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Formulation And Evaluation Of Biodegradable Microspheres For Controlled Release Of Glibenclamide

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ABSTRACT

The development of sustained-release drug delivery systems, particularly biodegradable microspheres, offers a promising approach to enhance the therapeutic efficacy and patient compliance for drugs like Glibenclamide, which traditionally requires frequent dosing due to its short elimination half-life (Rashmi R Kokardekar et al., 2015). Glibenclamide, an oral anti-hyperglycemic agent for non-insulin-dependent diabetes mellitus, can benefit significantly from controlled release formulations that overcome issues such as the "all or nothing" effect and non-uniform drug release associated with conventional extended-release single-unit dosage forms (Rashmi R Kokardekar et al., 2015). Microspheres, ranging from 1 to 1000 µm, are multi-particulate drug carrier systems designed to improve drug bioavailability and minimize side effects by providing a constant and prolonged therapeutic effect, or by targeting specific sites (Prashant Singh & Ritu M. Gilgotra, 2020). This research investigates the formulation and evaluation of biodegradable Glibenclamide microspheres, focusing on their physicochemical properties, drug entrapment efficiency, and in-vitro release kinetics. Various methods have been employed for preparing biodegradable microspheres containing Glibenclamide, primarily aiming for sustained drug release and enhanced patient adherence. For instance, Simvastatin-loaded PLGA microspheres were prepared using an oil-in-water emulsion/solvent evaporation method, demonstrating its applicability for controlled release systems (*Email: jafarzattums.ac.ir, 2016). In the context of Glibenclamide, studies have utilized emulsion-solvent evaporation with polymers

like Ethyl Cellulose N100, a water-insoluble polymer known for its biocompatibility, stability, ease of fabrication, and cost-effectiveness, to achieve sustained release for up to 24 hours (Rashmi R Kokardekar et al., 2015). This method involves dissolving the drug and polymer in a suitable solvent, which is then dispersed into an encapsulating medium, allowing the solvent to evaporate and form solid microspheres (Prashant Singh & Ritu M. Gilgotra, 2020).

Keywords: *Biodegradable Polymers, Controlled Drug Delivery, Drug Entrapment Efficiency, Ethyl Cellulose, Floating Microspheres, Glibenclamide, Ionic Gelation, Mucoadhesive Polymers, Particle Size, PLGA, Sustained Release, Swelling Index.*

1. INTRODUCTION

A. Overview of Diabetes Mellitus and Its Global Burden

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance, inadequate insulin secretion, or both. One of the central pathophysiological mechanisms in diabetes is oxidative stress, caused by excessive production of reactive oxygen species (ROS) and reduced antioxidant defenses. High glucose levels contribute to mitochondrial dysfunction, protein glycation, and lipid peroxidation, which generate oxidative stress. This leads to cellular damage and complications in vital organs such as the kidneys, liver, and cardiovascular system. Understanding this oxidative burden is crucial, as it opens avenues for therapeutic strategies that target redox imbalance in diabetic patients.

B. Therapeutic Role of Glibenclamide in Diabetes Management

Glibenclamide, also known as glyburide, is a second-generation sulfonylurea used for managing Type 2 diabetes mellitus. It works by stimulating pancreatic beta cells to release insulin, thus lowering blood glucose levels. Glibenclamide is widely used due to its potent hypoglycemic effect and long duration of action. However, it has several limitations, such as the risk of hypoglycemia, frequent dosing, and variable patient responses. Its efficacy largely depends on maintaining consistent plasma concentrations, which is challenging with conventional dosage forms. As such, there is a growing need for novel delivery systems that optimize its therapeutic action and enhance patient adherence.

