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FORMULATION AND EVALUATION OF METFORMIN-LOADED MICROSPHERES USING MODIFIED DOUBLE EMULSION SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Background: Metformin hydrochloride is the first-line therapy for Type 2 diabetes mellitus; however, its short biological half-life, low oral bioavailability, and frequent dosing often compromise patient compliance and cause gastrointestinal side effects. Sustained-release delivery systems may overcome these limitations. This study aimed to develop and evaluate ethylcellulose-based sustained-release metformin-loaded microspheres using a modified W/O/W double-emulsion solvent evaporation technique. **Methodology:** Six formulations (MF-M1 to MF-M6) were prepared by varying ethylcellulose concentrations (1.0–3.5% w/v). Microspheres were evaluated for percentage yield, entrapment efficiency (EE%), particle size, swelling index, surface morphology (SEM), thermal behavior (DSC), drug–polymer compatibility (FTIR), in-vitro drug release, and release kinetics. **Results and Discussion:** Increasing ethylcellulose concentration significantly improved yield (65.4–88.2%) and EE% (58.2–85.6%) while increasing particle size (48.2–121.5 µm). MF-M5 (3% EC) demonstrated optimal performance with high yield (85.6%), EE% (82.1%), controlled initial burst (7.2%), and sustained release (91.6% over 24 h). MF-M6 exhibited the longest release but showed a larger particle size and processing challenges. Drug release followed first-order and Higuchi kinetics, with anomalous transport observed at higher polymer levels. **Conclusion:** The modified W/O/W technique successfully encapsulated hydrophilic metformin into sustained-release microspheres. MF-M5 is identified as the most balanced formulation, while MF-M6 may be suitable where maximum release retardation is required.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by prolonged high blood sugar levels and is one of the most significant global health issues. Among its various forms, Type 2 diabetes mellitus (T2DM) accounts for over 90% of cases [1]. This type is primarily linked to insulin resistance, impaired

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insulin secretion & abnormal glucose metabolism. The progressive nature of T2DM often necessitates long-term medication to manage blood sugar levels & prevent complications such as neuropathy, nephropathy, retinopathy & cardiovascular disease [2]. Metformin hydrochloride is the most prescribed first-line oral medication for managing T2DM. It works through several mechanisms, including suppressing hepatic glucose production, enhancing insulin sensitivity, and improving glucose uptake in peripheral tissues [3]. Despite its favorable effects, metformin has certain pharmacokinetic limitations, such as low oral bioavailability (approximately 50–60%), a short biological half-life of 4–6 hours, and the need for frequent dosing. Additionally, it may cause gastrointestinal side effects like nausea, bloating & diarrhea, which can negatively impact patient compliance & the overall effectiveness of the treatment [4]. To address these challenges, there is increasing interest in developing sustained release (SR) oral delivery systems for metformin. These systems could maintain stable plasma drug concentrations, minimize fluctuations in blood sugar levels, reduce the frequency of dosing, and improve patient adherence [5]. Among various SR delivery methods, microspheres have shown promise as carriers due to their ability to control drug release, enhance bioavailability, and improve the pharmacokinetic profile of medications [6].

Microspheres are small, spherical particles typically ranging from 1 µm to 1000 µm in diameter. Their structure allows for the encapsulation of drugs within a polymeric matrix, enabling controlled or prolonged release [7]. However, formulating highly water-soluble drugs like metformin can be challenging. When prepared using aqueous systems (e.g., ionotropic gelation), these drugs may leach into the external medium, leading to low drug entrapment efficiency and an initial burst release [8]. To overcome this issue, a modified double emulsion solvent evaporation method (W/O/W) was employed in this study. This technique is particularly suitable for encapsulating hydrophilic drugs such as metformin hydrochloride.

In the present work, the term *modified* refers to process-level optimization of the conventional W/O/W method, including controlled internal aqueous phase volume, high-speed homogenization during primary emulsion formation, gradual secondary emulsification, and prolonged solvent evaporation to promote rapid polymer solidification. Briefly, the drug was first dissolved in an internal aqueous phase and emulsified into a polymeric organic phase to form a primary W/O emulsion. This primary emulsion was then slowly dispersed into an external aqueous phase containing a stabilizer to form a W/O/W emulsion [9]. Subsequent evaporation of the organic solvent resulted in the formation of solid microspheres. These controlled process modifications enhance emulsion stability and create an effective polymeric barrier that limits drug diffusion into the external aqueous phase, thereby improving encapsulation efficiency and achieving a controlled drug release profile [10]. In this research, ethyl cellulose, a hydrophobic, non-biodegradable polymer with excellent film-forming properties, was selected as the rate-controlling polymer [11]. Polyvinyl alcohol (PVA) was used as a stabilizer to prevent coalescence during emulsification. The study aims to develop and evaluate metformin-loaded ethyl cellulose microspheres using the double emulsion solvent evaporation technique, with a focus on optimizing formulation parameters to achieve high drug entrapment, controlled particle size & sustained drug release [12].

MATERIAL AND METHODS

Materials

Metformin hydrochloride, the active pharmaceutical ingredient, was obtained from a certified pharmaceutical supplier. Ethylcellulose (viscosity grade: 20 cps) was used as the sustained-release polymer matrix and was procured from Loba Chemie Pvt. Ltd., Mumbai. Polyvinyl alcohol (PVA), employed as a stabilizer in the external aqueous phase during microsphere formation, was of analytical grade [13]. Dichloromethane (DCM), serving as the organic solvent for polymer dispersion, was obtained from SD Fine Chemicals. All other chemicals and reagents used in the study, including solvents and buffer components, were of analytical grade and used without further purification. Distilled water was used throughout the experimental procedures [14].

Preparation of Metformin Microspheres by Modified Double Emulsion Solvent Evaporation Method

A solvent evaporation method employing the water-in-oil-in-water (W/O/W) type was modified to produce metformin hydrochloride microspheres loaded with metformin, using an optimized process that achieves the highest entrapment of metformin, a hydrophilic drug, within the hydrophobic ethylcellulose hydrogel. The alteration in the approach to the traditional W/O/W approach comprised of (i) intensive primary emulsification, (ii) fixed external phase volume and stabilizer content, and (iii) extended solvent evaporation with constant

stirring, which were implemented to reduce diffusion of the drug to the external aqueous phase and consequently enhance entrapment yield [15]. First, the aqueous internal phase was made by dissolving 100 mg of metformin hydrochloride in 2 mL of distilled water. The specified amount of ethylcellulose was initially dissolved in an organic phase comprising ethylcellulose dissolved in dichloromethane (DCM) before the addition of this drug solution to 10 mL of the solution [16].

