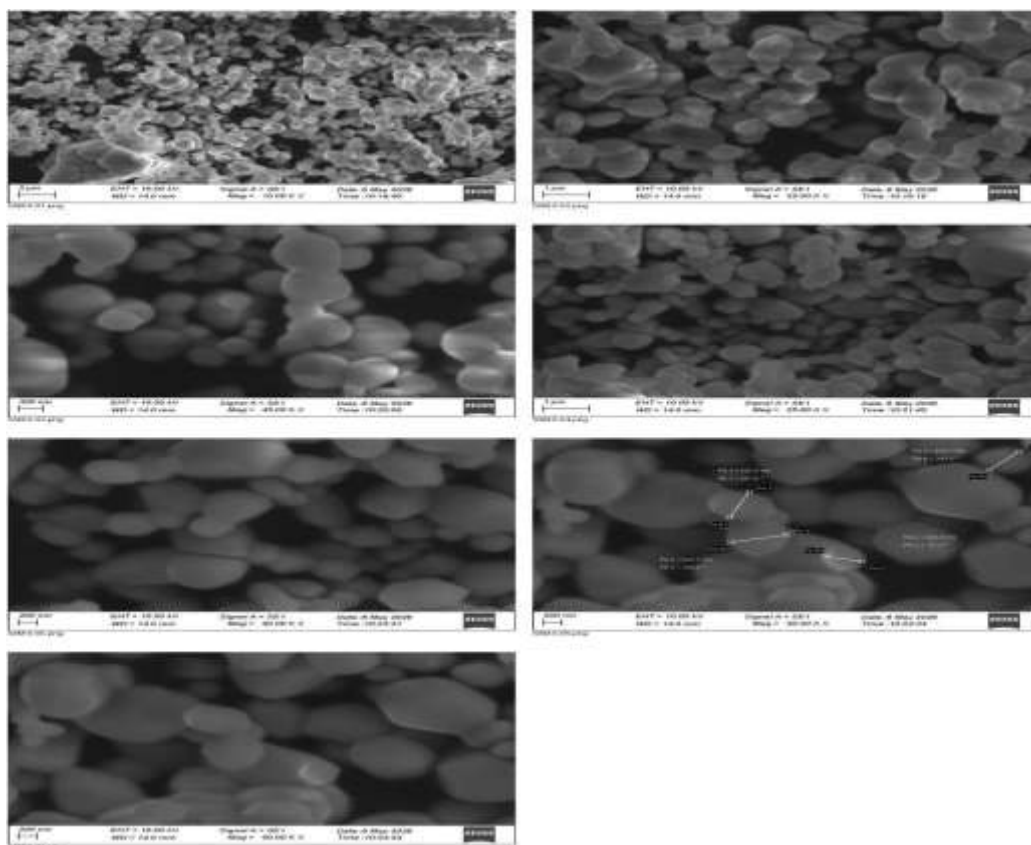


Fig 3: Representative SEM micrographs of gliclazide–chitosan/sodium alginate microspheres (optimized F4).

SEM examination (Figure 3) showed predominantly rounded/sub-spherical microspheres with comparatively smooth surfaces and some aggregation/heterogeneity.

In-Vitro Drug Release

Drug release was progressively retarded with increasing polymer concentration. F4 released 9.0% of gliclazide at 1 h and 94.2% at 24 h. The optimized formulation showed $T_{50\%}$ of 9.11 h, $T_{80\%}$ of 17.45 h, mean dissolution time of 9.28 h and dissolution efficiency at 24 h of 57.77%.

Table 2. Cumulative in-vitro release of gliclazide from microsphere formulations F1–F6.

