Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : https://ijpsdronline.com/index.php/journal

Research Article

Fabrication and Optimization of Glibenclamide Drug Delivery System Using Pulsatile Approach for Hyperglycemia

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ARTICLE INFO

Article history:
Received: 06 July, 2024
Revised: 04 October, 2024
Accepted: 18 October, 2024
Published: 30 November, 2024

Keywords:
Glibenclamide, Pulsatile delivery, Solid dispersion, Soluplus®, *Aloe barbadensis* millers

DOI:
10.25004/IJPSDR.2024.160601

ABSTRACT

Diabetes mellitus is characterized by persistently high blood sugar levels, and glibenclamide is commonly used to manage these levels. Pulsatile formulations of glibenclamide offer controlled, timed release to address early morning hyperglycemia, enhancing glucose management and reducing complications. Incorporating *Aloe barbadensis* miller spray-dried powder as a solid plug in the pulsatile capsule design may help control morning glucose spikes and reduce elevated triglyceride levels in diabetic patients. The present study utilized the Pulsincap® system, which incorporates ethyl cellulose (EC)-coated capsules containing optimized glibenclamide tablets and a swellable plug. Solid dispersions (SDs) were developed using Soluplus® to enhance the poor aqueous solubility of glibenclamide, with compatibility confirmed *via* fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Capsules (size '000'), coated with 10% w/v ethyl cellulose in methanol and dibutyl phthalate solution, achieved sustained release over 12 hours. Immediate-release (IR) tablets, formulated via wet granulation, exhibited rapid disintegration within 2 minutes. Sustained-release (SR) tablets, optimized using a 3^2 full factorial design with varying concentrations of HPMC K4M and HPMC K100M CR, demonstrated release profiles of 16 to 37% at 1-hour, 33 to 74% at 4 hours and 44 to 100% at 8 hours. The erodible plug, composed of HPMC K15M, guar gum, and aloe vera, provided swelling and controlled lag times ranging from 7 to 12 hours. The pulsatile delivery system effectively enhanced glibenclamide bioavailability and modulated its release, offering potential improvements in glycemic management for diabetic patients.

Introduction

Diabetes mellitus (DM) poses a significant global health challenge, characterized by persistent elevation in blood glucose levels. This metabolic disorder encompasses two primary types: type 1, involving the degradation of insulin-producing pancreatic β-cells, and type 2, more prevalent among older adults and associated with insulin deficiency and resistance.[1,2] Morning hyperglycemia, termed the dawn phenomenon or liver dump, is a common complication of diabetes, marked by excessive glucose release from the liver due to hormonal imbalances, particularly between 4 am and 8 am.[3,4] Maintaining stable blood glucose levels throughout the day is essential for the overall health and well-being of individuals with diabetes. Innovative approaches to medication delivery and management are essential to address the therapeutic needs of diabetic patients. Pulsatile drug delivery, synchronized with the body's circadian rhythms, presents a promising strategy. By releasing medication rapidly after a lag period, known as chronotherapy, this approach optimizes drug effectiveness precisely when it is most needed, such as during the critical morning hours when

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

morning hyperglycemia is prevalent. Thus, exploring pulsatile technology for diabetes management holds significant potential for improving patient outcomes.

Glibenclamide is a second-generation sulfonylurea derivative and is used in managing type 2 diabetes by enhancing insulin secretion, with the added benefit of convenient once or twice-daily dosing. Its long duration of action helps to provide consistent blood sugar control throughout the day. The study designed and characterized a novel pulsatile drug delivery system for a biguanide antidiabetic drug[5] and demonstrated significant promise *in-vitro*, showcasing the potential of such delivery mechanisms to enhance therapeutic outcomes. It highlighted the feasibility and effectiveness of pulsatile drug delivery systems in addressing the unique challenges of diabetes management.

