Empagliflozin-Loaded Floating Density-Modulated Drug Delivery System as a Novel Approach for Sustained Therapy in Type 2 Diabetes Mellitus with Sodium-Glucose Co-Transporter-2 Inhibition

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Abstract

The development of a density-modulated drug delivery system (DMDDS) for Empagliflozin aims to enhance gastric retention and ensure sustained drug release for effective management of Type 2 Diabetes Mellitus. This study evaluated five formulations (EMF1 to EMF5) based on micromeritic properties, weight and drug content uniformity, in vitro floatation, and drug release kinetics. Among the formulations, EMF1 demonstrated superior flowability, as evidenced by its lowest Carr's Index (8.49%) and Hausner Ratio (1.09), and the most consistent weight uniformity (1.28% CV). Drug content uniformity for EMF1 was exceptionally high (99.98 ± 1.79%), ensuring accurate dosing. In vitro floatation studies revealed that EMF1 remained buoyant for over 12 hours without lag time due to its hydrophilic polymer matrix, facilitating prolonged gastric retention. Drug release kinetics of EMF1 aligned with zero-order and Higuchi models (R^2 = 0.945 and 0.967, respectively), with non-Fickian transport (n = 0.781) indicating a controlled release mechanism. These results highlight EMF1 as the optimal formulation, offering a reliable system for prolonged drug release and enhanced therapeutic efficacy. This study underscores the potential of DMDDS in improving bioavailability and patient compliance for gastric-retentive drug delivery.

Keywords: Empagliflozin, Density-modulated drug delivery system (DMDDS), In Vitro Drug Release, Sustained Release, Micromeritic Properties, Type 2 Diabetes

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive beta-cell dysfunction, leading to hyperglycemia. It is a growing global health concern, affecting millions of individuals and imposing significant economic and social burdens. Effective management of T2DM often requires sustained blood glucose control through the use of pharmacological agents. Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, has emerged as a promising therapeutic option for T2DM (Zinman et al., 2015, 2016). It works by reducing renal glucose reabsorption, promoting glycosuria, and improving glycemic control. Despite its efficacy, conventional formulations of Empagliflozin are limited by rapid drug release and absorption, resulting in fluctuations in plasma drug levels, reduced bioavailability, and frequent dosing, which may compromise patient compliance (S et al., 2024, Bantounou et al., 2024, Patel et al., 2024).

Gastric retention has gained significant attention as a means to overcome these challenges. Prolonged retention of drug formulations in the stomach can enhance bioavailability, especially for drugs with a narrow absorption window in the upper gastrointestinal (GI) tract. A density-modulated drug delivery system (DMDDS) is a novel approach that combines controlled release with enhanced gastric retention. By ensuring the drug remains in the

stomach for an extended period, DMDDS can improve therapeutic efficacy, minimize dosing frequency, and enhance patient compliance (Patel et al., 2024, Reddy and Murthy, 2002).

The development of hydrodynamically balanced systems and floating drug delivery systems (FDDS) has been integral to achieving gastric retention. These systems rely on low-density polymers and excipients that enable buoyancy in gastric fluid. Upon contact with gastric fluid, these systems form a swollen polymeric matrix that remains afloat, ensuring sustained drug release over time. Incorporating hydrophilic polymers such as Medium Molecular Mass Chitosan (MMMCH) and Xanthan Gum (XG) in DMDDS formulations has been shown to optimize floatation and release behavior. These polymers hydrate and swell upon contact with gastric fluid, forming a gel matrix that regulates drug release and prevents rapid dissolution (Singh and Kim, 2000, Patel et al., 2024, Erni and Held, 1987).

This study focuses on the formulation and evaluation of a DMDDS for Empagliflozin, employing a combination of MMMCH and XG as the release-modulating polymers. Five formulations (EMF1 to EMF5) were developed and evaluated for micromeritic properties, weight and drug content uniformity, in vitro floatation, and drug release kinetics. Micromeritic properties such as bulk density, tapped density, Carr's Index, and Hausner Ratio were assessed to ensure efficient processing and capsule filling. Weight and drug content uniformity tests were conducted to confirm consistent drug dosing, while in vitro floatation studies examined the buoyancy and gastric retention potential of the formulations. Drug release kinetics were analyzed using mathematical models (zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell) to understand the release mechanism. This research aims to identify an optimized formulation capable of sustaining drug release over 12 hours while maintaining gastric retention. Such a formulation would address the limitations of conventional drug delivery, improving the therapeutic efficacy and patient compliance for Empagliflozin in managing T2DM. By integrating floating mechanisms and controlled-release technology, this study highlights the potential of DMDDS as a transformative approach in drug delivery for chronic diseases.

2. MATERIAL AND METHODS

All materials and chemicals utilized in this research were procured from trusted and reputable suppliers to ensure high-quality and consistent results. Each material was of analytical grade, meeting the stringent requirements necessary for pharmaceutical research. Empagliflozin, the active pharmaceutical ingredient, was obtained from Avin Pharmaceuticals, a well-known manufacturer recognized for its commitment to quality and reliability. Xanthan Gum and Medium Molecular Mass Chitosan, critical excipients in the formulation, were sourced from Loba Chemical Private Limited, a supplier known for providing premium-grade pharmaceutical raw materials. Lactose, an essential diluent, along with Talc and Magnesium Stearate, used as glidants and lubricants respectively, were purchased from Sigma Aldrich, a global leader in supplying high-grade chemicals for research and development. Barium Sulphate, required for specific analytical or formulation purposes, was also procured from Sigma Aldrich. The size 000 empty hard gelatin capsules, employed as the dosage form container, were supplied by Tisco Traders, located in Karnal, India. This supplier is recognized for its consistent supply of high-quality capsule shells suitable for pharmaceutical applications. In addition to these core materials, any supplementary chemicals or equipment required during the research process were acquired only from commercially validated and certified vendors. These vendors were selected based on their proven track record for supplying reliable and high-quality products. Ensuring the quality and authenticity of all materials used in this research was a fundamental step in maintaining the integrity and reproducibility of the study.