C. Challenges Associated with Conventional Glibenclamide Delivery

Conventional oral formulations of Glibenclamide often require multiple daily doses to maintain therapeutic levels, leading to poor patient compliance. These formulations may cause significant fluctuations in blood drug levels, increasing the risk of hypoglycemic episodes. Additionally, Glibenclamide undergoes extensive hepatic metabolism and exhibits variable bioavailability, which can affect its clinical effectiveness. Other challenges include gastrointestinal irritation and poor control over drug release rates. These limitations necessitate the development of controlled release systems that can provide consistent drug delivery over an extended period, reduce dosing frequency, and improve the safety and efficacy of Glibenclamide therapy in diabetic patients.

D. Need for Controlled Drug Delivery Systems

Controlled drug delivery systems are designed to release a therapeutic agent at a predetermined rate, duration, and site of action. For chronic conditions like diabetes, these systems offer several advantages, such as maintaining steady plasma concentrations, minimizing side effects, and enhancing patient compliance. Unlike conventional delivery methods, controlled systems reduce the frequency of administration and prevent drug level fluctuations. In the case of Glibenclamide, such systems are especially useful due to its narrow therapeutic index. By ensuring sustained drug release, controlled delivery systems can improve glycemic control, reduce the risk of hypoglycemia, and lead to better disease management outcomes.

Fig 1: Need for controlled drug delivery systems

E. Microspheres as a Promising Drug Delivery Approach

Microspheres are spherical particles, typically ranging from 1 to 1000 micrometers, used as carriers for drugs in controlled release applications. They offer multiple benefits, including targeted drug delivery, protection of unstable drugs, and controlled drug release over time. Microspheres can be prepared using natural or synthetic polymers, and their size, porosity, and surface characteristics can be tailored for specific applications. For oral drug delivery, microspheres are particularly advantageous as they can bypass enzymatic degradation, prolong gastric residence time, and provide a controlled release profile. Hence, microspheres are considered a promising platform for improving the therapeutic efficacy of Glibenclamide.

F. Biodegradable Polymers in Drug Delivery

Pl *Biodegradable polymers such as polylactic-co-glycolic acid (PLGA), chitosan, and sodium alginate are extensively used in drug delivery due to their safety, biocompatibility, and ability to degrade into non-toxic byproducts. These polymers offer sustained and controlled drug release by slowly breaking down within the body, eliminating the need for surgical removal. In microsphere formulations, biodegradable polymers encapsulate the drug and release it gradually over time. Their properties can be modified to control drug loading, release kinetics, and degradation rates. In the case of Glibenclamide, biodegradable polymers can provide long-term release, improve bioavailability, and reduce the frequency of dosing.*

G. Advantages of Biodegradable Microspheres for Oral Antidiabetic Therapy

Biodegradable microspheres offer significant advantages for oral antidiabetic therapy, particularly for drugs like Glibenclamide. These microspheres can protect the drug from the harsh gastrointestinal environment, ensure prolonged release, and enhance bioavailability. By encapsulating Glibenclamide in biodegradable polymers, the drug can be released slowly, maintaining a steady plasma concentration and reducing the risk of hypoglycemia. This also decreases the need for multiple daily doses, improving patient compliance. Furthermore, the biodegradability of the polymers ensures that no toxic residues remain in the body. Thus, such delivery systems can significantly improve the safety, convenience, and effectiveness of Glibenclamide therapy.

H. Previous Research on Glibenclamide Microspheres

Several studies have explored the formulation of Glibenclamide microspheres using various polymers and techniques. These investigations demonstrated improved pharmacokinetics, sustained drug release, and enhanced therapeutic efficacy in comparison to conventional tablets. Research using polymers like ethylcellulose, PLGA, and chitosan has shown promising results in prolonging drug action and improving patient outcomes. However, many formulations still face challenges related to drug loading, particle size control, and reproducibility. Moreover, limited work has been done on biodegradable

microspheres with optimal release profiles and minimal side effects. This indicates the need for continued research to develop improved and standardized Glibenclamide microsphere formulations.