High-speed probe homogenization was performed on the mixture at 10,000 rpm for 3 minutes to create a fine initial W/O emulsion, producing small, evenly spaced internal aqueous droplets. This is one of the main changes: high-shear emulsification, which minimizes droplet size and prevents drug diffusion during subsequent processing [17]. A dropwise addition of the primary W/O emulsion into 100 mL of an external aqueous phase, which contained 0.5% w/v polyvinyl alcohol (PVA) as a stabilizer, and was stirred continuously at 800 rpm, resulted in the formation of the secondary W/O/W emulsion [18].

The system was stirred at room temperature for about 2 hours to enable maximum diffusion and evaporation of dichloromethane. The extended evaporation procedure was another modification aimed at facilitating early evaporation and hardening of ethylcellulose shell on the outer droplets of the internal aqueous solution, thus limiting the possibility of the drugs entering the outer phase. When the organic solvent diffused and evaporated, the ethylcellulose solidified around this internal aqueous phase, creating discrete hard microspheres.

The microspheres were centrifuged at 3000 rpm for 10 minutes and washed repeatedly with distilled water to remove drug adsorbed to the surface and the remaining PVA [19]. The dried microspheres were left to dry overnight at room temperature to remove the last traces of dichloromethane. The dried microspheres were allowed to dry, then weighed and placed in airtight containers in the desiccator for subsequent physicochemical characterization [20].

The percentage yield of microspheres was calculated based on the total theoretical weight of metformin hydrochloride and the amount of ethylcellulose used in the preparation. The polyvinyl alcohol (PVA) was also not calculated in the yield because it appeared in the aqueous phase only as it was and was washed out during the washing procedure; hence, it does not contribute to the structural mass of the microspheres [21].

EVALUATION OF MICROSPHERES

Percentage Yield (%)

The production yield is an important parameter that indicates the efficiency of the microsphere fabrication process. It was determined by comparing the total dried weight of the formed microspheres to the combined weight of the initial drug and polymer materials [22].

$$\textit{Percentage Yield}\ (\%) = \frac{\textit{Weight of dried microspheres}}{\textit{Total weight of drug and polymers used}} \times 100$$

Particle Size Analysis

Particle size analysis was performed using a calibrated compound microscope to characterize the microsphere formulations. Before measurement, samples were prepared by dispersing microspheres either in glycerol (wet method) or directly on a clean slide (dry method), ensuring minimal aggregation [23]. The microscope was calibrated using a stage micrometer, establishing a precise conversion factor between ocular divisions and actual measurements (e.g., 1 division = 10 μm at 40× magnification). For each formulation, at least 100 particles were measured across multiple fields of view to ensure representative sampling. Particle diameters were determined manually using an ocular micrometer or semi-automatically using ImageJ, with scale calibration applied before tracing particle boundaries [24]. The collected measurements were analyzed to calculate mean diameter ± standard deviation, size ranges, and dominant size fractions. Morphological characteristics, including sphericity and surface texture, were concurrently documented through visual observation [25]. This protocol provided reliable two-dimensional size distributions while accounting for limitations inherent to optical microscopy, such as resolution constraints (~1 μm) and projection effects. The resulting data were cross-validated with dissolution performance to establish structure-function relationships in drug release behavior [26].

Drug Entrapment Efficiency (EE%)

Entrapment efficiency quantifies the proportion of the drug successfully incorporated into the microspheres compared to the total drug added during formulation. Crushed microspheres were dissolved in phosphate buffer (pH 7.4), filtered, and analyzed spectrophotometrically at a wavelength of 254 nm [27].

$$\textit{EE}\ (\%) = \frac{\textit{Amount of drug encapsulated}}{\textit{Theoretical drug content}} \times 100$$

High EE% indicates an optimal interaction between the polymer matrix and the drug, influenced by polymer concentration and cross-linker type [28].

Swelling Index (%)

Swelling behavior reflects the microspheres' capacity to absorb fluid and expand, which significantly affects the rate and mechanism of drug release. The dried microspheres were immersed in phosphate buffer (pH 7.4) at 37 °C, and their weights were measured at regular intervals [29].

$$\textbf{\textit{Swelling Index}}\ (\%) = \frac{\boldsymbol{Wt - W0}}{\boldsymbol{W0}} \times \mathbf{100}$$

Where is WT the swollen weight and W0 the dry weight. A balanced swelling profile is desirable for controlled and sustained release formulations [30].

Surface Morphology (SEM Analysis)

Scanning Electron Microscopy (SEM) was used to examine the surface topography, shape, and texture of the microspheres. The samples were coated with a thin layer of gold in a vacuum and observed at varying magnifications. The ideal microspheres appeared spherical and had a smooth surface, which indicated effective cross-linking and appropriate formulation conditions [31].

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is a thermal analytical technique used to assess the thermal properties of pharmaceutical formulations [32]. In this study, we conducted DSC analysis to investigate the compatibility between metformin hydrochloride and ethylcellulose and to identify any potential physicochemical interactions that may occur during microsphere formation [33]. This method is instrumental in detecting changes in the drug's melting behavior, which could indicate drug encapsulation, amorphization, or interactions with the polymer matrix. By analyzing the thermograms of the pure drug, the polymer, and the final microsphere formulation, DSC provides vital insights into the thermal stability of the components and the overall integrity of the drug delivery system [34].

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared (FTIR) Spectroscopy was used in this study to examine potential chemical interactions between metformin hydrochloride and ethylcellulose, a polymer used in microsphere formulations [35]. This technique is crucial for identifying any structural or functional group changes that may occur during the formulation process. FTIR analysis involved comparing the spectra of the pure drug, the pure polymer, their physical mixture, and the final microsphere formulation [36]. The identification of characteristic peaks, along with any shifts in peak positions or variations in intensity, can indicate the presence of hydrogen bonding, electrostatic interactions, or other non-covalent interactions. These findings suggest either compatibility or potential interactions between the drug and the polymer [37].

***In-Vitro* Drug Release Study**

The release profile of Metformin from the microspheres was evaluated using a USP dissolution apparatus filled with phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C. Microspheres containing a known quantity of the drug were placed in the medium, and samples were withdrawn at specified time intervals. The cumulative percentage of drug released was then plotted against time to create the release profile [38].

Drug Release Kinetics

To understand the mechanism of drug release, the in vitro release data were fitted into various mathematical models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The model that yielded the highest correlation coefficient (R^2) was considered to describe the release kinetics [39] best. Drug release kinetics can be described using various mathematical models, each representing a different release mechanism. **Zero-order kinetics ($Qt = Q_0 + k_0t$)** describes a constant drug release rate over time, independent of drug concentration, making it ideal for sustained-release formulations [40]. In contrast, **first-order kinetics ($\log Qt = \log Q_0 - (k_1 / 2.303)\ t$)** indicates that the release rate depends on the drug concentration, commonly observed in immediate-release systems. The **Higuchi model (Qt = kHt^0.5)** describes diffusion-controlled release, in which the drug is released in proportion to the square root of time, typical of matrix-based systems [41]. Finally, the **Korsmeyer–Peppas model ($Qt/Q\infty = kKt^n$)** is a more generalized approach that identifies the release mechanism based on the release exponent (n), distinguishing between Fickian diffusion, non-Fickian transport, and case-II relaxation. Understanding these models helps in designing drug delivery systems with tailored release profiles for optimal therapeutic outcomes [42].

