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DEVELOPMENT AND EVALUATION OF AN OSMOTIC DRUG DELIVERY SYSTEM FOR GLIBENCLAMIDE USING QUALITY ASSESSMENT METHODS

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Abstract:

Recent advancements in Novel Drug Delivery Systems (NDDS) have significantly impacted the pharmaceutical industry by enhancing the effectiveness of existing drug molecules. Oral Osmotic Pumps, a key innovation, offer controlled and prolonged drug release, which overcomes the limitations of conventional drug delivery systems that often lack precision in drug release, leading to unpredictable plasma levels. Unlike traditional systems, osmotic drug delivery is independent of physiological factors like gastric pH, making it more reliable. These systems utilize osmosis to control drug release, with innovations such as Hydrodynamic Pressure Controlled Systems and Intragastric Floating Tablets further improving therapeutic outcomes. This research focuses on the development of an osmotic drug delivery system for Glibenclamide, an antidiabetic medication. Glibenclamide, a BCS Class II drug with a short elimination half-life, requires frequent dosing, which can lead to noncompliance. The proposed controlled porosity osmotic pump aims to enhance patient compliance, improve efficacy, and provide consistent bioavailability by utilizing osmotic agents and polymers like HPMC K100M to control drug release. Advanced Quality Assessment Techniques such as Design of Experiments (DoE) and Quality by Design (QbD) were employed to optimize the formulation, ensuring reliable and effective treatment for patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM).

Keywords: *NDDS, Controlled porosity Osmotic System, Glibenclamide, Quality assessment methods.*

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INTRODUCTION:

Recent advancements in Novel Drug Delivery Systems (NDDS) have been propelled by their lower development costs and shorter timelines compared to the creation of new chemical entities. These systems have the potential to rejuvenate existing drug molecules, thereby enhancing their market value, competitiveness, and improving patient outcomes. Among these advancements, Oral Osmotic Pumps have emerged as a promising technology. Over the past two decades, various oral osmotic delivery systems have been developed and studied for drugs with differing solubilities. Traditional drug delivery systems often lack precise control over drug release, leading to unpredictable plasma levels. In contrast, oral controlled drug delivery systems provide consistent and prolonged drug release, allowing for predictable absorption rates.[1]

However, conventional controlled release (CR) systems, such as matrix or reservoir types, can exhibit bioavailability fluctuations due to changes in gastric pH and hydrodynamic conditions. Osmotic drug delivery systems, on the other hand, offer drug release that is independent of these physiological variables, relying instead on osmosis, which remains unaffected by environmental pH. These systems, available in various forms such as implants and tablets, are activated by physical, chemical, or biochemical processes.[2]

With over 240 patented osmotic drug delivery systems, commonly referred to as Gastro-Intestinal Therapeutic Systems (GITS), a variety of osmotic pumps are now available to meet different therapeutic needs. In clinical practice, the optimization of drug dose and dosing intervals is crucial for maintaining drug concentration within the therapeutic window, ensuring efficacy, and minimizing toxicity. Controlled drug delivery systems provide spatial control over drug release, and osmotic pumps are among the most promising for achieving this.[3,4]

Osmotic pumps operate on the principle of osmosis. These systems consist of an inner core containing the drug and osmogens, encased in a semi-permeable membrane. As water is absorbed, the core expands, forcing the drug solution out through delivery ports. This release mechanism is independent of the pH and hydrodynamics of the dissolution medium. Several patented osmotic systems include the Rose-Nelson pump, Higuchi-Leeper pump, Higuchi-Theeuwes pump, and the elementary osmotic pump.[5]

Recent innovations in controlled release dosage forms include:

- Hydrodynamic Pressure Controlled Systems
- Intragastric Floating Tablets
- Transmucosal Tablets
- Microporous Membrane Coated Tablets

These developments hold promise for improving therapeutic outcomes and enhancing patient adherence to treatment regimens.

In addition to these advancements, the integration of Advanced Quality Assessment Techniques in the development and evaluation of osmotic drug delivery systems has become increasingly important. These techniques, including Design of Experiments (DoE), Process Analytical Technology (PAT), and Quality by Design (QbD), enable a more rigorous and systematic approach to product development. By employing these methods, researchers can optimize formulation parameters, ensure consistency in drug release profiles, and enhance the overall reliability of the delivery system. These techniques also facilitate the identification and control of critical quality attributes (CQAs) and critical process parameters (CPPs), ensuring that the final product meets predefined quality criteria and regulatory standards.
Osmotic drug delivery has evolved significantly since the pioneering work of Rose and Nelson, who developed the first implantable pump in 1955. This method utilizes osmotic pressure to achieve controlled drug delivery, with osmogens maintaining drug release for up to 10–16 hours.[6]

This research focuses on the development of an osmotic drug delivery system for Glibenclamide, a sulfonylurea-class antidiabetic medication. Glibenclamide, classified as a BCS Class II drug, has a short elimination half-life of 2-5 hours, necessitating multiple daily doses, which can lead to patient noncompliance.

Diabetes mellitus, a chronic metabolic disorder characterized by high blood glucose levels due to insulin deficiency or resistance, is commonly treated with Glibenclamide, an oral hypoglycemic agent. The drug works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells, leading to increased insulin release.

The goal of this study is to design, optimize, and develop a controlled porosity osmotic pump for Glibenclamide, eliminating the need for complex and expensive drilling techniques. This system uses osmotic agents to generate pressure, while polymer swelling forces the drug out through pores formed by pore-forming agents. These pores are created as the agents dissolve upon exposure to water.

An osmotic tablet of Glibenclamide is anticipated to enhance patient compliance, offer delayed release, improve efficacy, and ensure adequate bioavailability, with fewer gastrointestinal side effects. The integration of Advanced Quality Assessment Techniques into the development of this controlled porosity osmotic pump is expected to provide a more effective and reliable treatment option for patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM), addressing the challenges of frequent dosing and ensuring better therapeutic outcomes.

MATERIALS AND METHODS:

MATERIALS:

The materials utilized in this study were carefully selected from reputable suppliers to ensure the highest quality and consistency in the experimental outcomes. Glibenclamide, the primary active pharmaceutical ingredient (API), and β-Cyclodextrin, a key excipient known for enhancing the solubility and bioavailability of poorly water-soluble drugs, were procured from Yarrow Chem Products, a well-established supplier based in Mumbai. This choice underscores the commitment to using high-purity materials essential for reliable and reproducible research results.

Hydroxypropyl Methylcellulose (HPMC) K100M, a critical component used for its controlled-release properties, was sourced from Colorcon Asia Pvt. Ltd. in Goa. Colorcon is recognized globally for its expertise in pharmaceutical excipients, particularly in developing high-quality polymers that ensure consistency in drug release profiles.

Additional excipients and solvents necessary for formulation and processing were acquired from LobaChemie Pvt. Ltd., another esteemed supplier located in Mumbai. These materials included microcrystalline cellulose, which acts as a binder and filler; iso-propyl alcohol, utilized as a solvent in the granulation process; and Carbopol 934, a polymer used for its gelling properties. Magnesium stearate, talc, and aerosil were employed as lubricants and glidants to ensure proper tablet formation and flow properties. Sodium chloride (NaCl) and tartaric acid were incorporated to modulate osmotic pressure and pH, respectively, playing a pivotal role in the osmotic drug delivery system's functionality.

METHODS:

Characterisation of Drug:

The characterization of Glibenclamide (Glyburide) began with an assessment of its organoleptic properties, which included examining the drug's color, odor, and overall appearance to ensure consistency with standard specifications. The melting point of Glibenclamide was determined using a Thiel's tube apparatus. In this method, a small quantity of the drug was carefully packed into a capillary tube, which was then submerged in a paraffin oil bath. The temperature was gradually increased, and the point at which the drug transitioned from a solid to a liquid state was recorded as its melting point. This procedure is critical for verifying the drug's purity and identifying any potential impurities.