Preparation of Empagliflozin Density-modulated drug delivery system (DMDDS)

The preparation of the Empagliflozin density-modulated drug delivery system (DMDDS) was meticulously carried out following a structured protocol. Initially, all required materials, including Empagliflozin, Xanthan Gum (XG), Medium Molecular Mass Chitosan (MMMCH), Lactose, Talc, and Magnesium Stearate, were accurately weighed based on the predetermined formulation design. To ensure uniformity in particle size, all components were passed through a #40 sieve. The process began by blending Empagliflozin with Lactose in a mortar and pestle for approximately 10 minutes. This step was crucial to ensure the uniform distribution of the active pharmaceutical ingredient (API). Subsequently, Xanthan Gum and MMMCH were incrementally added to the mixture. The geometric dilution method was employed, which involved systematic mixing to achieve a homogenous blend. This mixing process was extended for an additional 15 minutes to ensure thorough integration of all ingredients. Following this, Talc and Magnesium Stearate were incorporated into the powder blend. These excipients were added to enhance the flow properties and lubrication of the mixture, facilitating smooth processing during capsule filling. This final mixing step was carried out for another 5 minutes, ensuring that the blend was consistent and free-flowing. The prepared powder blend was then encapsulated using size 000 hard gelatin capsules. The filling process was executed either manually or with the aid of a capsule filling machine, depending on the scale of production. Each capsule was carefully filled with a precise amount of the powder blend, ensuring uniformity in dosage and adherence to the desired formulation characteristics. After filling, the capsules were sealed to prevent powder leakage. This was achieved by moistening the cap with a small amount of water or a specialized capsule-sealing solution. Once sealed, the capsules were left to dry completely at room temperature

to ensure the integrity of the seal. The dried, sealed capsules were then subjected to further evaluation to assess their physicochemical and performance characteristics, ensuring their suitability for density-modulated drug delivery.

Table 1: Composition of Empagliflozin Density-modulated drug delivery system (DMDDS)

	Formulation Code				
Ingredients (mg)	**EMF 1**	**EMF 2**	**EMF 3**	**EMF 4**	**EMF 5**
Empagliflozin	100	100	100	100	100
Medium Molecular Mass Chitosan (MMMCH)	25	50	75	100	125
XG (Xanthan Gum)	125	100	75	50	25
Lactose	85	85	85	85	85
Talc	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10

Determination of Micromeritic Properties

The determination of micromeritic properties plays a pivotal role in the development of density-modulated drug delivery system (DMDDS) capsules. This step is essential to ensure the efficient processing, handling, and performance of powders, including the active drug (Empagliflozin), polymers, excipients, and their mixtures. Micromeritic properties provide crucial insights into the flowability, compressibility, and packing behavior of these powders, which directly impact the formulation's consistency, production efficiency, and overall quality of the final product.

Understanding the flowability of the powders is particularly critical as poor flow characteristics can lead to significant challenges during manufacturing. These challenges include uneven filling of capsules, weight variations, inconsistent drug content, and production delays due to clogging or sticking in the capsule-filling equipment. Conversely, powders with excellent flow properties ensure smooth operation, allowing the blend to flow seamlessly into the filling machine, thereby enhancing production efficiency and product consistency. The compressibility and packing behavior of the powder blend also play a vital role in ensuring the mechanical integrity of the capsules. Proper compressibility ensures that the powders maintain their stability during processing, preventing segregation or breakage, while uniform packing behavior minimizes air gaps and enhances capsule uniformity. This contributes to maintaining the quality of the product throughout its shelf life, ensuring reliable performance during storage and use. To comprehensively evaluate these characteristics, various micromeritic parameters are measured. These include bulk density, which reflects the powder's ability to settle under its weight; tapped density, which indicates the powder's compressibility after tapping; Carr's index, which assesses the flowability based on the difference between bulk and tapped densities; Hausner ratio, a measure of cohesiveness; and the angle of repose, which provides a visual and quantitative assessment of flowability. These parameters collectively characterize the powder blend and determine its suitability for encapsulation in DMDDS formulations. By thoroughly analyzing micromeritic properties, formulators can optimize the powder blend to ensure consistent capsule filling, precise dosing, and high-quality product outcomes. This evaluation ultimately contributes to the development of an efficient and reliable density-modulated drug delivery system that meets stringent pharmaceutical standards (Mohapatra et al., 2020).

Bulk Density (BD): The determination of micromeritic parameters is a fundamental step in evaluating the properties of powders used in pharmaceutical formulations, particularly for density-modulated drug delivery systems (DMDDS). Bulk density, an important parameter, measures the volume occupied by a powder when loosely packed. To determine bulk density, a known quantity of powder is weighed and transferred into a graduated cylinder. The initial volume of the powder is recorded without applying any external force, and bulk density is calculated using the formula: Bulk Density (g/cm³) = Weight (g) / Volume (cm³). This parameter provides insights into the powder's ability to settle under its weight and forms the baseline for further assessments.

Tapped Density (TD): Tapped density evaluates the powder's packing behavior under mechanical tapping, which mimics the effect of external forces during processing. For this parameter, a known quantity of powder is weighed and placed in a graduated cylinder. The cylinder is tapped a fixed number of times, typically using a tapped density tester, until a constant volume is reached. The final tapped volume is recorded, and tapped density is calculated using the formula: Tapped Density (g/cm³) = Weight (g) / Tapped Volume (cm³). This parameter helps assess the powder's compressibility and packing potential.

Carr's Index (Compressibility Index): Carr's Index, also known as the Compressibility Index, is derived from the difference between tapped density and bulk density, providing a measure of the powder's flowability and compressibility. It is calculated using the formula: Carr's Index (%) = [(Tapped Density - Bulk Density) / Tapped Density] × 100. A lower Carr's Index indicates good flowability, while higher values suggest poor flow properties.

Hausner Ratio: The Hausner Ratio is another important parameter that evaluates the cohesiveness of the powder. It is determined by dividing the tapped density by the bulk density, using the formula: Hausner Ratio = Tapped

Density / Bulk Density. A Hausner Ratio closer to 1 indicates excellent flow properties, while values significantly higher than 1 indicate poor flowability, which may require additional processing aids or adjustments.

Angle of Repose: The angle of repose is a widely used parameter to assess the flowability of powders. This is determined by allowing the powder to flow through a funnel onto a flat surface, forming a cone. The height and radius of the cone are measured, and the angle of repose is calculated using the formula: Angle of Repose (θ) = $\tan^{-1}$ (Height / Radius). Powders with lower angles of repose exhibit good flowability, while those with higher angles may pose challenges during processing due to poor flow characteristics.

