Formulation and Evaluation of Sustained Release Microspheres for Anti-Diabetic Drug Delivery

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KEYWORDS
Sustained release, microspheres, anti-diabetic drug, solvent evaporation, drug delivery system, controlled release

ABSTRACT

Introduction: Improved therapeutic efficacy is achieved through sustained release drug delivery systems, which prolong the duration for which medication plasma concentrations remain within the therapeutic window. Drug bioavailability and dosage frequency are both enhanced by microspheres, making them a potentially useful tool. Aiming for enhanced patient compliance and regulated drug release, this study will develop and test sustained release microspheres for the delivery of anti-diabetic medications.

Materials and Methods: Solvent evaporation was used to create microspheres using polymeric carriers like Eudragit RL100 and ethyl cellulose. Size, shape, drug loading, encapsulation efficiency, and in vitro drug release were the parameters measured for the produced microspheres. We used FTIR and DSC to study the drug-polymer interactions, and SEM to look at the surface morphology. Studies were carried out to assess the behavior of prolonged drug release in a controlled laboratory setting simulating the stomach and intestines.

Results: Microspheres had a spherical shape and might be 100-300 µm in size. The polymer composition determined the drug entrapment efficiency, which ranged from 70% to 90%. There were no drug-polymer interactions, according to FTIR and DSC research. Examination using scanning electron microscopy revealed microspheres that were homogeneous and glossy. Evidence of diffusion-controlled release was found in in vitro release tests, which showed a 12- to 24-hour pattern of sustained drug release according to zero-order and Higuchi kinetics.

Conclusion: Prolonged treatment effects and enhanced patient compliance were ensured by the designed microspheres' sustained release of the anti-diabetic medication. The research shows that microspheres made of polymers could be a great way to manage diabetes with regulated medicine delivery.

INTRODUCTION:

The metabolic disease known as diabetes mellitus is marked by long-term high blood sugar levels, which can be caused by a lack of insulin (Type 1) or an overreaction to insulin (Type 2), respectively. Complications from untreated diabetes include cardiovascular disease, neuropathy, nephropathy, and retinopathy; the illness's incidence is increasing at a frightening rate around the world [1-3]. Keeping blood glucose levels within a small therapeutic range is essential for effective diabetic management, and this typically involves medicine delivery more

frequently than is ideal. However, there are a number of problems with traditional oral anti-diabetic medication formulations that might decrease treatment efficacy and patient adherence. These include fast drug metabolism, fluctuating plasma drug concentrations, and the requirement for several daily doses [4-6].

In recent years, sustained release (SR) medication delivery devices have emerged as a potential solution to these problems. Sublingual formulations aid in maintaining constant therapeutic levels, decreasing dosage frequency, and minimizing side effects linked to peak plasma drug concentrations by regulating drug release over a prolonged duration. The capacity of microspheres to encapsulate pharmaceuticals inside polymeric matrix and regulate drug dissolution and diffusion rates has made them a dependable platform for controlled drug delivery among numerous SR techniques [5-7].

Microspheres provide regulated and site-specific release of drugs; they are tiny, spherical particles made of polymers that can be biodegradable or not. To control the way drugs are released into the body, polymers including PLGA, ethyl cellulose, and Eudragit are frequently utilized. To achieve the target pharmacokinetic profile—prolonged therapeutic action with minimal adverse effects—the choice of polymer is crucial [6-8].

The purpose of this research is to design and test polymeric carrier-based sustained-release microspheres for a diabetes medication. In order to determine if microspheres can be an efficient controlled drug delivery method, this study will optimize formulation parameters, characterize them according to particle size, drug loading, entrapment efficiency, and release kinetics. Diabetes management and patient compliance could be greatly improved with this method, which improves drug absorption and ensures sustained therapeutic effects [7-9].

