RESEARCH ARTICLE

Design, Optimize and Evaluate Dapagliflozin Sustained Release Microspheres using Box-Behnken Design

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ABSTRACT
This study aimed on optimizing dapagliflozin microspheres for sustained release to improve efficacy over the marketed product. Microspheres were formulated by a Solvent Evaporation method involving sodium alginate, ethyl cellulose and HPMC K 100. The process was optimized through Box- Behnken statistical experimental model, adjusting polymer concentration, surfactant amount and rotational speed. Seventeen formulations were formulated and the optimized formulation (F2) was investigated for its micromeritic characteristics, SEM, in-vitro release, kinetic modeling, and stability. FT-IR study showed no negative correlation among the drug and polymers. F2 exhibited maximum yield (81.78%), entrapment efficiency (82.21%) with optimum particle size (278.69 µm). Increased concentration of polymer improved yield and efficiency of drug entrapment while stirring rate decreased particle size. SEM analysis revealed rough, porous and spherical microspheres, and the release was sustained, with 98.02% of the drug released over 20 hours. The optimized microspheres showed prolonged drug release under gastrointestinal conditions, offering increased efficacy and potentially enhancing patient adherence by lowering dosing compared to the marketed product.
Keywords: Dapagliflozin, Box- Behnken, Independent, Dependent variables
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INTRODUCTION
Chronic hyperglycemia occurs when food remains unabsorbed, gets accumulated in the blood and eliminated through urine due to scarce release of insulin.[1,2] Microspheres, small spheroid granules (1µm to 1000 µm) made from soluble polymers, provide controlled release of drug improved effectiveness, minimized toxicity, and strengthen patient compliance.[3,4] Dapagliflozin, a Sodium-glucose co-transporter 2 (SGLT2) inhibitor often used with diet and exercise, minimizes the risk of heart failure by stimulating urinary glucose excretion hence decreasing plasma glucose.[5-7] Ethyl cellulose widely used in modified release formulations is non-biodegradable, stable, hydrophobic and biocompatible polymer having non-toxic nature.[8] HPMC (hydroxypropyl methylcellulose), a non-ionic, swellable with versatile physicochemical properties and its matrix gel systems are in widespread use due to their flexibility and affordability to modify the profile of drug release.[9,10] It controls drug release through diffusion or gel erosion, making it suitable for hydrophilic as well as hydrophobic drugs.[11] Sodium alginate is biocompatible, biodegradable with excellent thickening properties and reduced toxicity making it ideal for mucoadhesive and multi-particulate systems.[12]

MATERIAL AND METHODS
Dapagliflozin was obtained from Sun Pharma (Mumbai, India), and HPMC K 100, ethyl cellulose, sodium alginate, and Tween 80 from CDH Laboratory Reagents, New Delhi. Additional chemicals, solvents, reagents employed were of pharmaceutical grade.

Pre-Formulation Studies
Pre-formulation studies conducted included a calibration curve for dapagliflozin and drug-polymer compatibility testing utilizing FT-IR technique.[13, 14]

Standard Calibration Curve
The calibration curve was created by serially diluting dapagliflozin in phosphate buffer (pH 7.4), and absorbance was measured at 233 nm.[15, 16]

Drug Polymer Compatibility Assessment
Drug-excipient compatibility was assessed using FT-IR spectrophotometry (4000-400 cm-1 range), analyzing dapagliflozin alone and with polymers.[17]

Preparation of Microspheres using Solvent Evaporation Method
Dapagliflozin microspheres were formulated employing the solvent evaporation method. Polymeric solutions of sodium alginate, ethyl cellulose, and HPMC K 100 were mixed with a drug-containing aqueous solution and a dichloromethane-acetone mixture, with Tween 80 as a