The present research aimed to investigate the application of pulsatile technology using glibenclamide, a second-generation sulfonylurea known for its ability to increase insulin secretion and tissue sensitivity, ultimately leading to reduced blood glucose levels.[6,7] However, glibenclamide's therapeutic efficacy is hindered by its poor solubility, limiting its bioavailability. To address this challenge, solubility enhancement techniques, such as solid dispersion (SD), were employed. Specifically, the incorporation of Soluplus®, a polymeric carrier with solubility-enhancing properties, facilitated the formation of SDs with glibenclamide. However, recent updates in recommendations for first-line therapy emphasize the importance of tailoring treatment based on patient-specific factors and comorbidities factors to reduce elevated triglyceride levels in diabetic patients

Additionally, the study explored the development of a pulsatile drug delivery system utilizing ethyl cellulose-coated capsules, optimized immediate-release (IR) and sustained-release (SR) tablets, and a swellable plug. Notably, aloe vera and guar gum. Notably, aloe vera gel spray dried powder and guar gum are incorporated into the formulation as solid plugs, leveraging their synergistic effects with glibenclamide to enhance therapeutic efficacy. Clinical trials investigating the combination of glibenclamide with aloe vera spray dried powder have shown promising results in reducing fasting blood glucose levels and triglycerides in diabetic patients, supporting the potential use of aloe vera in diabetes treatment. Yongchaiyudha S *et al.* (1996) revealed that the combination of glibenclamide and aloe vera juice significantly reduced fasting blood glucose as well as triglycerides in diabetic patients, further validating the potential benefits of this combination in diabetes management.[8] Importantly, no prior reports of this approach have been documented, highlighting the novelty and potential impact of this research on advancing diabetes treatment. The specific objectives include developing a pulsatile drug delivery system employing a Pulsincap® design with ethyl cellulose-coated capsules to achieve controlled release of glibenclamide, with Soluplus® utilized to enhance solubility. The optimization of immediate-release (IR) and sustained-release (SR) formulations of glibenclamide tablets using experimental design approaches and evaluating the formulated tablets and a swellable plug for quality control parameters to ensure precise drug release. The results of the study could significantly advance the treatment of diabetes by providing a more effective and targeted delivery system.

Materials And Methods

Materials

Cadila Healthcare Ltd., Goa, supplied glibenclamide. Otto Chemie Pvt. Ltd., Mumbai, was the supplier of hydroxypropyl methylcellulose (HPMC) K15M, while Ultrapure Lab Chem India was the source of ethyl cellulose. Soluplus® was achieved from BASF Pvt. Ltd., Mumbai. Neelkanth Finechem, Jodhpur, provided the aloe vera powder, while H. B. Gum Industries Pvt. Ltd., Kalol, provided the guar gum. Other materials used were of IP grade.

Methods

Preparation of SD

Micronization may not significantly affect the solubility or bioavailability of oral drugs, but it can increase the cohesiveness of powder materials, leading to particle agglomeration. The SD of glibenclamide with Soluplus® was prepared to enhance solubility and dissolution. The kneading method was employed to prepare SD, with three ratios of glibenclamide to Soluplus® (1:1, 1:2, and 1:3). After passing through a 44# mesh, weighed quantities of the drug and Soluplus® (graft copolymer containing polyvinyl caprolactam 57%, polyvinyl acetate 30%, and polyethylene glycol 600 13%) were mixed in a mortar pestle and kneaded for 30 minutess.[9]

Phase solubility study

The method outlined by Connors and Higuchi, a phase solubility study of glibenclamide, was used.[10] Excess SD was added to acidic pH 1.2 and a phosphate buffer solution (PBS) at pH 6.8. Then, it was agitated for 24 hours at 100 rpm until equilibrium was attained. After filtration, absorbance was analyzed at λmax (223 nm) against a blank solution using a UV-vis spectrophotometer.

The thermodynamic parameter of Gibbs free energy (ΔG°) was determined utilizing the below mentioned equation.

$$\Delta G^\circ = -2.303RTlog\left(\frac{Sc}{So}\right)$$

Where, ΔG°= Gibbs free energy of transfer;
R= Gas constant (8.314 J/K-mole);
T= Temperature in kelvin;
Sc/So = molar solubility ratio of SD[11]

Characterization of SD

Flow properties of SD are crucial in pharmaceutical processes like powder blending, tablet compression, and capsule filling. Various parameters were utilized to evaluate the pre-compression parameters.[12]

FTIR spectroscopy

FTIR (Spectrum GX-FTIR, PerkinElmer, USA) was used for the spectroscopic examination of the SD and untreated glibenclamide samples. Spectra were obtained in the 4000 to 400 cm^{-1} range. The material was dispersed in KBr and then gently shaken as part of the process. The spectrum was scanned at a speed of 20 scans per second, with a resolution of 0.15 cm^{-1}.