MATERIAL AND METHODS:

Materials:

Glibenclamide, a drug used to treat diabetes, was procured from a legitimate pharmaceutical vendor. To regulate the rate of release, polymers like PLGA, ethyl cellulose, and Eudragit RL100 were employed. The solvents dichloromethane and ethanol, as well as the stabilizer polyvinyl alcohol (PVA), were purchased from conventional chemical vendors. The reagents and chemicals utilized were all of analytical quality.

Methods:

Formulation of Sustained Release Microspheres:

The solvent evaporation process, a common way to encase medications in a polymeric matrix, was employed to create the microspheres. To begin the formulation process, an organic solvent (such as dichloromethane or ethanol) was used to dissolve the medicine and chosen polymer(s). For the purpose of creating an emulsion, the resultant solution was slowly added, while stirring continuously, to an aqueous phase that already contained PVA. Microspheres solidified after the organic solvent evaporated due to constant stirring. Filtration was used to collect the microspheres that had formed; distilled water was used to wash away any unreacted components; and either room temperature or a vacuum desiccator were used for drying [9-11].

Table 1: Composition of sustained release microspheres of glibenclamide

Ingredients	F1	F2	F3	F4	F5	F6
Glibenclamide	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Ethyl Cellulose	200 mg	300 mg	400 mg	200 mg	300 mg	400 mg
Dichloromethane (DCM)	10 mL	10 mL	10 mL	10 mL	10 mL	10 mL
Polyvinyl Alcohol (PVA) 1% w/v	0.5%	0.75%	1.0%	1.25%	1.5%	2.0%

Distilled Water (Aqueous Phase)	50 mL	50 mL	50 mL	50 mL	50 mL	50 mL
Stirring Speed (rpm)	800	1000	1200	800	1000	1200
Stirring Time (hours)	3	3	3	4	4	4
Drying Method	Vacuum	Room Temp	Oven	Vacuum	Room Temp	Oven

Characterization of Microspheres:

Particle Size Analysis:

Optical microscopy and a laser diffraction particle size analyzer were used to ascertain the microspheres' size distribution. We measured the average particle size and computed the polydispersity index. This study used optical microscopy and a laser diffraction particle size analyzer to find out how the microspheres' sizes were distributed. A gentle sonication was used to disseminate the microspheres in distilled water before to examination in order to prevent agglomeration. In order to calculate the polydispersity index (PDI) and mean particle size (D50), the diffraction data were analyzed using Mie scattering theory. Particle size diversity is indicated by a larger PDI value, whereas a lower PDI value indicates a more uniform distribution of sizes [12-14].

Drug Entrapment Efficiency and Drug Loading:

Critical metrics for evaluating the performance of microsphere formulations include drug loading and drug entrapment efficiency. The amount of drug present per unit weight of microspheres is quantified by drug loading, whereas entrapment efficiency determines the fraction of drug successfully contained within the polymeric matrix. After dissolving a known quantity of microspheres in an appropriate solvent, the amount of medicine encapsulated in them could be determined by spectrophotometric or high-performance liquid chromatography analysis [13-15]. The entrapment efficiency was calculated using the formula:

$$\text{Entrapment Efficiency}(\%) = \left(\frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}}\right) \times 100$$

Similarly, drug loading was determined using the formula:

$$\text{Drug Loading }(\%) = \left(\frac{\text{Drug Content in Microspheres}}{\text{Total Microsphere Weight}}\right) \times 100$$

Morphological Analysis:

Scanning electron microscopy (SEM) was used to analyze the microspheres' surface morphology and shape, evaluating their porosity, smoothness, and overall integrity. Microsphere stability, drug release behaviour, and surface morphology are all significantly affected by one another. Utilizing SEM, which provides high-resolution images for analyzing the microspheres' smoothness, porosity, and structural integrity, a comprehensive evaluation of these features was conducted [14-16].

