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Research Article

Advanced Osmotic Drug Delivery of Glipizide: Formulation Optimization and Release Kinetics of Controlled Porosity Tablets

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Abstract

Background: Diabetes mellitus is a long-term illness that needs sustained therapy to keep glycemic control intact. Glipizide is an effective second-generation sulfonylurea but has a short half-life, thus requiring prolonged dosing that compromises compliance in patients. Controlled-release drug delivery systems provide an answer by delivering constant drug levels over a long duration of time. Osmotic controlled-release tablets, specifically, facilitate drug delivery irrespective of gastrointestinal motility and pH, which makes them suitable for drugs such as Glipizide.

Objective: Innovative drug delivery systems have advanced oral controlled-release systems, offering benefits over immediate-release forms by maintaining consistent drug concentration, reducing dosing frequency, and improving patient adherence.

Methods: Tablet cores were prepared via wet granulation and coated with cellulose acetate and potassium chloride for semipermeable membranes. Pre-compression parameters of the granules indicated excellent flow properties, while post-compression parameters such as weight variation, hardness, friability, and drug content met the required standards. In-vitro dissolution studies revealed variable drug release profiles among different formulations, attributed to the choice and concentration of osmotic agents. The F-02 formulation, containing Mannitol and Fructose, demonstrated extended drug release over 12 hours.

Results- in the Kinetic analysis of drug release indicated that most formulations followed zero-order kinetics, with an Anomalous non-Fickian diffusion mechanism. This suggests that the release of Glipizide from OCR tablets is not solely governed by Fickian diffusion but is also influenced by other mechanisms.

Conclusion: The development of Glipizide OCR tablets offers a promising approach to improve drug delivery, reduce dosing frequency, and enhance patient compliance in treating diabetes.

Keywords: Osmotic controlled-release (OCR), Glipizide, Oral drug delivery, Zero-order kinetics, Anomalous diffusion, Excipients

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease defined by the presence of a hyperglycemia.The diabetes mellitus (DM) is a chronic metabolic disease defined by the presence of a hyperglycemia, due to a defect in the insulin secretion, insulin action or both. Type 2 diabetes mellitus (T2DM) is a major health and economic issue that has become extensively prevalent in the world in recent decades.[1] Severe complications from long-term hyperglycemia include cardiovascular diseases, nephropathy, retinopathy, neuropathy and peripheral vascular disorders. Thus, a key therapeutic target in diabetes is to maintain optimal glycemic control.[2]

Glipizide, a second generation sulfonylurea, has a strong insulin-secretagogic effect and is well utilized in the management of T2DM. This medication reduces blood sugar by making insulin released by working β-cells in the pancreas. [3]Although effective, Glipizide has a relatively short elimination half-life of 2-5 h, requiring multiple daily doses to maintain therapeutic plasma levels. Standard, conventional, immediate release formulations are typically associated with wide fluctuations in plasma drug levels, therapeutic failure due to poor compliance and a higher risk of hypoglycemic events. These restrictions have led to a significant amount of interest in the development of controlled drug delivery systems that can deliver a sustained therapeutic level for longer periods of time.[4]

The problems with traditional dosage forms have taken on great significance and have been solved with the development of controlled drug delivery technologies.

Several methods have been studied to obtain sustained drug release such as matrix tablets, reservoir systems, multiparticulate systems, microspheres and osmotic systems.[5] Osmotic drug delivery systems (ODDS) are of significant interest of these technologies, as they can yield predictable and reproducible drug release profile which is relatively independent of physiological parameters like gastrointestinal pH, motility, food intake, and enzymatic activity. In contrast to diffusion controlled formulations, in osmotic formulations the drug release is mainly driven by the osmotic pressure, leading to a more predictable in vivo performance.[6]

The key to osmotic drug delivery is that the water is moving in response to an osmotic gradient across a semi-permeable membrane. When it comes in contact with gastrointestinal fluids, this water dissolves through the membrane to the drug and osmotic agents in the core of the tablet. This osmotic pressure in turn pushes the drug solution out of the system at a predetermined rate. The release mechanism is predominantly osmotic independent of the environmental conditions, making it possible to obtain near zero-order release rates and sustained therapeutic action for extended periods of time.[7]