DSC analysis

The thermal behavior of the untreated glibenclamide and SD samples was evaluated using a calibrated differential scanning calorimeter (DSC-PYRIS-1, Phillips, Netherlands). Using dry nitrogen to remove moisture, this analysis was conducted in an inert environment. About 2 to 4 mg of sample was added to a hermetically sealed aluminum flat bottom PAN, which was then filled with nitrogen at a flow rate of 20 mL/min. The samples were then scanned at a rate of 10°C/min up to 200°C from a starting temperature of 25°C. Aluminum trays were used for standard measures. Samples for DSC experiments were collected in aluminum pans with a nitrogen gas flow rate of 50 mL/min and a scanning rate of 20°C/min.[13]

Development of glibenclamide Pulsincap®

The Pulsincap® manufacturing process comprises 4 stages: 1. The inside and outside of the capsule body should be coated, 2. Improving the performance of IR and SR tablets, 3. To achieve the specified latency period swellable plug is prepared, 4. Tab-SR, tab-IR, and erodible plug filling and assembly into the capped-coated capsule.

Capsule coating and optimization

The process started with the hard gelatin capsules; the caps and bodies were split. EC was dissolved in methanol along with DBP to prepare the coating solution in which the DBP was regarded as a plasticizer. It would only be the capsule bodies that were placed in the above solution. The number of coatings was strategically applied to enhance the survivability of the capsules for a minimum of 12 to 14 hours, corresponding to the pulsatile delivery requirements (Figs 1 and 2). The stability of the coated capsules was checked by placing them in 900 mL of the acidic solution of pH 1.2, then washed with a phosphate buffer of pH 6.8 for 12 hours [14].

Optimization of IR and SR tablets

IR tablets were formulated by the wet granulation method. Firstly, the glibenclamide granules mixture was dried in the oven at 50°C until dried granules to a loss of drying

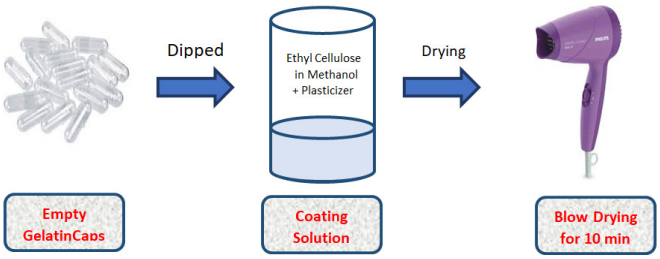

Fig. 1: Coating of finished formulation

Fig. 2: Coated finished formulation

value is < 2%. Dried granules were mixed with external granular phase excipients and the tablets were punched. The composition of all the formulations is shown in Table 1. The design of the experiment chosen was full factorial 3^2 because its usage is statistical and is aimed at optimizing the polymer concentration in SR tablets. The proposed approach enabled to definition of the dependencies between the activity factors and their values, as well as the combinations with the necessary characteristics for SR tablets. The values of formulation variables and their actual form are shown in Table 2.

As a part of the full factorial 3^2 design, the independent factors were HPMC K4M concentration (X1) and HPMC K100M concentration (X2). Each was examined at three levels -1, 0, +1. The total number of runs was 9 using the Design Expert version 11 software. SR tablets were compressed using the standard procedures of drug formulation. These tablets were later compared concerning their percentage cumulative drug release (%CDR) available at 1 hour (Y1), 4 hours (Y2) and 8 hours (Y3).[15]

The ANOVA and MLR analyses were conducted in this study using Design Expert software and major research aim was to establish the interaction between two IVs: X1 and X2: and three DVs, Y1, Y2, and Y3.Comparing various MLR outcomes, such as correlation coefficients and coefficient values, as well as ANOVA criteria like Fisher's ratio and similar *p-values*, was necessary in order to determine which mathematical prediction model was the best. These acted as a guideline when selecting the right model for the human resource management of the organisation.

Table 1: Composition of IR formulation

Ingredient name	*Binder level (+) & %fluid uptake (+)*	*Binder level (-) & %fluid uptake (-)*	*Disintegrant level (-)*	*Disintegrant level (+)*	*Lubricant level (-)*	*Lubricant level (+)*
	% w/w	*% w/w*	*% w/w*	*% w/w*	*% w/w*	*% w/w*
Glibenclamide	4.17	4.17	4.17	4.17	4.17	4.17
Lactose MH	65.83	67.50	67.42	65.92	67.71	66.17
Maize starch	16.67	16.67	16.67	16.67	16.67	16.67
Croscarmellose sodium	3.75	3.75	3.00	4.50	3.75	3.75
Povidone K30	4.17	2.50	3.33	3.33	3.33	3.33
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Colloidal silicon dioxide (Aerosil)	0.67	0.67	0.67	0.67	0.67	0.67
Croscarmellose sodium	3.75	3.75	3.75	3.75	3.75	3.75
Magnesium stearate	1.00	1.00	1.00	1.00	0.50	1.50
Total	100%					

Each batch of tablets has the same weight of 120 mg.