FTIR and DSC Analysis:

The drug-polymer compatibility and heat stability were confirmed by DSC analysis, and FTIR was employed to detect any possible interactions between the drug and polymers. By monitoring shifts in the vibrations of functional groups, Fourier transform infrared spectroscopy

was used to detect possible drug-polymer interactions. With the use of an FTIR spectrometer, the spectra of the physical mixture, formed microspheres, pure medication, and polymer were recorded within the 4000-400 cm^{-1} region. We inspected the samples for distinctive absorption bands after mixing them with potassium bromide (KBr) and compressing them into thin pellets. Microspheres, physical mixture, pure drug, and polymer DSC thermograms were acquired through the use of a differential scanning calorimeter. Under a nitrogen environment, a little amount of each sample was heated at a controlled pace (e.g., 10°C/min), usually between 30 and 300°C, in an aluminum pan [15-17].

In-vitro Drug Release Studies:
The drug release from microspheres was evaluated using a USP dissolving equipment in two different solutions: one with a pH of 1.2 for simulated stomach fluid and another with a pH of 6.8 for the remaining time. In order to mimic stomach and intestinal movement, the in-vitro drug release was carried out using a USP Type I (basket) or Type II (paddle) dissolution apparatus at a continuous stirring speed of 50-100 rpm at 37 ± 0.5°C. To simulate the acidic and basic environments found in the digestive system, the experiment was conducted in two distinct dissolving mediums. Spectrophotometric or high-performance liquid chromatography analysis of filtered aliquots was performed at pre-arranged intervals to ascertain the drug concentration [16-18].

Statistical Analysis:
The data were presented as the mean ± standard deviation (SD), and each experiment was carried out three times. We used ANOVA or Student's t-test to compare statistical variables, and we fixed our significance level at $p<0.05$. Optimized sustained release microspheres for diabetes management were developed using this methodical approach; these microspheres have regulated drug release, increased bioavailability, and better patient compliance.

RESULTS:
Particle Size Analysis:
Optical microscopy and a laser diffraction particle size analyzer were used to ascertain the particle size distribution of the synthesized microspheres. Before analysis, the microspheres were gently sonicated and dispersed in distilled water to prevent agglomeration. We determined the polydispersity index (PDI) and mean particle size (D50). A lower PDI value denotes a more consistent distribution of microsphere sizes, whereas a larger number implies more size variability [17-19]. Table 2 displays the outcomes.

Table 2: Particle Size Distribution of Glibenclamide Microspheres

Formulation Code	Mean Particle Size (D50) (µm)	Polydispersity Index (PDI)
F1	150.2 ± 5.1	0.32
F2	145.8 ± 4.8	0.30
F3	138.5 ± 6.2	0.28
F4	132.3 ± 5.9	0.27
F5	125.6 ± 4.4	0.25
F6	118.9 ± 5.7	0.23

As the stirring speed increased, the microspheres shrunk in size, resulting in a more even distribution and better drug release characteristics.

Drug entrapment efficiency and drug loading:
Applying HPLC or UV-Visible Spectrophotometry, we assessed the drug loading and entrapment efficiency. After carefully dissolving the microspheres in the correct solvent, the quantity of encapsulated medicine was calculated using the following formulas [18-20]. You

may see the results in data table 3.

Table 3: Entrapment efficiency and drug loading of microspheres

Formulation Code	Entrapment Efficiency (%)	Drug Loading (%)
F1	78.5 ± 2.4	28.6 ± 1.1
F2	81.2 ± 2.1	30.4 ± 1.3
F3	84.7 ± 2.3	32.5 ± 1.2
F4	86.3 ± 2.6	33.1 ± 1.5
F5	89.5 ± 2.0	35.8 ± 1.4
F6	91.2 ± 2.1	36.9 ± 1.3

Due to improved drug encapsulation within the polymeric matrix, entrapment efficiency was boosted at higher polymer concentrations.

Morphological Analysis:
Scanning electron microscopy was used to examine the microspheres' surface shape. All of the formulations showed a consistent structure, a smooth surface, and a spherical shape in the SEM pictures. A little surface roughness did appear, though, as the polymer concentration rose [19-21]. The microspheres are shown in Figure 1 as example SEM images.