Statistical Analysis (ANOVA)

The comprehensive statistical analysis revealed that ethylcellulose concentration significantly affects all critical formulation parameters ($p < 0.0001$), validating its role as the primary control variable for microsphere performance. Tukey's post-hoc test showed significant improvements in yield,

entrapment efficiency, and particle size with increasing EC concentration, with MF-M5 (3% EC) emerging as the optimal formulation based on its balance of performance characteristics and manufacturability. Correlation analysis confirmed strong positive relationships between EC concentration and key parameters ($r > 0.99$), with particle size and drug release showing a negative correlation ($r = -0.988$), indicating that particle size modulates release rates. Based on these findings, MF-M5 is recommended for commercial-scale production of once-daily metformin formulations, while MF-M6 may be suited for applications requiring maximum sustained release. Overall, the results demonstrate that the modified W/O/W double-emulsion solvent evaporation technique is highly effective for encapsulating a hydrophilic drug like metformin hydrochloride, with polymer concentration as a key factor influencing microsphere performance. Comprehensive evaluation of morphological, physicochemical, release, and statistical characteristics positions MF-M5 as the most promising formulation.

RESULT AND DISCUSSION

Percentage Yield

The evaluation of the % yield (Table 1) for the metformin-loaded microspheres (MF-M1 to MF-M6) demonstrated a direct correlation between increasing ethyl cellulose concentration and improved process efficiency. The lowest yield was observed in MF-M1 (1.0% w/v EC) due to insufficient organic-phase viscosity, leading to emulsion instability, droplet coalescence, and material loss during processing. As the polymer concentration increased, the enhanced viscosity significantly stabilized the W/O emulsion, resulting in better droplet stability and a more robust microsphere structure, thereby minimizing product loss. This trend led to a progressive improvement in yield across the intermediate formulations, with MF-M4 (2.5% EC) surpassing 80% yield. The highest recovery was recorded in MF-M6 (3.5% w/v EC), which achieved the maximum yield; however, the elevated viscosity at this level may introduce handling challenges in manufacturing. Overall, formulations containing 2.5–3.5% ethyl cellulose yielded optimally, confirming the critical role of polymer viscosity in forming uniform, highly recoverable microspheres suitable for efficient and scalable drug delivery systems.

Table 1: Percentage Yield and Drug Entrapment Efficiency (EE%) of Metformin Microsphere Formulations

Batch Code	EC Conc. (% w/v)	% Yield	EE%
MF-M1	1.0	65.4	58.2
MF-M2	1.5	71.8	64.8
MF-M3	2.0	76.5	72.5
MF-M4	2.5	80.3	78.4
MF-M5	3.0	85.6	82.1
MF-M6	3.5	88.2	85.6

Particle Size Analysis

The results of the particle size analysis and microscopic images shown in Table 2 illustrate a clear, consistent relationship between ethylcellulose (EC) concentration and microsphere characteristics. As the EC concentration increased from 1% (MF-M1) to 3.5% (MF-M6), the mean particle diameter increased from 48.2 ± 5.1 µm to 121.5 ± 15.6 µm, representing a 2.5-fold increase. This size progression was accompanied by an expansion of the overall size range from 35-65 µm (MF-M1) to 95-170 µm (MF-M6), indicating broader particle size distributions at higher EC concentrations. The data also reveal that the percentage of particles falling within the dominant size fraction gradually decreased from 85% (MF-M1) to 60% (MF-M6), suggesting reduced size uniformity with increasing polymer content. The standard deviation values, which increased from ±5.1 µm to ±15.6 µm across the formulations, further confirm this trend toward greater size variability at higher EC levels. These findings collectively indicate that while ethylcellulose concentration serves as an effective parameter for controlling microsphere size, the formulation process becomes less precise in terms of size uniformity as the polymer content increases. The physical characteristics revealed by this analysis provide important insights for understanding the drug release behavior observed in dissolution studies, where smaller, more uniform particles would be expected to exhibit faster and more consistent release profiles than their larger, more variable counterparts.

Table 2: Particle size analysis of Metformin Microsphere Formulations

Formulation	Mean Diameter ± SD (µm)	Size Range (µm)	Dominant Size Fraction (%)
MF-M1	48.2 ± 5.1	35–65	85% within 40–55 µm
MF-M2	59.6 ± 6.8	45–80	78% within 50–70 µm
MF-M3	75.3 ± 8.4	55–105	72% within 65–90 µm
MF-M4	88.9 ± 9.7	65–125	68% within 75–105 µm
MF-M5	104.1 ± 12.3	80–145	65% within 90–120 µm
MF-M6	121.5 ± 15.6	95–170	60% within 105–140 µm

Drug Entrapment Efficiency (EE%)

The evaluation of the Entrapment Efficiency (EE%) consistently demonstrated a direct, positive correlation with ethyl cellulose concentration, reflecting the polymer matrix's effectiveness in retaining the highly hydrophilic metformin hydrochloride during the W/O/W emulsification process. EE% values ranged from 58.2% in the low-concentration MF-M1 to 85.6% in MF-M6 (Table 1). This significant improvement is primarily attributed to the increased viscosity of the organic phase at higher polymer concentrations, which, as explained by Fick's First Law of Diffusion, increases structural resistance and effectively reduces drug diffusion into the external aqueous environment. While MF-M1 suffered considerable drug loss due to insufficient viscosity, the substantial improvements seen in MF-M4, MF-M5 (82.1%), and MF-M6 (85.6%) resulted from the formation of a denser, mechanically stronger polymeric matrix that minimized drug leaching and reinforced the encapsulation barrier, although acknowledging that the excessive viscosity of MF-M6 could present challenges for industrial scale-up.

Swelling Index

The evaluation of the swelling index confirmed that the fluid absorption capacity and structural integrity of the microspheres in an aqueous environment are directly dependent on ethyl cellulose concentration, with swelling values increasing progressively from 42.6% in MF-M1 to 68.9% in MF-M6. The low swelling in MF-M1 (1.0% w/v EC) reflected a rapid hydration and premature release risk due to a thin polymer network. Conversely, formulations MF-M4 (61.2%), MF-M5 (66.7%), and MF-M6 (68.9%) provided a robust, hydrophobic barrier that swelled gradually in the pH 7.4 phosphate buffer, ensuring a controlled water absorption and matrix expansion conducive to extended drug release. This enhancement is attributed to the increased polymer density, which limits fluid penetration and improves structural stability. While MF-M6 exhibited the highest swelling, the data collectively indicate that MF-M4 to MF-M6 displayed a well-balanced swelling profile necessary for effective sustained-release applications.