Table 2: Actual and coded values of formulation parameters for 3^2 full factorial design

Independent variables	*Coded and actual values*		
	-1	*0*	*+1*
Concentration of HPMC K4M (mg) (x_1)	2	6	10
Concentration of HPMC K100M (mg) (x_2)	15	20	25
Dependent variables	Constraints		
Y_1 = %cdr at 1 hours	Nmt 40%		
Y_2 = %cdr at 4 hours	40–80%		
Y_3 = %cdr at 8 hours	Nlt 85%		

A comprehensive analysis of statistical parameters, including the coefficient of variation (CV), multiple correlation coefficient (r^2), adjusted multiple correlation coefficient (adjusted r^2), and predicted residual sum of squares (PRESS), was used to determine which mathematical model was most appropriate. A model's goodness of fit to the given data was indicated by its PRESS value, where a smaller PRESS value denoted a better fit. The best model for the analysis was chosen with the help of proper evaluation.

Characterization of prepared IR and SR tablets

Pre-compression characteristics of each tablet, such as size, hardness, weight fluctuation, friability, and disintegration, were recorded. The USP apparatus II was used to carry out the *in-vitro* dissolution. PBS pH 6.8 and 7.4 were used as the media for SR tablets, while phosphate buffer pH 1.2 was utilized for IR tablets.[16]

Disintegration time of IR tablets

The disintegration of IR tablets was assessed using a disintegration apparatus. Two different media were employed to simulate gastric conditions: 900 mL of 0.1 N HCl and PBS pH 6.8, both maintained at a temperature of 37 ± 0.5°C. Six tablets, randomly chosen, were placed into individual glass tubes and subjected to the disintegration process. The disintegration time, noted as n = 6, was meticulously recorded to represent the mean time required for complete tablet disintegration. It was ensured that no residue remained on the sieve after disintegration.

In-vitro dissolution studies

In-vitro drug release analysis was done with the help of USP apparatus II, which rotates with a speed of 75 rpm carrying 500 mL of PBS solution with a pH of 6. 8 and 7. 4 for sustained-release (SR) formulations and 0. IR 1 N HCl for all the immediate-release formulations, kept at 37 ± 0.5°C. Portion sample was taken at different time intervals and were run through the HPLC method.

Preparation of erodible plug

By directly compressing the aforementioned polymers, HPMC K15M, guar gum, and aloe vera, using the appropriate punch and die of a rotary tablet punching machine, an erodible plug was created to seal the capsule body. Following preparation, the coated gelatin capsule containing the erodible plug was placed inside after optimization of the capsule's influencing factors. Table 3 provides the following information regarding the various plugs' compositions.

Characterization of erodible plug

Friability and hardness were two examples of pre- and post-compression characteristics that were measured.

Table 3: Composition of erodible plug

Batch	*Aloe vera (mg)*	*Guar gum (mg)*	*HPMC K15M (mg)*
A1	50	50	80
A2	50	50	90
A3	50	50	100
A4	40	40	100
A5	40	40	90
A6	40	40	80

Swelling index cement used in the preparation of erodible plug

Single erodible plugs were weighed at the beginning (W1) and placed in one petri dish. After every hour, the erodible plugs were taken out of the petri dish, the surface water of the plugs, which again became swollen, was blotted with tissue paper and then the same plugs were weighed (W2). According to the formula provided, the swelling index was obtained based on the data recorded previously.

$$\%\ Swelling\ Index = \frac{W2 - W1}{W2} * 100$$

%Erosion of erodible plug

The plug's initial weight, W1, was noted. The swollen plugs were then stored in a desiccator for 48 hours after being dried in an oven for 24 hours at 60°C. The plugs were then weighed again (W3). The given formula[17] was used to compute the percentage matrix erosion.

