ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Development of Osmotic Drug Delivery System to Control the Release Pattern of Drug Repaglinide

Paras Pophalkar, Sarita Karole*

Faculty of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

Article History:

Received on: 08 May 2023
Revised on: 10 Jun 2023
Accepted on: 13 Jun 2023

Keywords:

Novel drug delivery systems,
drug delivery,
bioavailability,
osmotic pump,
drug solubility,
osmotically controlled drug delivery systems

ABSTRACT

The osmotic drug delivery system is a specific type of drug delivery system that regulates the medication release pattern using osmotic pressure. The components of this system include a drug core, a semipermeable membrane, and an osmotic agent. Water is transferred into the osmotic agent across the semipermeable membrane when the drug delivery system is placed in an aqueous environment. This causes the osmotic agent to expand and put pressure on the drug core. This pressure causes the medicine to be released under regulated conditions via a tiny opening in the semipermeable membrane. In comparison to conventional drug delivery methods, the development of osmotic drug delivery systems provides a number of benefits, including increased therapeutic effectiveness, less toxicity, and enhanced patient compliance. The semipermeable membrane's composition, the type and amount of the osmotic agents being employed, as well as the size and number of orifices, may all be changed to easily adjust the rate at which medications are released. In the present work, an osmotic drug delivery system of Repaglinide drug had been developed and characterized with various parameters. This drug delivery system showed potential results to improve drug delivery in the patients.

*Corresponding Author

Name: Sarita Karole
Phone:
Email: ritak000123@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v14i3.4287

Production and Hosted by

IJRPS | https://ijrps.com

INTRODUCTION

Significant progress has been achieved in the field of innovative drug delivery systems (NDDS) during the last three decades. The main focus of pharmaceutical research and development is NDDS. Thus, applying an NDDS to a novel chemical entity just requires a little investment of time and money in development [1, 2]. The development of pharmaceuticals has largely depended on the controlled drug delivery system, one of the several NDDS currently on the market. This is because patient comfort and compliance have improved, steady state plasma level variation has decreased, the severity of local or systemic adverse effects has decreased, and the safety margin for high strength medications has increased [3, 4]. Control release (CR) systems have a maximum drug utilisation, allowing for a decrease in the total dosage given and the delivery of pharmaceuticals with a short biological half-life [5, 6].

One of the most promising drug delivery technologies, osmotically controlled drug delivery systems (OCDDS), uses osmotic pressure as a driving factor for the controlled distribution of pharmaceuticals. Due to the semipermeable nature of the rate-controlling membrane and the design of the deliver orifice employed in osmotic systems, drug release from OCDDS is independent of pH and hydrodynamic conditions of the body, leading to a high

degree of in vitro/in vivo correlation. In comparison to other diffusion-based systems, it is also feasible to achieve larger release rates in these ones [7].

Controlled porosity osmotic pump tablets are typically made in an OCDDS by spray coating a semipermeable membrane with substances that may leach into the pores [8]. These devices lack an aperture through which pharmaceuticals may be released, but instead accomplish drug release via holes created in situ during surgery in the semipermeable membrane [9]. In these systems, the drugs are released from the osmotic pump tablet by hydrostatic pressure and diffusion via holes made possible by the dissolution of pore formers included into the membrane after the drug has been dissolved within the core. After water has been ingested over the semipermeable barrier, either an osmotic agent, the medicine itself, or the components of the tablet produce hydrostatic pressure [10].

Drugs having a shorter biological half-life (2–6 hours) such as nifedipine, verapamil, and glipizide are suitable candidates for osmotic administration since very strong medications are often needed for sustained treatment of illnesses [11]. OCDDS formulations also need critical osmogens in order to sustain the osmotic gradient across the membrane. Additionally, they provide a driving force for water absorption and help to maintain the drug homogeneity in the hydrated formulation. Repaglinide, a nonsulfonyl urea, decreases the plasma glucose concentrations in patients with type 2 diabetes by boosting glucose-stimulated insulin release from the pancreatic beta cells, making it a unique, short-acting insulin secretagogue. In the present study effort, we designed a controlled porosity osmotic pump tablets to release the repaglinide medicine at zero order release.

MATERIALS AND METHODS

Materials

Repaglinide pure drug were received as a gift sample from Torrent Pharmaceuticals Ltd. Gangtok, Sikkim. Microcrystalline cellulose, PEG 4000 and polyvinyl pyrrolidone were taken from Laboratory Reagent, Research lab Mumbai; cellulose acetate, PEG 400, potassium chloride, sodium chloride, magnesium stearate and isopropyl alcohol were taken from Thomas Baker Chemicals Ltd. Mumbai. All other chemicals used were of analytical grade.

Preformulation study of drug

One of the crucial steps in the creation of any drug delivery system is the preformulation research. It provides the details required to specify whether the medication release is diffusion or dissolution. Therefore, preformulation investigations of the drug repaglinide for identification have been carried out in this research work, including solubility analysis, melting point determination, FTIR study of the drug, determination of λ max, construction of calibration curve, etc. [10].

