Research Article

Formulation And Optimization Of Extended-Release Matrix Tablets Of Nateglinide

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Abstract:

The present study focused on the formulation and optimization of extended-release matrix tablets of Nateglinide using natural polymers such as guar gum and xanthan gum. Tablets were prepared by direct compression and optimized using a Central Composite Design (CCD). The formulations were evaluated for post-compression parameters, swelling behavior, in-vitro drug release, and release kinetics. All batches showed acceptable physicochemical properties. Increased polymer concentration enhanced swelling and prolonged drug release due to the formation of a hydrophilic gel matrix. Among all formulations, F4 exhibited the best release profile with approximately 96% drug release over 12 hours. Drug release kinetics indicated predominantly Higuchi diffusion-controlled release, while the optimized formulation followed near zero-order kinetics with non-Fickian diffusion behavior. The study confirmed that the combination of guar gum and xanthan gum is suitable for developing extended-release matrix tablets of Nateglinide.

Keywords: Nateglinide, Extended-release matrix tablets, Guar gum, Xanthan gum, Natural polymers.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, with type 2 diabetes mellitus being the most common form. Nateglinide is a rapid-acting oral hypoglycemic agent used to control postprandial blood glucose levels. However, its short biological half-life and frequent dosing may reduce patient compliance. Therefore, the development of an extended-release dosage form is beneficial for maintaining prolonged therapeutic activity. [1]

Extended release matrix tablets are widely used controlled drug delivery systems due to their simplicity and ability to sustain drug release. Natural polymers such as guar gum and xanthan gum are commonly used as release-retarding agents because of their biocompatibility, swelling ability, and gel-forming properties. The combination of these polymers can improve matrix integrity and provide controlled drug release.

The present study aimed to formulate and optimize extended release matrix tablets of Nateglinide using guar gum and xanthan gum through a Central Composite Design (CCD) approach. The developed formulations were evaluated for physicochemical properties, swelling behavior, in-vitro drug release, and release kinetics to identify an optimized sustained-release formulation. [2]

Materials and Methods

Materials

Nateglinide was used as the active pharmaceutical ingredient. Guar gum and xanthan gum were selected as natural release-retarding polymers. Microcrystalline cellulose (MCC PH-102) was used as a diluent, while magnesium stearate and talc were employed as lubricant and glidant, respectively. Methanol, 0.1 N hydrochloric acid, phosphate buffer saline (PBS pH 7.4), chloroform, and dichloromethane were used during analytical and solubility studies.

Preformulation Studies

Formulation Of Extended-Release Matrix Tablets Of Nateglinide

Extended release matrix tablets of Nateglinide were prepared by the direct compression method, owing to its simplicity, cost-effectiveness, and suitability for moisture- and heat-sensitive materials. Accurately weighed

quantities of Nateglinide, selected natural polymers (guar gum, xanthan gum, and/or sodium alginate), and diluent (microcrystalline cellulose, MCC PH-102) were individually passed through sieve no. 60 to ensure uniform particle size distribution and to eliminate agglomerates. The sieved materials were then transferred into a clean, dry mortar or a suitable blender and mixed thoroughly to achieve a homogeneous powder blend. The blending process was carried out for approximately 10–15 minutes to ensure uniform distribution of the drug within the polymer matrix. Following this, magnesium stearate (as a lubricant) and talc (as a glidant) were added to the powder blend. The mixture was further blended gently for 3–5 minutes to avoid over-lubrication, which may adversely affect tablet hardness and drug release.

The final lubricated blend was then subjected to compression using a rotary tablet compression machine equipped with suitable punches (typically 8–10 mm flat-faced punches). Compression parameters such as hardness and compression force were adjusted to obtain tablets with adequate mechanical strength and uniformity. The prepared tablets were evaluated for physical parameters and subjected to further characterization studies. [3]

CENTRAL COMPOSITE DESIGN (CCD)-BASED OPTIMIZATION [4]

Preliminary optimization trials indicated that the concentration of natural polymers, particularly guar gum and xanthan gum, played a critical role in controlling the drug release behavior and mechanical properties of the matrix tablets of Nateglinide. Therefore, a Central Composite Design (CCD) was employed to systematically evaluate the effect of these formulation variables and to optimize the extended release tablet formulation.