$$\%\ Matrix\ Erosion = \frac{W1 - W3}{W3} * 100$$

Analysing lag time

Lag time analysis was performed with the help of a sustained-release tablet combined with an erodible plug, and then with a capsule body coated and *in-vitro* drug release was further studied. A cap that dissolves in water effectively hermetically seals the capsule body. It was discovered that the medication was released in PBS with a pH of one. That is 2 for 2 hours, approximately 6.8 for 3 hours, and 7.4 for the rest of the periods, using USP apparatus II. During the experiment at each hourly interval, aliquots of the samples were collected, media was replaced with fresh solutions and the samples were used for spectrophotometric analysis.[18]

Fabrication of optimized formulation

After the optimization of both IR and SR tablets, an optimized formulation was prepared. The erodible plug and SR tablet included in the optimized formulation were inserted into the coated capsule body to achieve the produced formulation. The erodible plug was positioned with the IR tablet on top so that it would fit properly when the plug was packed into the coated capsule body. Later on, the shell it coated was sealed hermetically with the cap, made from the same material, but without any coating. The optimized formulation was subjected to *in-vitro* dissolution studies, after which the following procedure was carried out.

Stability studies of optimized formulation

Carefully placing a suitable quantity of capsules into the glass bottles, they were sealed with rubber corks. After that, the bottles were kept in stability chambers with a temperature of 40 ± 2°C and a relative humidity of 75 ± 5%. These comprised the samples that were examined for drug release *in-vitro* after 0, 1, 2, 4, 8, and 16 hours.

Results And Discussion

Improvement of Solubility

Phase-by-phase solubility analysis

The purpose of this study was to predict the behavior of polymers at various concentrations. A solubility investigation was conducted at pH values of 1.2 and 6. Fig. 3 showed the solubility was enhanced by 2.23 times with Soluplus®. This type of solubility improvement may be ascribed to Soluplus®'s action as a surfactant, which lowers surface tension and increases solubility. When the medication and Soluplus® have the same quantity at 1:1. The results in effective distribution of drug within the polymer matrix. Hence, it was deduced that solubility is enhanced with improved exposure of the compound's surface area.

Characterization of SD

Pre-compression parameters were set in order to get good SD flow qualities that were correlated with pure drugs. This was achieved by dispersing the drug throughout the polymer matrix and preventing drug particle agglomeration.

FTIR spectroscopy

The FTIR peak of glibenclamide revealed absorption bands at specific wavenumbers: 3313.11 cm^{-1} for O-H stretching,

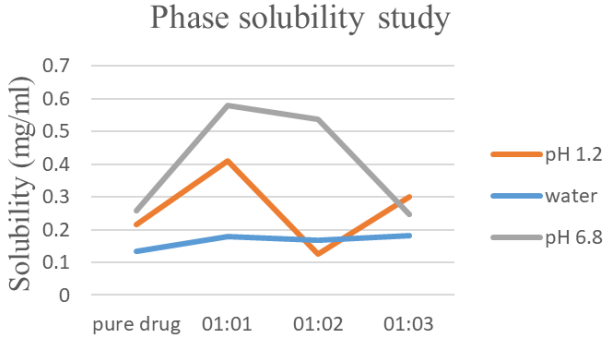

Fig. 3: Phase solubility study of SD

1712.48 cm^{-1} for C=O stretching, 1616.06 cm^{-1} for C=C stretching, 1346.07 cm^{-1} for S=O stretching, 1025.94 cm^{-1} for C-N stretching, and 821.527 cm^{-1} for C-Cl stretching, as depicted in Fig. 4. Similarly, the FTIR spectra of the SD also displayed these distinct peaks of glibenclamide, as shown in Fig. 5. Though with only minor adjustments to their placements. This change suggests a little widening of the peaks, signifying the establishment of strong hydrogen bonds between the medication and Soluplus®. Because of these hydrogen bonds, glibenclamide is more soluble and forms a dispersion more easily. Moreover, the lack of a peak was noted, suggesting that the medication under investigation is amorphous. According to this FTIR analysis, the polymer and medication don't appear to interact, which makes it appropriate for use in formulation development.

DSC analysis

Glibenclamide's DSC thermogram showed an endothermic, single, abrupt melting peak at 176°C (Fig. 6). On the other hand, Fig. 7 shows a shift and reduction in the DSC peak of the SD, indicating that the medication remained amorphous for a considerable period of time. The medication dissolves more quickly when it changes from a crystalline to an amorphous state. This finding implies that there was no interaction between the medicine and the excipient.