Determination of Weight Uniformity

The determination of weight uniformity is a crucial quality control step in the development of capsules, ensuring consistency in dosage and formulation across the batch. This parameter is particularly important as it directly impacts the accuracy of the drug dose delivered to patients, contributing to the overall efficacy and safety of the pharmaceutical product. To evaluate weight uniformity, 20 capsules from each formulation are randomly selected as a representative sample. Each capsule is carefully weighed individually using a high-precision analytical electrical balance. The individual weights are meticulously recorded to allow for further statistical analysis. The average weight, or mean, of the capsules is then calculated by summing the weights of all 20 capsules and dividing the total by the number of capsules (Verma et al., 2017). Once the mean weight is established, the uniformity of the weights is assessed by calculating the percentage coefficient of variation (% CV). This is a widely recognized method for evaluating variability within a dataset. The

% CV is calculated using the formula:

% Coefficient of Variation = (Standard Deviation / Mean Weight) × 100

The standard deviation quantifies the dispersion or variability of the individual capsule weights from the mean, while the % CV expresses this variability as a percentage of the mean weight. A low % CV indicates minimal variation between the capsule weights, signifying excellent weight uniformity. This ensures that each capsule delivers a consistent and accurate dose of the active ingredient. Conversely, a high % CV suggests significant variability in capsule weights, which could lead to dosage inaccuracies and inconsistencies in therapeutic performance. Weight uniformity testing is a critical part of the quality assurance process, as it ensures that manufacturing processes are operating within acceptable limits. Any deviations identified during this assessment may indicate issues in the formulation, blending, or encapsulation processes, requiring corrective actions to maintain product quality. By adhering to stringent weight uniformity standards, manufacturers can uphold the reliability and effectiveness of their drug delivery systems, meeting both regulatory requirements and patient expectations (Verma et al., 2017).

Evaluation of Drug Content Uniformity

The evaluation of drug content uniformity is a critical step in ensuring that the Empagliflozin density-modulated drug delivery system (DMDDS) meets the required standards for consistent drug dosing. This test ensures that each capsule within a batch contains the appropriate amount of the active pharmaceutical ingredient (API), thus guaranteeing uniform therapeutic efficacy and patient safety. To perform this evaluation, 10 capsules from each formulation are randomly selected as a representative sample. Each capsule is carefully emptied into a beaker containing simulated gastric fluid (SGF) with a pH of 1.2, which mimics the acidic environment of the stomach. This fluid serves as the dissolution medium, allowing the complete release of the drug from the formulation. The beaker's contents are stirred continuously using a magnetic stirrer, with the temperature maintained at 37 ± 0.5°C to replicate physiological conditions. The stirring speed is set at 500 rpm, ensuring uniform mixing and facilitating the complete dissolution of the drug. The stirring process is conducted for 1 hour, which is sufficient to ensure that the drug is fully released into the medium. After the stirring period, the solution is filtered using Whatman Grade I filter paper to remove any undissolved particles, excipients, or capsule shell fragments. This step ensures that the resulting solution is clear and suitable for analysis. The filtered solution is then subjected to drug content analysis using a double beam UV-VIS spectrophotometer, an analytical tool known for its accuracy and precision in quantifying drug concentrations. The absorbance of the sample solution is measured at a specific wavelength of 230 nm, which is the characteristic absorption maximum (λmax) for Empagliflozin. A blank solution of simulated gastric fluid is used as the reference to nullify any background absorbance. The absorbance values obtained from the spectrophotometer are compared against a standard calibration curve for Empagliflozin, allowing for the quantification of the drug content in each capsule. The measured drug content for each capsule is then compared to the theoretical drug content specified in the formulation. The results are expressed as a percentage of the theoretical content, ensuring compliance with acceptable pharmacopeial limits (typically 85–115% of the labeled amount). Consistency across the capsules is evaluated to confirm uniform drug distribution within the formulation. This methodical approach ensures that the drug content is uniform across the entire batch of capsules, which is critical for maintaining the intended therapeutic effect. Any deviation identified during the evaluation may indicate issues in the blending, encapsulation, or formulation process, necessitating further investigation and corrective action to uphold the quality of the DMDDS.

In Vitro Drug Release and Kinetic modelling

The in vitro drug release of the Empagliflozin density-modulated drug delivery system (DMDDS) was evaluated using a USP Type II dissolution apparatus in a medium of 0.1N HCl (pH 1.2), simulating gastric fluid. The dissolution study was conducted under controlled conditions, with the apparatus set to maintain a stirring speed of 50 rpm and a temperature of 37 ± 0.5°C to replicate physiological environments. One Empagliflozin capsule was carefully placed into a dissolution vessel containing 900 mL of 0.1N HCl, and the paddle was rotated to ensure uniform exposure of the capsule to the medium. At predefined intervals, 5 mL aliquots of the dissolution medium were withdrawn for analysis, and an equivalent volume of fresh 0.1N HCl was added to the vessel to maintain sink conditions. The withdrawn samples were filtered through Whatman Grade I filter paper to eliminate any undissolved particles or excipients. The filtered samples were diluted as necessary and analyzed for the amount of Empagliflozin released using a double beam UV-VIS spectrophotometer. Absorbance measurements were taken at a wavelength of 230 nm, corresponding to the λmax of Empagliflozin. A blank solution of 0.1N HCl was used as a reference to eliminate any background interference. The amount of drug released at each time point was quantified by comparing the absorbance values to a pre-constructed calibration curve for Empagliflozin. This allowed for the construction of the drug release profile over time. To understand the drug release behavior, the release data were analyzed using various mathematical models to evaluate the release kinetics and mechanisms. These models included zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell equations. Each model provided specific insights into the drug release characteristics.

The zero-order model assumes a constant release rate of the drug, independent of the concentration remaining in the formulation, ideal for achieving steady-state drug delivery. The first-order model, on the other hand, describes a concentration-dependent release, where the rate slows as the drug depletes. The Higuchi model was applied to describe the drug release as a diffusion-controlled process based on Fick's law, particularly useful for systems involving a porous or matrix-based design.