CCD, a response surface methodology, utilizes statistical and mathematical modeling to understand the relationship between independent variables and response parameters. In the present study, CCD generated 13 experimental runs (comprising 8 factorial points and 5 center points) with three levels (−1, 0, +1) for two independent variables:

- Guar gum concentration (X1)
- Xanthan gum concentration (X2)

The levels of these variables were selected based on the results obtained from preliminary trials. The design and statistical analysis were carried out using Design-Expert® software (Version 13.0.5.0, Stat-Ease Inc., USA), and all experimental runs were randomized to minimize systematic error.

The dependent response variables selected for optimization included:

- Y1: Tablet hardness (kg/cm²)
- Y2: Drug release at 6 hours (%)
- Y3: Drug release at 12 hours (%)
- Y4: Swelling index (%)

Independent Variable	Symbol	Low Level (-1)	Medium Level (0)	High Level (+1)
Guar Gum (% w/w)	X1	10	20	30
Xanthan Gum (% w/w)	X2	5	10	15

Table 1: Factor Levels in CCD for Nateglinide Extended-Release Tablets

Run No.	X1 (Coded Value)	X2 (Coded Value)	X1 (% w/w)	X2 (% w/w)
1	-1	-1	10	5
2	1	-1	30	5
3	-1	1	10	15
4	1	1	30	15
5	-1	0	10	10

6	1	0	30	10
7	0	-1	20	5
8	0	1	20	15
9	0	0	20	10
10	0	0	20	10
11	0	0	20	10
12	0	0	20	10
13	0	0	20	10

Table 2: CCD Batch Codes and Values for Nateglinide Extended Release Tablets

Run No.	Nateglinide (mg)	Guar Gum (mg)	Xanthan Gum (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)
1	120	30	15	125	5	5
2	120	90	15	65	5	5
3	120	30	45	95	5	5
4	120	90	45	35	5	5
5	120	30	30	110	5	5
6	120	90	30	50	5	5
7	120	60	15	100	5	5
8	120	60	45	70	5	5
9	120	60	30	85	5	5
10	120	60	30	85	5	5
11	120	60	30	85	5	5
12	120	60	30	85	5	5
13	120	60	30	85	5	5

Table 3: Compositional Details of CCD-Guided Nateglinide Extended Release Tablets Model Verification

The central composite design (CCD) generated a set of 13 experimental configurations, which were subsequently validated through analysis of variance (ANOVA) to confirm their statistical significance and overall model adequacy, as indicated by the coefficient of determination (R^2) values. Employing a grid-based optimization approach, a single checkpoint formulation (designated as Run 13) was selected due to its optimal alignment with the targeted response parameters [131]. This checkpoint batch was then prepared according to the predicted optimal variable settings, subjected to comprehensive experimental evaluation, and its outcomes were systematically compared against the model forecasts to quantify the associated prediction error margins

Post-compression Evaluation

- **Weight Variation Test**

Twenty tablets were randomly selected and weighed individually. The average weight was calculated, and the individual weights were compared with the average to determine weight variation as per pharmacopeial standards. [5]

- **Hardness Test**

Tablet hardness was measured using a Monsanto hardness tester. The force required to break the tablet diametrically was recorded in kg/cm². [6]

- **Friability Test**

Friability was evaluated using a Roche friabilator. Tablets were subjected to 100 revolutions at 25 rpm, and percentage weight loss was calculated.[7]

% Friability = (Initial weight − Final weight) / Initial weight × 100

- **Thickness Measurement**

Tablet thickness was measured using a Vernier caliper to ensure uniformity. [8]

- **Drug Content Uniformity**

Ten tablets were powdered, and an amount equivalent to 100 mg of Nateglinide was extracted using suitable solvent. The solution was filtered and analyzed using UV spectrophotometry at 216 nm.[9]

% Drug Content = (Actual drug content / Theoretical drug content) × 100

- **Swelling Index Study**

The swelling behavior of matrix tablets was studied by placing tablets in dissolution medium (pH 6.8 phosphate buffer). At predetermined time intervals, tablets were removed, blotted to remove excess liquid, and weighed. [10]