Development of Glibenclamide Pulsincap®

Coating and optimization of capsule body

A hard gelatine capsule of size '000' non-soluble gelatine capsule was chosen for Pulsincap® preparation. Ethylcellulose, a hydrophobic polymer (for a high extent of water resistance) was used to prepare thin semi-permeable films. Besides enhancing mechanical strength, flexibility

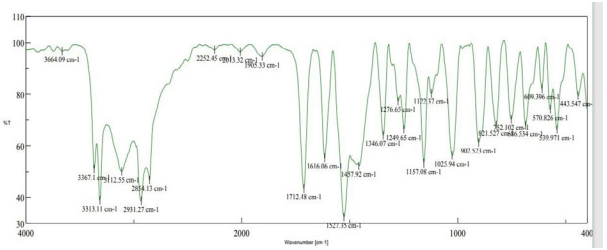

Fig. 4: FTIR spectra of drug

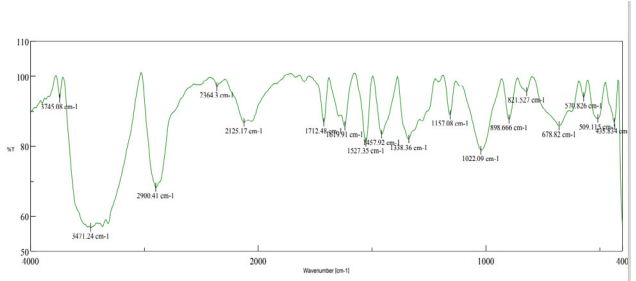

Fig. 5: FTIR spectra of SD

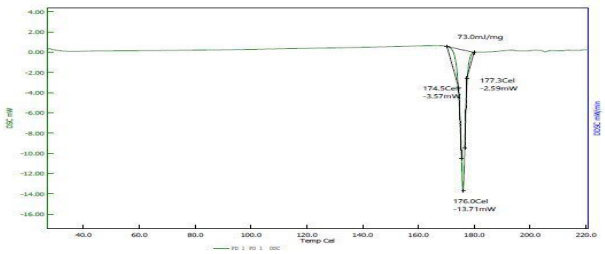

Fig. 6: DSC thermogram of drug

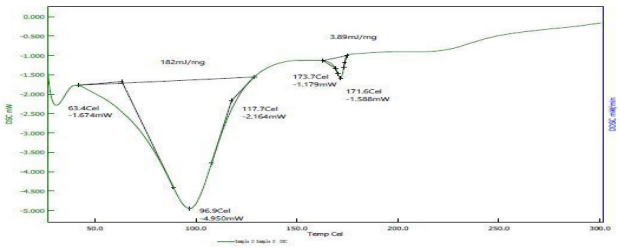

Fig. 7: DSC thermogram of SD

and thermoplasticity, dibutyl phthalate also played a plasticizer role, respectively. Hence, double coating to give a capsule integrity of 14 hours at 10% w/v ethyl cellulose in methanol with 0.5% dibutyl phthalate was performed on the capsules body alone.[14,15] This prolonged durability meets the requirements for controlled chronotherapeutic drug release, concluding that applying two coatings optimized the capsules' performance.

Characterization of prepared IR tablets

The pre-compression parameters of prepared IR tablets were assessed, demonstrating favorable flow characteristics. The tablets maintained a hardness of 3 kg/cm^2, facilitating rapid disintegration without exceeding friability limits (< 1%). The tablets were uniformly flat and circular, with thicknesses of 4.2 mm and a diameter of 5 mm. They also exhibited consistent weights within acceptable variation limits as per IP specifications. The disintegration time for IR tablets was observed to be within 2 minutes. All the prepared tablets were analyzed for %drug release using the HPLC method. pH 3.0. Buffer: Acetonitrile (60:40% v/v) was optimized as a mobile phase. All the tablets showed 98 to 100% drug release in less than 15 minutes. The polymer concentration was optimized based on *in-vitro* drug release. A 3.33% w/w binder, 3.75% w/w disintegrant and 1% w/w lubricant was optimized.