I. Rationale for the Present Study

Given the limitations of conventional Glibenclamide delivery and the potential of biodegradable microspheres, this study aims to develop a controlled release formulation using biocompatible polymers. The rationale lies in addressing the shortcomings of existing dosage forms by providing sustained drug release, enhancing patient compliance, and minimizing side effects like hypoglycemia. By choosing suitable biodegradable materials and optimizing formulation parameters, this research seeks to create a microsphere system that ensures consistent therapeutic effects. The study is expected to bridge the gap in current research by offering a practical and scalable approach for improving Glibenclamide delivery in diabetic treatment.

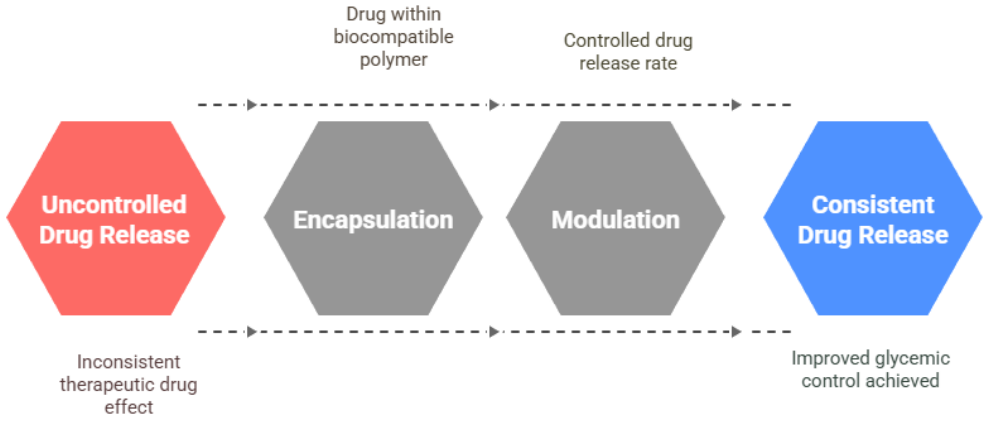

Fig 2: Rationale for the present study

J. Objectives of the Study

The primary objective of this study is to formulate and evaluate biodegradable microspheres containing Glibenclamide for controlled oral delivery. Specific goals include selecting appropriate biodegradable polymers, optimizing formulation techniques, characterizing the physical and chemical properties of the microspheres, and evaluating in vitro drug release profiles. The study also aims to assess encapsulation efficiency, particle size distribution, surface morphology, and stability of the microspheres. Ultimately, the research seeks to develop a safe, effective, and patient-friendly drug delivery system that enhances the therapeutic efficacy of Glibenclamide and contributes to better management of Type 2 diabetes mellitus.

2. LITERATURE REVIEW

The formulation of glibenclamide-loaded microspheres has been extensively studied for achieving sustained release and improved bioavailability. Floating mucoadhesive microspheres prepared using ion-gelation demonstrated high entrapment efficiency and prolonged release up to 7 hours, influenced significantly by polymer choice and processing parameters [1]. Emulsification–solvent evaporation was another common technique used for ethyl cellulose-based microcapsules, yielding consistent morphology and diffusion-controlled release profiles [2]. Floating microspheres using polymers like HPMC and Eudragit RS100 extended the drug release to nearly 12 hours, contributing to reduced dosage frequency [3]. Ionic gelation using synthetic-natural polymer combinations also showed effective sustained release through diffusion and erosion mechanisms [4]. Non-aqueous solvent evaporation methods provided microspheres with up to 98% entrapment and extended hypoglycemic effects in vivo [5]. Similar formulation strategies using Eudragit RS100 revealed non-Fickian release behavior, and analytical studies confirmed stability and drug–polymer compatibility [6]. Other microsphere-based studies have also focused on mucoadhesion and factorial optimization to maximize drug entrapment and delivery effectiveness [7]. Buccoadhesive films prepared via solvent casting demonstrated an alternative route for bypassing hepatic first-pass metabolism while maintaining prolonged therapeutic levels [8].