The Korsmeyer-Peppas model further analyzed the release mechanism by calculating the release exponent (n). The value of n is crucial for determining the predominant mechanism of drug release:

- $n \leq 0.5$: Fickian diffusion, indicating that release is predominantly diffusion-controlled.
- $0.5 < n < 1$: Non-Fickian (anomalous) transport, suggesting a combination of diffusion and polymer relaxation.
- $n \geq 1$: Case II transport, dominated by swelling or relaxation of the polymer, often associated with zero-order release.

Additionally, the Hixson-Crowell model examined the release kinetics based on changes in the surface area and particle diameter of the drug as it dissolved. This model provides insights into systems where the dissolution process alters the surface area over time. By fitting the release data to these models, a comprehensive understanding of the release kinetics and mechanisms of the Empagliflozin DMDDS was obtained. This evaluation was instrumental in optimizing the formulation, ensuring consistent drug release, and achieving the desired therapeutic effects. The results from this analysis provide critical data for improving the performance and reliability of the DMDDS formulation (Verma et al., 2017, Nayak et al., 2013).

Characterization by FTIR: Drug-Excipient Interaction study

The Fourier Transform Infrared (FTIR) spectroscopy study was conducted to evaluate potential drug-excipient interactions in the formulation of Empagliflozin density-modulated drug delivery system (DMDDS). FTIR spectra were recorded for pure Empagliflozin, individual excipients (Xanthan Gum, Medium Molecular Mass Chitosan, Lactose, Talc, and Magnesium Stearate), and their physical mixtures. Approximately 2–3 mg of each sample was mixed with dry potassium bromide (KBr) in a 1:100 ratio and compressed into a transparent pellet using a hydraulic press. The pellets were analyzed using an FTIR spectrophotometer in the spectral range of 4000–400 cm^{-1}, with a resolution of 4 cm^{-1}. The spectra were recorded and compared to identify any shifts, disappearance, or appearance of new peaks, which could indicate potential chemical interactions. The analysis focused on the retention of characteristic peaks of Empagliflozin in the physical mixtures, ensuring compatibility between the drug and the excipients used in the formulation.

In Vitro Floatation

The in vitro floatation study is a crucial test for assessing the floating ability of the Empagliflozin density-modulated drug delivery system (DMDDS), which is designed to prolong gastric retention and ensure sustained drug release. The optimized formulation, designated as VC4, was selected for this evaluation. The study aimed to determine the buoyancy and floating behavior of the formulation in simulated gastric fluid. To conduct the test, a single VC4 capsule was immersed in 500 mL of 0.1N HCl (pH 1.2), simulating gastric fluid, contained in a transparent glass beaker. The dissolution medium was maintained at a constant temperature of 37 ± 0.5°C, replicating the physiological conditions of the stomach. The setup was closely monitored to observe the capsule's behavior upon immersion in the medium. The floating ability of the capsule was evaluated by two parameters: the floating lag time and the total floating time. The floating lag time was recorded as the duration required for the capsule to rise to the surface of the medium and achieve buoyancy. This parameter indicates the efficiency of the formulation in initiating floatation, which depends on the density-modulating components within the capsule.

Once the capsule achieved buoyancy, it was continuously monitored for the duration it remained afloat, referred to as the total floating time. This parameter reflects the capsule's ability to maintain its position on the surface of the gastric fluid over time, a critical characteristic for prolonged gastric retention. Throughout the study, the capsule's floating behavior was visually observed and documented to assess its stability in the medium. The capsule's ability to float for an extended period ensures that the drug remains in the stomach for a prolonged time, facilitating controlled and sustained drug release. The floating mechanism is primarily attributed to the inclusion of low-density excipients and gas-generating agents within the formulation, which create buoyancy. This test provided valuable insights into the formulation's suitability for achieving extended gastric retention, a key feature for enhancing therapeutic efficacy. Prolonged gastric residence allows for sustained drug release at the site of absorption, improving bioavailability and ensuring consistent drug levels in the bloodstream over time. By demonstrating efficient floatation behavior, the VC4 formulation confirmed its potential as a robust density-modulated drug delivery system (DMDDS), meeting the desired design criteria for improved patient outcomes (Verma et al., 2017).

Statistical Analysis

The release data from the formulations, along with additional experimental results, were systematically analyzed to ensure reliability and precision. All data were reported as mean values, accompanied by their respective standard deviations (SD), derived from multiple independent determinations. This approach ensured that the results accounted for variability and provided a robust representation of the observed trends. To evaluate the significance of differences between the experimental groups, statistical analysis was carried out using the GraphPad Prism software, a widely recognized tool for advanced statistical and graphical analysis in scientific research. The unpaired "t" test was employed for this purpose, as it is particularly suitable for comparing the means of two independent groups. This test determines whether the differences observed between the groups are statistically significant or merely due to random variation. A significance threshold of $p < 0.05$ was applied, indicating that any differences with a p-value below this level were considered statistically significant. This means that there was less than a 5% probability that the observed differences occurred by chance, thereby providing confidence in the validity of the results. The use of rigorous statistical analysis ensured that the conclusions drawn from the experimental data were both accurate and scientifically reliable. This approach not only validated the findings but also provided critical insights into the performance of the formulations, contributing to a deeper understanding of their behaviour and guiding further optimization efforts.

3. RESULTS AND DISCUSSION

Micromeritic Properties

The micromeritic properties of the different density-modulated drug delivery system (DMDDS) formulations of Empagliflozin, as presented in Table 2, provide valuable insights into their flowability, compressibility, and suitability for capsule formulation. Bulk density (BD) and tapped density (TD) values vary across the formulations, with EMF1 showing the highest bulk and tapped densities (0.539 g/cm³ and 0.589 g/cm³, respectively), indicating better packing and flow characteristics compared to other formulations. Conversely, EMF5 exhibits the lowest bulk and tapped densities (0.397 g/cm³ and 0.498 g/cm³, respectively), suggesting a more loosely packed powder. Carr's Index (CI), a measure of compressibility, increases progressively from EMF1 (8.49%) to EMF5 (20.28%), indicating a decline in flowability and increased cohesiveness in formulations with lower densities. EMF1, with the lowest CI, is indicative of excellent flowability, whereas EMF5, with a CI of 20.28%, falls into the category of poor flow properties. This is further corroborated by the Hausner Ratio (HR), which increases from 1.09 in EMF1 to 1.25 in EMF5, reflecting reduced ease of flow as the HR value moves further from the ideal range (<1.2). The angle of repose (AOR), which directly assesses the flowability of powders, also follows a similar trend, increasing from 15.869° in EMF1 to 22.876° in EMF5. A lower AOR indicates better flowability, suggesting that EMF1 has superior handling properties compared to the other formulations, while EMF5 exhibits the poorest flow characteristics. Overall, the data reveal that EMF1 demonstrates the most favorable micromeritic properties, including low CI, HR, and AOR, making it the most suitable candidate for efficient processing and capsule filling. In contrast, EMF5, with higher CI, HR, and AOR values, may pose challenges during manufacturing due to poor flowability and cohesiveness, requiring additional processing aids or modifications to improve its performance. These findings highlight the importance of optimizing micromeritic properties to ensure consistent drug delivery and manufacturing efficiency in the DMDDS formulations of Empagliflozin.