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Table 1: Summary of Design

Runs	Dapagliflozin (mg)	Polymer concentration (SA+EC+HPMC)(mg)		Surfactant concentration (%)		Stirring speed (rpm)	
F1	5	-1	70	-1	0.5	0	1000
F2	5	1	100	1	1.5	0	1000
F3	5	0	85	1	1.5	-1	800
F4	5	0	85	-1	0.5	1	1200
F5	5	-1	70	1	1.5	0	1000
F6	5	0	85	1	1.5	1	1200
F7	5	1	100	-1	0.5	0	1000
F8	5	1	100	0	1	-1	800
F9	5	0	70	0	1	0	1000
F10	5	0	70	-1	0.5	-1	800
F11	5	1	100	0	1	1	1200
F12	5	0	85	0	1	0	1000
F13	5	0	85	0	1	0	1000
F14	5	0	85	0	1	0	1000
F15	5	-1	70	0	1	-1	800
F16	5	0	85	0	1	0	1000
F17	5	-1	70	0	1	1	1200

surfactant. The solution was added dropwise to the aqueous phase under stirring at 800, 1000, and 1200 rpm for 2 hours to allow solvent evaporation, forming spherical microspheres which were then washed, dried, and stored.[18]

Design of Experiment (DOE) in Optimization

The Box-Behnken design optimized dapagliflozin microspheres, with polymer concentration, surfactant amount, and stirring speed as independent variables, and particle size, yield, and drug encapsulation efficiency as dependent variables. The factors were tested at three levels each: polymer concentration (70 mg, 85 mg, 100 mg), surfactant concentration (0.5%, 1%, 1.5%), and stirring speed (800 rpm, 1000 rpm, 1200 rpm). Data were analyzed using Design-Expert software, with 17 experimental runs conducted as presented in Table 1.[19,20]

Table 2: Responses of the various batches of Dapagliflozin microspheres

Runs	R_1 Particle dimension (in µm)	R_2 Percentage Production (in %)	R_3 Encapsulation Efficiency (in %)
F1	277.29	78.25	72.12
F2	278.69	81.78	82.21
F3	283.47	77.42	60.44
F4	272.84	70.24	54.76
F5	276.63	76.24	65.23
F6	268.25	74.54	64.51
F7	293.45	77.82	78.82
F8	287.47	75.17	76.74
F9	278.14	72.41	74.25
F10	284.68	70.23	71.46
F11	280.72	69.78	65.36
F12	276.55	80.14	76.52
F13	274.28	78.36	69.84
F14	275.68	77.42	68.76
F15	278.45	67.12	55.51
F16	274.86	73.45	71.32
F17	270.57	62.14	57.42

The responses for all 17 formulations were analyzed using linear, 2FI, cubic, and quadratic models. ANOVA identified significant factors with p-values < 0.05. Positive values indicated a complementary effect, while negative values showed an inhibitory effect. High R-squared values (> 0.90) demonstrated strong correlations between estimated and corrected experimental values. P-values greater than 0.1000 were non-significant and those less than 0.0500 were significant.

The polynomial equation for Response 1 (R_1) - Particle Size is:

Particle size $(R_1) = 275.38 + 4.39 \times A - 3.34 \times B - 5.60 \times C - 3.33 \times AB + 0.37 \times AC + 0.41 \times BC + 5.08 \times A^2 + 1.29 \times B^2 + 0.17 \times C^2$

Here, R1 represents particle dimension in µm, A is the quantity of polymer, B is amount of surfactant, and C is rotational speed. The model's F-value of 29.91 indicates significance (P<0.0001), with A, B, C, AB and A^2 being notable terms. The Lack of fit F- value is 3.42 with a p-value of 0.1704 shows that it is insignificant. The model showed good reliability with a Signal-to-Noise Ratio of 20.94 and an estimated R^2 of 0.7220, lower than the corrected R^2 of 0.9421. Three-dimensional response surface plots for R1 are presented in Fig. 1.

The polynomial equation for Response 2 (R_2) - Percentage yield is:

Percentage yield $(R_2) = 77.48 + 2.72 \times A + 1.33 \times B - 2.00 \times C + 1.48 \times AB - 0.11 \times AC + 0.22 \times BC - 2.42 \times A^2 + 3.58 \times B^2 - 6.89 \times C^2$

Here, R_2 is the percentage yield in %. The Quadratic Model F-value of 15.95 suggests statistical importance with A, C, A^2, B^2, C^2 as important key terms. The lack of fit (1.98) was unsignificant with a p-value of 0.3001. The estimated R^2 value (0.4606) was lower than the corrected R^2 value (0.8937), and the model's Signal-to-Noise Ratio of 16.24 indicates suitability for further analysis. Three-dimensional response surface plots for R_2 are presented in Fig. 2.