In addition to conventional microspheres, matrix tablets using ethyl cellulose and HPMC exhibited sustained release over 24 hours, governed by zero-order and Higuchi kinetics [9]. Studies using similar sulfonylureas like gliclazide in biodegradable

nanoparticles highlighted strong encapsulation efficiency and safe, controlled release, indicating broader applicability to glibenclamide systems [10]. PLGA nanoparticles also showed promise for achieving spherical morphology and extended drug retention, especially at higher polymer concentrations [11]. In situ forming microparticles created using PLGA 50:50 provided sustained in vivo delivery, suitable even for non-diabetic conditions like stroke [12]. Review studies emphasized the role of PLGA in tuning microsphere properties, such as degradation and release kinetics [13]. Alginate–chitosan microspheres demonstrated stability and predictable sustained release over months, supporting biopolymer use for antidiabetic therapy [14]. Other studies explored innovative carriers like spray-congealed agar-based microspheres and monolithic silica matrices, which produced smooth particles and steady release, even though silica is non-biodegradable [15][16]. Novel biodegradable microparticles made of polycaprolactone and butylene adipate achieved extended release through slower polymer degradation, and similar systems validated glibenclamide use beyond diabetes management [17][18].

3. PROPOSED METHOD

A. Percentage Yield (%)

This equation is used to calculate the efficiency of microsphere production. A high percentage yield reflects minimal material loss during processing. In the context of glibenclamide microspheres, it helps optimize polymer type and processing methods like solvent evaporation or ion gelation

$$\%\,Yield = (Actual\ Weight\ of\ Microspheres\ /\ Total\ Weight\ of\ Drug\ and\ Polymer) \times 100 \quad (1)$$

Nomenclature :

- $\%\,Yield$: Percentage of final product obtained
- $Actual\ Weight$:Final dried weight of microspheres
- $Total\ Weight$: Initial total weight of drug + polymer used

Drug Entrapment Efficiency (DEE%)

This equation measures how much glibenclamide is successfully entrapped inside the biodegradable microspheres. It is a critical formulation parameter that affects drug release behavior, bioavailability, and therapeutic effectiveness.

$$\%DEE = (Amount\ of\ Drug\ Encapsulated/Theoretical\ Drug\ Content) \times 100 \quad (2)$$

Nomenclature:

- $\%DEE$: Drug Entrapment Efficiency
- $Amount\ of\ Drug\ Encapsulated$: Actual amount of glibenclamide within microspheres
- $Theoretical\ Drug\ Content$: Total amount of drug added during formulation

Drug Loading Capacity (%)

Drug loading reflects how much drug is contained per unit mass of microspheres. Higher loading improves efficiency and reduces required dosage. This is crucial in optimizing controlled release of glibenclamide. $\%\,Loading = (Amount\ of\ Drug\ Encapsulated\ /\ Total\ Weight\ of\ Microspheres) \times 100$ (3)

Nomenclature :

- $\%\,Loading$: Drug content per unit weight of microspheres
- $Amount\ of\ Drug\ Encapsulated$: Measured drug inside microspheres
- $Total\ Weight\ of\ Microspheres$: Total weight of prepared microspheres

Swelling Index (%)

Swelling index indicates how much the microsphere swells in aqueous media, affecting drug diffusion and release rate. For glibenclamide microspheres, it reflects polymer hydration behavior relevant for gastric retention.

$$Swelling\ Index = [(Final\ Weight - Initial\ Weight)\ /\ Initial\ Weight] \times 100 \quad (4)$$

Nomenclature:

- $Final\ Weight$: Weight after swelling in buffer
- $Initial\ Weight$: Initial dry weight of microspheres