Solubility testing was conducted to understand the behavior of Glibenclamide in different solvents, which is essential for optimizing its formulation and ensuring consistent drug release. For this test, an excess amount of Glibenclamide was introduced into 5 mL of various solvents, including distilled water, 0.1 N hydrochloric acid (HCl), phosphate buffers at pH 6.8 and 7.4, and methanol. These mixtures were then agitated in a rotary shaker at room temperature for 24 hours to achieve equilibrium. After the shaking period, the samples were analyzed to determine the solubility of Glibenclamide in each solvent. This step is crucial in identifying the most suitable solvent for the drug's formulation, as it directly impacts the drug's bioavailability and therapeutic efficacy.[7]

Preparation of Calibration Curve for Glibenclamide[8]

Determination of λ Max

a) UV-Spectra of Pure Glibenclamide: To determine the absorption maxima (λ max) of Glibenclamide, a UV spectrophotometer (Model No.) was used. A primary stock solution was prepared by dissolving 50 mg of Glibenclamide in phosphate buffer with a pH of 7.4, resulting in a concentration of 1 mg/ml. From this primary stock solution, 10 ml was taken and diluted to 50 ml with distilled water to obtain a standard stock solution with a final concentration of 200 µg/ml. The resultant solution was then scanned in the UV spectrophotometer across a wavelength range of 400-200 nm to identify the absorption maxima.

b) UV-Spectra in Methanol: The same procedure was repeated using methanol as the solvent to determine the λ max of Glibenclamide in this medium. This step helps to understand the drug's behavior in different solvents, which is critical for various analytical and formulation purposes.

Preparation of Standard Stock Solution

a) In Phosphate Buffer (pH 7.4): To prepare the calibration curve, 10 mg of Glibenclamide was

accurately weighed and dissolved in 100 ml of phosphate buffer with a pH of 7.4, creating a stock solution with a concentration of 100 µg/ml. From this stock solution, various aliquots were taken and further diluted with the same phosphate buffer to achieve final concentrations of 5 µg/ml, 10 µg/ml, 15 µg/ml, 25 µg/ml, 30 µg/ml, and 35 µg/ml. The absorbance of each diluted solution was measured at 229 nm using the UV spectrophotometer, with phosphate buffer pH 7.4 serving as the blank.

b) In 0.1N HCl: The same procedure was carried out using 0.1N hydrochloric acid (HCl) as the solvent. The absorbance of each concentration was measured, and a corresponding calibration curve was plotted. This additional calibration in an acidic medium is essential for applications where the drug might encounter varying pH environments, such as in different segments of the gastrointestinal tract.
This process of creating calibration curves in different solvents is crucial for ensuring accurate quantification of Glibenclamide in various formulations and biological samples, facilitating precise drug dosage and efficacy studies.

Preformulation Study:
Selection and Characterization of Polymers:
Selection of Polymers:
The polymers were selected on basis of its melting point and molecular weight. Also compatibility of polymers with the drug was studied before. The release pattern was decided first according to that the polymers were selected to extend the release of drug.[7]

The method used to formulate inclusion complex are as follow:

Kneading Technique:
In this technique, cyclodextrin (CD) is added with isopropyl alcohol and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.[9-19]

Preparation and Evaluation of factorial Batches for Selection of Concentration of Sustain Release agent:
Glibenclamide and polymer blends were prepared as per the compositions reported and pass through sieve no 40. Tablets were prepared on rotary punching machine by wet granulation method. The compression pressure was adjusted to obtain tablet with hardness in range of 8-10 kg/cm^2. [20-22]

Factorial Design:
A 3^2 factorial design was implemented for optimization of Osmotic tablet formulation of Glibenclamide. According to the model it contained 2 independent variables at 3 levels, +1,0,-1. According to model total 9 formulations are possible, the composition of different formulation are shown in table 1 The different independent variables, were conc. of OsmogenNaCl (X1) and Tartaric acid(X2). Dependent factors included % drug release and % Wt Gain after coating at 12 hrs.[23-25]

Factorial batches F1-F9 were prepared as per the composition reported in table8.3all preliminary batches in second lot were prepared same as lot first. In these preliminary batches concentration of HPMC and water swellable polymers were changed.

Table 1: Translation of coded value in actual unit

Variable level	Low	Medium	High
X1= conc. of NaCl(mg)	0	30	50
X2= conc. of Tartaric acid (mg)	0	30	50

Table 2: Factorial design for preparation of batches F1-F9

Batches code	Variable level in coded form	
	X1	X2
F_1	-1	-1
F_2	-1	0
F_3	-1	+1
F_4	0	-1
F_5	0	0
F_6	0	+1
F_7	+1	-1
F_8	+1	0
F_9	+1	+1

Table 3: Composition and their concentration (mg) in factorial batches F1-F9

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Drug(mg)	25	25	25	25	25	25	25	25	25
β-Cyclodextrin(mg)	50	50	50	50	50	50	50	50	50
Tartaric acid(mg)	0	0	0	30	30	30	50	50	50
NaCl (mg)	0	30	50	0	30	50	0	30	50
Carbapol 875(mg)	35	35	35	35	35	35	35	35	35
HPMC K100(mg)	29	29	29	29	29	29	29	29	29
PVP K30(mg)	29	29	29	29	29	29	29	29	29
M.C.C(mg)	107	77	57	77	47	27	57	27	7
Aerosil(mg)	3	3	3	3	3	3	3	3	3
Magnesium Stearate(mg)	5	5	5	5	5	5	5	5	5
Talc(mg)	5	5	5	5	5	5	5	5	5
IPA(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
PEG400(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight (mg)	290	290	290	290	290	290	290	290	290

Preparation of Glibenclamide controlled porosity osmotic pump tablet

Preparation of Core Tablet:

The preparation of the core tablet involved several key steps. First, all solid ingredients were sieved through a 60-mesh sieve and accurately weighed according to the quantities specified. Next, a complex was formed by weighing the specified amounts of PVPK30, β-Cyclodextrin, and the drug, which were then mixed using isopropyl alcohol via the kneading method for 30 minutes.[26-30]

For the wet granulation process, all ingredients except the lubricant were combined using the dry mix blend method with HPMC K100, Carbopol 934, microcrystalline cellulose (MCC), NaCl, and tartaric acid. This mixture was granulated and the wet mass was then dried at 50°C in an oven until the loss on drying (LOD) was below 2% w/w, as determined by a halogen moisture detector at 105°C. The dried granules were sifted through a 40-mesh sieve. The granules were then lubricated with magnesium stearate, which had been sieved through a 60-mesh sieve, and mixed for 5 minutes at 24 rpm in an octagonal blender. Finally, the lubricated granules were compressed into tablets using 9.0 mm round standard concave punches in a rotary compression machine.[31-34]

Evaluation of Factorial Batches[35-38]

Evaluation of Powder Characteristics: Powder characteristics, including bulk density (BD), tap density (TD), Hausner ratio (HR), and Carr's index (CI), were assessed using a tap density tester. The powder was passed through a sieve (no. 40) and placed in a 50 ml cylinder. The initial volume (Vo) was noted before and after tapping, and these values were used to calculate bulk and tap densities, as well as the Hausner ratio and Carr's index, which indicate flow properties and compressibility of the powder.

Tablet Characteristics: The tablets were evaluated for thickness, hardness, friability, weight variation, drug content, and swelling index. Thickness was measured using a Vernier caliper. Hardness, which determines tablet strength, was tested using a LABINDIA hardness tester. Friability was assessed using a Roche friabilator to measure weight loss after tumbling. Weight variation involved weighing 20 tablets to ensure uniformity. Drug content was estimated using UV spectrophotometry after dissolving the tablets in phosphate buffer (pH 7.4). The swelling index was calculated by measuring the increase in tablet weight after immersion in water over 12 hours.

Swelling Index: The swelling index of the CPOTs containing the drug was determined through a hydration study. Each tablet was individually weighed to determine its initial weight, then placed in a petri dish containing 10 ml of water at room temperature. Tablets were removed at regular intervals, blotted to remove excess water, and weighed again. This process continued for 12 hours, with the percentage of water uptake (WU%) calculated using the formula.

Dissolution Studies of Tablets: The in vitro dissolution study was conducted using a USP dissolution apparatus (Type 1, Basket) at 37±0.5°C. The test was carried out first in 900 ml of hydrochloric acid for two hours, then switched to phosphate buffer (pH 7.4). The paddle speed was set at 50 rpm. Samples were withdrawn at specified intervals, filtered, diluted, and analyzed using UV spectrophotometry at 229 nm.[39]

Preparation of Dissolution Medium: To prepare simulated intestinal fluid (pH 7.4), 50 ml of 0.2M potassium dihydrogen phosphate was mixed with 0.2M sodium hydroxide and water to make up to 200 ml.