Solubility analysis

An evaluation of the drug's solubility prior to formulation, which included choosing the best solvent to dissolve it, was conducted. In order to determine the solubility, the solute was added to a predetermined volume of solvents in small, incremental volumes. After each addition, the system was decisively agitated, and any undissolved solute particles were visually checked. The entire quantity added up to this point served as an estimate of the solubility when part of the solute is not completely dissolved [12].

Determination of melting point

To verify the sample's purity, the drug's melting point was determined using the Thiele tube technique. A capillary tube containing repaglinide was filled and sealed at one end before being connected to the thermometer's base. The liquid paraffin collected in the tube was used to submerge the thermometer and capillary tube. Burner was used to gradually heat the tube's bottom. The reading was taken as soon as the sample began to melt.

Determination of wavelength

Repaglinide was made by combining 10 mg of the drug with 100 ml of methanol to produce a stock solution of 100 g/ml. This stock solution served as the basis for the working standard. Then, using UV Agilent technology, carry 60 UV-Visible spectrophotometers to scan the spectrum in the region of 200-400 nm to identify the drug's maximum wavelength.

Calibration curve of Repaglinide

In 0.1 N HCL Solution

Repaglinide was carefully weighed at 100 mg per 100 ml in a volumetric flask before being diluted with 0.1 N HCL solution to the proper concentration in order to create the standard stock solution (1000 g/ml). Then, 10 ml of the stock solution was diluted in a 100 ml volumetric flask with 0.1N HCL until the desired concentration of 100 g/ml of repaglinide was achieved. In order to create concentrations in the range of 5 to 25 g/ml, various stock solution aliquots of 5, 10, 15, 20, and 25 were made up to 100 ml with 0.1 N HCL.

In pH 6.8 buffer

A precisely weighed 100 mg of repaglinide was

placed in a 100 ml volumetric flask to create the standard stock solution of repaglinide (1000 g/ml), which was then diluted with pH 6.8 buffer to the desired strength. Repaglinide solution containing 100 g/ml was created from the standard stock solution by diluting 10 ml in a 100 ml volumetric flask to the proper pH 6.8. In order to create concentrations in the range of 5 to 25 g/ml, various stock solution aliquots of 5, 10, 15, 20, and 25 were made up to 100 ml with 0.1 N HCL.

FTIR spectroscopy

Fourier transform infrared (FT-IR) study has been performed to identify the repaglinide drug, excipients and their physiochemical compatibilities with the help of Agilent Technology Cary 630.

Formulation of osmotic tablets

With the exception of PVP K30, Talc, and magnesium stearate, all of the ingredients for the core tablet went through Sieve No. 85. All materials were measured out precisely, and PVP K30 was dissolved in enough isopropyl alcohol. The process of wet granulation was used to create the granules. The produced granules were sieved through No. 18 after drying at 500°C for an hour. The produced granules were combined with the talk and magnesium stearate after which the mixture was compacted into tablets using a tablet punching machine.

Preparation of coating solution

All chemicals, including cellulose acetate as a polymer, PEG 400 as a plasticizer, and PEG 4000 as a pore-forming agent, were precisely weighed. For the preparation, required amount of acetone and methanol were added to weighed amount of PEG 4000 (30%) and 40% of cellulose acetate. Stirred and dissolved completely in the solvents. Then, PEG 400 was added slowly to 20% of cellulose acetate. This mixture was again agitated with a mechanical stirrer at a speed of 100 rpm after the addition was complete. After that, the sunset yellow pigment was carefully blended to provide a clear sunset yellow color solution.

Coating of core tablet

In a standard laboratory type stainless steel 15 cm pear-shaped baffled coating pan, 20 batches of tablets were coated. The coating solution was manually applied to the tossing bed of tablets using a spray pistol at a pan speed of 25 rpm. Spraying and drying procedures were carried out manually, and the input air temperature was kept between 40 and 45 °C. The percentage weight growth of the tablet compared to the actual weight of the core tablet was used to regulate the coat weight and coating thickness. The coated tablets were then given time to finish drying in a hot air oven set at 60°C.

Evaluation of tablets

Evaluation of granules

Bulk density

After being blended, a precisely weighed powder was obtained, gently agitated to separate any agglomerates, and then added to a measuring cylinder. The powder's volume was measured to determine its bulk volume. Powder's bulk density (BD) was calculated using the formula below [13];

Bulk density=Wt. of powder gm Bulk volume of powder cm3

Tapped density

After mixing, a precisely weighed powder was obtained, gently shook to eliminate any remaining agglomerates, and then placed into a measuring cylinder. The measuring cylinder was tapped until there was no longer any volume change, at which point the tapped volume was obtained. Using the following formula, the powder's tapped densities (TD) were calculated.

Tapped density=Wt. of powder gm Tapped volume of powder cm3

Angle of repose (θ)

Solid material flow characteristics are described using the angle of repose. It is a distinctive technique that deals with inter-particle friction or resistance to particle movement. The following formula was used to obtain the angle of repose (θ) for powder;

$\tan \theta = h/r$

Where, angle of repose is presented by θ, the height of the pile of powder is h (h=1), and the radius of the base of cone is presented via r.