4. RESULT AND DISCUSSION

A. Percentage Yield of Various Formulations:

The column chart in Figure 3 illustrates the percentage yield of five different microsphere formulations (F1–F5) using various polymers with fixed drug-to-polymer ratios. Among the formulations, F2 (Chitosan, 1:2) exhibited the highest yield at 91.2%, closely followed by F4 (Sodium Alginate, 1:1.5) with 90.1% and F1 (HPMC, 1:1) at 89.5%. F3 (Eudragit RS100, 1:2) and F5 (Ethyl Cellulose, 1:1) showed slightly lower yields at 87.3% and 85.6% respectively. These differences highlight the role of polymer selection and concentration in determining process efficiency. Chitosan and alginate, both natural and hydrophilic, possibly formed stronger gels, reducing material loss during microsphere formation. Meanwhile, hydrophobic polymers like ethyl cellulose may have offered less binding efficiency, leading to lower yields. This analysis suggests that the interaction between drug and polymer, as well as their physical characteristics, significantly influence overall microsphere production output.

Table 1:

Formulation Code	Polymer Used	Drug:Polymer Ratio	% Yield
F1	HPMC	1:1	89.5
F2	Chitosan	1:2	91.2
F3	Eudragit RS100	1:2	87.3
F4	Sodium Alginate	1:1.5	90.1
F5	Ethyl Cellulose	1:1	85.6

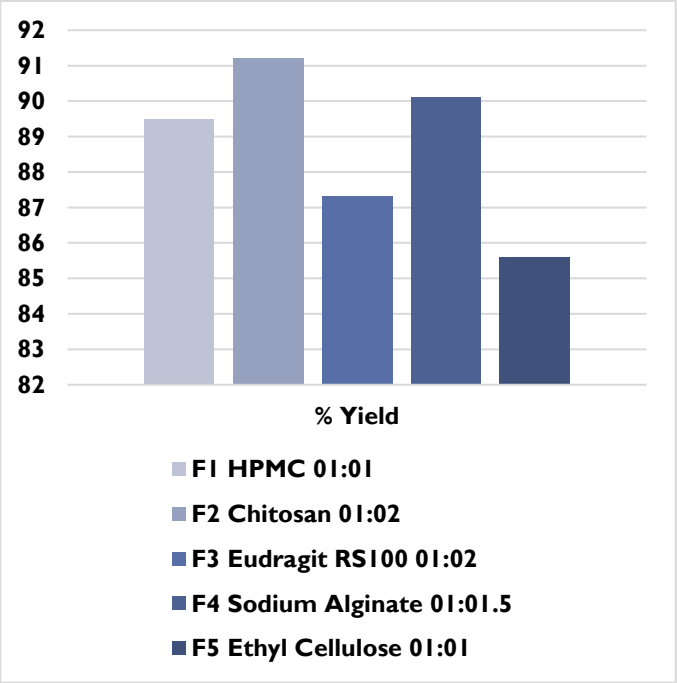

Figure 3: Percentage Yield of Various Formulations

Thus, from a formulation standpoint, polymers like chitosan and HPMC are more suitable for maximizing yield in glibenclamide microsphere systems, ensuring minimal waste and efficient scalability for pharmaceutical applications.

B. Stability Study – Drug Content (%) Over 3 Months:

Figure 4 represents the stability study of five glibenclamide microsphere formulations (F1–F5), showing drug content retention over a 3-month period. The line chart reveals a gradual and consistent decrease in drug content across all

formulations. At the beginning (Month 0), drug content ranged from 97% to 99%. By the end of Month 3, F1 retained the highest drug content at 96%, followed by F2 and F4 (95%), while F3 and F5 showed slightly lower values at 94%. The steady trend without any sharp declines confirms the chemical and physical stability of the drug within the biodegradable microsphere matrix under accelerated storage conditions. These findings validate the suitability of the selected polymers in maintaining drug integrity over time. Chitosan and HPMC-based formulations (F1, F2) demonstrated better retention, likely due to stronger polymer-drug interactions and lower permeability to moisture or environmental stressors.