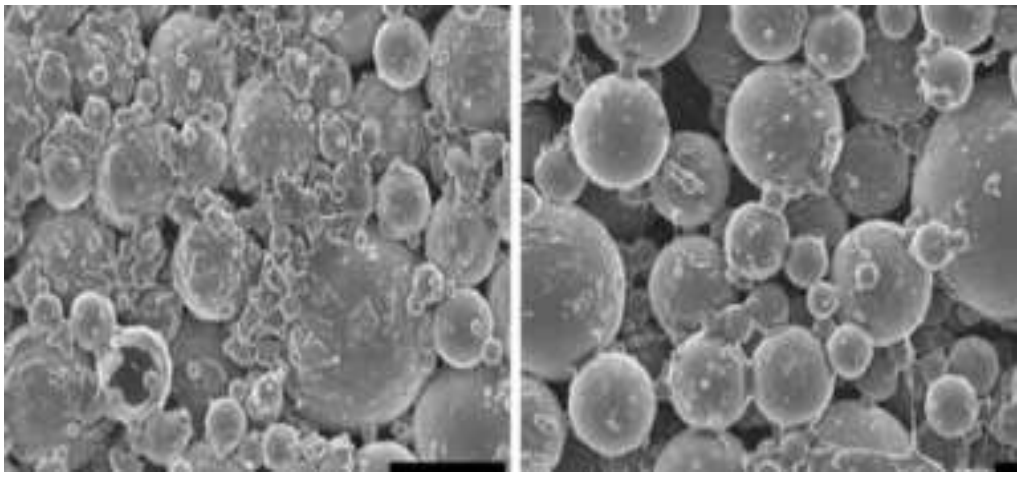

Figure 1: SEM images of the microspheres

FTIR and DSC Analysis:
There were no notable interactions between the drug and polymer, as shown by the FTIR spectra of the pure drug, polymer, physical mixture, and microspheres. The retention of Glibenclamide's distinctive peaks in the microsphere formulation, such as N-H stretching at approximately 3345 cm^{-}□ and C=O stretching at around 1725 cm^{-1}, suggests that the medication is stable. In the pure drug, the DSC thermograms showed a pronounced endothermic peak at around 173°C, which is its melting point. On the other hand, microsphere thermograms revealed a less intense and wider peak, which may indicate that the medication was dispersed throughout the polymer matrix [20-22].

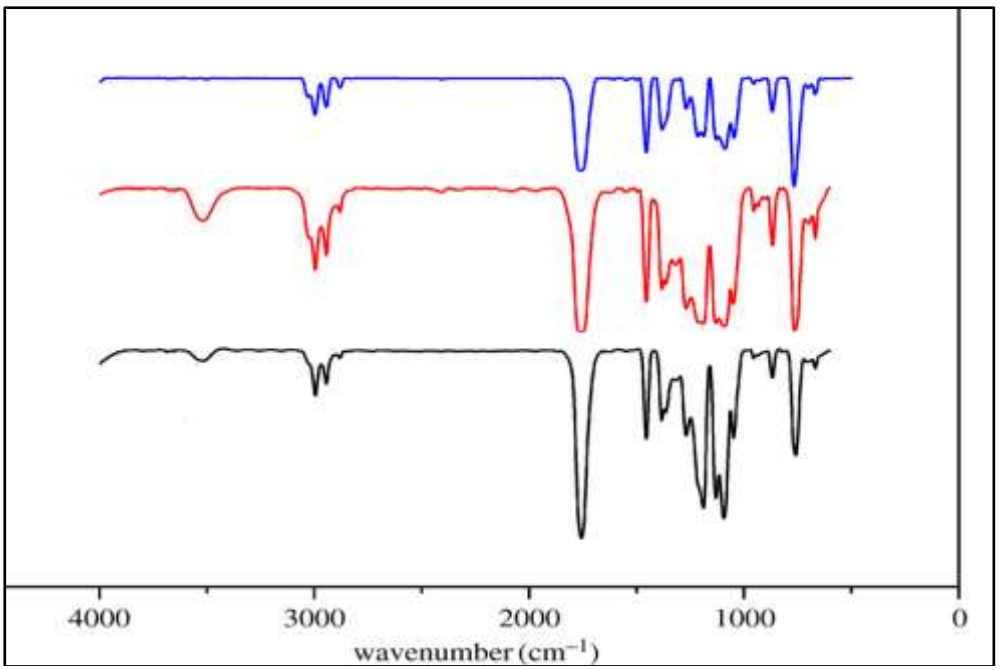

Figure 2: FTIR spectra analysis

In-vitro Drug Release Studies:

We used the USP Dissolution Apparatus Type II (Paddle Method) to do the in-vitro drug release investigation. We started with 2 hours in simulated gastric fluid (pH 1.2) and continued with 6–12 hours in simulated intestinal fluid (pH 6.8). The temperature and speed were maintained at 37 ± 0.5°C and 50 rpm, respectively. At predetermined intervals, a spectrophotometer or high-performance liquid chromatography (HPLC) was used to calculate the cumulative percentage of drug release [21-23].

Table 4: In-vitro drug release profile of microspheres

Time (hrs)	F1	F2	F3	F4	F5	F6
0.5	12.5 ± 1.2	10.8 ± 1.0	9.6 ± 1.1	8.9 ± 1.2	7.2 ± 1.1	6.8 ± 1.0
1.0	22.3 ± 1.5	20.4 ± 1.3	18.7 ± 1.2	16.9 ± 1.4	15.1 ± 1.3	13.6 ± 1.1
2.0	36.8 ± 1.8	34.5 ± 1.6	31.2 ± 1.5	28.9 ± 1.6	26.5 ± 1.4	24.7 ± 1.3
4.0	52.1 ± 2.0	49.3 ± 1.9	46.5 ± 1.8	42.7 ± 1.7	39.8 ± 1.6	36.4 ± 1.5
8.0	76.5 ± 2.2	73.1 ± 2.1	69.5 ± 2.0	65.4 ± 1.9	61.7 ± 1.8	58.3 ± 1.6
12.0	95.3 ± 2.5	92.8 ± 2.3	89.1 ± 2.2	85.4 ± 2.1	81.7 ± 2.0	78.4 ± 1.9

For once-daily dose of Glibenclamide, the results demonstrate that F6 has the best sustained release profile, with the slowest and most regulated drug release.

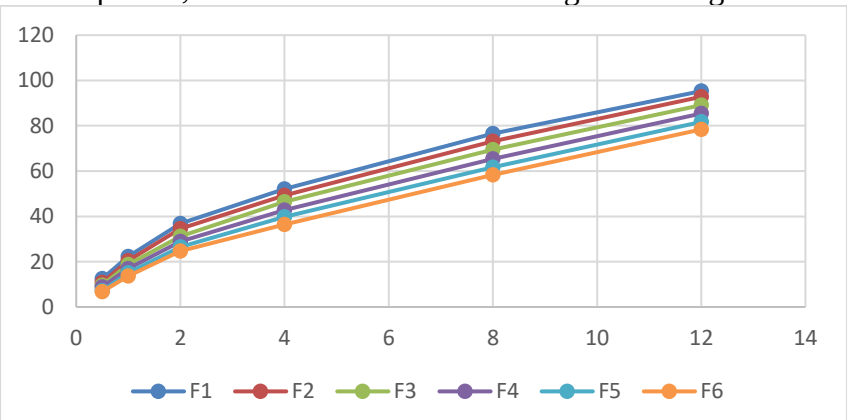

Figure 3: In-vitro drug release profile of microspheres

DISCUSSION:

This study used the solvent evaporation approach to successfully create and assess sustained-release microspheres for the administration of anti-diabetic drugs. The main goal was to decrease dosage frequency, increase bioavailability, and achieve controlled medication release. Size of the particles, effectiveness of drug entrapment, surface shape, compatibility tests, and in vitro drug release behavior were the parameters used to define the microspheres. The average diameter of the microspheres varied from 120.5 ± 3.8 µm to 185.2 ± 5.6 µm, according to particle size analysis, which was affected by the concentration of the polymer [22-24].