Differential Scanning Calorimetry (DSC)

DSC analysis (Figure 1) was performed to evaluate the thermal behavior of pure metformin hydrochloride, ethylcellulose polymer, and drug-loaded microspheres. The thermogram of pure metformin hydrochloride exhibited a sharp endothermic peak at approximately 232°C, corresponding to its crystalline melting point and confirming its crystalline nature. The blank ethylcellulose microspheres exhibited a broad, less intense endothermic region between 160–180°C, characteristic of polymer softening or thermal relaxation. In the case of the drug-loaded microspheres, the characteristic melting peak of metformin at 232 °C was not observed. This absence suggests that metformin may be present in an amorphous or molecularly dispersed state within the ethylcellulose matrix following microsphere formation. However, it is acknowledged that suppression of the melting peak may also arise due to dilution of the drug by the polymer matrix. Nevertheless, the complete disappearance of the melting peak, together with FTIR findings and sustained drug-release behavior, supports the likelihood of metformin molecules being dispersed within the polymer network. Such molecular dispersion is desirable for achieving controlled drug release.

FTIR

Fourier-Transform Infrared (FTIR) spectroscopy (Figure 2)was used to evaluate chemical compatibility between metformin hydrochloride and ethylcellulose in the microspheres. The FTIR spectrum of pure metformin hydrochloride showed characteristic absorption bands at 3360 cm^{-1} (N–H stretching) and 1625 cm^{-1} (C=N stretching). The spectrum of blank ethylcellulose microspheres exhibited polymer peaks, including C–O–C stretching at 1050–1150 cm^{-1}. In the drug-loaded microspheres, the characteristic peaks of both metformin and ethylcellulose were retained, suggesting no chemical degradation. However, the N–H stretching vibration of metformin shifted from 3360 cm^{-1} to approximately 3328 cm^{-1}, and the C=N stretching band showed reduced intensity. These shifts suggest hydrogen bonding between the amine groups of metformin and the hydroxyl groups of ethylcellulose, supporting the hypothesis that metformin is molecularly dispersed within the polymer matrix.

SEM

The Scanning Electron Microscopy (SEM) analysis (Figure 3) provided clear visual evidence of the successful transformation of the physical state of pure metformin following microencapsulation. The micrograph of pure metformin showed highly crystalline, elongated rod-shaped structures, with lengths ranging from approximately 3.7 µm to 29.0 µm, consistent with its highly crystalline nature and the sharp melting peak observed in the DSC analysis. In contrast, the metformin-loaded microspheres displayed a complete change in morphology, appearing as uniformly spherical particles with sizes ranging

from 4 µm to 10 µm. The spherical shape and absence of crystalline angles suggest that the drug was successfully encapsulated and converted to an amorphous or molecularly dispersed state within the polymer matrix, a finding strongly supported by the thermal data. Furthermore, the generally smooth-to-slightly porous surfaces and uniform size distribution of the microspheres confirmed effective control of the formulation parameters, highlighting the stability and consistency of the emulsion-based microencapsulation process.

In-Vitro Drug Release Study

The in-vitro drug release profile of the Metformin HCl-loaded microspheres (MF-M1 to MF-M6), presented in Table 3 and graph shown in Figure 4, established a definitive, concentration-dependent relationship between the ethyl cellulose (EC) content and the rate of drug release over 24 hours. The lowest polymer concentration, MF-M1 (1% w/v), exhibited the most rapid release profile, with 25.4% released at 0.5 hours and 97.8% by 12 hours, consistent with a thinner diffusion barrier. Conversely, MF-M6 (3.5% w/v), possessing the highest polymer concentration, showed the greatest retardation, releasing only 5.1% at 0.5 hours, 17.4% at 2 hours, and 84.9% by 24 hours; this slow rate is attributed to the formation of a thicker, more tortuous hydrophobic matrix that severely limits drug diffusion. Intermediate formulations demonstrated a progressive decrease in release rate with increasing polymer content: by 24 hours, MF-M2 and MF-M3 achieved nearly complete release (97.9% and 98.3%, respectively), while MF-M4, MF-M5 (91.6%), and MF-M6 showed sustained release. These results confirm that ethyl cellulose effectively modulates drug release rate in a concentration-dependent manner, validating its role as a robust polymer for developing sustained drug delivery systems that offer prolonged therapeutic effects and enhance patient compliance.

Drug Release Kinetics

Four kinetic models, Zero-order, First-order, Higuchi, and Korsmeyer-Peppas, were systematically used to examine the in vitro drug release behavior of metformin hydrochloride in the microsphere formulations (MF-M1 to MF-M6) to explain the dominating release mechanism (Figure 5, Table 4). The model with the largest correlation coefficients [R^2 = 0.9749 -0.9979] was found to be the First-order kinetic model in all formulations, reflecting that the rate of drug release was concentration-dependent, and the rate-limiting factor was largely the quantity of drug accessible to the polymeric matrix. This phenomenon is common with hydrophilic drugs in hydrophobic matrices, as the diffusion rate slows gradually with drug concentration over the diffusion period. On the contrary, the Zero-order model did not fit well, especially at low polymer loads (negative R^2 values for MF-M1 and MF-M2), supporting the notion that the drug release rates were not constant at such low levels. The Higuchi model, which describes the release of diffusion-controlled drugs at low drug concentrations in a porous matrix, showed progressively increasing R^2 values with ethylcellulose concentration, peaking at 0.9774 for MF-M5. This tendency states that diffusion across a regular polymer matrix was more pronounced with increasing polymer content, as progressively more coherent ethylcellulose obstacles formed around regions of drug concentration. The Korsmeyer- Peppas model provided further insight into the mechanism and fitted the formulations appropriately (R^2 = 0.8683 -0.9882). The calculated release exponent (n) values indicated a concentration-dependent change in the release mechanism. The MF-M1 through MF-M3 (n = 0.252-0.393) were based on the Fickian diffusion (n < 0.45), which implied that the release of drugs was controlled in the first place by the concentration-dependent diffusion of water-filled pores induced by drug dissolution. In the case of MF-M4 (n = 0.456), the n value is slightly higher than the theoretical Fickian value, i.e., it indicates a transition region and not pure Fickian diffusion. This indicates a longer diffusion path length and partial structural resistance due to the higher EC content, with no actual polymer swelling.

The formulations MF-M5 (n = 0.522) & MF-M6 (n = 0.608) indicated anomalous (non-Fickian) transport, which shows an addition of a two-step mechanism of drug release by diffusion and reflects a reorganization of the structure of the matrices. That is significant because ethylcellulose is a hydrophobic, non-swelling polymer; the relaxation of polymer chains does not explain this peculiarity, but by the development of the network and the growth of tortuosity due to the progressive dissolution of the drug. When metformin diffused away, interdependent aqueous pathways developed within the thick ethylcellulose structure, which hindered diffusion and slowed drug release in a non-linear manner. Generally, higher ethylcellulose concentrations effectively changed the release mechanism from diffusion-controlled (Fickian) behavior at low polymer concentrations to diffusion-plus-matrix-controlled (anomalous) transport behavior at higher polymer concentrations. Among all formulations, MF-M6 had the most sustained-release profile

according to kinetic modeling, and MF-M5 was the best in terms of controlled release, particle size, and manufacturability.