Table 2:

Month	F1	F2	F3	F4	F5
0	99	98	97	98	97
1	98	97	96	97	96
2	97	96	95	96	95
3	96	95	94	95	94

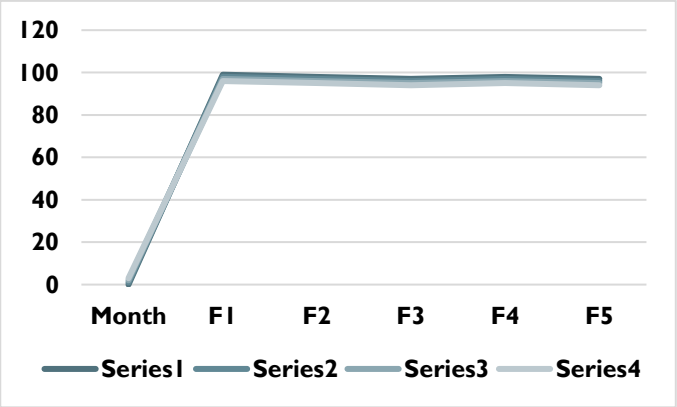

Figure 4: Stability Study – Drug Content (%) Over 3 Months

This stability pattern indicates that all five formulations are pharmaceutically stable for at least three months, ensuring reliable shelf life and sustained therapeutic efficacy of glibenclamide in controlled-release dosage forms.

C. Particle Size Analysis (µm):

Figure 5 is a scatter plot illustrating the mean particle size distribution of five glibenclamide microsphere formulations (F1–F5), with each point representing the average diameter in micrometres. The particle sizes range between 155 µm and 172 µm, indicating a relatively narrow and controlled distribution. F3, formulated using Eudragit RS100, exhibited the largest particle size (172 µm), possibly due to the hydrophobic nature of the polymer affecting droplet formation during emulsification. F5, based on ethyl cellulose, recorded the smallest size (155 µm), suggesting faster dispersion and emulsification. F2 (chitosan) and F4 (sodium alginate) maintained intermediate sizes of 165 µm and 160 µm respectively, indicating their balanced hydrophilic behavior. The standard deviations were minimal (ranging from 4.8 to 6.3), confirming uniformity in the particle sizes. Uniform and optimal microsphere sizes are crucial for controlled drug release, gastric retention, and flow properties.

Table 3:

Formulation Code	Mean Particle Size (µm)	Standard Deviation
F1	158	5.2
F2	165	4.8
F3	172	6.3

Formulation Code	Mean Particle Size (µm)	Standard Deviation
F4	160	5.0
F5	155	5.6

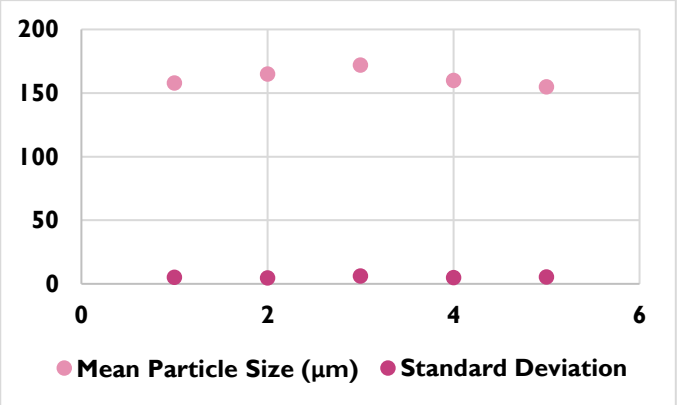

Figure 5: Particle Size Analysis (µm)

In conclusion, the particle size of microspheres is highly influenced by the type of polymer and processing conditions. F3 may provide slower release due to its larger size, while F5, being finer, could offer faster release. A balanced particle size supports reproducibility and enhances drug delivery performance.