Optimization of SR tablets

For the 3^2-full factorial design, 9 experiments were conducted with two factors at three levels each. Pre- and post-compression studies were performed on all formulations, revealing good flow properties, weight variation within IP specifications, and friability within acceptable limits (<1%). Tablet hardness was maintained at 4.5 kg/cm^2, with uniformly flat and circular tablets

measuring 3.5 mm thickness and 5 mm diameter. In order to achieve the maximum percentage CDR at 1-hour, 4 and 8 hours for continuous delivery, the formulations were created to optimize the levels of independent variables and their interaction with dependent variables. As shown in Table 4, %CDR ranged between 16 to 37% at 1 hour, 33 to 74% at 4 hours, and 44 to 100% at 8 hours, with adequate precision (>4) and a CV% of less than 10%, confirming model reliability with a p <0.05. Regression statistical analysis and 2D/3D plots illustrated the effect of independent factors on each response, as shown in Fig. 8. Increasing HPMC K4M, concentration increased %CDR, while a simultaneous increase in HPMC K100M CR retarded drug release due to thicker gel-like layer formation around the minitablet via slow erosion. The regression statistical analysis of 3 responses is shown in Table 5.

The polynomial equations are as follows:

Y_1 (% CDR at 1 h) = 20.81+ 4.12*A- 3.93*B- 4.50*AB

Y_2 (% CDR at 4 h) = 41.67+ 7.43*A- 7.44*B- 9.62*AB

Y_3 (% CDR at 8 h) = 60.05+ 10.42*A- 9.14*B- 14.79*AB

Response 1 had an NMT 40% aim, response 2 had a 40 to 80% goal, and response 3 had an NLT 85% drug release target. In summary, 7.11 mg HPMC K4M and 14.92 mg HPMC K100M CR satisfied the requirements of an optimum formulation and got the targeted percentage CDR.

Evaluation of erodible plug

Guar gum exhibits the highest swelling capacity but lacks binding properties, while HPMC K15M demonstrates excellent binding capabilities. Therefore, a combination of HPMC and guar gum was utilized to maintain the integrity of the plug. Additionally, aloe vera, known for its swelling capacity and therapeutic effects in diabetes treatment, was incorporated into the erodible plug formulation to achieve therapeutic levels during the lag time. The plugs exhibited hardness ranging from 3 to 6 kg/cm^2, %swelling between 60 and 75%, and lag time durations of 7 to 12 hours. Among the formulations, the plug composed of 90 mg HPMC K15M, 50 mg guar gum, and 50 mg aloe vera demonstrated the best results, meeting the desired criteria.

Fabrication of optimized formulation

An *in-vitro* drug release evaluation was done on the optimized formulation whereby the SR tablet was filled into the coated capsule and then erodible plug. In this experiment, the IR tablet was housed inside the water-soluble cap, which encapsulated its body. After 5 to 7 minutes of starting up, the IR tablet moved out since it was inside a water-soluble cap that dissolved within this time period (Fig. 8). The first pulse initiated by drug release from IR tablet began after 15 minutes, while medication release from the SR tablet caused the second pulse 7 to 8 hours later. The attainment >90% for both tablets emphasized on robustness of the therapeutic performance of the fabricated system.

Investigation of the enhanced formulation's stability

Fig. 9 displayed the results of stability tests performed on the optimized Pulsincap®. The percentage CDR at one and eight hours each week was measured while the capsules were stored according to the guidelines. Additionally, an assessment of any possible deterioration indications was incorporated into the formulation. These findings suggested that the formulation was stable throughout the study period rather than breaking down.

In the present study, we developed a chronotherapeutic system for glibenclamide. Initially, FTIR and DSC studies were conducted to assess potential drug-polymer interactions (compatibility study), confirming compatibility for formulation development. SD was formulated to enhance drug solubility, using Soluplus® as a carrier through physical mixing. The 1:1 drug/Soluplus® ratio was found optimal, as equal amounts facilitated better drug dispersion within the matrix. Ratios of 1:2 and 1:3 led to excess polymer, potentially resulting in poor drug

Table 4: Experimental runs for 3^2 full factorial design and their observed responses