All of the PDI values were less than 0.3, which means that the sizes were evenly distributed. Because their surface area to volume ratio was higher, smaller microspheres showed signs of a quicker medication release rate, whereas bigger microspheres showed signs of a slower drug release rate. Microspheres with a smooth surface morphology and a spherical shape were verified by scanning electron microscopy (SEM) at lower polymer concentrations. As the solvent evaporated, the surface roughness rose slightly at higher polymer concentrations, likely due to the increased viscosity and solidification effects [23-25].

The polymer-to-drug ratio had a substantial impact on the drug entrapment efficiency, which varied between 72.8 ± 2.3% and 89.4 ± 3.1%. Better drug encapsulation was observed in formulations with a higher polymer content. This is because, during emulsification, a more stiff polymer matrix is formed, which inhibits drug diffusion into the external aqueous phase. The formulations were successful in encapsulating the ideal quantity of medicine within the microspheres while preserving their structural integrity, as evidenced by drug loading values ranging from 18.2 ± 1.1% to 26.7 ± 1.5% [24-26].

The results of the FTIR measurement showed that the medication and polymer did not interact chemically in any meaningful way. The molecular integrity of the medicine was conserved, as the spectra of the formed microspheres showed characteristic peaks of the pure drug without any substantial changes. Similarly, differential scanning calorimetry (DSC) thermograms demonstrated that the drug's melting point was 215.3°C throughout the experiment, indicating that the drug kept its crystalline structure inside the polymeric matrix and that there was no notable interaction between the drug and polymer [25-29].

The drug was released in two phases during the in-vitro drug release trial. The first phase was a rapid burst release of 24.6 ± 1.8% in the first two hours. The second phase was a steady release that lasted up to twenty-four hours. The rapid release of the drug was thought to have occurred because the microspheres were in close proximity to the drug particles, whereas the slower release was due to the drug diffusing through the polymer matrix [30-36].

Based on the results of this investigation, the created microspheres have features that make them ideal for long-term medication administration in diabetes treatment. A single dose of the tailored microspheres may be able to sustain therapeutic medication levels for 24 hours, in contrast to traditional immediate-release formulations that typically necessitate numerous doses daily. Potential benefits include less variation in plasma medication concentration, fewer adverse effects, and better treatment adherence for patients. The formulation is a good candidate for additional in-vivo pharmacokinetic and pharmacodynamic research because it is safe and effective because biocompatible and biodegradable polymers are used [37-44].

The results show that the formulation was successful, but more research is needed to find the best combination of polymers and drug loading to improve stability and bioavailability. Confirming the microspheres' therapeutic efficacy and pharmacokinetic characteristics should be the focus of future in-vivo studies [45-51]. To further evaluate the formulation's potential for the long run, stability tests under accelerated settings are required. Reducing dosage frequency and increasing therapeutic effects in diabetes treatment may be possible with the help of the sustained-release microspheres created in this study, which offer a dependable and effective method for the administration of anti-diabetic drugs [52-57].

CONCLUSION:

The researchers in this work used solvent evaporation to create microspheres that release anti-diabetic drugs over time. With a drug entrapment efficiency ranging from 72.8 ± 2.3% to 89.4 ± 3.1%, the microspheres displayed a consistent size distribution (120.5 ± 3.8 µm to 185.2 ± 5.6 µm). The spherical shape and smooth surfaces were confirmed by morphological analysis, and investigations using FTIR and DSC showed no significant drug-polymer interactions. The Korsmeyer-Peppas model was followed by the in-vitro drug release, which began with a burst of 24.6 ± 1.8% and continued for 24 hours with a steady release of 82.7 ± 3.8%. Patient compliance and treatment efficacy can be improved with the optimized formulation's approach to delayed medication release. Clinical validation requires more in-vivo investigations.

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Conflict of Interest:
None

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