Hausner's Ratio

Hausner's ratio is a proximate indicator of powder flow simplicity. Better flow qualities are indicated by a lower Hausner's ratio (<1.25) than by a greater one (>1.25). Bulk density and tapped density measurements were made, and following formula was used to get the Hausner's ratio;

Hausner's ratio=Tapped densitygmcm3Bulk densitygmcm3

Compressibility Index

The small amounts of powder may be used to estimate the compressibility index. The more flow attributes a material possesses, theoretically, the less compressible it is. The formula below is used to calculate the compressibility indices of the powder mixtures,

% Compressibility=ρ_t-$\rho_0\rho_t \times 100$

Where, ρ_0 = Bulk density, ρ_t =Tapped density.

Evaluation of uncoated tablet

Before coating, the uncoated tablets underwent a number of tests to assess their hardness, friability, weight consistency, content uniformity, and thickness.

Weight variation test

20 tablets were subjected to a weight variation test by being individually weighed, the average weight being determined and the individual tablet weights being compared to the average USP weight variation test.

Friability

The purpose of a friability test is to evaluate how friction and shocks may affect a tablet and often lead it to chip, cap, or shatter . The friability was examined using the Roche friabilator. Utilizing the following formula, the percentage of friability of the tablets was calculated;

%F= {1-Wo-W}×100

where, friability in percentage (% F), initial weight of tablet (Wo), and weight of tablets after revolution (W).

Content uniformity

For the content uniformity test, 10 tablets were broken down into powder using a mortar and pestle, and a quantity equal to 10 mg of Vildagliptin was then dissolved in 100 mL of phosphate buffer with a pH of 6.8. Following filtering, the absorbance at 230 nm of the solution was measured using a UV spectrophotometer to determine the amount of Vildagliptin present. Content uniformity was calculated with the help of following formula;

Content uniformity= Conc. in mcg/ml×100×dilutionfactor1000

The percentage content uniformity is calculated by:

% Content uniformity= Practical yield×100Theoretical yield

Hardness

Tablets need to be strong enough to withstand the mechanical shocks that occur during production, packing, and shipment. A tablet hardness tester (Monsanto type) was used to gauge the tablets' hardness.

In this, the pressure needed to break the tablet diametrically was measured after the tablet had been inserted between the plungers and tightened from one end. In kg/cm2, the hardness was determined.

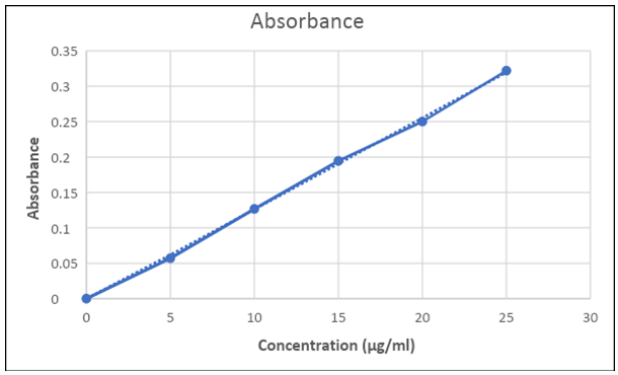

Figure 1: Calibration curve for Repaglinide in 0.1 N HCl

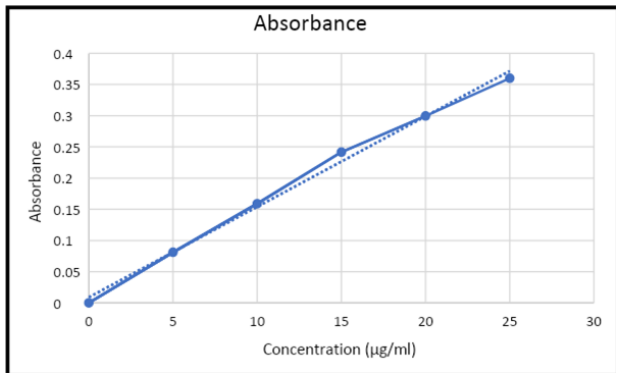

Figure 2: Calibration curve for Repaglinide in phosphate buffer pH 6.8

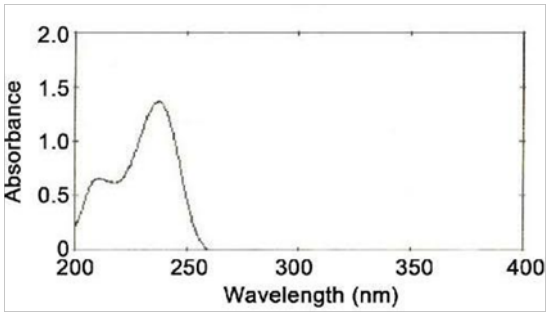

Figure 3: Determination of λ max of Repaglinide

Uniformity of thickness

Using a Digital Vernier calliper, the thickness of the tablets was measured consistently.

Evaluation of osmotic tablets

Osmotic tablets were coated and then tested for weight uniformity, dissolving in the produced formulas, tablet and film thickness, and tablet thickness.

Thickness of tablets

After coating, all tablets were first given the go-ahead to have their thickness measured using a digital Vernier calliper. Three copies of each measurement were taken.