The mathematical relation obtained for Response 3 (R_3) - Entrapment efficiency is:

Entrapment efficiency $(R_3) = 72.02 + 5.73 \times A - 0.95 \times B - 3.13 \times C + 3.00 \times AB - 2.90 \times AC + 5.93 \times BC + 2.70 \times A^2 + 0.72 \times B^2 - 10.12 \times C^2$

Here, R_3 is the entrapment efficiency in %. The Quadratic model F-value of 8.66 and a p-value of 0.0047 shows significant result with A, C, BC, and C^2 as key terms. The lack of fit was non-significant, with a p-value of 0.4865. The estimated R^2 (0.6731) is close to the corrected R^2 (0.8117), indicating a good model fit. The Signal-to-Noise Ratio of 10.53 suggests the model is suitable for further analysis. Three-dimensional response surface plots for R_3 are presented in Fig. 3.

Characterization of Dapagliflozin Microspheres

Micromeritic Attributes of Microspheres

The optimized microspheres were evaluated for its micromeritic characteristics like loose and compacted densities, critical angle, carr's compressibility indicator and flowability ratio.[22]

Particle Dimension Measurement

The particle dimensions of the microspheres were measured through optical microscopy by means of ocular and stage micrometres, and the average size was determined.[23]

Percentage Production Estimation

The percentage amount of the dapagliflozin microspheres was assessed through comparing the dried microspheres weight to the initial weight drug and polymers employed, by the formula mentioned below.[23, 24]

$$Yield\ (\%) = \left[\frac{Dried\ microsphere\ mass}{Total\ mass\ of\ drug\ and\ polymers}\right] x100$$

Determination of entrapment efficiency

Dapagliflozin microspheres (25 mg) were weighed, crumbled and dissipated in phosphate buffer (100 ml, pH 7.4), sonicated for 20 mins, and filtered. The refined solution obtained was analysed for drug concentration by U.V spectrophotometry at 233 nm, and proficiency of drug entrapment was computed using the appropriate formula given below: [24]

$$Retention\ Efficiency = \left[\frac{Actual\ drug\ content}{Hypothetical\ drug\ content}\right] x100$$

Surface Morphology (SEM Testing)

The optimal microspheres (F2) were attached to brass stubs, and images were captured utilizing a JEOL JSM 6700 F SEM microscope to determine its topography.

In-Vitro Drug Release Characterization

Drug release testing from the optimized dapagliflozin microspheres was conducted through a USP type II apparatus in phosphate buffer (pH 7.4) at 37 °C and 100

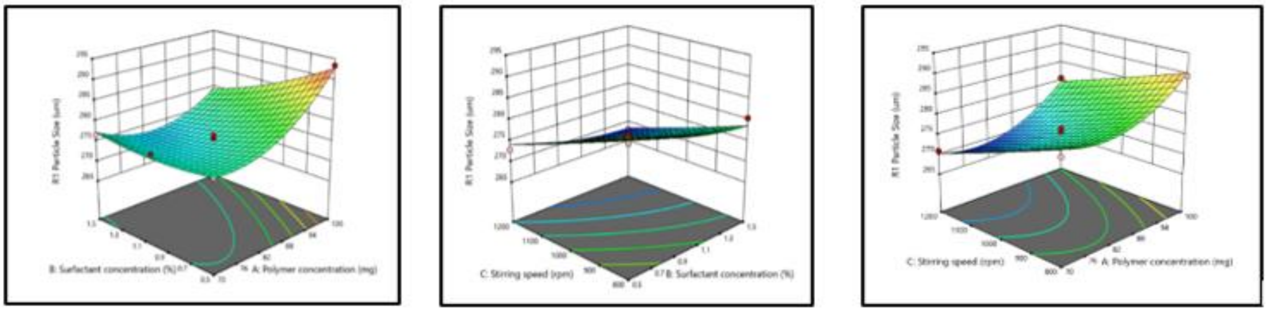

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Figure 1: 3D contour diagrams illustrate the effects of different factors on particle magnitude: (a) polymer concentration and concentration of surfactant; (b) surfactant concentration and rotational speed; (c) polymer and rotational speed