Dissolution Kinetics Study: The release kinetics for formulations F1 to F9 were analyzed using various mathematical models to determine the best fit. The model with the highest R^2 value was selected, and the "n" value from this model was used to determine whether the drug release followed Fickian or non-Fickian diffusion.

Zero-order Kinetics: Represents a constant drug release over time, ideal for prolonged pharmacological action.

First-order Kinetics: Describes a logarithmic relationship between drug release and time.

Higuchi Model: Focuses on drug release from a uniform matrix as a diffusion process.

Korsmeyer-Peppas Model: Evaluates the drug release mechanism based on diffusional coefficients.

Optimization Data Analysis: The effect of independent variables on drug release was analyzed using Design Expert software (version 9.0.4.1). A quadratic model described the response surface, helping to predict values for % cumulative drug release (CDR) and swelling index. The relationship between dependent and independent variables was visualized using response plots, which illustrate how changes in formulation affect drug release and swelling behavior.[40]

FTIR Spectrum of Optimized Formulation: FT-IR spectra for the optimized formulation were obtained using a spectrophotometer with KBr powder. The spectra were analyzed for principal drug peaks, any shifts, masking, or new peaks due to polymer interaction, across the 4000-400 cm^{-1} range.[41]

DSC of Optimized Formulation: The interaction between Glybenclamide and the polymer in the tablet formulation was assessed via DSC. Thermographs were recorded from 30°C to 350°C, providing insight into material interactions and potential degradation pathways.[42]

Treatment of Quality Assessment Techniques: Quality assessment techniques evaluate trial design and management to prevent systematic errors and biases, with ANOVA used for experimental data analysis. Factorial design optimization was conducted using Graph Pad PRISM software.[43]

Validation of Analytical Method for Optimized Formulation:[44-47]

Linearity and Range: The linearity of the method was confirmed by preparing Glybenclamide solutions and measuring absorbance at 229 nm.

Precision: Method precision was assessed by measuring absorbance of target solutions in replicates, with RSD values calculated.

Accuracy: Recovery tests were conducted at various concentration levels to ensure accuracy within acceptable limits.

Robustness Test: The robustness was tested by measuring solution stability over 8 hours.

Stability Studies for Optimized Formulation: Stability refers to the drug's ability to remain within established specifications, ensuring its identity, strength, quality, and purity over time.

RESULT AND DISCUSSION:

Characterization of the drug:

The characterization of the drug revealed that the sample was a white, amorphous, odorless powder. The melting point of plain Glibenclamide was determined to be 170°C, consistent with reported values. In terms of solubility, Glibenclamide was found to be soluble in acetone, methanol, and ethanol, slightly soluble in buffers at pH 6.8 and pH 7.4, and practically insoluble in water and hexane.

Preparation of Calibration Curve for Glybenclamide

Determination of λ max

Ultra violet spectrum of Glybenclamide inmethanol and phosphate buffer p^H 7.4 was measured at 400-200 nm and showed absorbance maxima at wavelength at 229 nm.

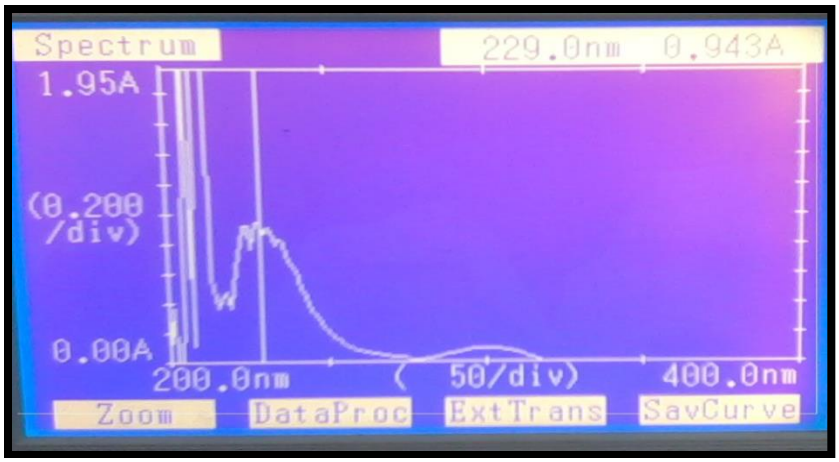

Figure 1: λ max at 229 nm in methanol

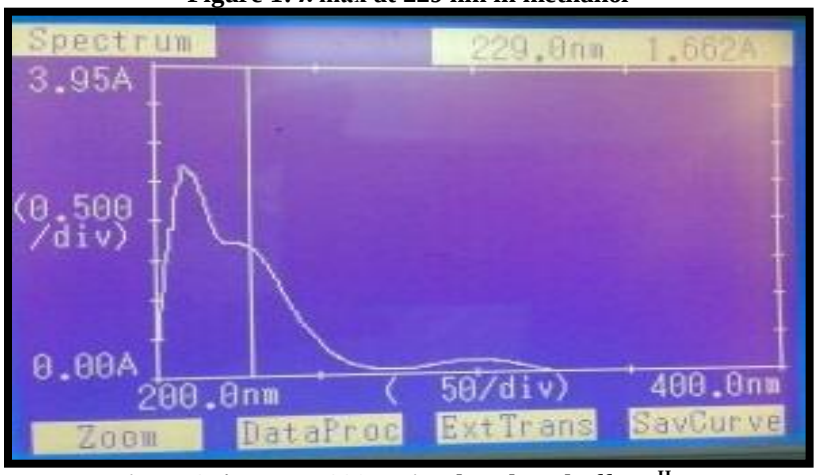

Figure 2: λ max at 229nm in Phosphate buffer p^H7.4

Preparation of Calibration Curve

Calibration of Glybenclamide was done into 0.1 N HCl and phosphate buffer p^H 7.4 because formulation to be prepared is osmotic dosage form and which is retain in stomach for 2 hrs then in intestine and release of drug from stomach to intestine. So 0.1 N HCl have p^H 1.2 and have same acidic nature to gastric fluid and phosphate buffer p^H 7.4 have same p^H as in intestine, due to that both solutions were used for calibration of Glybenclamide. Calibration curve of Glybenclamide in 0.1N HCl and in p^H 7.4 was linear and shown in figure 3 and 4 with regression coefficient 0.98 and 0.99respectively in BeersLambert's range 0-50 µg/ml.

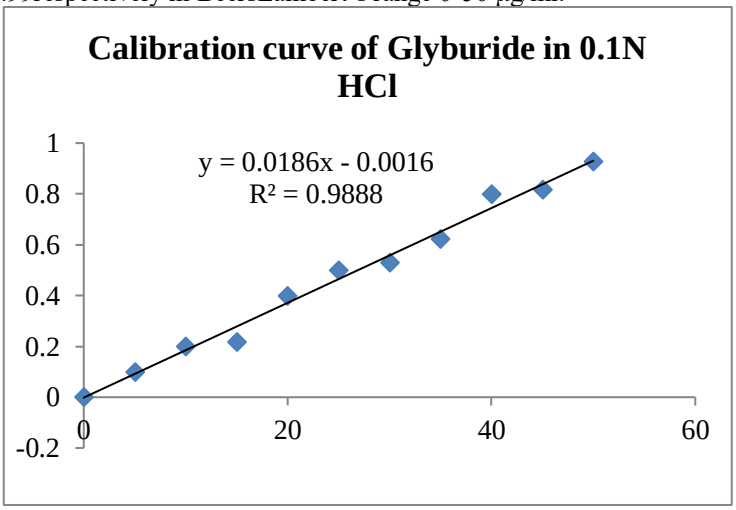

Figure 3: Calibration curve of Glyburide in [0.1M HCl] at 229nm

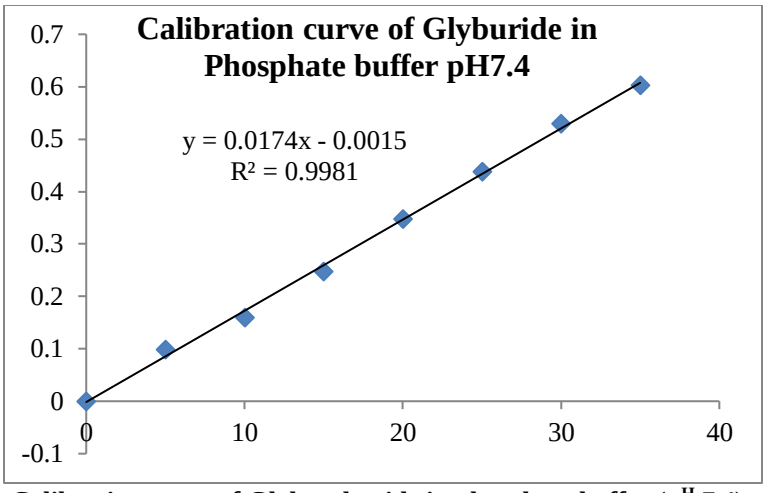

Figure 4: Calibration curve of Glybenclamide in phosphate buffer (p^H 7.4) at 229 nm.