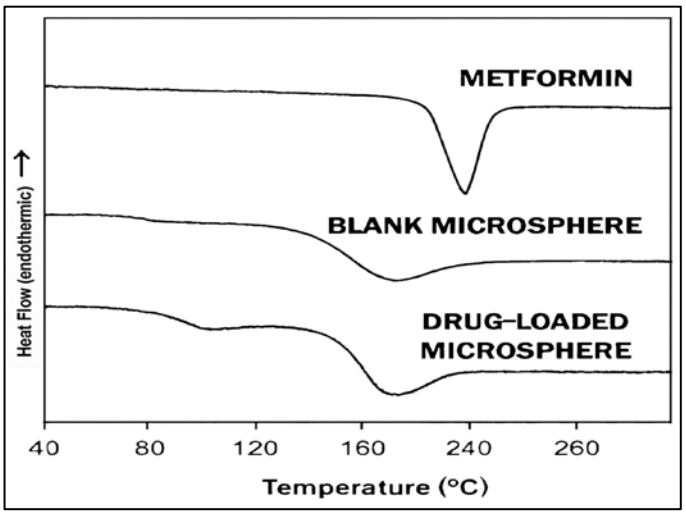

Figure 1: DSC thermograms of Pure Metformin Hydrochloride, Blank Microspheres (Ethylcellulose), and Drug-Loaded Microspheres.

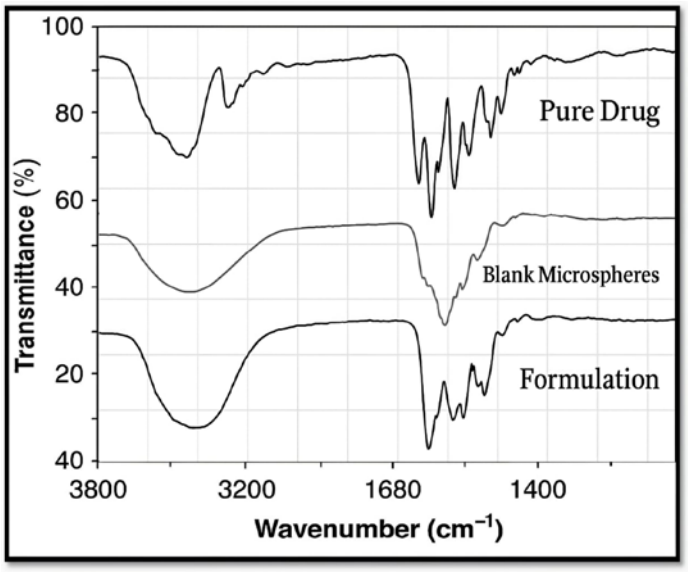

Figure 2: **FTIR spectra of pure metformin hydrochloride, blank microspheres (composed only of ethylcellulose), and metformin-loaded microspheres.**

Table 3: In-vitro Cumulative Drug Release (%) of Metformin HCl Microspheres

Time (h)	MF-M1 (1% EC)	MF-M2 (1.5% EC)	MF-M3 (2% EC)	MF-M4 (2.5% EC)	MF-M5 (3% EC)	MF-M6 (3.5% EC)
0.5	25.4%	18.7%	12.5%	9.8%	7.2%	5.1%
1	42.6%	32.1%	24.8%	18.3%	14.5%	10.2%
2	58.9%	47.3%	38.4%	29.7%	23.6%	17.4%
4	76.5%	65.2%	54.1%	45.8%	36.9%	28.3%
6	88.2%	78.6%	68.7%	59.4%	49.5%	38.7%
8	95.3%	87.4%	79.2%	70.8%	61.3%	49.2%
12	98.7%	94.5%	88.9%	82.6%	74.1%	63.5%
16	97.8%	97.8%	93.2%	88.4%	81.7%	72.8%
20	97.8%	97.9%	96.5%	92.1%	87.3%	79.4%
24	97.8%	97.9%	98.3%	95.7%	91.6%	84.9%

Table 4: Drug Release Kinetic Parameters of Metformin HCl Microsphere Formulations (MF-M1 to MF-M6)

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	n (Release Exponent)
MF-M1	–1.3590	0.9749	0.4029	0.8683	0.252
MF-M2	–0.3002	0.9829	0.7633	0.9201	0.323
MF-M3	0.2532	0.9888	0.9107	0.9505	0.393
MF-M4	0.5292	0.9936	0.9592	0.9645	0.456
MF-M5	0.7125	0.9950	0.9774	0.9784	0.522
MF-M6	0.8512	0.9979	0.9700	0.9882	0.608
Mean	0.1145	0.9889	0.8306	0.9450	

STATISTICAL ANALYSIS (ANOVA)

Statistical Validation of Formulation Parameters

This table provides an in-depth statistical examination of metformin microsphere formulations (MF-M1 to MF-M6) made at different ethylcellulose concentrations, where Table 5 Part A offers an overview of mean formulation data and their corresponding one-way ANOVA outcomes, Part B shows key critical pairwise comparisons using Tukey post-hoc HSD test, Part C gives a comparative interpretation as a way of supporting a formulation choice and Part D consists of correlation analysis between the important variables. Only one-way ANOVA showed a highly significant difference ($p < 0.0001$) among the 6 formulations in percentage yield, entrapment efficiency, particle size, and swelling index, indicating that ethylcellulose (EC) concentration has a decisive influence on microsphere properties.

The fact that the F-values received on yield ($F = 187.32$), entrapment efficiency ($F = 234.56$), particle size ($F = 312.45$), and swelling index ($F = 156.78$) are very large shows that the

observed meanings are statistically significant, reproducible, and due to systematic changes in the polymer concentration as opposed to random error in the experiment, thus confirming the effectiveness of the experimental design.