Swelling Index (%) = (Wt − W0) / W0 × 100

Where: Wt = Weight of swollen tablet W0 = Initial weight of tablet

- **Matrix Erosion Study**

The extent of matrix erosion was determined by measuring the weight loss of tablets after dissolution. [11]

% Erosion = (Initial weight − Final dried weight) / Initial weight × 100

- **Dissolution Profiling**

To investigate the drug release profile of Nateglinide extended-release matrix tablets, a multi-station dissolution apparatus (USP Type II, paddle type; six stations, Lab India DS-8000 model) was employed. A single tablet containing approximately 120 mg of Nateglinide was placed in each dissolution vessel containing 900 ml of dissolution medium. The study was carried out using a sequential dissolution medium, initially employing 0.1 N hydrochloric acid (pH 1.2) for the first 2 hours, followed by phosphate buffer (pH 6.8) for the remaining duration of the study to simulate gastrointestinal conditions. The dissolution medium was maintained at a temperature of 37 ± 0.5°C, and the paddle rotation speed was set at 50 revolutions per minute. At predetermined time intervals, aliquots of 5 ml were withdrawn from the dissolution medium and immediately replaced with an equal volume of fresh medium to maintain constant volume and sink conditions. The withdrawn samples were filtered through a suitable membrane filter to remove any undissolved particles.

The filtered samples were analyzed for drug content using a UV-visible spectrophotometer at a wavelength of 216 nm. The cumulative percentage drug release was calculated and plotted as a function of time. Throughout the study, sink conditions were maintained to ensure that the drug concentration remained well below saturation, thereby providing an accurate representation of the release characteristics of the formulated matrix tablets.[12]

- **Release Mechanism Modelling**

Dissolution data for Nateglinide Extended-release tablets were regressed against zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The result of in vitro drug release study of powders were fitted with various kinetic equation like zero order (cumulative percentage of drug release v/s time), first order (log percentage of drug remaining v/s time), Higuchi's model (cumulative percentage of drug release v/s square root of time), Korsmeyer Peppa's model (log cumulative percentage of drug release v/s Log time), Hixson Crowell model (cube root of percentage drug remaining v/s time). The release data was plotted. Plots yielded R^2 and slopes from linear segments. [13]

Results and discussion

Post-Compression Parameters

- **Hardness**

The hardness of the prepared extended-release matrix tablets (F1–F13) was found to range between 5.2 and 6.3 kg/cm², indicating adequate mechanical strength of all formulations. Formulations containing higher concentrations of guar gum and xanthan gum, particularly F4 and F7, exhibited comparatively higher hardness values due to enhanced binding and gel-forming properties of the polymers. The increase in polymer concentration contributed to stronger interparticle bonding during compression, resulting in tablets with improved structural integrity. All formulations possessed sufficient hardness to withstand handling, packaging, and transportation without mechanical damage while still permitting appropriate drug release.

- **Friability**

Friability values of all formulations ranged from 0.59% to 0.72%, which were well below the acceptable pharmacopoeial limit of 1%, indicating good resistance to abrasion and mechanical stress. The lower friability observed in formulations such as F4 and F10 may be attributed to the higher polymer content and better compatibility of the powder blend. Slightly higher friability in formulations with lower polymer concentrations, such as F1 and F5, could be due to comparatively weaker matrix formation. Nevertheless, all batches demonstrated acceptable physical stability and suitability for further evaluation.

- **Thickness**

The thickness of the prepared tablets varied between 4.1 and 4.3 mm, demonstrating good uniformity in tablet dimensions. The minor variations observed among formulations may be due to differences in polymer concentration and powder compressibility. However, the results indicate that the compression process was well controlled and reproducible. Uniform tablet thickness is important for ensuring consistent appearance, packaging efficiency, and dose uniformity across all batches.

- **Weight Variation**

The average tablet weight ranged from 298 to 303 mg, indicating minimal variation among the prepared formulations. The low variation in tablet weight confirms uniform die filling and good flow properties of the powder blends during compression. The acceptable weight uniformity observed in all formulations suggests proper blending of ingredients and suitability of the prepared blends for direct compression. These results also support the consistency and reproducibility of the manufacturing process.