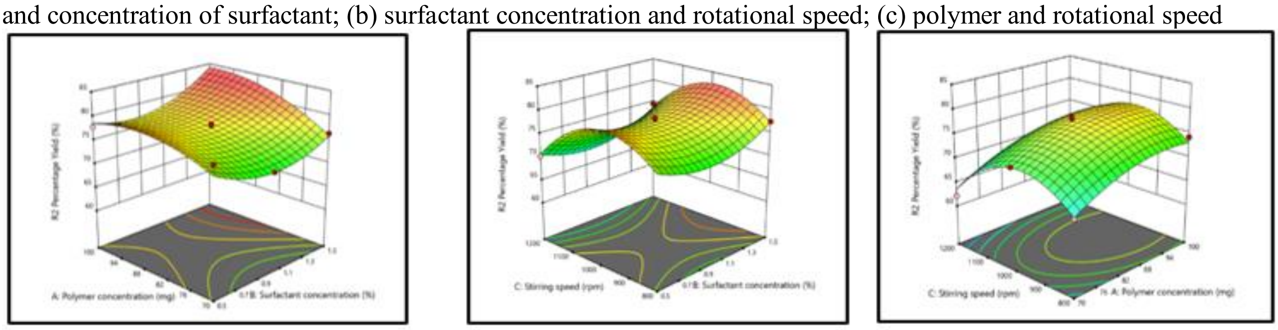

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Figure 2: 3D contour diagrams demonstrate the influence of different factors on percentage yield: (a) polymer concentration and surfactant; (b) surfactant concentration and rotational speed; (c) polymer and rotational speed.

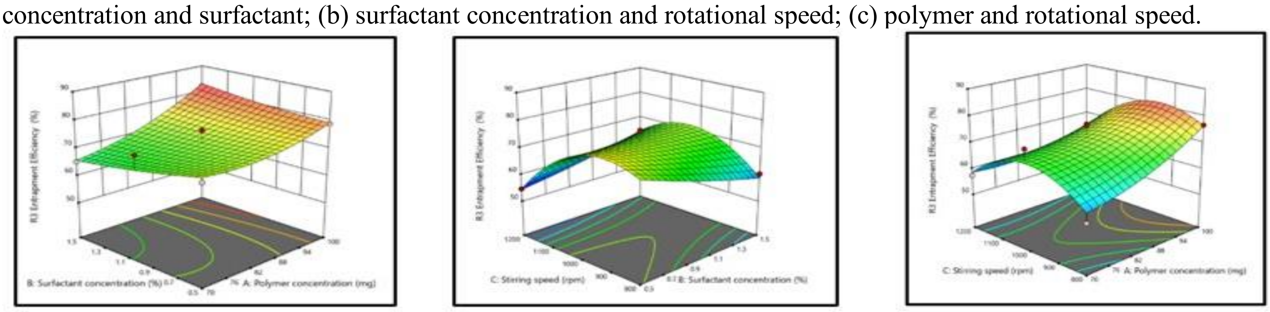

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Figure 3: 3D contour diagrams illustrating relationship among the various factors on drug encapsulation efficiency: (a) polymer and concentration of surfactant; (b) surfactant concentration and rotational speed; (c) polymer and rotational speed

Table 3: Cumulative drug liberation from the optimized microspheres and commercial SR tablets

Time (Hours)	Dapagliflozin Microspheres (F2)	Dapagliflozin SR Tablet (5mg)
0	0	0
1	5.8	18.17
2	6.9	25.02
3	7.42	34.03
4	10.62	40.69
5	18.78	51.12
6	23.61	60.76
7	31.74	68.71
8	42.60	71.52
9	58.16	81.10
10	62.89	89.39
11	75.31	92.18
12	77.10	95.41
13	80.12	-
14	85.15	-
15	88.04	-
16	90.17	-
17	92.08	-
18	93.76	-
19	96.21	-
20	98.02	-
21	-	-
22	-	-
23	-	-
24	-	-

rpm, with 5 ml aliquots collected over 24 hours, and analysed by UV-VIS spectroscopy.[25]

Comparison of Optimized Formulation (F2) with Marketed Product Dapagliflozin 5mg SR tablet (Glidapaflozin)

The release profile of F2 was compared to marketed Dapagliflozin 5mg SR tablets (Glidapaflozin), using the similarity factor (f2) mathematical equation given below.