There are a number of osmotic technologies that have been developed such as the elementary osmotic pump, the push-pull osmotic pump, the sandwiched osmotic system, and the controlled porosity osmotic pump (CPOP) tablets. Controlled porosity osmotic tablets are attractive and commercially viable because of their relatively simple design and manufacturing process among these. CPOP systems use a semipermeable membrane containing water soluble pore-forming agents that surround the drug containing core. The pore formers dissolve upon contact with the aqueous media and leach from the membrane creating a microporous channel for the dissolved drug to be released from the membrane. The in situ pore formation does not require laser-drilled delivery orifices typically required in conventional osmotic pumps, making it easier to manufacture and lower manufacturing costs.[8]

For a controlled porosity osmotic system to be a success, there are several formulation variables such as membrane type, coating thickness, pore-forming agents and the concentration of osmogen. Of these, type and degree of osmogens are the most important in influencing water influx, osmotic pressure generation and drug release properties. Osmogens create an osmotic gradient, which leads to a better water uptake to the tablet core and controlled drug release.[9] Common pharmaceutical osmogens include mannitol, fructose, dextrose, lactose and inorganic salts, with each having unique solubility and osmotic properties which can have a significant impact on the performance of a formulation.[7,10]

Mannitol is used extensively in the osmotic system due to its high aqueous solubility, chemical stability and good compatibility with active pharmaceutical ingredients. Fructose and dextrose also have high osmotic activity and dissolution rate properties, so they are also well suited to be used as the core to create osmotic activity. Lactose is one of the most widely-used excipients in the pharmaceutical industry and can, in addition to the development of osmotic pressure, also enhance powder flow and compressibility. Different osmogens can be used to control release rate and provide opportunities to fine-tune the osmotic pressure to meet the therapeutic needs. The effect of single and combination of osmogen systems on release pattern of Glipizide from controlled porosity tablet is yet to be studied extensively.[11]

To realize the robust performance on the osmotic drug delivery, formulation variables need to be optimized. The water permeation rate, osmotic pressure generation, membrane integrity and drug release rate are in an ideal osmotic tablet in a balanced state. Too little osmotic activity can result in poor drug release and too much can cause instability of the membrane and change the drug release rate. So, there is a need for systematic evaluation of osmogen selection and concentration to determine formulations which release Glipizide in a controlled and reproducible way for a prolonged period of time.[12]

Besides formulation optimization, the knowledge of drug release in controlled release systems is essential in their rational development. Mathematical modelling of dissolution data offers useful information about the mechanism of drug dissolution and aids in comparing dissolution data from different formulations. The zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell equations are often used to describe release behavior and to investigate the relative contribution of diffusion, erosion, and osmotic pumping mechanisms. This kinetic analysis can play a crucial role in the development of osmotic systems, where the release rate and pattern must be sustained and predictable to achieve therapeutic success.[2,13]

There have been many formulations of Glipizide, but limited studies of multi-combination of osmogen controlled porous osmotic tablets. In addition, there are only a few comparative studies that assess the effect different osmogen systems have on release kinetics and formulation performance. This deficit can offer insights that can be used for the design of optimized formulations of osmotic type with better therapeutic outcome.[14]

Thus the objective of the present study was to develop and optimize the controlled porosity osmotic tablet of Glipizide with different combination of osmogen like mannitol, fructose, dextrose and lactose. The prepared formulations were found to have comparable physicochemical properties, in vitro dissolution profile and release kinetics to find an optimized system that can provide sustained and predictable drug release. The results of this investigation will aid in the development of osmotic drug delivery and help develop successful once-daily antidiabetic products.

2. MATERIAL AND METHOD

2.1 Material

Materials used for the experimental work are shown in Table .1

Table 1: List of Drugs and Excipients

Sr.No	Name of material	Specification	Category
1.	Glipizide	USP	Anti- Diabetic Drug
2.	Microcrystalline cellulose	AR	Diluent
3.	Mannitol	AR	Osmogent
4.	Fructose	AR	Osmogent
5.	Dextrose	AR	Osmogent
6.	Lactose	AR	Osmogent
7.	Polyvinyl pyrroialK-30	AR	Binder
8.	Talc	AR	Lubricant
9.	Magnesium stearate	AR	Lubricant