Table 2: Micromeritic Properties of Different Density-modulated drug delivery system (DMDDS) of Empagliflozin

Formulation Code	Bulk Density (BD) (g/cm³)	Tapped Density (TD) (g/cm³)	Carr's Index (CI) (%)	Hausner Ratio (HR)	Angle of Repose (AOR) (°)

EMF1	0.539	0.589	8.49	1.09	15.869
EMF2	0.481	0.548	12.23	1.14	18.784
EMF3	0.452	0.501	9.78	1.11	19.887
EMF4	0.427	0.503	15.11	1.18	21.692
EMF5	0.397	0.498	20.28	1.25	22.876

Note: Data are presented as mean values, n = 3. All formulations are part of the Density-modulated drug delivery system (DMDDS) for Empagliflozin.

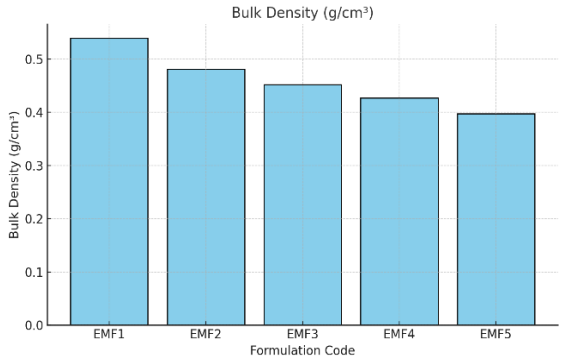

Figure 1a. Bulk Density (BD) (g/cm³) and Tapped Density (TD) (g/cm³)

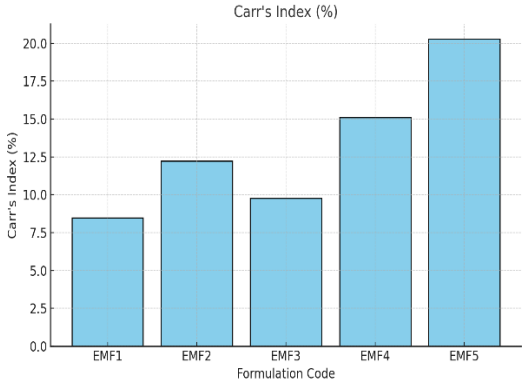

Figure 1b. Tapped Density (TD) (g/cm³)

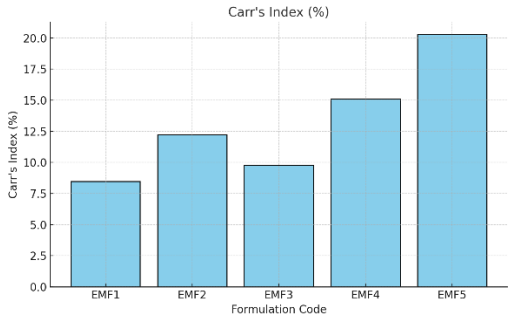

Figure 2. Carr's Index

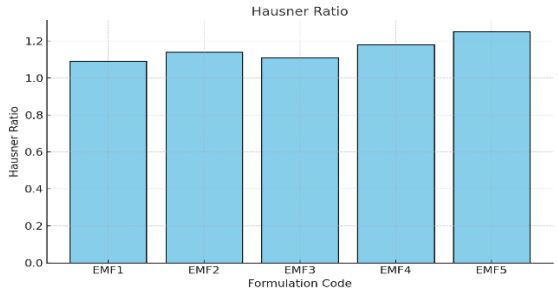

Figure 3. Hausner Ratio of Different Formulations

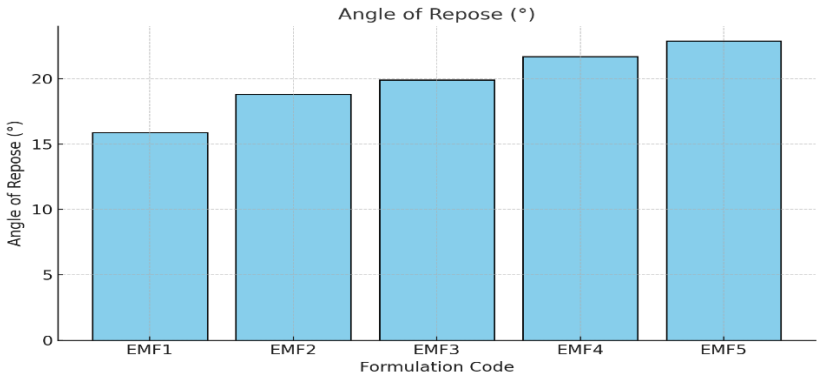

Figure 4. Angle Of Repose of Different Formulations

Weight Uniformity Test and Coefficient of Variation (%)

The results of the weight uniformity test and coefficient of variation (CV) for different density-modulated drug delivery system (DMDDS) formulations of Empagliflozin, as presented in Table 3, indicate the consistency and precision of the encapsulation process.