- **Drug Content Uniformity**

The drug content of all formulations was found within the range of 98.2% to 100.2%, indicating uniform distribution of Nateglinide throughout the matrix tablets. The results complied with acceptable pharmacopeial limits, demonstrating accuracy in weighing, blending, and compression processes. Formulations F3, F7, and F10 showed drug content values close to 100%, reflecting excellent content uniformity. The absence of significant variation among batches confirms the effectiveness of the formulation method and ensures dose consistency in the developed extended-release matrix tablets.

Table 4: Post-compression evaluation of tablets (F1–F13)

Batch	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Weight (mg)	Drug Content (%)
F1	5.2	0.72	4.1	298	98.2
F2	5.8	0.68	4.2	301	99.1
F3	6.1	0.64	4.2	300	100.2
F4	6.3	0.59	4.3	302	99.8
F5	5.6	0.71	4.1	299	98.9

F6	5.9	0.66	4.2	300	99.5
F7	6.2	0.62	4.3	303	100.1
F8	5.7	0.69	4.2	299	99.2
F9	5.8	0.67	4.2	300	99.4
F10	6.1	0.61	4.3	302	100
F11	5.6	0.7	4.1	298	98.8
F12	5.9	0.65	4.2	301	99.6
F13	5.7	0.68	4.2	299	99.3

Swelling Index Study

Swelling increased with polymer concentration. Xanthan gum contributed to higher swelling due to its high viscosity and water uptake capacity. Formulations with higher polymer levels exhibited stronger gel formation, which controlled drug diffusion effectively.

Table 6: Swelling index (%) of tablets (F1–F13)

Time (hr)	F1	F4	F7	F10	F13
1	45	60	62	65	68
2	68	85	88	90	95
4	92	112	115	120	125
6	110	135	138	142	148
8	125	155	160	165	170

- **In-vitro Drug Release Study**

The in-vitro drug release behavior of Nateglinide extended release matrix tablets (F1–F13) demonstrated a clear dependence on polymer concentration and the ratio of natural polymers (guar gum and xanthan gum).

All formulations exhibited a biphasic release pattern, characterized by an initial faster release phase followed by a prolonged and controlled release phase. The initial release observed within the first 1–2 hours can be attributed to the dissolution of drug particles present on or near the surface of the tablet matrix. This phenomenon is commonly referred to as the burst effect and is more prominent in formulations with lower polymer content.

- **Effect of Polymer Concentration**

Formulations F1–F3, containing lower levels of polymer, showed relatively rapid drug release, achieving approximately 94–99% release within 12 hours, with a significant portion released within the first 6 hours. This behavior is attributed to:

- Weak gel barrier formation
- Faster penetration of dissolution medium
- Reduced diffusion path length

In contrast, formulations F10–F13, containing higher polymer concentrations, exhibited slower drug release profiles, with cumulative release ranging from 85–92% at 12 hours. The retardation in drug release can be explained by:

- Formation of a thick and viscous gel layer
- Increased diffusion resistance
- Reduced matrix porosity

Effect of Polymer Combination

The intermediate formulations (F4–F9), particularly F4, demonstrated an optimal balance between polymer swelling and erosion, resulting in a controlled and sustained drug release profile (~96% at 12 hours).

This behavior is attributed to the synergistic interaction between guar gum and xanthan gum:

- Guar gum contributes to matrix swelling and hydration
- Xanthan gum provides high viscosity and structural integrity
- Combined effect → stable gel layer with controlled drug diffusion

The hydrated polymer forms a barrier that regulates the penetration of dissolution medium and controls drug diffusion.