2.2 Compatibility Study Drug and Polymer

The physical interaction between the Glipizide, Mannitol, Fructose, Dextrose, MCC, Magnesium stearate, and Talc was studied in the stability chamber at a temperature of 40 °C C± 2 °C at dry conditions, and with 75%± 5% RH, for two weeks. [15] Samples kept were as follows (Table 2) These samples were kept for compatibility study and observed for caking, liquefaction, color change, or any other incompatibility

Table 2: Samples for compatibility study

Sr.No	Physical mixture	Initial Observation
1.	Glipizide	White color powder
2.	Glipizide: Mannitol(1:1)	White color powder
3.	Glipizide: Fructose(1:1)	White color powder
4.	Glipizide: Dextrose(1:1)	White color powder
5.	Glipizide: Lactose(1:1)	White color powder
6.	Glipizide: Microcrystalline cellulose(1:1)	White color powder
7.	Glipizide: Magnesium stearate(1:1)	White color powder
8.	Glipizide: Talc(1:1)	White color powder
9.	Glipizide :Mannitol: Fructose: Dextrose: Lactose	White color powder

2.3. Preparation Method

2.3.1 Preparation of Tablet Core

All ingredients required for the tablet core, except polyvinylpyrrolidone K-30 (PVP K-30), talc, and magnesium stearate, were accurately weighed and passed through a sieve. 80 to ensure uniform particle size. They were then mixed thoroughly to obtain a homogeneous blend. PVP K-30 was weighed separately and dissolved in a sufficient quantity of isopropyl alcohol to form a binding solution. A wet granulation technique was employed, in which the drug-excipient mixture was wetted with the PVP solution to form a damp mass. The resulting wet mass was passed through sieve no. 8 to form granules. These granules were dried at 50 °C for one hour, followed by screening through sieve no. 16 to achieve a uniform granule size. Finally, the dried granules were blended with talc and magnesium stearate, and the mixture was compressed into tablets using a rotary tablet compression machine fitted with 6 mm deep concave punches. The detailed composition of the tablet core formulation is presented in Table 3: Preparation of Core Tablets.

Table 3: Preparation of core tablets

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Glipizide	5	5	5	5	5	5	5	5	5	5
Mannitol	25	15	25	15	25	15	15	15	15	15
Fructose	15	25	-	-	-	-	13	-	13	9
Dextrose	-	-	15	25	-	-	13	13	-	9
Lactose	-	-	-	-	15	25	-	13	13	9
MCC	35	35	35	35	35	35	35	35	35	35
PVPK-30	8	8	8	8	8	8	8	8	8	8
Mg. Sterate	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1

***All quantities in mg**

2.3.2 Preparation of coating solution

To prepare the coating solution, cellulose acetate and potassium chloride were accurately weighed and mixed uniformly. Polyethylene glycol 400 (PEG 400) was then added to this dry blend, followed by continuous stirring for approximately 10 minutes to ensure proper homogenization. A solvent mixture comprising acetone and methanol was then added gradually with continuous agitation to form a clear and uniform coating solution. The detailed composition of the coating formulation is provided in Table 4: Coating Solution of the Tablet Core.

Table 4: Coating solution of the tablet core

Ingredients	C-I
Cellulose acetate(mg)	**3**
PEG-400(ml)	**2.5**
Potassium chloride (mg)	**0.2**
Acetone(ml)	**80**
Methanol(ml)	**20**

3. EXPERIMENT

3.1 Pre-compression Parameter Evaluation

The prepared granules and powder blends were evaluated for the flow properties by following the tests.[16]

3.1.1 Angle of Repose

For every powder formulation, the angle of repose, the greatest angle at which a pile of powder stays stable on a horizontal surface, was determined using the funnel technique. This was letting the powder run from a funnel onto a flat sheet of paper. Next, the behind equation was used to get the angle of repose utilizing the base radius (R) and the pile height (H). .[17,18]

$\tan \theta = H / R$

Therefore; $\theta = \tan^{-1}(H / R)$

3.1.2 Carr's index:

The Hausner ratio and compressibility index are well-liked, easy-to-use, and effective methods for assessing the flow properties of powders. Because the compressibility index reflects a wide range of influencing elements, it is recommended to utilize it as an indirect measure of bulk density, particle size and shape, surface area, moisture content, and material cohesiveness. The compressibility index and Hausner ratio are calculated using the powder's bulk volume and tapped volume as input. [19,20]

The following formula was used to obtain each formulation's Carr's index.