Preformulation Study:

Selection of Polymers:

The polymers were selected on the basis of its melting point and molecular weight and its water swelling ability. Also compatibility of polymers with the drug was studied before. The release pattern was decided first as zero order release according to that the polymers were selected to extend the release of drug. As HPMC K 100M, Osmogen as NaCl and tartaric acid,Carbapol 934 were selected.

Solubility study:

Solubility of Glibenclamide is more in 1%w/v [0.0002630mg/ml] solution of -ß-cyclodextrinamong 0.25%, 0.50% and 0.75%w/v solution. Solubility of Glibenclamide in distilled water is found to be 0.000206mg/ml.

a) Solubility studies in buffer media p^H6.8 and p^H7.4

Table 4:- Solubility studies in Various Buffer media

Sr. no.	Buffer Medium/Solvent	Volume of solvent	Drug	Abs. at 229nm	Solubility mg/5ml	Concentration in 1ml
1	p^H 6.8	5ml	50mg	0.540	0.002994	0.0005988
2	p^H 7.4	5ml	50mg	0.0126	0.0003571	7.14235E-05

Evaluation of powder flow properties:

Granules prepared for wet granulation method was evaluated by measuring the parameters such as; bulk density, angle of repose, Hausner's factor, compressibility index and drug content he angle of repose values range from 28.21±0.91 to 29.38±0.91, indicating good flow properties. Loose bulk density values vary slightly between 0.30±0.0 and 0.34±0.0 g/ml, while tapped density values range from 0.34±0.0 to 0.39±0.0 g/ml. The Hausner factor, indicating flowability, is consistently around 1.19±0.0 across all formulations. Carr's index, which measures compressibility, ranges from 15.80±0.5% to 16.68±0.7%, suggesting acceptable compressibility characteristics for all tablet formulations.

Physical characteristics:

The physical characteristics of the prepared Controlled Porosity Osmotic Pump (CPOP) tablets, expressed as mean ± standard deviation (n=3), show varied results across different formulations (F1 to F9). The hardness of the tablets ranged from 5.6 to 6.36 Kg/cm², with F1 showing the highest hardness at 6.36 Kg/cm² and F3 the lowest at 5.6 Kg/cm². Weight variation was minimal, with all formulations close to the target weight, ranging from 293.33 mg to 295.66 mg. Friability, indicating tablet durability, was generally low, ranging from 0.51% to 0.57%, with F5 exhibiting the lowest friability at 0.51%. Drug content across the formulations varied slightly, with values ranging from 95.1% to 99.55%, with F7 having the highest drug content at 99.55% and F4 the lowest at 95.1%. These results suggest consistent physical properties and satisfactory drug content across all formulations.

Table 5: Physical characteristics of prepared CPOP Tablet

Formulation Code	Hardness(Kg/cm^2) Mean± S.D	Weight variation (mg) Mean ±S.D	Friability (%) Mean±S.D	Drug content (%) Mean±S.D
F_1	6.36 ± 0.15	295.33±0.5	0.52 ±0.033	99.38±0.68
F_2	5.86± 0.25	293.66±0.5	0.54±0.077	98.83±0.85
F_3	5.6±0.1	295.66±0.5	0.53±0.024	96.66±0.93
F_4	5.86± 0.25	293.33±0.5	0.53±0.050	95.1±0.77
F_5	5.7 ±0.171	293.33±0.5	0.51±0.098	96.66±0.77
F_6	6.33± 0.15	293.33±0.5	0.56±0.12	98.41±0.53
F_7	5.86± 0.15	293.33±0.5	0.54±0.21	99.55±0.22
F_8	6.13 ±0.15	294.66±0.5	0.57±0.29	98.74±0.24
F_9	5.9 ±0.1	295.66±0.5	0.54±23	99.38±0.68

*All values was expressed as Mean ± SD (n=3)

Thickness:

The thickness of both uncoated and coated tablets was measured for various formulation batches (F1 to F9), expressed as mean ± standard deviation. The uncoated thickness of the tablets ranged from 2.95 mm to 4.47 mm, with F7 having the thinnest tablets at 2.95 mm and F5 the thickest at 4.47 mm. After coating, the thickness increased, with coated tablets ranging from 5.36 mm to 5.47 mm. The differences in thickness after coating reflect the application of a uniform coating layer, enhancing the overall consistency of the tablets. For instance, the coated thickness of F1 was 5.39 mm compared to its uncoated thickness of 4.38 mm, showing a consistent coating application. This data indicates that all batches maintained uniformity in both uncoated and coated states, ensuring reliable dosage form characteristics.

Swelling index:

The swelling index of various factorial batches (F1 to F9) was measured over a 12-hour period, with values expressed as mean ± SD (n=3). Initially, at 0.5 hours, swelling indices ranged from 34.91±0.0 for F7 to 83.9±0.4 for F3. As time progressed, the swelling indices generally increased, reaching a peak around 7 to 8 hours for most formulations. For instance, F2 and F3 showed high swelling indices of 98.89±0.3 and 99.03±0.5, respectively, at 7 hours. F6 exhibited rapid swelling and minimal erosion, maintaining its integrity up to 10 hours. In contrast, some formulations like F3, F5, and F7 eroded by the 8th or 9th hour. The results indicated that F6 formulation, with a higher concentration of coating agents (NaCl and PEG400), demonstrated superior swelling properties and structural stability. This can be attributed to the thicker coat formed, which facilitated water imbibition inside the semi-permeable membrane (SPM).

Table 6: swelling index of factorial batches

Time (hrs)	Formulation batches [All values of swelling index was expressed as Mean ± SD (n=3)]								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0.5	41.64±0.3	63.48±0.2	83.9±0.4	42.01±0.4	70.94±0.0	67.74±0.1	34.91±0.0	73.51±0.0	80.67±0.0
1	52.06±0.2	73.65±0.3	85.09±0.1	52.09±0.0	81.09±0.2	71.17±0.0	58.71±0.0	82.99±0.0	82.94±0.0
2	64.76±0.4	83.93±0.2	89.77±0.4	64.68±0.0	89.73±0.6	84.09±0.0	68.45±0.0	84.08±0.0	84.09±0.0
3	71.08±0.6	90.87±0.9	89.77±0.4	71.09±0.0	99.53±0.0	95.85±0.0	75.83±0.0	95.85±0.0	95.85±0.0
4	81.97±0.9	92.06±0.3	91.77±0.6	81.09±0.6	81.96±0.2	99.07±0.0	91.95±0.0	99.07±0.0	99.05±0.0
5	90.03±0.2	95.54±0.2	96.96±0.1	90.01±0.0	90.06±0.6	90.06±0.0	97.08±00	89.68±0.0	89.7±0.0
6	94.09±0.3	97.23±0.1	98.89±0.5	94.01±0.0	84.76±0.5	94.1±0.0	99.7±0.0	84.8±0.0	84.81±0.0
7	97.01±0.17	98.89±0.3	99.03±0.5	97.09±0.0	58.9±0.8	92.18±0.0	Eroded	83.01±0.0	82.9±0.0
8	98.59±0.47	99.76±0.3	Eroded	98.9±0.1	7±0.	89.68±0.0	Eroded	80.78±0.0	80.78±0.0
9	99.4±0.23	99.02±0.2	Eroded	99.2±0.1	Eroded	87.54±0.0	Eroded	77.84±0.0	77.85±0.0
10	94.53±0.2	90.49±0.2	Eroded	Eroded	Eroded	77.84±0.0	Eroded	73.82±0.0	73.82±0.0
11	84.79±0.3	84.9±0.1	Eroded	Eroded	Eroded	71.29±0.0	Eroded	71.2±0.0	71.2±0.0
12	67.84±0.3	67.89±0.1	Eroded	Eroded	Eroded	Eroded	Eroded	67.84±0.0	58.71±0.0