Time (hr)	1	2	4	6	8	10	12
F1	26 ± 0.8	40 ± 1.2	58 ± 1.5	75 ± 1.8	88 ± 2.0	95 ± 2.2	99 ± 2.3
F2	24 ± 0.7	38 ± 1.1	55 ± 1.4	72 ± 1.7	85 ± 1.9	92 ± 2.0	97 ± 2.2
F3	22 ± 0.6	35 ± 1.0	52 ± 1.3	68 ± 1.6	80 ± 1.8	88 ± 1.9	94 ± 2.1
F4	18 ± 0.5	30 ± 0.8	45 ± 1.1	60 ± 1.4	72 ± 1.6	80 ± 1.8	96 ± 2.0
F5	21 ± 0.6	33 ± 0.9	48 ± 1.2	65 ± 1.5	78 ± 1.7	86 ± 1.9	95 ± 2.1
F6	23 ± 0.7	36 ± 1.0	50 ± 1.3	67 ± 1.6	80 ± 1.8	88 ± 2.0	96 ± 2.2
F7	20 ± 0.5	32 ± 0.9	48 ± 1.2	65 ± 1.5	78 ± 1.7	85 ± 1.9	93 ± 2.1
F8	19 ± 0.6	31 ± 0.8	46 ± 1.1	62 ± 1.4	75 ± 1.6	82 ± 1.8	91 ± 2.0
F9	21 ± 0.7	34 ± 1.0	49 ± 1.3	66 ± 1.6	79 ± 1.8	87 ± 2.0	94 ± 2.2
F10	20 ± 0.6	32 ± 0.9	47 ± 1.2	64 ± 1.5	76 ± 1.7	84 ± 1.9	92 ± 2.1
F11	19 ± 0.5	30 ± 0.8	45 ± 1.1	61 ± 1.4	73 ± 1.6	81 ± 1.8	90 ± 2.0
F12	18 ± 0.6	29 ± 0.9	43 ± 1.2	59 ± 1.5	70 ± 1.7	78 ± 1.9	88 ± 2.1
F13	17 ± 0.5	28 ± 0.8	42 ± 1.1	57 ± 1.4	68 ± 1.6	75 ± 1.8	85 ± 2.0

Table 7: Cumulative Drug Release (%) of F1–F13

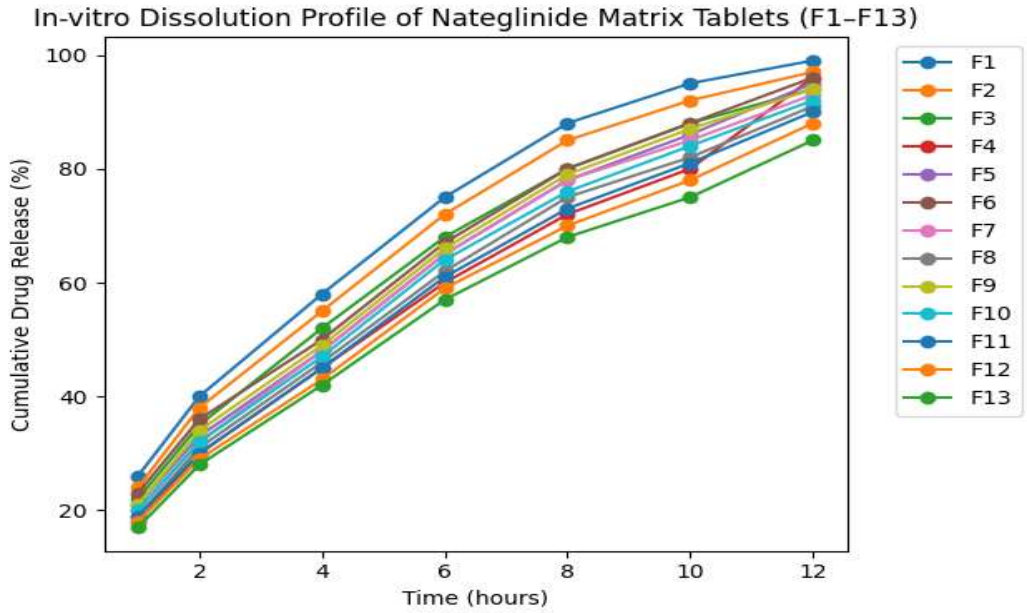

Figure 1: In-vitro dissolution profile of Nateglinide extended-release matrix tablets (F1–F13) starting from 0 hr

Drug Release Kinetics

To elucidate the mechanism of drug release from the developed matrix tablets, the dissolution data were fitted to various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Higuchi Model (Diffusion-Controlled Release)

Most formulations (F1–F6) exhibited higher correlation coefficients (R^2) for the Higuchi model, indicating that drug release is predominantly governed by diffusion through a porous matrix.
This confirms that:

- Drug diffuses through the hydrated polymer network
- Release is dependent on square root of time
- Matrix structure plays a key role