$\%\ \text{Compressibility} = V_o - V_f \times 10 / V_o$

Where,

Vo Tapped amount of powder

Vf Bulk amount of powder

3.1.3 Hausner Ratio:

Hausner Ratio = Tapped Density / Bulk Density

3.2 Evaluation of Osmotic Controlled Tablet of Glipizide:

The prepared tablets were evaluated based on several criteria, including Weight fluctuation, drug content, drug release, thickness, hardness, and friability.[21]

3.2.1. General Appearance:

For a tablet to be accepted by consumers, its overall design, visual identity, and "elegance" were crucial. A tablet's overall appearance is determined by measuring many characteristics, including its size, shape, color, odor, surface roughness, and distinguishable marks.[22]

3.2.2 Weight Variation

The tablets were checked to ensure the proper weight. As of each batch, twenty pills were chosen arbitrarily, weighed separately, and the middling weight was determined. The % variation is then calculated. [23]

3.2.3 Thickness

A screw gauge was used to measure the tablet thicknesses. Five tablets were selected at random and used for each formulation. The unit of thickness is millimeters.

3.2.4 Hardness:

The degree of resistance that tablets have to break when being handled, stored, and transported before being used is known as their tablet hardness. The hardness of each formulation's tablet was measured with a Monsanto hardness tester, and the results were reported in kg/cm^2.

3.2.5 Friability

Friability evaluates a tablet's durability. The following technique was used to examine this attribute with the Roche Friabilator: Before being put in the sinking apparatus, which rotates at 25 rpm and drops the tablets six inches with each revolution, the tablets were precisely weighed. The pills were reweighed after four minutes to calculate the proportion of weight loss. Conventionally, compressed tablets are deemed acceptable if they lose less than 0.5 to 1.0% of their weight.[22]

% Loss = (Initial wt. of tablets – Final wt. of Tablets) X 100 / Initial wt. of tablets

3.3. Drug Content

The drug content of all batches was determined. The percent medicine content was found by following the procedure.

3.3.1. In-Vitro

After precisely weighing three pills, they were crushed into a fine triturate. This powder was added to a 100 ml volumetric flask in a quantity equal to 30 mg of Glipizide. pH 6.8 phosphate buffer was partially added to the flask, which was then sonicated and agitated for 10 min. After adding more phosphate buffer to get the amount up to 100 ml, the mixture was filtered using Whatman filter paper no. 41. A spectrophotometer calibrated at 276 nm was used to measure the drug concentration of the filtrate after it had been diluted as necessary. The blank solution used for the analysis was a pH 6.8 phosphate buffer. Throughout 12 hours, the Glipizide release rate from osmotic tablets was ascertained using the USP-type II dissolving testing device, also known as the paddle type. 900 cc of pH 6.8 phosphate buffer was spun at 50 rpm for 12 hours to conduct the dissolving test. At predefined intervals during the 12-hour trial, 5 mL samples were taken out of the dissolving apparatus and replaced with fresh dissolving liquid. Following filtration, a Japanese Shimadzu UV-1800 UV/Vis double-beam spectrophotometer was used to measure the concentration of Glipizide in these samples at 276 nm.[24] The formula that was developed from a standard curve was used to compute the collective percentage of drug release.

3.3.2. FTIR Study

FTIR of optimized formulation F-2 Mannitol: Fructose (30:50) was carried out using compartment and scanned between wave number4000^{-1} to 600 cm^{-1} using a Shimadzu Mode l8400 FTIR with ATR. 24 The formulation spectrum peaks at 3282.84 cm^{-1} for N-H stretching, 2902.87cm^{-1} for[C=O]carboxylic acid, 1425.40 cm^{-1} for – CH bend, 1280.73 cm^{-1} for – [S=O] Sulfonyl,1649.14cm^{-1}for Amides group are seen. (fig 01) These are quite identical to the reported wave numbers. These peaks are identical to those obtained in individual spectra of the drug and excipients. Thus, it establishes the compatibility between drugs and excipients.