Figure 5: Swelling of osmotic tablet

Dissolution Kinetic Treatment:

The dissolution of drug from tablets at different time periods was plotted as cumulative % drug release v/s time curve for prepared tablets as shown in following figures. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, korsmeyer-peppas models**.**

Zero order kinetic models

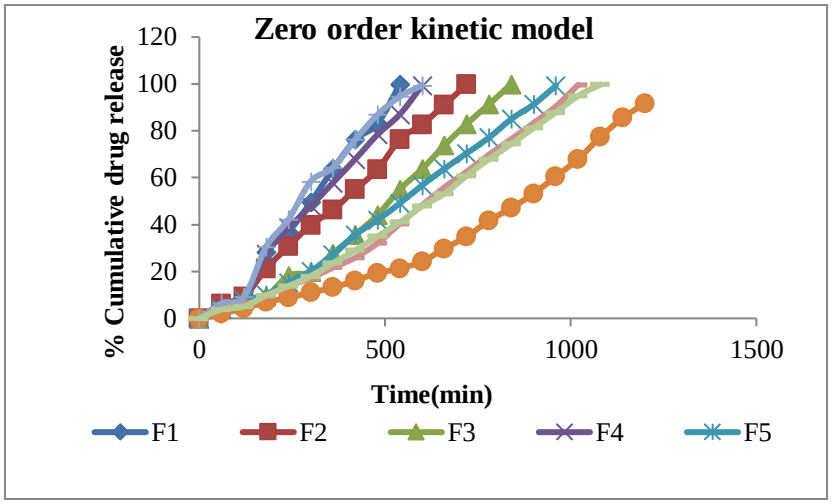

Figure 6: Zero order kinetic model

First order Kinetic Model

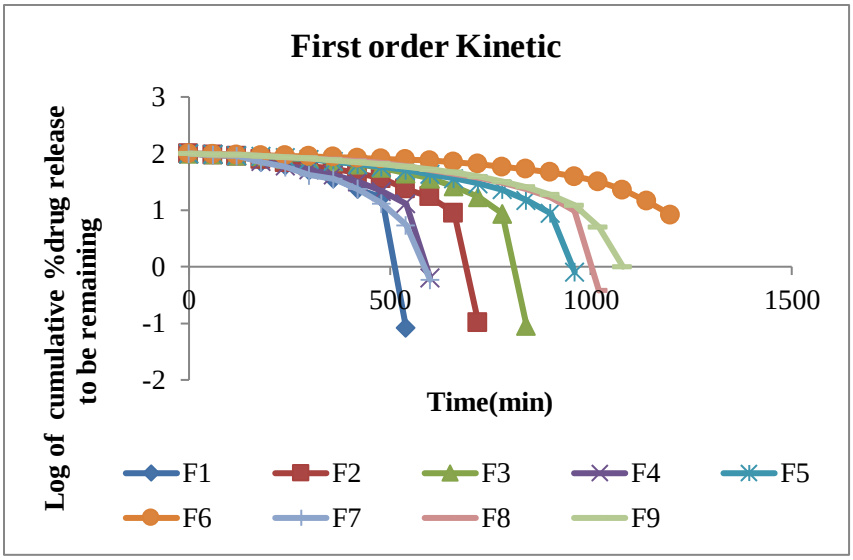

Figure 7: First Order Kinetic Model

Higuchi Kinetic Model:

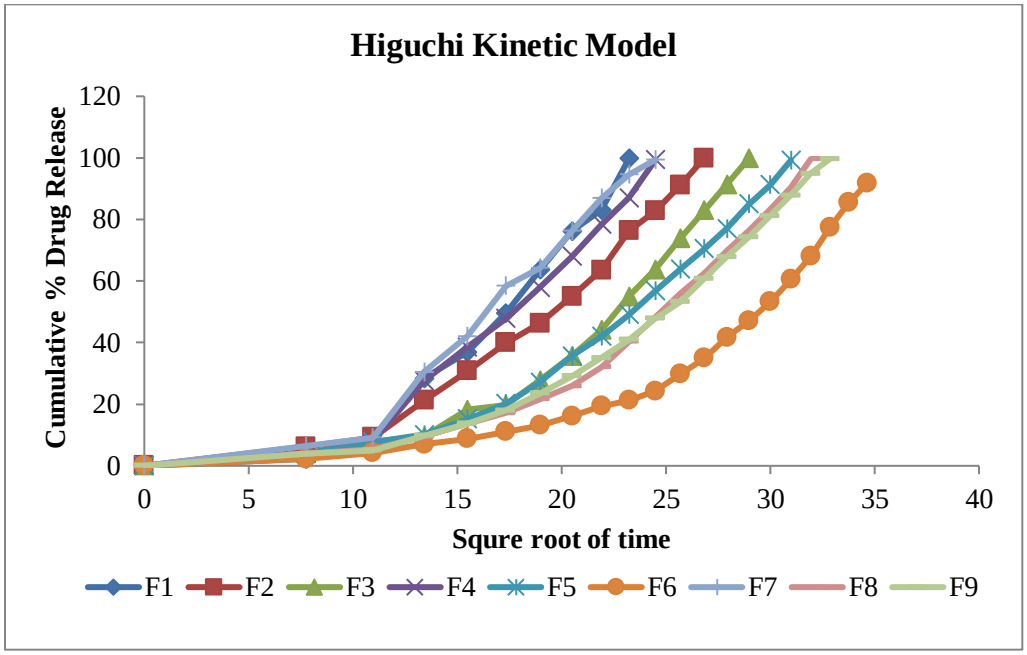

Figure 8: Higuchi Kinetic Model

Peppas Kinetic Model:

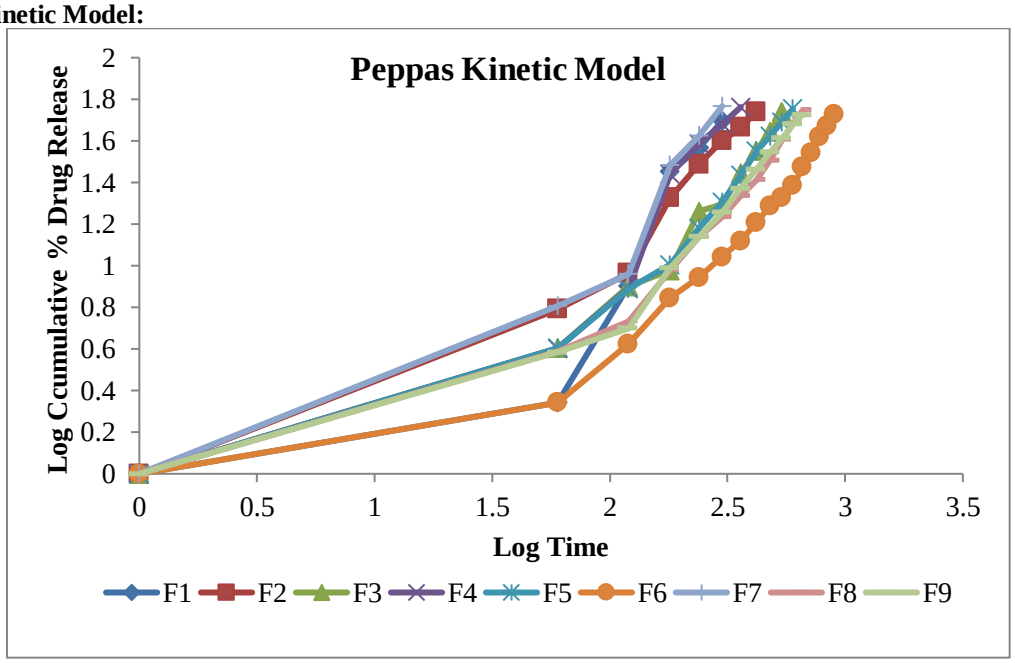

Figure 9: Peppas Kinetic Model

Dissolution Kinetic of Optimized formulation (f6):