Table 1: Evaluation of prepared granules

Formulatic code	Angle of repose	Bulk density mean ±S.D.	Tapped density mean ±S.D.	Compressibility index (%) mean ±S.D.	Hausner's ratio mean ±S.D.
F1	28.96±0.026	0.3818±0.007	0.4789±0.06	11.56±0.026	1.23±0.056
F2	28.29±0.025	0.3731±0.007	0.4372±0.05	13.69±0.016	1.22±0.066
F3	27.90±0.012	0.3696±0.088	0.4598±0.029	16.05±0.061	1.31±0.081

*All the values were represented as mean ±S.D. (standard deviation)(n=3)

Table 2: Evaluation of uncoated tablet

Formulation	Average Weight (mg) *** mean ±SD	Hardness (kg/cm2) **Mean ±SD	Thickness (mm) * Mean ±SD	Friability (%) *** Mean ±SD	Diameter (mm) *Mean ±SD	Drug content (%) * Mean ±SD
B1	155.63±0.01	6.30±0.16	3.21±0.03	0.47±0.01	4.01±0.01	98.82±0.6
B2	155.80±0.01	6.28±0.15	3.31±0.03	0.45±0.01	4.03±0.01	96.57±0.7
B3	155.36±0.01	6.00±0.16	3.02±0.02	0.46±0.01	4.00±0.01	98.74±0.9

All the values were represented as mean ± SD = (n=3), **= (n=5), ***=(n=20)

Table 3: Evaluation of Osmotic Tablets

Formulation Code	Average weight (mg) *** mean ±SD	Thickness of coated tablet (mm) * mean ±SD	Diameter(mm) * mean ±SD	Drug content (%) *mean ±SD
B1C1	161.6±0.08	4.09±0.035	5.70±0.01	97.82±0.614
B1C2	164.4±0.08	4.90±0.032	5.80±0.05	98.57±0.782
B1C3	162.9±0.07	3.59±0.026	5.70±0.018	98.74±0.974
B1C4	165.9±0.09	4.50±0.035	5.80±0.013	97.82±0.614
B2C1	163.1±0.05	3.50±0.032	5.70±0.021	96.57±0.782
B2C2	164.1±0.08	4.19±0.026	5.80±0.016	98.74±0.974
B2C3	161.9±0.06	4.00±0.035	5.70±0.02	98.74±0.974
B2C4	164.9±0.09	4.70±0.032	5.80±0.03	97.82±0.614
B3C1	162.2±0.08	3.59±0.026	5.70±0.02	96.57±0.782
B3C2	165.01±0.07	3.90±0.035	5.80±0.04	97.74±0.974
B3C3	163.1±0.07	4.10±0.032	5.70±0.03	97.82±0.614
B3C4	166.1±0.07	4.90±0.026	5.80±0.02	98.57±0.782

Weight uniformity

According to the procedure outlined in the Indian Pharmacopoeia, the weight variation of the coated tablets was estimated by weighing each of the 20 tablets separately and calculating their average weight.

Dissolution test

This test is intended to ascertain if solid dosage forms intended for oral administration comply with the dissolving requirement. Due to the enteric coating on the tablet, both buffer pH and acidic pH were used for the dissolution. Dissolution tests were conducted using the I-IP (Electrolab TDT 08L) dissolution test device.

Evaluation of optimized formulation

The optimized batch was selected on the basis of model Kinetic model fitting method which showed that the release pattern of osmotic tablet whether it follow the required drug release kinetic or not.

To study the effect of pH on drug release of optimized formulation

The osmotic tablet should not be affected by changing the pH in GIT. Therefore, these tablets have been introduced to different pH of 0.1 N HCl, pH 6.8 buffer,

Table 4: Cumulative % Drug Release of B1C1-B1C4

Time (hr)	Cumulative % drug release			
	B1C1	B1C2	B1C3	B1C4
1	30.16	20.91	32.07	29.99
2	39.74	45.49	40.7	49.05
3	48.06	45.81	43.69	51.44
4	56.93	57.96	60.37	64.47
5	59.59	60.02	67.11	77.44
6	69.86	70.78	76.32	77.73
7	80.11	81.69	82.96	83.64
8	89	83.31	88.37	88.17
9	90.29	90.24	89.35	89.54
10	91.06	93.57	94.77	94.90
11	92.76	93.68	95.54	95.77
12	92.99	93.88	95.54	95.77

Table 5: Cumulative % Drug Release of B2C1-B2C4

Time (hr)	Cumulative % Drug release			
	B2C1	B2C2	B2C3	B2C4
1	10.49	20.78	17.27	26.54
2	21.19	23.44	31.75	29.5
3	32.73	33.86	39.28	40.38
4	38.91	35.04	48.82	51.66
5	46.02	50.7	60.08	53.88
6	49.37	66.63	63.91	60.54
7	53.28	71.32	70.98	66.71
8	59.42	84.69	78.64	71.96
9	59.59	89.73	79.28	76.94
10	73.08	91.71	84.89	80.42
11	73.91	99.34	89.73	90.93
12	85	99.22	93.06	98.93

Table 6: Cumulative % Drug Release of F3C1-F3C4

Time (hr)	Cumulative % Drug release			
	B3C1	B3C2	B3C3	B3C4
1	28.54	38.21	26.34	40.21
2	38.91	41.81	38.99	44.26
3	43.29	50.65	44.46	51.22
4	49.9	56.45	50.9	58.92
5	57.29	60.39	58.21	61.28
6	62.26	68.93	69.08	70.76
7	70.33	69.37	74.75	76.9
8	73.92	72.88	74.29	72.91
9	75.29	74.99	79.33	74.39
10	79.1	80.91	86.29	88.29
11	91.21	92.69	93.21	94.24
12	98.29	99.29	97.11	96.64