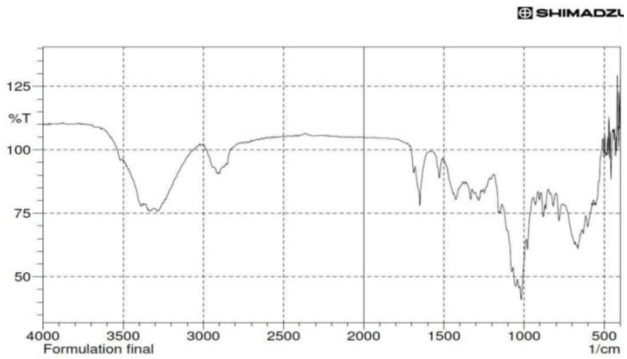

Fig. 1 Infrared spectrum of optimized formulation

3.4. The Kinetics of Drug Release

Drug release kinetics is assessed by combining data from in vitro release in several kinetic models.[25]

3.4.1Zero Order Kinetics

The rate of drug release is dependent upon concentration, as demonstrated by tracking the cumulative percentage of drug release over time.[26]

C=Kθt

Here, t is the time in hours, and Kθ is the zero-order rate constant in concentration units/time.

3.4.2. Kinetic model of first-order

Plotting the drug's log cumulative percentage remaining against time showed that the relief rate is concentration-dependent. [15]

Log C =logC0-Kt/2.3030

where,

K is the first-order persistent, t is the time in hours, and C0 is the drug's initial concentration.

3.4.3. Higuchi kinetics

Based on Fickian diffusion principles, Higuchi's model explains the time-dependent pattern of drug release from an insoluble matrix. In this approach, the release rate is determined by the square of the time. When the cumulative drug release is plotted against the square root of time, a linear graph is produced.[27,28]

$$Q=Kt_{1/2}$$

Where systemt1/2=time in hours and K=constant reflection design variable.

The drug release rate and the reciprocal of the square root of time are exactly proportionate. A dosage form is considered to follow Higuchi kinetics of drug release if its plot displays a straight line with a slope of one.

3.4.4. Hixson-Crowell erosion equation

The Hixson-Crowell rate equation was used to investigate the link between differences in surface area and particle span and their implications on the drug release mechanism. Plotting the cube root of the remaining drug % in the matrix versus time resulted in the creation of a graph.[29,30]

$$\sqrt[3]{Q0}-Qt=K_{HC}t.$$

Where,

Qt: Quantity of drug released in time

tQ0= First amount of drug in tablet.

K_{HC}=Rate perpetual for Hixon Crowell rate equation.

3.4.5.Korsmeyer-Peppas equation

To examine the drug relief process, the data were then graphed using Peppa's equation, which involved charting the logarithm of the cumulative percentage of the medication released against the logarithm of time.[31,32]

Mt/Mα=K t n,

Log Mt/Mα=log K+ n logt

Where,

Mt/Mα=Drug release fraction at period t; K=Kinetic rate perpetual
t=Time of release
n=Diffusion proponent suggestive of the drug release mechanism

When many release mechanisms are at work or the release process is unclear, this model is used to evaluate the release of pharmacological polymeric dosage forms. The slope of the plot of the logarithm of the cumulative percentage of medication released vs. the logarithm of time can be used to calculate the n value 34,35

4. RESULT

4.1 Pre-compression Parameters

The fixed funnel technique revealed that the granules had exceptional flow properties, with angle of repose values ranging from 25° to 28°. The findings for the compressibility index, tapped density, and loose bulk density are shown in the Table 5. With a range of 7.91±0.19 to 11.5±0.085 for the compressibility index, the granules' flow qualities are excellent, too good

Table 5: Pre-compression parameters of Granules in all Formulations

Formulation No.	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Compressibility Index (%)	Hausners Ratio	Angle of Repose(θ)
F1	0.3807±0.002	0.4303±0.003	11.5±0.085	1.12±0.0057	26.23±0.59
F2	0.3969±0.001	0.4396±0.006	9.6±1.458	1.1±0.0173	27.54±0.31
F3	0.3867±0.003	0.4252±0.003	9.03±1.285	1.09±0.015	26.7±0.12
F4	0.3849±0.007	0.4264±0.0011	9.73±0.326	1.10±0.0052	28.79±0.07
F5	0.3924±0.0005	0.4361±0.0012	10.0±0.2433	1.10±0.0057	28.10±0.36
F6	0.3877±0.0012	0.4426±0.0053	8.94±1.108	1.09±0.005	27.91±0.05
F7	0.3963±0.0010	0.4392±0.0062	9.74±1.14	1.1±0.017	25.85±0.11
F8	0.3947±0.0028	0.4305±0.0004	8.35±0.5200	1.08±0.0057	25.70±0.15
F9	0.3813±0.0006	0.4270±0.0017	10.66±0.413	1.11±0.005	28.76±0.15
F10	0.3964±0.001	0.4305±0.004	7.91±0.19	1.08±0.0057	28.89±0.08

4.2. Post-Compression Parameters

Post-compression results (Table 6) confirmed uniform weight, acceptable hardness (5.66–6.16 kg/cm^2), and consistent thickness (3.3–3.5 mm). Drug content ranged from 94.9% to 99.2%, with friability well below 1%, ensuring mechanical stability.