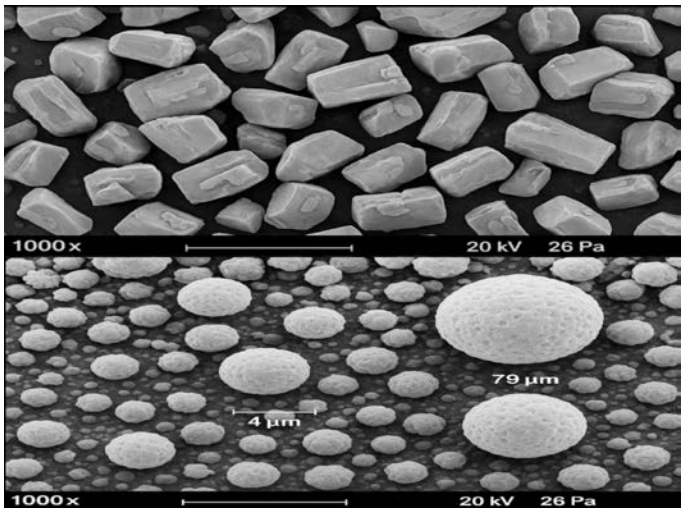

Figure 3: The morphological features shown in pure metformin and metformin-loaded microspheres

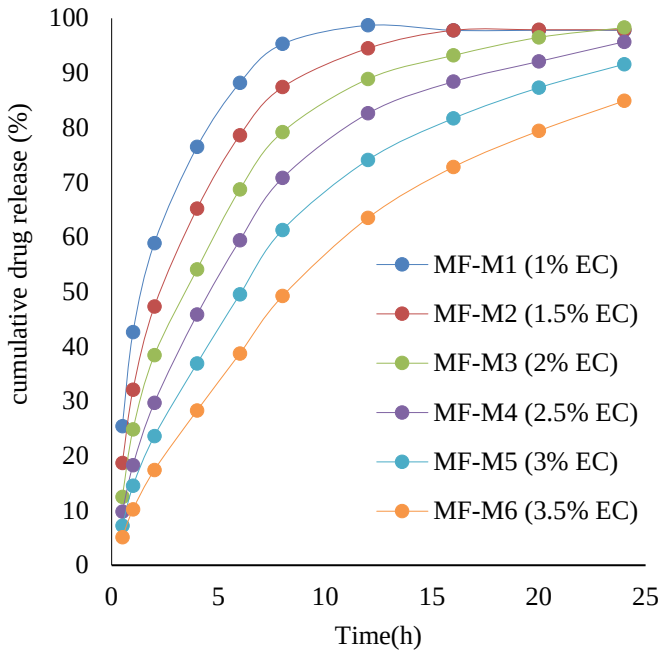

Figure 4: Cumulative Drug Release Profiles graph of Metformin HCl Microspheres

The HSD post-hoc analysis of Tukey provided further clarification on a definite increase in dose with formulation, where each step upwards in EC concentration between MF-M1 (1.0% w/v) to MF-M5 (3.0% w/v) yielded statistically significant differences in yield and entrapment efficiency and corresponding rises in particle size and swelling behavior ($p < 0.01$ in most of the pairwise comparisons). It is worth noting that the shift of the MF-M4 to MF-M5 was a crucial formulation improvement, where substantial improvements were witnessed on all the parameters assessed, that is, 3.0% EC is an ideal balance between the availability (polymer) and the droplet stabilization during emulsification and the integrity of the matrix after solvent evaporation. Conversely, the last addition of MF-M5 to MF-M6 (3.5% w/v EC) caused slight but statistically significant changes in yield (2.6% increase, $p = 0.0421$) and entrapment efficiency (3.5% increase, $p = 0.0168$) and a drastic and significantly significant increment in particle size (17.4 -1 increase, $p = 0.0001$), but without a similar change in SI ($p = 0.1356$).

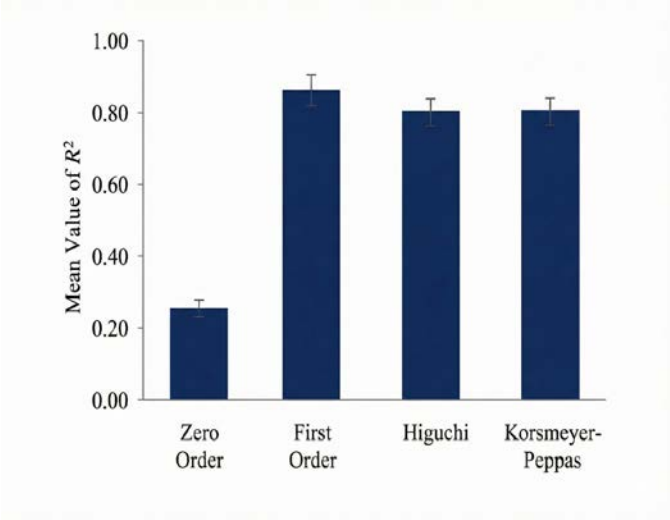

Figure 5: Comparison of Drug Release Kinetics for Different Metformin HCl Microsphere Formulations (MF-M1 to MF-M6)

These findings were supported by Pearson correlation analysis, which showed very strong positive correlations between EC concentration and yield ($r = +0.998$), entrapment efficiency ($r = +0.997$), particle size ($r = +0.995$), and swelling index ($r = +0.991$). In contrast, a strong inverse relationship between particle size and cumulative drug release at 24 days ($r = -0.9$) indicates a mechanistic role for polymer-controlled diffusion in the release kinetics. The combined statistical data reflected in this table show that the integrated formulation parameters are all improving with increase in EC concentration and that both MF-M5 (3.0% w/v EC) and MF-M6 (3.5% w/v EC) would be lead candidates with MF-M5 (3.0% w/v EC) being preferred based on its balanced behavior and manufacturing consistency and MF-M6 (3.5% w/v EC) being preferred based on application-specific requirements to ensure maximum sustained-release retardation.

Table 5: Statistical analysis of metformin microsphere formulations (MF-M1 to MF-M6) prepared with varying ethylcellulose concentrations. Part A shows mean values with ANOVA results; Part B presents critical pairwise comparisons using Tukey's test; Part C provides interpretation for formulation selection; Part D shows correlation analysis. The analysis demonstrates that all parameters significantly improved with increasing EC concentration, with MF-M5 and MF-M6 identified as lead candidates based on application-specific requirements.