Weight Uniformity

The mean weights for all formulations (EMF1 to EMF5) fall within a close range, indicating that the manufacturing process was consistent in terms of the amount of powder blend encapsulated in each capsule. The lowest mean weight was observed in EMF3 (842.77 mg), while the highest was in EMF5 (857.84 mg). The relatively small variations in mean weight across the formulations highlight a well-controlled encapsulation

process, essential for ensuring uniform drug dosing. The standard deviation (SD) values for weight uniformity, ranging from ±13.75 (EMF5) to ±17.56 (EMF2), reflect slight variability in the weights. However, these variations are within acceptable limits, indicating the process consistency for producing capsules of similar weights.
The coefficient of variation (CV), which provides a normalized measure of variability, is below 2% for all formulations, indicating excellent weight uniformity. EMF2 exhibited the lowest CV (1.24%), suggesting the highest consistency in weight distribution. On the other hand, EMF4 showed the highest CV (1.91%), indicating slightly more variability compared to the other formulations, but still within acceptable pharmaceutical limits. The weight uniformity and CV results demonstrate that all formulations meet the regulatory requirements for uniformity of dosage forms. The low CV values across formulations ensure consistent drug dosing, which is critical for maintaining therapeutic efficacy and patient safety. Although all formulations showed acceptable uniformity, EMF2 demonstrated the most precise weight consistency, making it slightly superior in terms of encapsulation accuracy. Variations among the formulations might be attributed to differences in powder flowability, bulk density, or slight inconsistencies during the filling process. In conclusion, the weight uniformity and coefficient of variation results confirm the reliability of the manufacturing process for these DMDDS formulations of Empagliflozin. The data ensures that each capsule contains a consistent amount of drug, contributing to the overall quality and therapeutic performance of the formulations.

Table 3: Weight Uniformity Test and Coefficient of Variation (%) of Different Density-modulated drug delivery system (DMDDS) of Empagliflozin

Formulation Code	Weight Uniformity (Mean± SD) *	Coefficient of Variation (%)
EMF1	854.46 ± 14.35	1.28
EMF2	855.59 ± 17.56	1.24
EMF3	842.77 ± 15.90	1.88
EMF4	846.91 ± 16.83	1.91
EMF5	857.84 ± 13.75	1.89

Drug Content Uniformity
The drug content uniformity results for the density-modulated drug delivery system (DMDDS) formulations of Empagliflozin, as presented in Table 4, provide insights into the consistency and accuracy of drug distribution across capsules. The mean drug content for all formulations is close to the theoretical value of 100%, indicating excellent control over the encapsulation process. The drug content ranges from 97.88% (EMF2) to 99.98% (EMF1), reflecting minimal variability in drug loading. The standard deviation values across the formulations are relatively low, ranging from ±1.58% (EMF3) to ±1.82% (EMF4). This indicates that the drug is uniformly distributed in the powder blend and encapsulated consistently, ensuring batch-to-batch reliability. All formulations fall within the acceptable pharmacopeial limits for drug content uniformity (85–115% of the labeled amount), confirming the accuracy and precision of the manufacturing process. The slightly lower mean drug content in EMF2 (97.88 ± 1.69%) still meets the regulatory criteria, but it is marginally lower compared to other formulations. EMF1 and EMF5, with mean drug contents of 99.98 ± 1.79% and 99.89 ± 1.77% respectively, show the highest accuracy and consistency, reflecting superior drug loading efficiency. The low variability (as indicated by the SD values) across all formulations ensures that each capsule contains the intended amount of drug, contributing to consistent therapeutic performance. The results indicate that the formulations are reliable, and the encapsulation process is robust, minimizing the risk of sub-therapeutic or supra-therapeutic dosing. The drug content uniformity results demonstrate that all formulations meet stringent quality control standards, ensuring accurate dosing and consistent drug release profiles. Among the formulations, EMF1 and EMF5 exhibit the highest uniformity, while EMF2, though slightly lower, remains within acceptable limits. These findings validate the suitability of the manufacturing process and confirm the reliability of the density-modulated drug delivery system for Empagliflozin.

Table 4: Result of Drug Content Uniformity for All Formulations of Empagliflozin

Formulation Code	Drug Content Uniformity (%)
EMF1	99.98 ± 1.79
EMF2	97.88 ± 1.69
EMF3	99.63 ± 1.58
EMF4	98.99 ± 1.82
EMF5	99.89 ± 1.77

Data are given as mean ± SD, n = 3.

Drug excipients compatibility study by FTIR
The Fourier Transform Infrared (FTIR) spectroscopy analysis was performed to evaluate potential drug-excipient interactions in the Empagliflozin density-modulated drug delivery system (DMDDS). The FTIR spectra of pure

Empagliflozin, individual excipients (Xanthan Gum, Medium Molecular Mass Chitosan, Lactose, Talc, and Magnesium Stearate), and their physical mixtures were analyzed and compared. The spectrum of pure Empagliflozin exhibited characteristic peaks corresponding to its functional groups, including a strong absorption band at ~3350 cm^{-1} for O-H stretching, peaks at ~1680 cm^{-1} and ~1605 cm^{-1} for C=O stretching and aromatic C=C stretching, and peaks at ~1215 cm^{-1} and ~1050 cm^{-1} for C-O-C stretching. The spectra of the physical mixtures showed these characteristic peaks without any significant shifts, alterations, or the emergence of new peaks, indicating the absence of chemical interactions between Empagliflozin and the excipients. This compatibility study confirms that the excipients do not chemically react with Empagliflozin during formulation, ensuring the stability of the drug and the integrity of the DMDDS. These results validate the suitability of the selected excipients for use in the formulation, supporting the development of a stable and effective drug delivery system

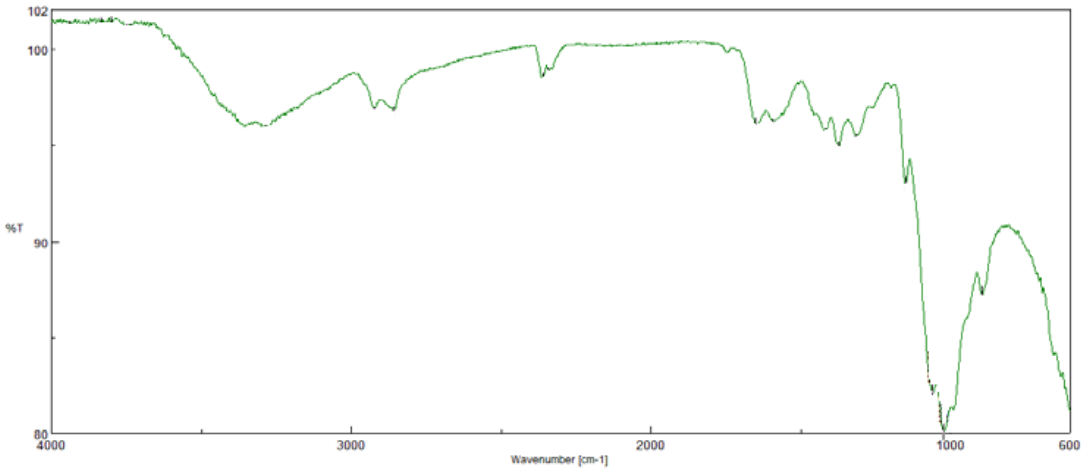

Figure 5. Compatibility of drug excipients employing FTIR spectra of Empagliflozin and excipients showing significant compatibility among ingredients and no significant interaction