Time (h)	F1	F2	F3	F4	F5	F6
1	22.0	17.2	12.3	9.0	6.8	5.4
2	36.0	29.5	22.0	16.0	13.0	10.2
4	55.0	45.5	36.0	27.0	22.8	18.0
6	70.0	59.0	49.0	36.0	32.5	26.0
8	82.0	71.5	61.5	45.0	41.5	33.0
10	89.0	80.0	70.5	54.0	49.5	39.5
12	94.0	87.0	78.5	63.0	57.0	45.5
16	98.0	93.0	87.5	76.0	67.5	54.5
20	99.3	96.5	93.0	87.0	75.5	62.0
24	99.8	98.2	97.0	94.2	83.0	70.5

The release profile of F1–F6 is illustrated in Figure 4.

Comparative In-vitro Drug Release Profiles of Formulations F1–F6

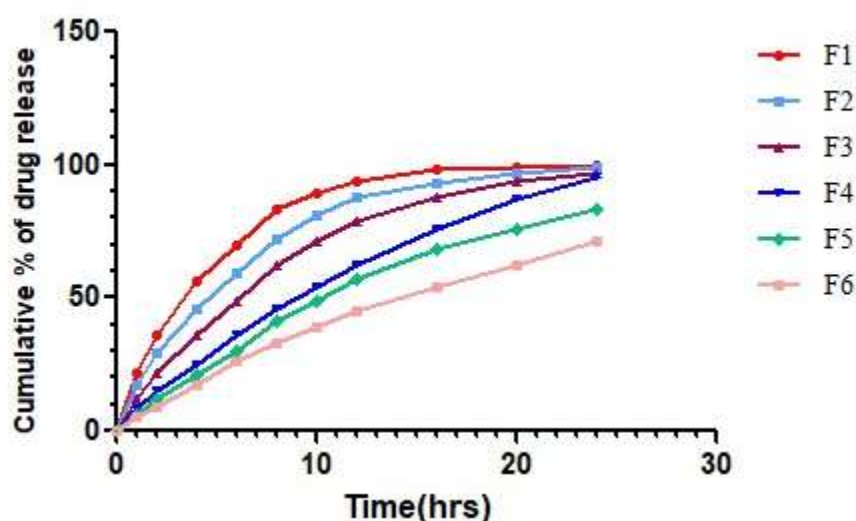


Fig 4: In-vitro cumulative release profiles of gliclazide from microsphere formulations F1–F6.

Release Kinetics and Comparative Dissolution

For F4, the Korsmeyer–Peppas model provided the best fit with $R^2 = 0.9994$ and $n = 0.769$, indicating anomalous/non-Fickian release behaviour consistent with combined drug diffusion and polymer relaxation/swelling. Compared with the marketed modified-release gliclazide product, F4 showed 94.2% release at 24 h versus 93.5% for the marketed product, with $f_1 = 1.38$ and $f_2 = 95.28$, indicating close in-vitro dissolution similarity.

Table 3. Release-kinetic parameters and optimized formulation characteristics of F4.

Parameter	F4
Yield (%)	92.4
Entrapment efficiency (%)	90.3
Drug loading (%)	10.86
Particle size (nm)	662.1
PDI	0.402
Zeta potential (mV)	-26.77 ± 0.25
Drug content (%)	99.13 ± 0.15
24-h release (%)	94.2
$T_{50\%}$ (h)	9.11
$T_{80\%}$ (h)	17.45
MDT (h)	9.28
DE_{24} (%)	57.77
Korsmeyer–Peppas R^2	0.9994
Release exponent, n	0.769
Marketed MR 24-h release (%)	93.5
f_1	1.38
f_2	95.28

Short-Term Stability

During 45 days of short-term stability assessment, particle size, PDI, entrapment efficiency, drug content and 24-h release showed only minor changes, indicating no major deterioration of the optimized formulation under the tested conditions.