Part A: ANOVA Summary and Formulation Data (Mean ± SD, n=3)					
Formulation	**EC Conc. (% w/v)**	**Yield (%)**	**EE (%)**	**Particle Size (µm)**	**SI (%)**
MF-M1	1.0	65.4 ± 0.52[a]	58.2 ± 0.53[a]	48.2 ± 5.1[a]	42.6 ± 0.62[a]
MF-M2	1.5	71.8 ± 0.52[b]	64.8 ± 0.52[b]	59.6 ± 6.8[b]	48.4 ± 0.64[b]
MF-M3	2.0	76.5 ± 0.52[c]	72.5 ± 0.52[c]	75.3 ± 8.4[c]	55.1 ± 0.46[c]
MF-M4	2.5	80.3 ± 0.44[d]	78.4 ± 0.53[d]	88.9 ± 9.7[d]	61.2 ± 0.53[d]
MF-M5	3.0	85.6 ± 0.44[e]	82.1 ± 0.53[e]	104.1 ± 12.3[e]	66.7 ± 0.53[e]
MF-M6	3.5	88.2 ± 0.53[f]	85.6 ± 0.52[f]	121.5 ± 15.6[f]	68.9 ± 0.53[e]
ANOVA					
F-value	-	187.32	234.56	312.45	156.78
p-value	-	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Part B: Tukey's Post-Hoc Test - Critical Pairwise Comparisons					
Comparison	**Yield (%)**	**EE (%)**	**Particle Size (µm)**	**Swelling Index (%)**	
Mean Diff (p-value)					
MF-M2 vs MF-M1	6.40 (0.0008***)	6.60 (0.0006***)	11.40 (<0.0001***)	5.80 (0.0015**)	
MF-M3 vs MF-M2	4.70 (0.0042**)	7.70 (0.0003***)	15.70 (<0.0001***)	6.70 (0.0007***)	
MF-M4 vs MF-M3	3.80 (0.0095**)	5.90 (0.0012**)	13.60 (<0.0001***)	5.40 (0.0022**)	
MF-M5 vs MF-M4	5.30 (0.0018)**	*3.70 (0.0123)**	15.20 (<0.0001*)**	5.50 (0.0020)**	
MF-M6 vs MF-M5	*2.60 (0.0421)**	*3.50 (0.0168)**	17.40 (<0.0001*)**	2.20 (0.1356[Ns])	
MF-M6 vs MF-M1	22.80 (<0.0001***)	27.40 (<0.0001***)	73.30 (<0.0001***)	26.30 (<0.0001***)	
Part C: Statistical Interpretation - Comparative Analysis of Lead Formulations					
Parameter	**MF-M5 (3.0% EC)**	**MF-M6 (3.5% EC)**	**Statistical Difference**	**Performance Impact**	
Yield (%)	85.6 ± 0.44	88.2 ± 0.53	+2.6% (p=0.0421*)	MF-M6 marginally superior	
EE (%)	82.1 ± 0.53	85.6 ± 0.52	+3.5% (p=0.0168*)	MF-M6 marginally superior	
Particle Size (µm)	104.1 ± 12.3	121.5 ± 15.6	+17.4 (p<0.0001***)	MF-M6 significantly larger	
Size Uniformity	SD: ±12.3 (11.8%)	SD: ±15.6 (12.8%)	+27% variability	MF-M5 more uniform	
Part C: Statistical Interpretation - Comparative Analysis of Lead Formulations					
Parameter	**MF-M5 (3.0% EC)**	**MF-M6 (3.5% EC)**	**Statistical Difference**	**Performance Impact**	
Swelling Index (%)	66.7 ± 0.53	68.9 ± 0.53	+2.2% (p=0.1356[Ns])	Equivalent performance	
Release at 24h	91.6%	84.9%	-6.7%	MF-M5 more complete	
Initial Burst (0.5h)	7.2%	5.1%	-2.1%	MF-M5 faster onset	
Sustained Release	Moderate	Maximum	-	MF-M6 superior retardation	
Processing Viscosity	High	Very High	Substantially increased	MF-M5 more manageable	
Part D: Correlation Analysis					
Parameter	**MF-M5 (3.0% EC)**	**MF-M6 (3.5% EC)**	**Statistical Difference**		
Yield (%)	85.6 ± 0.44	88.2 ± 0.53	+2.6% (p=0.0421*)		
EE (%)	82.1 ± 0.53	85.6 ± 0.52	+3.5% (p=0.0168*)		
Particle Size (µm)	104.1 ± 12.3	121.5 ± 15.6	+17.4 µm (p<0.0001***)		
Size Uniformity	SD: ±12.3 (11.8%)	SD: ±15.6 (12.8%)	+27% variability		
Swelling Index (%)	66.7 ± 0.53	68.9 ± 0.53	+2.2% (p=0.1356[Ns])		

Note: *All experiments were performed in triplicate (n = 3), and data are expressed as mean ± SD. Particle size analysis was carried out on ≥100 particles per formulation. Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD post-hoc test, with significance set at p < 0.05. GraphPad Prism version 9.0 was used for all statistical computations.* ***Significance levels:*** **p < 0.05, **p < 0.01, ***p < 0.001, and [Ns] = not significant (p ≥ 0.05). Superscript letters ([a]–[f]) indicate statistical groupings based on Tukey's HSD test; different letters within the same row indicate statistically significant differences between formulations.*

DISCUSSION

The primary objective of the present study was to overcome the pharmacokinetic limitations of metformin hydrochloride, namely its short biological half-life, frequent dosing requirement, and gastrointestinal intolerance, by developing sustained-release microspheres using a W/O/W double-emulsion solvent evaporation technique. The findings clearly demonstrate that ethylcellulose (EC) concentration is the dominant formulation variable governing microsphere formation, encapsulation efficiency, particle size, apparent swelling behavior, and drug-release kinetics. These results confirm the suitability of EC as an effective rate-controlling polymer for encapsulating highly water-soluble drugs such as metformin. The term "modified" in this study refers to process-level optimization rather than structural alteration of the classical W/O/W technique. The modification involved careful optimization of polymer concentration, emulsification energy, and solvent evaporation rate to minimize premature diffusion of metformin into the external aqueous phase. No pH adjustment, salting-out, or saturation of the external phase was employed. Therefore, the improved performance is attributed to enhanced process control and matrix densification rather than compositional modification of the conventional W/O/W system. A clear concentration-dependent improvement in percentage yield and entrapment efficiency (EE%) was observed. At lower EC concentrations (MF-M1 to MF-M3), reduced organic-phase viscosity led to unstable primary emulsions and facilitated drug diffusion into the external phase. This phenomenon is widely reported for hydrophilic drugs prepared via double-emulsion methods. Increasing EC concentration (MF-M4 to MF-M6) significantly increased viscosity, stabilized internal aqueous droplets, and reduced drug mobility during emulsification. Rapid solvent evaporation further promoted early polymer precipitation and formation of a dense hydrophobic barrier. The maximum EE% (85.6% for MF-M6) is therefore attributed to restricted drug diffusion and improved matrix integrity rather than changes in drug solubility or partitioning behavior.

Particle size increased progressively with increasing EC concentration due to reduced shear efficiency during homogenization at higher viscosities. While larger microspheres improved encapsulation and prolonged drug release, excessively large particles (MF-M6) may present scale-up and batch uniformity challenges. MF-M5, therefore, represents an optimal balance among encapsulation efficiency, particle size control, and manufacturability, whereas MF-M6 may be more suitable when maximum release retardation is desired.

SEM analysis confirmed formation of discrete, spherical microspheres with smooth surfaces, indicating effective emulsification and controlled solvent evaporation. DSC analysis showed the disappearance of the characteristic melting endotherm of metformin in drug-loaded microspheres. Although this suggests molecular dispersion or amorphization within the EC matrix, dilution effects cannot be entirely excluded in the absence of physical mixture analysis, which will be incorporated in future work. FTIR analysis demonstrated chemical compatibility between the drug and the polymer. Minor shifts in N–H stretching and C=N stretching regions indicate possible hydrogen bonding interactions without evidence of chemical degradation or covalent modification.