Table 7: Kinetic release of prepared Repaglinide osmotic tablet formulations

Formulation Codes	Zero Order	First order
B1C1	0.964924801	0.71285462
B1C2	0.963834286	0.7310254
B1C3	0.960506854	0.7101941
B1C4	0.934365187	0.68968937
B2C1	0.934365187	0.68968937
B2C2	0.988481105	0.80265683
B2C3	0.906273147	0.65028635
B2C4	0.967771625	0.72426156
B3C1	0.949826565	0.69548835
B3C2	0.908787741	0.65154527
B3C3	0.959438916	0.71181666
B3C4	0.906273147	0.65028635

Table 8: Cumulative % drug release of optimized batch

Time (hr)	Cumulative % drug release
1	20.78
2	23.44
3	33.86
4	35.04
5	50.7
6	66.63
7	71.32
8	84.69
9	89.73
10	91.71
11	99.34
12	99.22

Table 9: Cumulative % drug release of optimized formulation to study effect of pH

Time	Cumulative % Drug release		
	B2C2 0.1N HCL	B2C2 pH 6.8	B2C2 pH 7.4
1	20.61	19.78	21.52
2	25.5	23.94	23.29
3	29.91	33.86	29.81
4	37.67	35.14	36.66
5	41.97	50.7	37.07
6	49.56	67.63	46.86
7	52.91	77.32	52.98
8	68.7	88.69	69.71
9	82.28	89.73	74.12
10	86.9	94.71	89.92
11	94.98	99.84	91.1
12	97.82	99.22	98.2

Table 10: Agitation intensity on % drug release of optimized formulation B2C2 at 50 and 100 rpm

Time (hr)	Cumulative % drug release	
	B2C2 50 rpm	B2C2 100 rpm
1	20.78	22.64
2	23.44	25.81
3	33.86	29.69
4	35.04	38.69
5	50.7	49.89
6	66.63	57.26
7	71.32	75.99
8	84.69	88.01
9	89.73	92.21
10	91.71	96.41
11	99.34	98.16
12	99.22	99.06

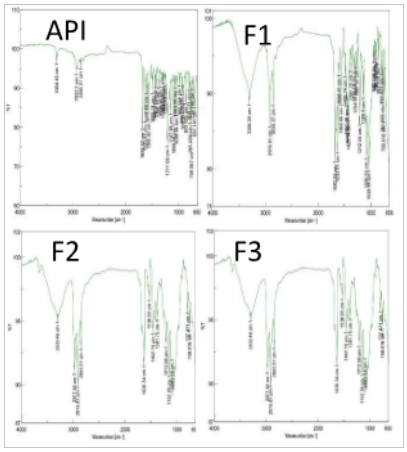

Figure 4: FTIR spectrum of Repaglinide and various excipients used during formulation of different samples

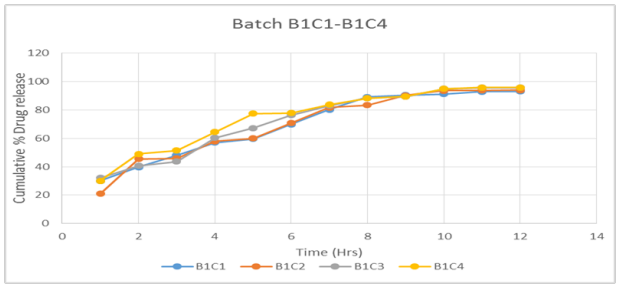

Figure 5: Drug release profile of B1C1 to B1C4

pH 7.4 buffer solution and then also performed a dissolution test.

To study effect of agitation intensity on drug release of optimized formulation

To assess the impact of agitation on the drug release, the osmotic tablets were tested at 50 and 100 rpm.