$$f2 = 50 \times \log\left([1 + \frac{1}{n}\sum_{j=1}^{n}(Rj - Tj)^2\ ]^{0.5}\ X\ 100\right)$$

The equation uses the sum of squared differences between reference formulation (Rj) and test formulation (Tj) values at time point (j) for 'n' total number of time points in the dissolution study. Values of f2 ranging closer to 100 indicates similar profiles.[26]

Stability Studies

Stability studies of F2 were conducted at 40°C and 75% humidity for 30 days, assessing entrapment efficiency and drug release 15- and 30-day intervals as per the International Council for Harmonisation (ICH) protocols.[27]

Kinetic Analysis

The drug release mechanism through the optimal preparation (F2) was evaluated using best-fitting kinetic models like zero-order, first-order, Higuchi, and Korsmeyer-Peppas.[28]

RESULTS AND DISCUSSION

Pre-formulation Studies

The various concentration of the test sample was calculated from the standard curve of dapagliflozin by use of obtained corresponding absorbance values.

Drug-Polymer Compatibility Study

The drug-polymer compatibility study showed that the IR spectra of dapagliflozin and its formulations with excipients revealed key functional peaks (O-H, C=C, C=O, S=O). No shifts in these bands indicated no adverse interactions between dapagliflozin and the polymers used.[29]

Statistical analysis

It showed variation in particle size (268.25 µm to 293.45 µm), percentage yield (62.14% to 81.78%), and entrapment efficiency (54.76% to 82.21%) across batches. Formulation F2, with 100 mg of polymer, 1.5% Tween 80, and 1000 rpm stirring speed, showed the best results: particle size of 278.69 µm, yield of 81.78%, and entrapment efficiency of 82.21% as depicted in Table 4.

Statistical analysis showed that higher polymer and surfactant concentrations improved entrapment efficiency, yield, and particle size, with F2 meeting the optimal criteria. Contour plots indicated that increased polymer and surfactant concentrations raised viscosity and particle size, while higher stirring speeds reduced particle size but lowered entrapment efficiency. Yield increased with polymer and surfactant concentrations, but excessive stirring speed decreased it. The optimal formulation balanced polymer and surfactant levels to improve entrapment efficiency and yield while controlling particle size.

Micromeritic Properties of Microspheres

The micromeritic characteristics of the optimized formulation (F2) show good flow properties, with a loose density of 0.39±0.42 g/cm³, compacted density of 0.35±0.18 g/cm³, and a critical angle of 25.13±0.56°. The compressibility indicator (15.26±0.21%) and flowability ratio (0.86±0.74) indicate good flow, with critical angle between 20-30°, compressibility indicator between 12-16%, and flowability ratio under 1.25.[30]

Scanning Electron Microscope Technique

SEM findings revealed that the microspheres had a spherical shape with rough- porous surface. The drug

Table 4: Release pattern profile of optimal formulation (F2) and Marketed product procured from various statistical models.

Formulation Units	Zero Order kinetics(R^2)	First-order kinetics (R^2)	Higuchi Equation (R^2)	Korsmeyer-peppas equation (R^2 value)	(n value)
F2	0.8533	0.9471	0.9880	0.9441	0.7941
Marketed Product	0.8646	0.9563	0.9759	0.9203	0.7801