DISCUSSION

The present study developed gliclazide-loaded chitosan–sodium alginate microspheres by ionic gelation as a sustained oral delivery system. The absence of major changes in FTIR and DSC characteristics indicated satisfactory compatibility between gliclazide and the selected polymers. Such compatibility is important for maintaining drug integrity during formulation and has also been reported in other gliclazide-loaded polysaccharide systems^{5,6,9,12,16,18}

The polymer composition substantially influenced formulation performance. F4 provided the most favourable balance of yield (92.4%), entrapment efficiency (90.3%), drug loading (10.86%) and swelling (106% at 8 h). The relatively high entrapment observed with the chitosan–alginate matrix is consistent with the ability of ionic and polyelectrolyte interactions to form drug-containing polymer networks. Chitosan–alginate systems are widely reported as useful carriers for controlled oral drug delivery because of their complementary ionic character and capacity for sustained release^{2,38,13,16,20}

The optimized formulation exhibited a particle size of 662.1 nm, PDI of 0.402 and zeta potential of -26.77 ± 0.25 mV. The particle characteristics reflect the influence of polymer concentration and ionic cross-linking on the formed matrix. Previous work on gliclazide–chitosan microparticles demonstrated that formulation and cross-linking conditions markedly affect particle characteristics and drug-release behaviour^{5,8,10,14,18}

The in-vitro release profile demonstrated a clear polymer-dependent retardation of gliclazide release. F4 released only 9.0% during the first hour and reached 94.2% at 24 h, with $T_{50\%}$ of 9.11 h and $T_{80\%}$ of 17.45 h. This prolonged release is consistent with the ability of chitosan–alginate matrices to restrict drug diffusion through hydrated polymer networks. Similar sustained gliclazide release has been reported from chitosan- and alginate-based particulate systems^{5,6,8,13,19,20}

The Korsmeyer–Peppas model gave the highest correlation ($R^2 = 0.9994$), with $n = 0.769$, indicating anomalous/non-Fickian release. This behaviour suggests that drug diffusion occurred together with polymer relaxation and swelling rather than through a single idealized release mechanism. The result is consistent with the mechanistic behaviour expected from hydrated, ionically cross-linked polysaccharide matrices.^{4,10,16,19}

The 24-h release of F4 (94.2%) was close to that of the marketed modified-release gliclazide product (93.5%), and the dissolution-comparison values ($f_1 = 1.38$; $f_2 = 95.28$) indicated close in-vitro dissolution similarity. This finding supports the ability of the optimized polymeric matrix to reproduce a prolonged release pattern; however, dissolution similarity should not be interpreted as evidence of bioequivalence or improved clinical efficacy. Modified-release gliclazide itself is designed to provide progressive drug release over an extended dosing interval.

Overall, F4 demonstrated a favourable combination of entrapment, particle characteristics, swelling and sustained drug release. The findings are in agreement with earlier research showing the potential of chitosan and alginate matrices for sustained oral delivery of gliclazide.^{5,6} Nevertheless, the present work is primarily an in-vitro formulation study; long-term stability and in-vivo pharmacokinetic/pharmacodynamic evaluation are required before drawing conclusions regarding in-vivo performance.^{8,13,14,18,20}

CONCLUSION

The present study successfully developed gliclazide-loaded chitosan–sodium alginate microspheres for sustained oral drug delivery. Among the formulations, F4 showed the most favourable overall performance, with 92.4% yield, 90.3% entrapment efficiency, 10.86% drug loading and 106% swelling at 8 h. The optimized formulation exhibited a particle size of 662.1 nm with a PDI of 0.402 and sustained drug release of 94.2% over 24 h. The release data followed the Korsmeyer–Peppas model ($R^2 = 0.9994$; $n = 0.769$), indicating anomalous/non-Fickian release behaviour. F4 also showed close in-vitro dissolution similarity with the marketed modified-release product ($f_1 = 1.38$; $f_2 = 95.28$) and remained stable during the 45-day short-term stability study. Overall, the developed microspheres demonstrated promising potential as a sustained-release delivery system for gliclazide. Further long-term stability and in-vivo studies are required to confirm its performance.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, methodology, formulation development, investigation, data analysis, interpretation of results, and preparation of the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY

The experimental data generated and/or analyzed during the current study, including formulation, evaluation, drug-release and stability data, are available from the corresponding author on reasonable request.

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