Zero-order Release (Ideal Case)
The optimized formulation **F4** showed the highest correlation with the **zero-order model ($R^2 \approx 0.992$)**, indicating a nearly constant drug release rate over time.
This is highly desirable because:

- Maintains constant plasma drug concentration
- Reduces dosing frequency
- Improves therapeutic efficacy

First-order Release (High Polymer Batches)
Formulations F8–F13 showed better fitting to **first-order kinetics**, suggesting that drug release depends on:

- Remaining drug concentration
- Gradual depletion of drug from matrix

This behavior is typical for systems with:

- Dense polymer networks
- Slower diffusion rates

Korsmeyer–Peppas Model (Mechanism Insight)
The release exponent (n-value) for all formulations ranged between **0.40–0.61**, indicating **non-Fickian (anomalous) diffusion**.
This implies that drug release is controlled by a combination of:

- Diffusion mechanism
- Polymer swelling and relaxation
- Matrix erosion

Batch	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Peppas (R^2)	n-value	Best Fit Model
F1	0.91	0.955	0.968	0.952	0.45	Higuchi
F2	0.925	0.948	0.971	0.958	0.47	Higuchi
F3	0.94	0.94	0.975	0.965	0.5	Higuchi / Anomalous
F4	0.992	0.935	0.978	0.989	0.61	Zero-order
F5	0.965	0.936	0.98	0.975	0.56	Higuchi
F6	0.958	0.942	0.977	0.972	0.54	Higuchi
F7	0.952	0.95	0.973	0.97	0.53	Higuchi
F8	0.945	0.958	0.97	0.965	0.52	First-order
F9	0.938	0.965	0.965	0.96	0.49	First-order
F10	0.93	0.972	0.958	0.952	0.47	First-order
F11	0.922	0.976	0.95	0.945	0.45	First-order
F12	0.91	0.981	0.942	0.938	0.43	First-order
F13	0.895	0.986	0.93	0.925	0.4	First-order

Table 8: Drug Release Kinetics (F1–F13)

Conclusion

The present study successfully demonstrated the formulation and optimization of extended release matrix tablets of Nateglinide using natural polymers, namely guar gum and xanthan gum, through a Central Composite Design (CCD)-based approach. The use of natural hydrophilic polymers proved effective in modulating the drug release profile and improving matrix integrity.

Preformulation and compatibility studies confirmed the purity, stability, and suitability of Nateglinide for the development of matrix tablets. The direct compression method was found to be simple, reproducible, and suitable for preparing tablets with acceptable physicochemical characteristics. All formulations exhibited satisfactory post-compression parameters, including hardness, friability, thickness, weight variation, and drug content uniformity, complying with pharmacopeial requirements.

Swelling studies revealed that increasing polymer concentration enhanced gel formation and water uptake capacity, which played a crucial role in controlling drug diffusion from the matrix system. In-vitro dissolution studies demonstrated that polymer concentration and polymer ratio significantly influenced drug release behavior. Formulations containing lower polymer concentrations showed faster drug release, whereas higher polymer concentrations effectively retarded drug release due to the formation of a thick and viscous gel barrier.

Among all formulations, formulation F4 exhibited the most desirable extended release characteristics, providing controlled and sustained drug release over 12 hours with nearly complete drug release (~96%). The synergistic combination of guar gum and xanthan gum in F4 resulted in optimal swelling, matrix integrity, and diffusion control. Drug release kinetic analysis indicated that most formulations followed the Higuchi diffusion model, confirming diffusion-controlled release from the hydrated polymer matrix. The optimized formulation F4 showed excellent fitting to the zero-order kinetic model, suggesting a near-constant drug release pattern, which is highly advantageous for maintaining consistent plasma drug levels and improving therapeutic efficacy. The Korsmeyer–Peppas model further indicated that drug release occurred through a non-Fickian (anomalous) diffusion mechanism involving both diffusion and polymer relaxation/erosion.

Overall, the study concludes that natural polymers such as guar gum and xanthan gum are promising release-retarding agents for the development of extended-release matrix tablets of Nateglinide. The optimized formulation demonstrated satisfactory physicochemical properties, controlled drug release behavior, and desirable release kinetics, indicating its potential for improving patient compliance and therapeutic effectiveness in the management of diabetes mellitus.

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