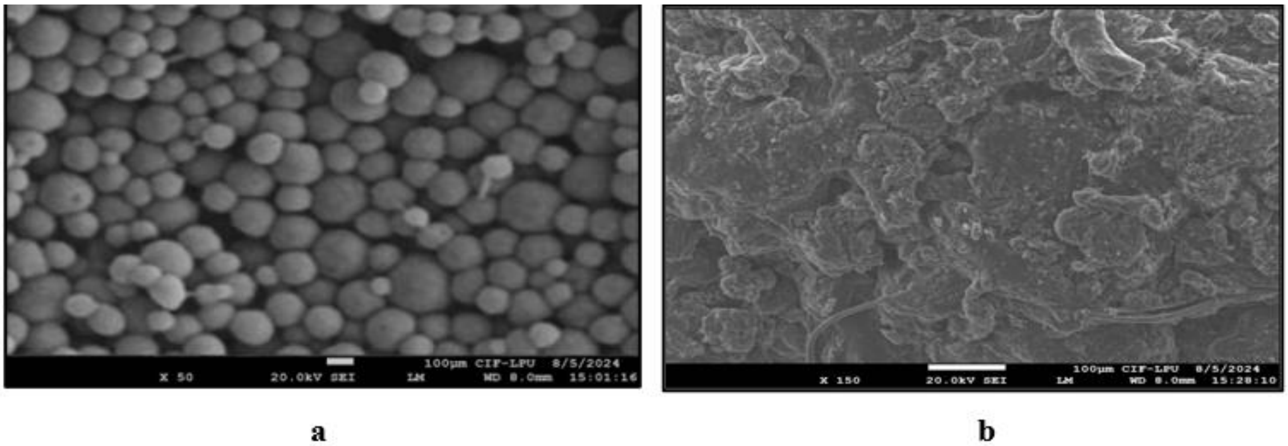

Figure 4: SEM images of optimized formulation (F2) (a) at 50 X (b) 150 X

release followed a diffusion-controlled mechanism, dependent on the number of pores. SEM images of the optimized dapagliflozin preparation are depicted in Fig. 4.

In-vitro Release Testing

In-vitro analysis of the optimized F2 formulation showed 98.02 % of drug release over 20 hours, compared to the commercial Glidapaflozin tablet, which released 95.41% of the drug within 12 hours. (as shown in Table 5). Cumulative % drug release pattern of Dapagliflozin microspheres (F2) and Marketed Formulation are shown in Fig. 5.

In vitro dissolution testing of the optimized F2 formulation and the marketed product was analyzed using statistical models, revealing that both followed the Higuchi model, indicating matrix diffusion. The Korsmeyer-Peppas model showed a non-Fickian diffusion mechanism (n value 0.45-0.89).[31] A comparison between F2 and the marketed Glidapaflozin tablet using the similarity factor (f2) test showed a value of 76.80%, indicating notable differences in drug release profiles as shown in Table 6.

Comparison between the Optimized Formulation (F2) and Marketed Dapagliflozin Formulation (Glidapaflozin tablet)

A comparison between F2 and the marketed Glidapaflozin tablet using the similarity factor (f2) test showed a value of 76.80%, indicating notable differences in drug release profiles.

Stability Assessment

The stability study of the optimized F2 formulation showed minimal changes over 30 days. With entrapment efficiency decreasing slightly from 82.21% to 81.72% and cumulative drug release reducing from 98.02% to 97.21%. This stability was attributed to the combined effects of HPMC K 100, ethyl cellulose, and sodium alginate, which provided mechanical strength and prolonged drug retention.

CONCLUSION

This research successfully developed prolonged-release dapagliflozin microspheres using a combination of sodium alginate, ethyl cellulose, and HPMC K 100 by employing emulsification (o/w) solvent evaporation technique. FT-IR

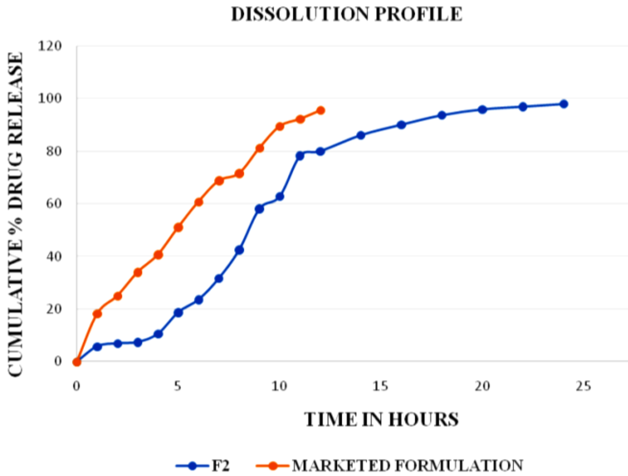

Figure 5: Comparative cumulative % drug release pattern of Dapagliflozin microspheres (F2) and Marketed Formulation.

studies demonstrated no negative drug-polymers interaction dynamics. The optimized formulation F2 (100 mg polymer, 1.5% surfactant, 1000 rpm) released 98.02% of the drug over 20 hours, outperforming the marketed tablet, which released 95.41% in 12 hours. The microspheres offer extended, uniform drug release, potentially improving diabetes management with increased efficacy and reduced dosing frequency.

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