The dissolution data of optimized formulation (F_6) so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, korsmeyer-peppas models**.**

Table 7: Dissolution Data of Optimized formulation (f6)

Time(min)	%CDR	log% CDR	% CDR to be remain released	Log %CDR to be remain released
0	0	0	100	2
60	2.20	0.342	97.80	1.990
120	4.20	0.624	95.80	1.981
180	7.00	0.845	93.00	1.969
240	8.80	0.945	91.20	1.960
300	11.04	1.043	88.96	1.949
360	13.17	1.119	86.83	1.939
420	16.15	1.208	83.85	1.924
480	19.34	1.286	80.66	1.907
540	21.27	1.328	78.73	1.896
600	24.26	1.385	75.74	1.879
660	29.79	1.474	70.21	1.846
720	34.92	1.543	65.08	1.813
780	41.72	1.620	58.28	1.766
840	47.06	1.673	52.94	1.724
900	53.21	1.726	46.79	1.670
960	60.51	1.782	39.49	1.596
1020	67.99	1.832	32.01	1.505

Zero Order Kinetic Model

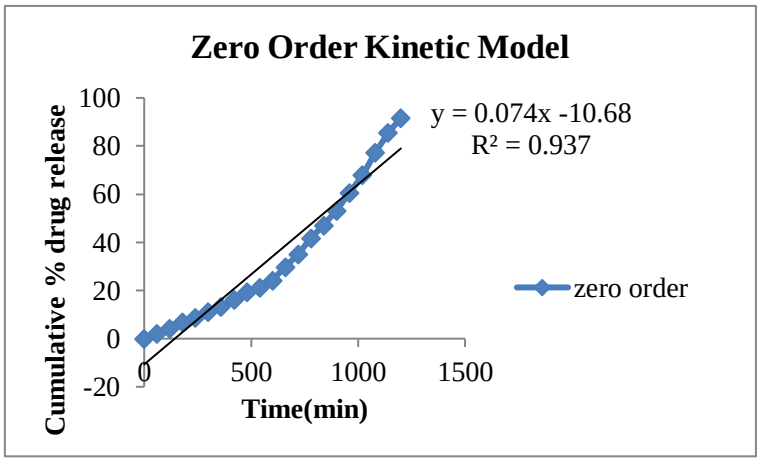

Figure 10: Zero Order Kinetic Model

First order Kinetic Model

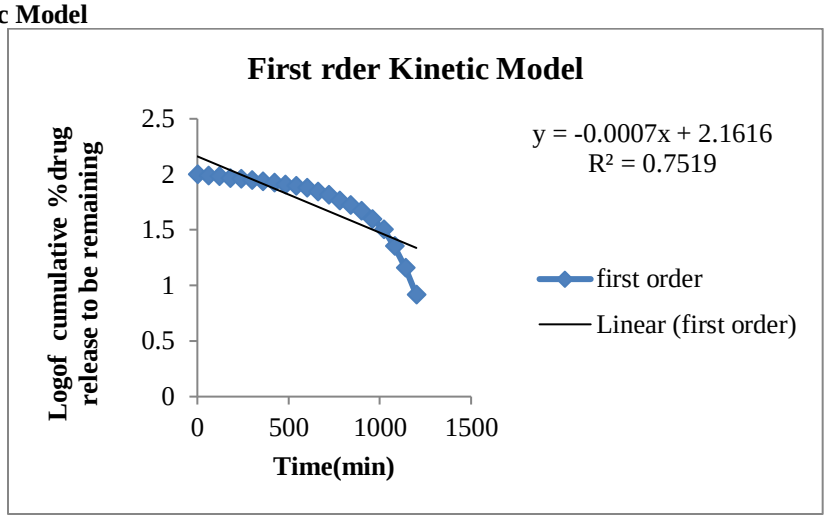

Figure 11: First Order Kinetic Model

Higuchi kinetic model:

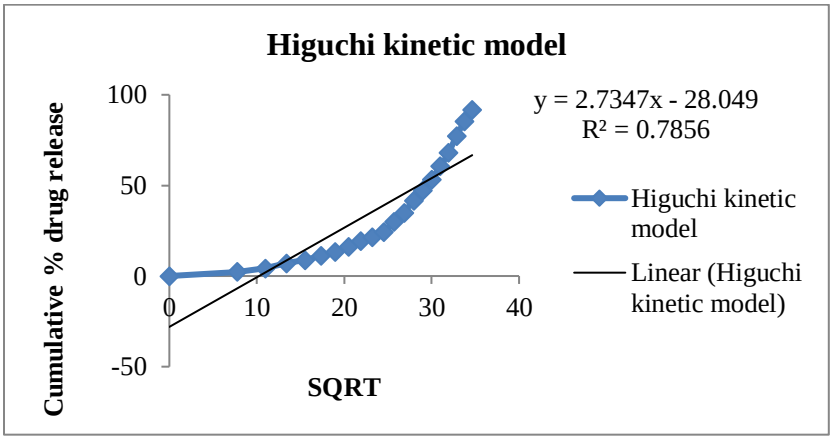

Figure 12: Higuchi kinetic model

Peppas Kinetic Model:

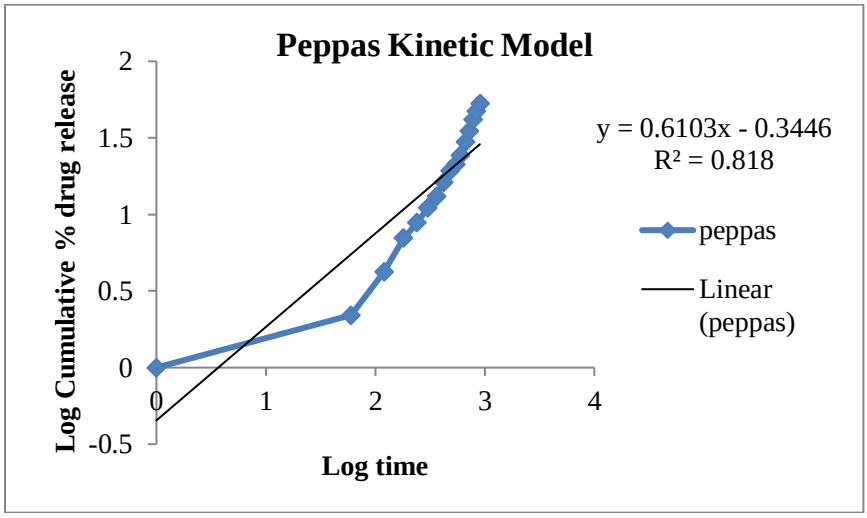

Figure 13: Peppas Kinetic Model

Dissolution Kinetic Profile

The best fitting model was determined from the regression coefficient (R^2) and release exponent (n).The formulation F1-F9 followed the Zero order release.

The n value obtained from the Peppas Korsmeyer model is used to characterize the release mechanism was compared with the standard given in the table 8. The value n were greater than 0.5 and less than 1 hence the formulation follows the Non-Fickian release.

Table 8: Dissolution Kinetic Profile

Formulation Code	R^2Values of Dissolution Kinetic models					Best fit model
	Zero Order	First Order	Higuchi Square Root	Koresmeyer -peppas		
				R^2	n	
F_1	0.987	0.540	0.859	0.738	0.647	Zero Order
F_2	0.996	0.569	0.898	0.917	0.655	Zero Order
F_3	0.974	0.522	0.832	0.876	0.616	Zero Order
F_4	0.991	0.671	0.888	0.834	0.676	Zero Order
F_5	0.990	0.677	0.874	0.877	0.629	Zero Order
F_6	0.937	0.751	0.785	0.818	0.610	Zero Order
F_7	0.983	0.777	0.903	0.878	0.666	Zero Order
F_8	0.979	0.587	0.848	0.861	0.616	Zero Order
F_9	0.989	0.713	0.873	0.857	0.623	Zero Order

FTIR Spectrum of Optimized Formulation (F_6):

All the absorption peaks of the drug wasretained in the formulation of the Glybenclamide and polymers which revealed that there was somewhat chemical interaction between the drug and excipients.