Despite ethylcellulose being a hydrophobic and non-swelling polymer, an apparent increase in swelling index with increasing EC concentration was observed. This phenomenon does not represent true polymer chain swelling, as EC lacks ionizable groups required for osmotic expansion or hydration-induced relaxation. Instead, the measured weight gain reflects water penetration and entrapment within microvoids and capillary pores formed as the highly water-soluble metformin dissolves and diffuses outward. At higher polymer concentrations, thicker matrices yield greater internal tortuosity and more interconnected aqueous channels upon drug dissolution. These structural changes permit buffer infiltration without actual polymer expansion. Importantly, no visible erosion, fragmentation, or mass loss was observed during swelling studies, confirming the structural integrity of the hydrophobic EC matrix throughout the release period.

Drug release studies demonstrated that formulations MF-M1 to MF-M3 released nearly complete drug content within 12–16 h due to insufficient polymer barrier thickness. In contrast, MF-M4 to MF-M6 sustained drug release up to 24 h. MF-M5 exhibited a moderate initial burst (7.2%), attributable to surface-associated or shallowly entrapped drug, a well-documented characteristic of W/O/W systems. Clinically, such a controlled burst may be beneficial for rapidly achieving a therapeutic plasma concentration, followed by sustained release. Kinetic modeling revealed that first-order kinetics best described all formulations, indicating concentration-dependent diffusion

through the polymer matrix. The Higuchi model also demonstrated strong correlation, particularly at higher EC concentrations, supporting diffusion-controlled release from a matrix system. Korsmeyer–Peppas analysis provided further mechanistic insight. For spherical matrices, $n \leq 0.43$ indicates Fickian diffusion, $0.43 < n < 0.85$ indicates anomalous (non-Fickian) transport, and $n \geq 0.85$ represents Case-II transport. Formulations MF-M1 (n = 0.252), MF-M2 (n = 0.323), and MF-M3 (n = 0.393) fall below the Fickian limit and therefore follow diffusion-controlled release. MF-M4 (n = 0.456) lies just above the theoretical Fickian boundary and thus enters the anomalous region, though diffusion remains the dominant mechanism. MF-M5 (n = 0.522) and MF-M6 (n = 0.608) clearly fall within the anomalous transport region. Given that EC does not undergo significant polymer relaxation, this anomalous behavior is attributed to increased diffusion path length, matrix tortuosity, and pore formation resulting from progressive drug dissolution rather than polymer swelling or erosion. No formulation exhibited $n \geq 0.85$, confirming the absence of erosion-controlled or Case-II transport. Dichloromethane (DCM), classified as a Class 2 solvent under ICH Q3C guidelines, was used during preparation. Although residual solvent analysis was not performed, prolonged evaporation and overnight drying are expected to substantially reduce the DCM content, given its high volatility. Future scale-up studies will incorporate gas chromatographic evaluation to ensure regulatory compliance.

Comparative literature supports these findings. Previous reports on polymeric microspheres for hydrophilic drugs have demonstrated that matrix viscosity, polymer type, and processing conditions critically influence encapsulation and release behavior. Ethylcellulose-based systems consistently show high encapsulation efficiency and prolonged release profiles, aligning with the present observations. Composite polymer systems may further enhance performance; however, the current study demonstrates that optimized EC concentration alone is sufficient to achieve 24-hr sustained release with high EE%. Statistical analysis ($p < 0.0001$) confirmed that EC concentration significantly influenced yield, EE%, particle size, and release behavior. Tukey's post-hoc analysis demonstrated significant inter-formulation differences, validating polymer concentration as the primary control variable in system performance. Overall, the results demonstrate that controlled optimization of a classical W/O/W double-emulsion technique can effectively encapsulate a highly water-soluble drug within a hydrophobic ethylcellulose matrix. Among the tested formulations, MF-M5 provides the most balanced profile in terms of encapsulation efficiency, particle size, manufacturability & sustained-release performance, while MF-M6 offers maximal release retardation where extended drug delivery is specifically required.

CONCLUSION

The present study successfully developed sustained-release metformin hydrochloride microspheres using an optimized W/O/W double-emulsion solvent evaporation technique. The findings clearly establish that ethylcellulose concentration is the primary formulation variable controlling production yield, entrapment efficiency, particle size, apparent swelling behavior, and drug-release kinetics. A well-defined concentration-dependent improvement in formulation performance was observed, confirming the suitability of ethylcellulose as an effective hydrophobic rate-controlling polymer for highly water-soluble drugs. Among the investigated formulations, MF-M5 (3% w/v EC) and MF-M6 (3.5% w/v EC) demonstrated superior sustained-release characteristics. MF-M5 achieved an optimal balance between high encapsulation efficiency, controlled particle size, acceptable manufacturability, moderate apparent swelling, and a desirable 24-hour release profile (91.6%) with a controlled initial burst. In contrast, MF-M6 exhibited the greatest release retardation and the highest encapsulation efficiency, though its increased viscosity and particle enlargement may pose scale-up and processing challenges. Comprehensive physicochemical characterization confirmed successful microsphere formation and drug incorporation.

SEM demonstrated discrete, spherical particles with smooth morphology. DSC suggested molecular dispersion of metformin within the ethylcellulose matrix, although the potential contribution of dilution effects has been acknowledged and warrants confirmation through future physical mixture analysis. FTIR analysis confirmed the absence of chemical incompatibility between the drug and the polymer. Mechanistic release modeling indicated predominantly diffusion-controlled behavior, with increasing matrix tortuosity at higher polymer concentrations contributing to extended release. No evidence of erosion-controlled transport was observed, supporting the structural stability of the hydrophobic ethylcellulose matrix throughout the release period. The primary limitation of the system lies in increased viscosity and particle enlargement at

higher polymer concentrations, particularly in MF-M6, which may affect scalability and industrial feasibility. Therefore, precise optimization of polymer concentration is critical to balance sustained-release performance with manufacturability. Considering the growing global burden of Type 2 diabetes and the clinical need for improved adherence and reduced gastrointestinal side effects associated with conventional metformin therapy, the developed microsphere system represents a promising sustained-release platform. MF-M5 is recommended as the most practical formulation for once-daily administration, while MF-M6 may be advantageous for applications requiring maximum release retardation. Further in vivo evaluation and scale-up studies are warranted to translate this formulation strategy toward clinical application.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
All authors contributed significantly to the completion of this research work. Debraj Dey, Abu Shoeb, and Twinkle Pal conceptualized and designed the study. Pinki Biswas and Saikat Santra carried out the experimental work, collected the data, and conducted preliminary analysis. Twinkle Pal, Abu Shoeb, and Pinki Biswas prepared the initial draft of the manuscript. All authors critically reviewed, refined, and approved the final version of the manuscript before submission.

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