Stability study of optimized formulation

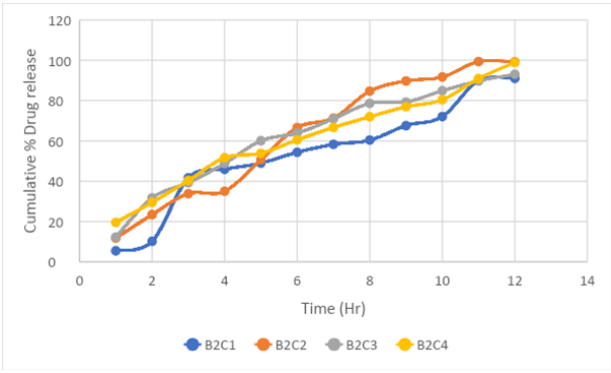

Figure 6: Drug release profile of F2C1 to F2C4

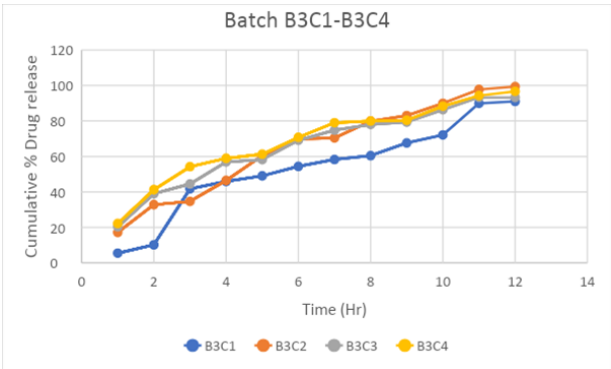

Figure 7: Drug release profile of B3C1-B3C4

On the vildagliptin osmotic tablets, short-term stability experiments were conducted over a three-month (90-day) period at a temperature of 402°C/75±5% RH. A sufficient quantity of tablets (15 tablets) was packaged in amber-colored rubber stopper vials and stored in a stability chamber with a temperature of 40±2°C and a relative humidity of 75±5%. After 90 days, samples were taken out, and a dissolution test was run to assess the drug release profile.

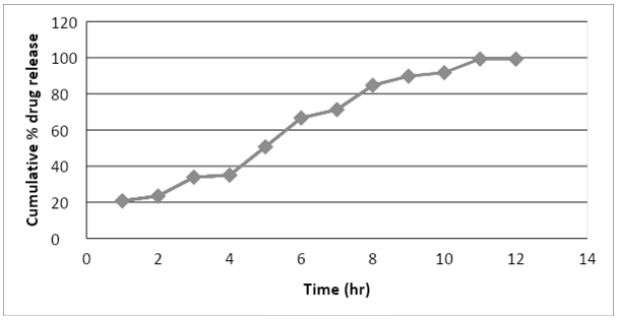

Figure 8: In vitro release of Optimized formulation of B2C2

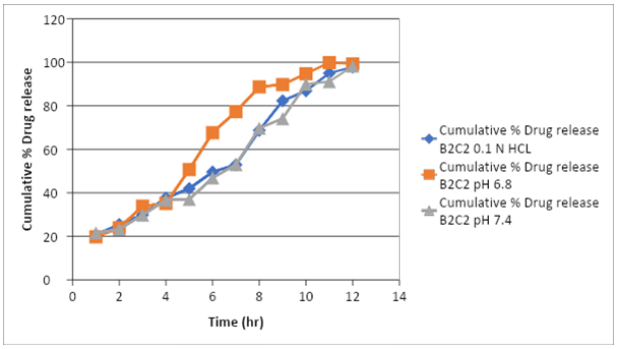

Figure 9: *In vitro* release of Repaglinide from B2C2 formulation in 0.1 N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4

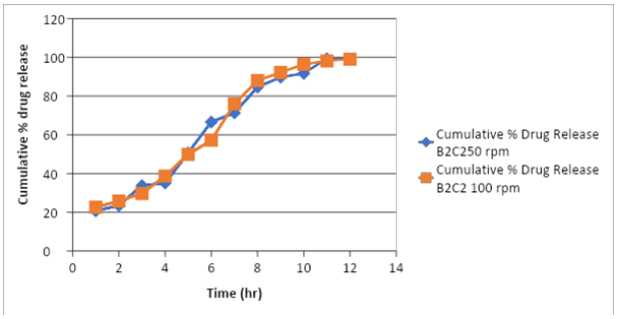

Figure 10: The results of agitation intensity on % drug release of optimized formulation B2C2

RESULTS

Characterization of Repaglinide

Physicochemical characterization and melting point determination

Repaglinide's physicochemical properties have been studied. The substance was discovered to be off-white in color and smell-free. The typical drug's melting point was discovered to be between 126 and 128 °C. The manufactured drug formulation was in accordance with the I.P. specification as shown by the organoleptic properties and melting point being determined to be standard for drugs.

Solubility analysis

Repaglinide's solubility in 10mg/10ml of solvent was tested, and the results showed that the medication was soluble in such solvents as well as in ethanol, methanol, DCM, chloroform, and phosphate buffer pH 6.8. Additionally, it was noted that the pure medication was easily soluble in acetone and phosphate buffer pH 9.0 and very minimally soluble in distilled water.

Standard calibration curve of Repaglinide

Standard calibration curve of Repaglinide in phosphate 0.1 N HCl and phosphate buffer pH 6.8.

Standard calibration curve of Repaglinide in phosphate 0.1 N HCl and phosphate buffer pH 6.8 have been developed at different concentrations of 5, 10, 15, 20, and 25 μg/ml (Figures 1 and 2 figure 1 and figure 2). A straight line has been drawn after taking the absorbances of different concentrations at 241 nm for the type of samples. The straight-line formulas for 0.1 N HCl and phosphate buffer pH 6.8 were y=0.0129x-0.0028 (R^2=0.999) and y=0.0145x+0.0089 (R^2=0.9949), respectively.

Determination of λ max

The drug Repaglinide used in the formulation has been scanned through UV spectrum in chloroform at 241 nm which showed maximum absorption at this wavelength (figure 3).

IR analysis of Repaglinide

FTIR of Repaglinide exhibited characteristic peaks of C-H stretching at wave number (cm^{-1}) 2933.2, OH stretching peak at 3304.43, C-N peak at 2850.27, C-O peak at 1633.41 cm^{-1}(Figure 4).