Table 6: Compression parameters of all Formulations.

Formulation No.	Weight Variation(n=20)	Hardness kg/cm2(n=3)	Thickness mm(n=3)	%Drug content (n=3)	%Friability (n=10)
F1	191.1±0.08	5.66±0.450	3.33±0.115	98.7±0.96	0.20
F2	182.1±0.72	5.96±0.115	3.43±0.057	99.2±0.62	0.15
F3	190.7±0.62	6.1±0.2	3.33±0.208	97.9±0.68	0.10
F4	190.48±0.56	6.06±0.152	3.46±0.05	97.4±0.66	0.10
F5	190.5±0.51	5.96±0.115	3.5±0.1	98.3±0.49	0.20
F6	191.5±0.89	6.16±0.115	3.36±0.05	96.06±0.92	0.31
F7	191.8±0.75	6.1±0.2	3.5±0.1	98.8±0.51	0.20
F8	191.3±0.48	6.06±0.152	3.43±0.05	98.06±0.55	0.26
F9	193.06±0.11	6.1±0.2	3.46±0.11	94.9±0.87	0.15
F10	193.2±0.2	5.9±0.1	3.4±0.1	98.8±0.60	0.15

4.3. In-Vitro Drug Release Study

The in vitro release profile (Table 7) F1, F2, F3, F4, F5, and F6 have very different release profiles. Due to the osmotic agents' concentrations, F1 and F2 displayed greater medication release than F3, F4, F5, and F6. Higher osmotic pressure was seen in F1 and F2, which contained fructose and mannitol. This led to increased medication release. Lower osmotic pressure in F3 and F4, which contained mannitol and dextrose, led to reduced medication release. In comparison to fructose and dextrose, F5 and F6, which contain mannitol and lactose, showed even poorer osmotic pressure and drug release. Higher osmotic pressure was seen in F7 and F9, which contained mannitol, fructose, and either lactose or dextrose. This led to a greater release of medication. Combinations of mannitol, dextrose, and lactose in F8 and F19 resulted in decreased osmotic pressure and decreased drug release.

Table 7: In-vitro drug release of formulation F1-F10 with coating-I

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	10.1±0.70	10.7±0.66	10.1±0.23	9.1±0.75	8.1±0.99	8.9±0.45	10.5±0.98	10.1±0.45	11.7±0.35	10.3±0.89
2	15.3±0.63	14.4±0.87	13.3±0.65	12.4±0.88	10.1±0.64	11.2±0.87	15.8±0.48	12.3±0.78	17.5±0.67	11.8±0.56
3	17.4±0.64	18.3±0.77	15.6±0.76	16.7±0.97	13.5±0.75	14.7±0.35	18.9±0.44	14.7±0.64	20.1±0.86	13.3±0.89
4	21.7±0.72	23.4±0.73	20.1±0.88	21.8±0.56	18.9±0.45	17.5±0.76	20.8±0.23	21.3±0.34	25.3±0.89	20.4±0.86
5	33.9±0.41	37.5±0.72	29.8±0.96	27.5±0.86	23.7±0.45	24.7±0.34	23.8±0.87	25.8±0.56	27.3±0.78	25.4±0.66
6	40.5±0.77	42.1±0.88	33.9±0.92	34.1±0.89	29.9±0.53	30.8±0.88	39.9±0.79	31.8±0.56	37.8±0.56	29.1±0.89
7	45.1±0.82	47.5±0.66	42.1±0.74	41.3±0.78	33.5±0.86	34.5±0.34	47.3±0.88	40.9±0.35	49.7±0.88	33.8±0.99
8	50.2±0.49	51.8±0.55	48.2±0.67	47.8±0.99	40.7±0.23	42.9±0.98	58.9±0.87	47.1±0.67	57.3±0.23	40.8±0.54
9	66.7±0.70	60.1±0.92	55.3±0.58	54.7±0.74	45.3±0.45	47.8±0.56	65.8±0.66	50.1±0.87	69.3±0.67	59.3±0.67
10	75.6±0.77	69.8±0.55	62.3±0.85	63.1±0.67	50.9±0.28	51.3±0.76	70.3±0.45	59.7±0.99	75.3±0.89	63.7±0.65
11	83.8±0.71	78.1±0.53	70.1±0.98	69.9±0.88	59.7±0.76	57.9±0.54	77.9±0.89	65.8±0.89	89.3±0.89	70.1±0.89
12	88.8±0.55	89.1±0.45	72.2±0.88	73.9±0.78	63.8±0.56	65.8±0.88	90.7±0.89	70.1±0.89	93.1±0.89	79.8±0.89