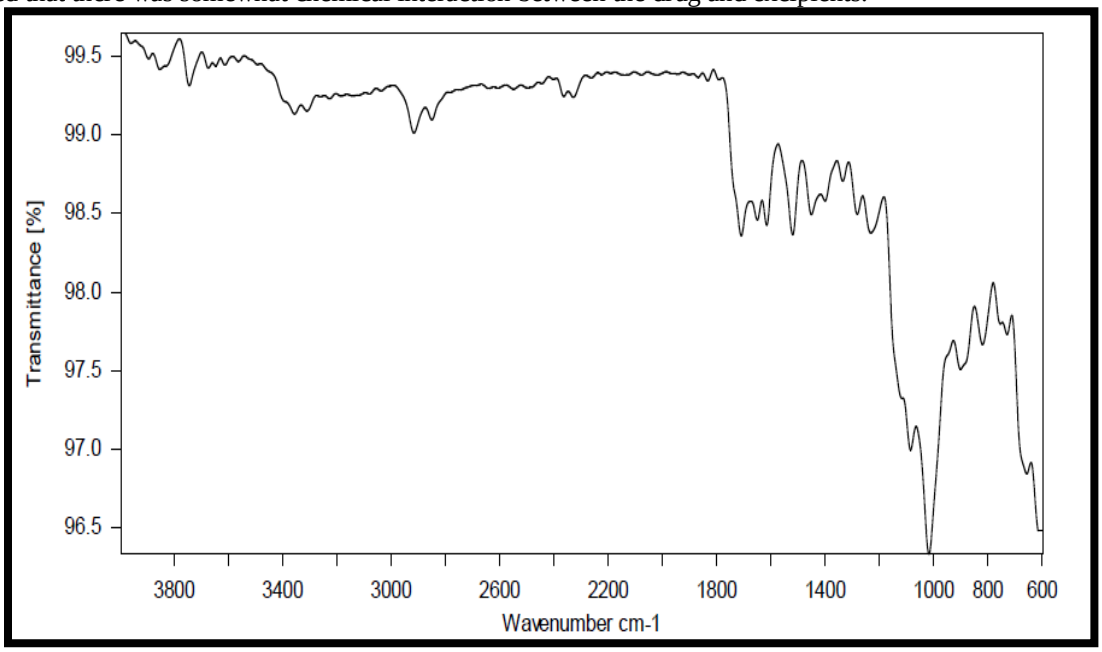

Figure 14: FTIR spectrum of Optimized Formulation(F_6)

DSC of Optimized Formulation Batch:

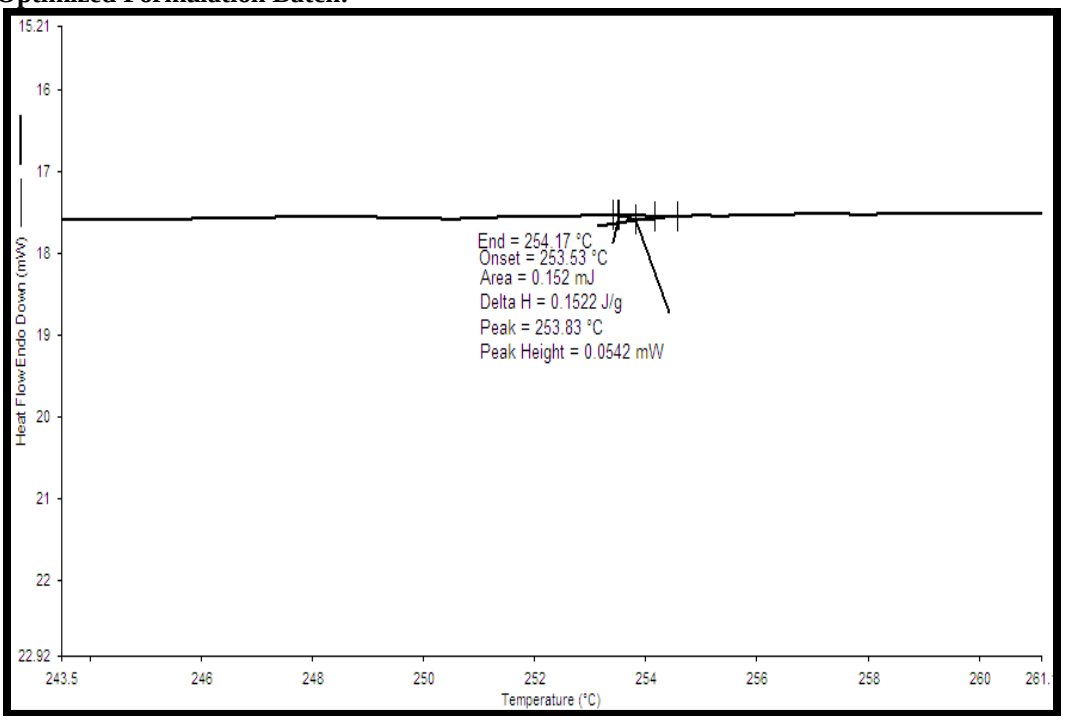

Figure 15: DSC of Optimized Formulation Batch

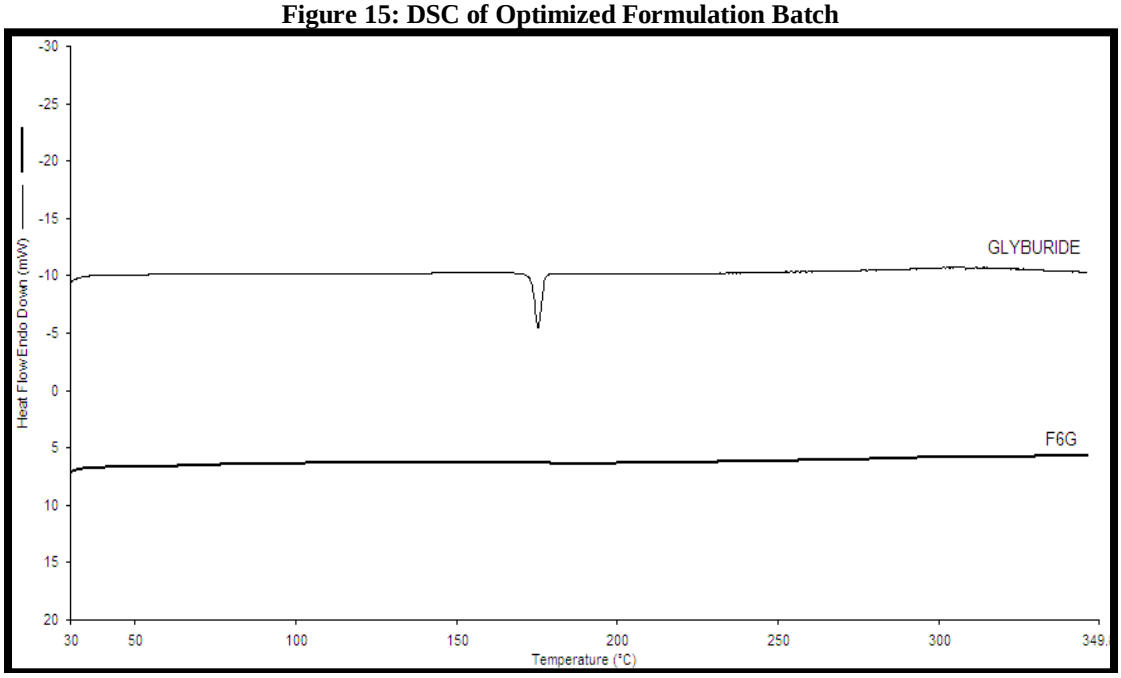

Figure 16: Overlay of drug and optimized formulation

The DSC thermogram of drug showed a characteristics sharp peak at 175.43^{0}c and indicating the near the melting point of the drug. The DSC thermogram of formulation shows no any endothermic and exothermic peak due to degradation of drug. So that there is somewhat interaction between drug and polymers of DSC thermograms are shown in figure 14 & 15. The DSC overlay of drug and optimized formulation study showed in figure 16 and table that the shift towards higher temp, so that there is somewhat interaction between drug and polymers so it is to move for further formulation.