These peaks have been matched with standard FTIR peaks of Vildagliptin which also exhibited characteristic peaks of C-H stretching at wave number (cm^{-1}) 2900.7, OH stretching peak at 3300-2500, C-N peak at 2294, and C-O peak at 1696.39 cm^{-1}.

These IR peaks confirmed the presence of Repaglinide in the prepared formulations. Besides, API formulation, three different formulations F1, F2 and F3 have been formulated with different excipients.

Evaluation of prepared formulations

Evaluation of prepared granules

The granules were weighted accurately and all the tests have been performed for bulk density, tapped density, angle of repose (θ), Hausner's ratio, compressibility index (%) (Table 1).

Evaluation of uncoated tablets

The tablets were examined for hardness, friability, weight variation, content consistency, and thickness prior to coating. Table 2 has the data.

Evaluation of osmotic tablets

Prepared osmotic tablets were evaluated via their average weight, thickness of coated tablets, diameter of tablets and percent drug content (Table 3).

In vitro drug release study of designed formulations

In this study effort, three different kinds of formulations have been developed. Table 4 and Figure 5 show the outcomes of the in vitro release of Repaglinide from formulations B1C1 to B1C4.

Table 5 and Figure 6 show the outcomes of the in vitro release of Repaglinide from formulation B2C1-B2C4.

Table 6 and Figure 7 show the outcomes of the in vitro release of Repaglinide from formulation F3C1-F3C4.

Dissolution kinetics

The dissolution kinetics of all type of formulation was calculated by PCP Disso model of kinetics (Table 7).

Repaglinide release from various osmotic tablets was interpreted using various kinetic treatments (zero order and first order treatment). Comparatively, the formulation batch B2C2's r2 value had the highest value, coming in at 0.9884. Osmotic tablet batch B2C2 among all zero-order kinetic batches was the best and most optimal formulation.

Optimized formulation B2C2

Calculations have been made on the optimised batch B2C2's cumulative percent drug release. The results are shown in Table 8 and Figure 8.

Evaluation of optimized formulation B2C2

To study effect of different pH on drug release of optimized formulation B2C2

Table 9 and Figure 9 show the outcomes of the in vitro release of Repaglinide from the optimized formulation B2C2 at various pHs using 0.1N HCl, buffer 6.8 and buffer 7.4.

The findings revealed that the optimised formulation B2C2's solubility data and dissolving profile in solutions of 0.1N HCl, pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer were almost identical. The pH of the dissolving medium has no discernible effect on the percentage drug release. This led to the conclusion that the pH change had no effect on the drug release from osmotic pump tablets.

To study the effect of agitation intensity on % drug release of optimized formulation B2C2

Table 10 and Figure 10 exhibit the findings of agitation intensity on the percent drug release of the optimized formulation B2C2 at 50 and 100 rpm to explore the influence of agitation.

At 50 and 100 rpm, the dissolution data and dissolution profile of the optimised formulation were conducted. At various levels of agitation, it was discovered that the % drug release rate was almost same. The drug release from osmotic pump tablets was shown to be independent of agitation intensity by the fact that the speed of the paddle's agitation had no discernible effect on the drug release. It is possible to anticipate that the created formulation's release will be unaffected by the body's hydrodynamic state.

Stability study of optimized formulation B2C2

The promising osmotic tablets of Repaglinide (formulation B2C2) were subjected to short-term stability testing for three months (90 days) at a temperature of 40°±2°C and 75°±5% RH. An adequate number of tablets (15) were packaged in amber-colored rubber stopper vials and housed in a stability chamber that was kept at 40±2°C and 75±5% RH. At intervals of three months, samples were collected. A dissolution test was conducted to ascertain the drug release profile at the conclusion of the three-month period.

DISCUSSION

The goal of the current study is to design and characterize an osmotically regulated oral medication delivery system for the model drug Repaglinide. Repaglinide might be given orally using an osmotically regulated drug delivery device in a zero-order way. Utilizing cellulose acetate as a polymer, PEG 4000 as a pore-forming agent, and PEG 400 as a plasticizer, the semipermeable membrane in the delivery system was created. This membrane is selective in nature and provides the flexibility needed for zero-order drug release.

Batches B1C1 to B1C4, B2C1 to B2C4, and B3C1 to B3C4 were made in the current experiment utilising 45 mg of KCl, NaCl, and fructose as osmogens with 30 to 40% w/w PEG-4000 and PEG-4 and 6% w/w cellulose acetate. Among the batches, B2C2 batch, which included 45 mg NaCl, 40% weight-to-weight PEG-400, 40% weight-to-weight PEG-4000, and 6% weight-to-weight gain increase of cellulose acetate, produced zero-order drug release, with 20.78% of the drug released after one hour and 99.22% after twelve.

In comparison to a semipermeable membrane, a microporous membrane releases drugs more quickly. The use of potassium chloride osmogens may speed up the release of the drug Repaglinide.

It has been discovered that the percentage of drug released from the osmotic pump is inversely propor-

tional to membrane thickness, which is connected to membrane weight.

The zero-order release may be anticipated using the drug release kinetic model fit, and batch B2C2 had the highest value of r2=0.973, indicating that it was an optimized batch.