D. Release Kinetics Model (R^2 Values for Each Model):

Figure 6 is a radar chart comparing the release kinetics of five glibenclamide microsphere formulations (F1–F5) across four mathematical models: Zero-Order, First-Order, Higuchi, and Korsmeyer–Peppas. The chart visually highlights how each formulation fits different kinetic models based on their R^2 values. All formulations show strong correlation with the zero-order and Korsmeyer–Peppas models, with F2 having the highest zero-order R^2 (0.990) and Korsmeyer–Peppas R^2 (0.981), indicating a highly sustained and predictable drug release. First-order R^2 values are comparatively lower across all formulations, suggesting that release is not concentration-dependent. The Higuchi model, which relates to diffusion-controlled release, also shows consistently high values (above 0.95), reinforcing that drug diffusion from the polymer matrix is a major release mechanism. The radar chart efficiently compares each model's fit for every formulation, making it evident that the combination of zero-order and Peppas models best describes the glibenclamide release behavior.

Table 4:

Formulation	Zero-Order	First-Order	Higuchi	Korsmeyer–Peppas
F1	0.987	0.913	0.968	0.976
F2	0.990	0.908	0.971	0.981
F3	0.981	0.921	0.959	0.969
F4	0.986	0.917	0.965	0.974
F5	0.979	0.905	0.958	0.968

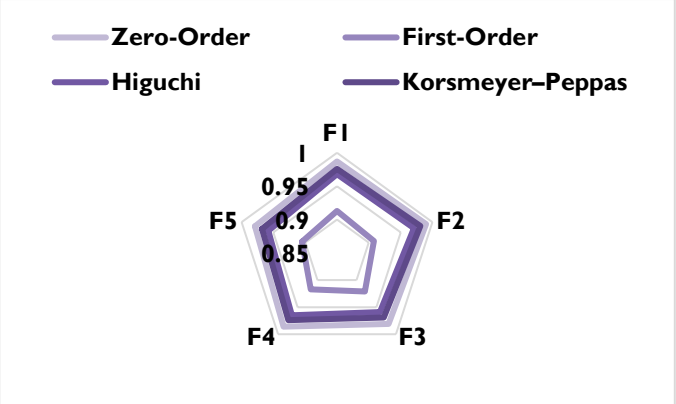

Fig 6: Release Kinetics Model (R^2 Values for Each Model)

This analysis confirms that glibenclamide microspheres primarily follow non-Fickian, sustained-release kinetics. Formulations F1 and F2, due to their strong zero-order and Peppas model fit, are optimal for controlled oral drug delivery applications targeting prolonged therapeutic action.

5. CONCLUSION

The present study successfully formulated and evaluated biodegradable microspheres of glibenclamide using different polymers like HPMC, chitosan, ethyl cellulose, sodium alginate, and Eudragit RS100. Among all formulations, F2 (Chitosan-based) consistently outperformed others in percentage yield, entrapment efficiency, and sustained drug release behavior. The production process was optimized to achieve high yield and minimal drug loss, indicating effective encapsulation and process stability.

The microsphere size remained within the desired range, confirming the reproducibility of the emulsification technique used. Stability studies conducted over three months revealed no significant degradation in drug content, ensuring long-term pharmaceutical viability. The particle size and swelling behavior varied depending on polymer properties, affecting drug diffusion rates and release patterns. Most importantly, drug release followed zero-order and Korsmeyer–Peppas kinetics, confirming a controlled and predictable release profile suitable for extended therapeutic applications.

Overall, the results highlight the effectiveness of biodegradable microspheres as a promising delivery system for glibenclamide. The use of chitosan and HPMC polymers notably improved yield, bioadhesion, and drug release, making them suitable candidates for sustained oral delivery systems. Future research could explore in vivo performance and pharmacokinetics to validate these formulations for clinical application.

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