4.4. Kinetics of Drug Release

The in-vitro drug release kinetics study indicated that formulations F-1, F-4, and F-9 had zero-order kinetics with (r^2) values ranging from 0.98 to 0.99. When Korsmeyer's equation was used, the release exponent (n) ranged from 0.62 to 0.88, indicating that the drug release from the osmotic tablets followed an unusual non-Fickian diffusion process ($0.45 < n < 0.89$).(Table no 8)

Table 8: Release kinetic parameters of the designed controlled-release osmotic Tablets of Glipizide with C-I.

Formulation No.	Zero-order(r2)	First Oder (r2)	Higuchi (r2)	Hixson Crowell (r2)	Korsmeyr Peppas (r2)	Korsmeyer Peppas(n)	Best Selected model
F1	0.981	0.884	0.976	0.968	0.962	0.762	Zero order
F2	0.983	0.887	0.992	0.968	0.937	0.784	Higuchi
F3	0.939	0.974	0.954	0.799	0.918	0.885	First order
F4	0.994	0.916	0.978	0.762	0.909	0.828	Zero order
F5	0.991	0.943	0.970	0.732	0.933	0.763	Zero order
F6	0.986	0.904	0.973	0.740	0.905	0.773	Zero order
F7	0.983	0.808	0.974	0.816	0.908	0.819	Zero order
F8	0.987	0.907	0.981	0.747	0.925	0.624	Zero order
F9	0.965	0.876	0.987	0.810	0.969	0.687	Zero order
F10	0.938	0.941	0.968	0.799	0.950	0.803	Higuchi

5. DISCUSSION

The pre-compression parameters established effective flow characteristics, providing consistent granulation and compressibility. Post-compression values were acceptable as per pharmacopeia, indicating good tablet design. F1 and F2 showed faster release of drugs as a result of increased osmotic pressure by fructose and mannitol, while F5 and F6 with mannitol and lactose released the drug slowly because of a lower osmotic driving force. The addition of dextrose in F4 and F10 comparatively increased the rate of release. F9 is the most effective release (93.1%) with the synergistic combination of mannitol, fructose, and dextrose. This indicates the function of optimised osmotic agents in facilitating extended and total drug release. Kinetic modeling validated that the release mechanism obeyed mostly zero-order kinetics in the majority of the formulations, exhibiting constant drug delivery rates that are best suited for controlled-release systems. Korsmeyer-Peppas analysis validated anomalous (non-Fickian) diffusion, which suggests that both diffusion and erosion controlled release. Systematic design of formulation with different combinations of osmotic agents greatly influenced drug release performance. Therefore, mannitol-fructose-based systems are potentially suitable for the development of osmotic-controlled oral tablets for Glipizide.

CONCLUSION

Controlled-release osmotic Glipizide pills were developed in an attempt to minimize adverse effects, minimize dosage frequency, and minimize expenses. These tablets were prepared using different osmotic agents, such as mannitol, fructose, lactose, and dextrose, either separately or in combination. The semipermeable membrane undercoat solution consisted of cellulose acetate, with PEG-400 serving as the pore-forming agent, and acetone-methanol as the solvent. Findings from in-vitro dissolution studies revealed that Dextrose and lactose, either alone or combined with Mannitol, failed to maintain drug release for up to 12 hours. Therefore, the inclusion of other osmogens, namely Mannitol and Fructose, was deemed necessary to achieve extended drug release. The F-02 formulation, which incorporated a combination of Mannitol and Fructose, successfully extended complete drug release for up to 12 hours.

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