Environmental factors such as the pH of the dissolving media, which was tested using various medium such as 0.1N HCl, pH 6.8 buffer, and pH 7.4 buffer, were shown to have no effect on the percent release of drug from the osmotic pump.

Agitation was carried out at various rpms of 50 and 100 rpm, however there were no changes in the drug release, leading to the conclusion that agitation had no impact on osmotic tablets. Additionally, it was discovered that the amount of agitation of the dissolving fluid was unaffected by the release rate.

Other findings from the experimental studies on Repaglinide osmotic tablets demonstrated that the drug's granules had good flow properties, that tablet evaluation tests were within acceptable ranges, that there was no interaction between the drug and its excipients, that the optimised formulation followed zero-order drug release kinetics, and that all formulations were stable after being kept for the 90 days. The study's overall findings, therefore, made it abundantly evident that the Repaglinide osmotically controlled release tablets offered controlled drug release at a predefined rate and time.

Future prospective

One of the finest formulations, highly patient compliance with reaching zero order since the pH and degree of agitation have no effect on the osmotic drug delivery system. The usage of pH-triggered osmotic pump pills has recently increased. Because of its superior benefits over traditional dose forms and higher patient compliance, the controlled porosity osmotic tablet (CPOT) may eventually replace the standard dosage form.

With this technique, it will eventually be feasible to construct two or more medications with excellent in-vivo and in-vitro correlation, different polymer-based systems to prolong the drug release, and formulations that combine different pharmaceuticals with osmogens.

CONCLUSION

Repaglinide tablets with osmotically regulated release were successfully created using a controlled porosity osmotic pump to release the drug at zero order for up to 12 hours. The quantity of pore-forming agents, cosmogenic concentration, and rise with reduction in weight-gaining agents have all been adjusted to maximise the rate of drug release from the formulation. Finally, it may be concluded that covering the core tablet with pore-forming chemicals, which is likely to be the most economical option, might simplify the formulations of osmotic pump tablets.

ACKNOWLEDGEMENT

Paras Pophalkar and Sarita Karole are thankful to Oriental Group of Institutions and Department of Pharmaceutical Sciences for their continuous support.

Authorship contribution statement

Conception and design of study and analysis and/or interpretation of data: Paras Pophalkar and Sarita Karole

Drafting the manuscript: Paras Pophalkar

Revising the manuscript critically for important intellectual content: Sarita Karole

Approval of the version of the manuscript to be published: Paras Pophalkar and Sarita Karole

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

Funding Suppport

The authors declare that they have no funding support for this study.

REFERENCES

[1] A S Bansode and K Sarvanan. Review on novel osmotic drug delivery system. *Journal of Drug Delivery and Therapeutics*, 8:87–93, 2018.

[2] S Saraf. Applications of novel drug delivery system for herbal formulations. *Fitoterapia*, 81(7):680–689, 2010.

[3] S K Kushwaha, A Rastogl, A K Rai, and S Singh. Novel drug delivery system for anticancer drug: a review. *International Journal of PharmTech Research*, 4(2):542–553, 2012.

[4] N M Hemed and N A Melosh. An integrated perspective for the diagnosis and therapy of neurodevelopmental disorders-From an engineering point of view. *Advanced Drug Delivery Reviews*, 194:114723–114723, 2023.

[5] A Makwana, K Sameja, H Parekh, and Y Pandya. Advancements in controlled release gastroretentive drug delivery system: A review. *Journal of Drug Delivery and Therapeutics*, 2(3), 2012.

[6] N R Gupta, A Mishal, Y Bhosle, and S Shetty. A review on recent innovation in osmotically controlled drug delivery system. *Indian Journal of Pharmaceutical and Biological Research*, 2(2):117–117, 2014.

[7] A Sharma, D Kumar, and N Painuly. A review on osmotically controlled drug delivery systems. *Asian Journal of Pharmaceutical Research and Development*, 6(4):101–109, 2018.

[8] K Praneet, K Narendra Kumar Reddy, and P. Swetha. Simultaneous estimation and method validation of Terbutaline sulfate and Guaifenesin in liquid dosage form by RP-HPLC. *Indian Journal of Research in Pharmacy and Biotechnology*, 5(1):36–40, 2017.

[9] P Bhateja, R Asija, Y Singh, and M Piplani. An Insight into Osmotic Drug Delivery Systems. *Letters in Drug Design & Discovery*, 20(1):16–30, 2023.

[10] M I Mohamed, A M Al-Mahallawi, and S M Awadalla. Development and optimization of osmotically controlled drug delivery system for poorly aqueous soluble diacerein to improve its bioavailability. *Drug Development and Industrial Pharmacy*, 46(5):814–825, 2020.

[11] H R Mene, N R Mene, D R Parakh, T B Ingale, D R Magar, and M R Mangale. Formulation aspects in the development of controlled porosity osmotic pump tablet. *Pharm. Biol. Eval*, 3(1):1–18, 2016.

[12] W Q T Tong and H Wen. Preformulation aspects of insoluble compounds. *Water-insoluble drug formulation*, pages 75–104, 2008.

[13] S K Roy, S Naskar, S Kundu, and K E Koutsu. Formulation and evaluation of sustained release bilayer tablets of propranolol hydrochloride. *Int J Pharm Pharm Sci*, 7:264–273, 2015.