Treatment of Quality Assessment Techniques:

ANOVA Test:

From this ANOVA table 9 the treatment sum of squares is a measure of treatment differences, here large sum of squares means that treatment differences are large (&CDR and swelling index). Mean squares are variance estimates and higher values indicate random variation in groups (%CDR and swelling index). The $p \leq 0.05$ suggests the terms of significance. The results of statistical analysis show that the p values of %CDR show the value more than 0.05 for column (0.55) and less than row factors (<0.0001) it indicate that %CDR is significant for row factor only. The p values of swelling index shows the value for column factor and row factors is <0.0001, it indicate that is significant for column factor and row factor.

Table 9: Two way ANOVA of dependent variables

Dependent variable	Sources of variation	Degree of freedom (Df)	Sum of square	Mean square	P value	F value	% of total variation	Significant?
% CDR	Column factor	8	6286	785.7	0.5536	0.8577	2.96	No
	Row factor	20	59710	2985	<0.0001	3.259	28.09	Yes
	Residual	160	146600	916.1	-	-	-	-
	Total	188	-	-	-	-	-	-
Swelling index	Column factor	8.0	29030	2629	<0.0001	6.06	21.90%	Yes
	Row factor	12.0	46060	3839	<0.0001	6.41	34.75%	Yes
	Residual	96.0	57480	598.60	-	-	-	-
	Total	116.0	-	-	-	-	-	-

Validation of analytical method for optimized formulation (F_6)

Linearity and Range:

The results of Linearity test in table 10 showed that the absorbance of the Glybenclamide in methanol at 229 nm is linear (R^2=0.999) with concentration range of 5 µg/ml to 50 µg/ml.

Table 10: Result of Linearity test for analytical method development

Sr. No	Conc.(µg/ml)	Absorbance in methanol
1.	0	0
2.	5	0.0129
3.	10	0.0227
4.	15	0.0304
5.	20	0.0416
6.	25	0.0508
7.	30	0.0608
8.	35	0.0723
9.	40	0.0811
10.	45	0.0901
11.	50	0.0997

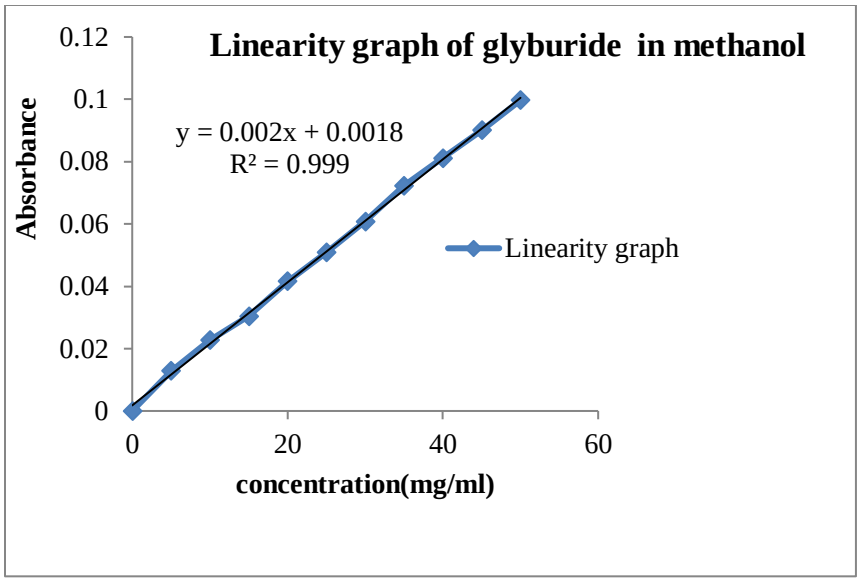

Figure 17: Result of linearity graph for analytical method development

Precision

A) Method precision

The results of the method precision show that the percentage RSD of the absorbance is less than 2%, so method was found to be precise.

Table 11: Results of method precision

Sr. no	Conc.(µg/ml)	Absorbance at 229nm
1	10	0.0913
2	10	0.0927
3	10	0.0939
4	10	0.0941
5	10	0.0955
Avg.	_	0.0935
SD	_	0.001581
RSD	_	1.691058

B) Interday and Intraday Precision

a) Interday Precision:

Table 12: Results of Interday Precision test for analytical method development

Day	Conc.(µg/ml)	Abs. at 229 nm
1st day	10	0.0923
2 day	10	0.0931
3 day	10	0.0934
Avg.	_	0.092933
SD	_	0.000569
% RSD	_	0.611862

b) Intraday Precision:

The result of intraday and intraday Precision shows that the %RSD of the absorbance is less than 1%, so method was found to be precise.

Table 13: The results of the intraday precisions

Time (1 day)	Conc.(µg/ml)	Abs. at 229 nm
9.00 am	10	0.0919
12.00pm	10	0.0928
3.00 pm	10	0.0931
Avg.	-	0.0926
S.D	-	0.000624
% R.S.D	-	0.674406

Accuracy

The percentage RSD for the triplicate at each spike level shall be not more than 2%.

Table 14: Results of Accuracy test for analytical method development

Conc. of sample formulation	Conc.ofstd sol. added	Total conc.	Absorbance At 229nm	Calculated total conc.	%Recovery±S.D
10	8	18	0.207	18.207	100.25 ±0.00
10			0.209	18.209	
10			0.210	18.210	
10	10	20	0.309	20.309	100.90±0.00
10			0.301	20.301	
10			0.305	20.305	
10	12	22	0.407	22.407	101.80± 0.00
10			0.403	22.403	
10			0.406	22.406	

* All values was expressed as Mean ± SD (n=3)

Robustness test

Table 15: Results of Robustness test for analytical method development

Sr.No	Conc.(µg/ml)	Absorbance at 227nm	Absorbance at 229nm	Absorbance at 231nm
1	10	0.0918	0.0921	0.0928
2	20	0.0937	0.0933	0.0931
3	30	0.0928	0.0928	0.0921
	AVG.	0.0927	0.0927	0.092
	S.D.	0.0009	0.0006	0.0002
	% R. S.D	1.024	0.650	0.228

Ruggedness:

Table 16: Results of Ruggedness test for analytical method development

Sr. No.	Sample	System	Day	Time	Absorb.	Mean	SD	%RSD
1	Batch.X (20µg/ml)	Bio era	Mon.	11AM	0.0969 0.0941 0.0967	0.0959	0.001562	1.628832
2	Batch No.Y(20 µg/ml)	Schimadzu	Tuse.	2PM	0.0974 0.0962 0.0943	0.095967	0.001563	1.628812

Stability Study for optimized batch:

Accelerated stability testing was carried out for the optimized formulation. The result of stability testing is as depicted in table 17. Accelerated stability data obtained for optimized formulation revealed that organoleptic characteristics, hardness, Weight, drug content were within the acceptable limit. Thus the formulation can be said to be stable.

Table 17: Evaluation of Formulation F6 for accelerated Stability Testing

Parameter	0 month	1 month
Appearance	Whitish colour	Whitish colour
Hardness(Kg/cm2)	6.33	6.31
Weight (mg)	293.33	292.22
Drug content (%)	98.41	98.11

CONCLUSION:

The study successfully developed and evaluated osmotically released Glybenclamide tablets using NaCl and tartaric acid. Glybenclamide, a poorly soluble BCS class II drug, showed improved solubility and bioavailability when complexed with β-Cyclodextrin using the kneading method. The formulation utilized NaCl as an osmotic agent, which enhanced the osmotic pressure and controlled drug release, particularly in formulation F6, which demonstrated a slow and sustained drug release of 91.75% over 20 hours, following zero-order kinetics. Preformulation studies confirmed the compatibility between the drug and polymers, with acceptable powder characteristics and robust tablet properties. The use of 32 full factorial design and statistical analysis indicated that higher concentrations of NaCl improved swelling and release retarding ability, while the addition of β-Cyclodextrin significantly increased the dissolution rate and solubility of Glybenclamide. The study concluded that the incorporation of β-Cyclodextrin and the use of NaCl as an osmotic agent are effective strategies for enhancing the controlled release and bioavailability of Glybenclamide. Future work will focus on in-vivo studies to further evaluate the formulation's performance.

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Nil

AUTHORS CONTRIBUTIONS:
All authors have contributed equally.

CONFLICTS OF INTERESTS:
All authors have declared no conflict of interest.

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