In vitro drug release study

The cumulative drug release data for Empagliflozin Density-modulated drug delivery system (DMDDS) formulations (EMF1 to EMF5) provide insights into their release profiles over 12 hours. The release patterns highlight differences in drug release rates, which are essential for evaluating the formulations' suitability for sustained-release applications. In the initial hours, all formulations exhibit a gradual increase in drug release, with EMF1 consistently showing the highest cumulative release at each time point. At the 1-hour mark, EMF1 releases 18.84% of the drug, compared to lower releases for EMF4 (15.89%) and EMF3 (15.98%), suggesting that EMF1 achieves faster initial release. By the 4-hour mark, EMF1 maintains its lead with 36.98% release, closely followed by EMF2 (37.91%), while EMF4 lags slightly behind at 35.77%. This trend indicates variations in polymer composition or density among formulations, influencing early-stage release kinetics. Between 5 to 8 hours, the drug release continues at a steady pace across formulations. EMF1 and EMF2 demonstrate comparable releases, reaching 47.77% and 45.87%, respectively, at 5 hours. By 8 hours, EMF1 achieves the highest release (65.67%), while EMF4 shows the lowest (62.55%). The differences suggest that EMF1 may have a more optimized balance of release-modulating excipients, facilitating sustained but faster drug release during this phase. In the final hours, all formulations approach complete drug release, with notable differences in their release rates. EMF1 maintains its superior release profile, achieving 97.89% at 12 hours, while EMF5 and EMF4 show comparatively lower releases of 91.32% and 92.19%, respectively. EMF2 and EMF3 also display high releases, at 96.11% and 94.21%, respectively, indicating their efficiency in approaching complete drug release within the desired timeframe. The standard deviation values across all time points remain relatively low for all formulations, indicating consistency in the drug release data. This consistency reflects the robustness of the formulation process and the uniformity of drug dispersion within the DMDDS. The data reveal that EMF1 exhibits the most rapid and consistent release profile throughout the 12-hour period, making it the most effective formulation for ensuring sustained release. EMF2 and EMF3 also demonstrate efficient release but lag slightly behind EMF1, particularly in the initial and final stages. EMF4 and EMF5 show relatively slower releases, which may be advantageous for applications requiring extended retention with delayed drug action. The release profiles highlight the influence of formulation composition and density on drug release behavior. EMF1 emerges as the most suitable candidate for achieving the desired sustained-release profile, ensuring near-complete drug release within 12 hours while maintaining consistency across replicates. This data is crucial for optimizing the DMDDS formulations to meet therapeutic goals and improve patient compliance.

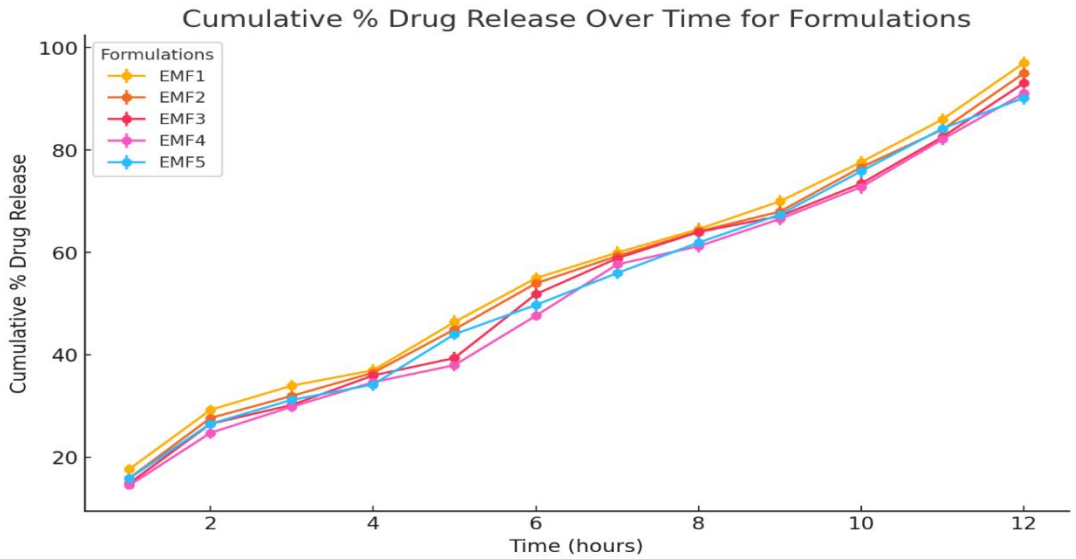

Figure 6. *In vitro* release of Empagliflozin from the DMDDS.

In Vitro Release Kinetics Modelling

The in vitro release kinetics data for the formulations of Empagliflozin provide valuable insights into the drug release mechanisms and behavior of the density-modulated drug delivery systems (DMDDS). The analysis of the regression coefficients (R^2 values) across different kinetic models and the release exponent (n) from the Korsmeyer-Peppas model allows for a detailed understanding of the release characteristics.

Zero-Order and First-Order Models

The R^2 values for the zero-order model range from 0.899 (EMF5) to 0.945 (EMF1), indicating a good fit, particularly for EMF1, which shows the highest R^2 value. This suggests that EMF1 predominantly follows a zero-order release pattern, where the drug is released at a constant rate, ideal for sustained drug delivery. In contrast, the first-order model, with R^2 values ranging from 0.893 to 0.911, shows a slightly better fit for EMF5, indicating that some formulations may exhibit concentration-dependent release behavior, where the release rate decreases as the drug content diminishes.

Higuchi Model

The Higuchi model consistently demonstrates the highest R^2 values across all formulations, ranging from 0.954 (EMF4) to 0.967 (EMF1). This strong fit indicates that drug release is primarily governed by diffusion mechanisms. The porous matrix or polymer system in the DMDDS facilitates drug release as per Fick's law, making this model the most representative for the tested formulations.

Korsmeyer-Peppas Model

The R^2 values for the Korsmeyer-Peppas model are comparatively lower, ranging from 0.799 (EMF5) to 0.852 (EMF1). The release exponent (n) values for all formulations fall between 0.741 and 0.781, suggesting a non-Fickian (anomalous) transport mechanism. This indicates that the drug release is influenced by a combination of diffusion and polymer relaxation or erosion. EMF1, with the highest n value (0.781), exhibits a stronger contribution from polymer relaxation compared to other formulations. The R^2 values for the Hixson-Crowell model are the lowest across all formulations, ranging from 0.711 (EMF5) to 0.778 (EMF1). This model accounts for changes in surface area and particle size during drug dissolution. The relatively low fit suggests that changes in the geometric surface area of the formulations have minimal influence on the drug release profile, with diffusion being the dominant mechanism. The kinetics data indicate that the drug release from all formulations is primarily diffusion-controlled, as evidenced by the high R^2 values for the Higuchi model. However, the Korsmeyer-Peppas model also reveals the involvement of polymer relaxation in the release process, indicating non-Fickian behavior. Among the formulations, EMF1 shows the best fit across the zero-order, Higuchi, and Korsmeyer-Peppas models, highlighting its superior performance in achieving sustained and consistent drug release. Formulations EMF4 and EMF5, with slightly lower R^2 values across all models, may exhibit less efficient release profiles, potentially requiring optimization to enhance performance. The data emphasize the need for a balanced formulation design that supports diffusion-driven release while leveraging polymer characteristics for controlled release. EMF1 emerges as the most optimal formulation based on its superior fit to the zero-order, Higuchi, and Korsmeyer-Peppas models, ensuring a sustained and controlled drug release profile. The non-Fickian release mechanism observed in all formulations underscores the combined roles of diffusion and polymer dynamics in the DMDDS system, contributing to its prolonged therapeutic efficacy. These findings provide critical guidance for further refinement and application of Empagliflozin DMDDS formulations.

Table 5: In Vitro Release Kinetics Data of All Formulations of Empagliflozin

Formulation Code	R^2 Value (Zero Order)	R^2 Value (First Order)	R^2 Value (Higuchi)	R^2 Value (Korsmeyer-Peppas)	R^2 Value (Hixson-Crowell)	n value (Korsmeyer-Peppas)
EMF1	0.945	0.893	0.967	0.852	0.778	0.781
EMF2	0.932	0.893	0.966	0.836	0.759	0.765
EMF3	0.925	0.909	0.962	0.827	0.729	0.761
EMF4	0.912	0.910	0.954	0.817	0.719	0.745
EMF5	0.899	0.911	0.956	0.799	0.711	0.741

***In vitro* floatation**

The in vitro floatation studies of the Empagliflozin Density-modulated drug delivery system (DMDDS) demonstrated exceptional buoyancy, with formulation EMF1 remaining afloat in an acidic medium (pH 1.2) for over 12 hours. Notably, EMF1 exhibited no floating lag time, indicating immediate buoyancy upon immersion. This enhanced flotation behavior is attributed to the synergistic effects of the two hydrophilic polymers, Medium Molecular Mass Chitosan (MMMCH) and Xanthan Gum (XG), used in the formulation. Upon exposure to the acidic medium, MMMCH and XG rapidly hydrated and swelled, forming a robust colloidal hydrogel around the capsule. This hydrogel facilitated the creation of a polymeric drug matrix, which significantly increased the medium's viscosity. The increase in viscosity not only reduced the capsule's density relative to the medium but also provided the structural integrity required for prolonged buoyancy. The swollen matrix acted as a barrier, preventing the ingress of gastric fluids into the capsule's core while allowing the gradual release of the drug over time. The floating mechanism of EMF1 is a hallmark of an effective hydrodynamically balanced system, essential for sustained drug delivery. The prolonged gastric retention afforded by the extended buoyancy ensures that the drug remains in the stomach for a longer duration, maximizing its absorption and therapeutic efficacy. Additionally, the integrity of the matrix over 12 hours supports controlled and sustained drug release, minimizing dose fluctuations and enhancing patient compliance. These results highlight the critical role of MMMCH and XG in optimizing the formulation's floatation properties. Their hydrophilic nature, rapid hydration, and gel-forming ability contribute to the development of a reliable and efficient DMDDS for Empagliflozin. This optimized system ensures that the drug is effectively delivered over an extended period, making it particularly beneficial for conditions requiring sustained therapeutic levels. The absence of floating lag time and the extended buoyancy period position EMF1 as a superior candidate for achieving prolonged gastric retention and improved bioavailability (Verma et al., 2017, Nayak et al., 2013, Verma et al., 2012).

4. CONCLUSION

This study successfully developed and evaluated a density-modulated drug delivery system (DMDDS) for Empagliflozin, targeting sustained drug release and prolonged gastric retention. Among the tested formulations, EMF1 emerged as the most promising due to its superior performance across all evaluation parameters. It exhibited excellent flow properties (Carr's Index: 8.49%, Hausner Ratio: 1.09), ensuring efficient manufacturing and capsule filling. EMF1 also demonstrated consistent weight and drug content uniformity (99.98 ± 1.79%), meeting stringent pharmaceutical standards. The in vitro floatation study confirmed EMF1's immediate and sustained buoyancy for over 12 hours, facilitated by the hydration and gel-forming properties of MMMCH and Xanthan Gum. The drug release profile of EMF1 followed zero-order and Higuchi models, indicating diffusion-driven controlled release. The Korsmeyer-Peppas analysis (n = 0.781) suggested a combination of diffusion and polymer relaxation mechanisms, ensuring consistent therapeutic drug levels. These findings validate EMF1 as an effective DMDDS formulation, addressing key challenges in drug delivery for gastric-retentive systems. Its prolonged gastric retention and controlled drug release make it a valuable approach for enhancing the therapeutic efficacy and bioavailability of Empagliflozin, ultimately improving patient compliance and treatment outcomes in Type 2 Diabetes Mellitus.

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