Batch	*Coded value*		*Uncoded value*		Y_1 *% CDR at 1st hours (%) n=3, (±S.D.)*	Y_2 *% CDR at 4 hours (%) n=3, (±S.D.)*	Y_3 *% CDR at 8 hours (%) n=3, (±S.D.)*
	X_1	X_2	X_1	X_2			
B1	-1	+1	2	25	18.62 ± 0.012	35.12 ± 0.062	49.42 ± 0.047
B2	0	+1	6	25	19.01 ± 0.043	36.93 ± 0.042	55.27 ± 0.035
B3	+1	+1	10	25	37.96 ± 0.022	74.36 ± 0.036	100 ± 0.058
B4	0	0	6	20	17.48 ± 0.061	40.96 ± 0.092	54.25 ± 0.028
B5	-1	0	2	20	20.67 ± 0.062	40.42 ± 0.087	56.9 ± 0.098
B6	+1	0	10	20	21.5 ± 0.071	45.53 ± 0.064	74.76 ± 0.052
B7	+1	-1	10	15	17.16 ± 0.042	33.91 ± 0.092	53.45 ± 0.025
B8	0	-1	6	15	16.35 ± 0.014	33.17 ± 0.054	51.51 ± 0.04
B9	-1	-1	2	15	18.5 ± 0.061	34.67 ± 0.034	44.89 ± 0.027

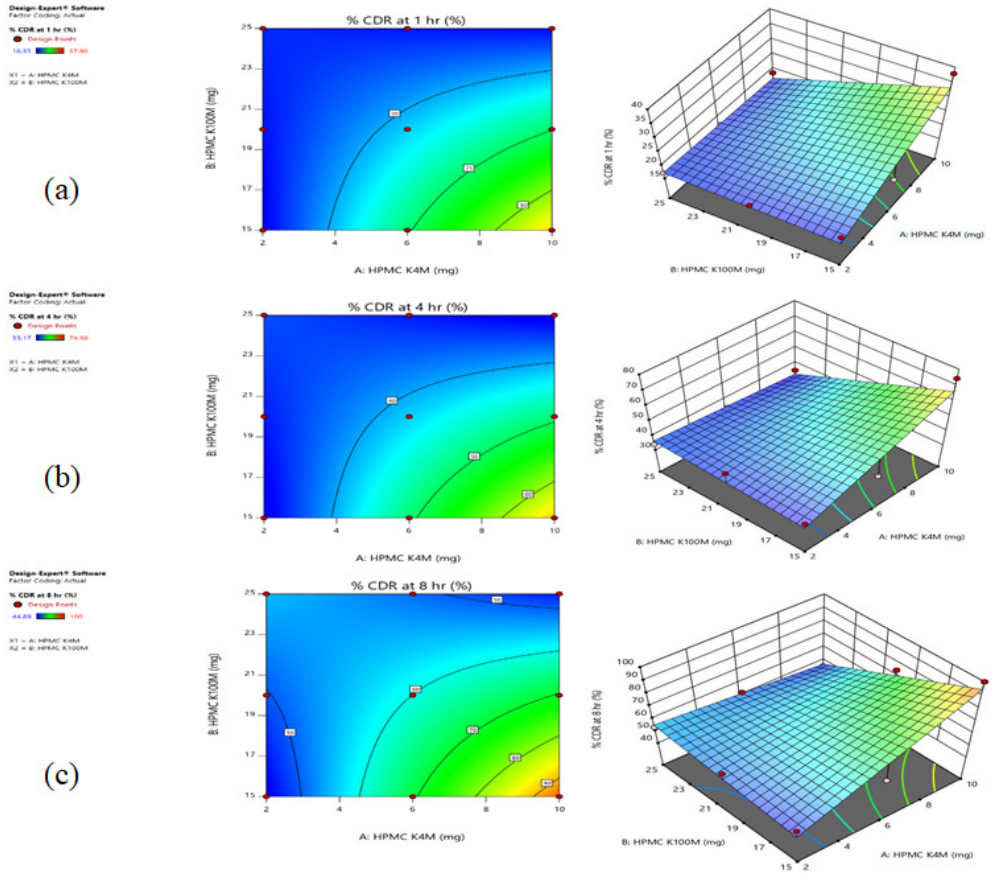

Fig. 8: 2D and 3D contour plot for: (a) Y_1 response (b) Y_2 response (c) Y_3 response

Table 5: Regression statistical analysis for the observed responses of 3^2 full factorial designs

	Response Y_1	*Response Y_2*	*Response Y_3*
R^2	0.7816	0.7758	0.8671
Adjusted R^2	0.6506	0.6412	0.7873
Predicted R^2	-0.2057	-0.0209	0.4958
F-value	5.96	5.77	10.87
p-value	0.0417	0.0444	0.0125
Coefficients			
β_0	20.81	41.67	60.05
$\beta_1(X_1)$	4.12	7.43	10.42
$\beta_2(X_2)$	-3.93	-7.44	-9.14
$\beta_{12}(X_1X_2)$	-4.5	-9.62	-14.79

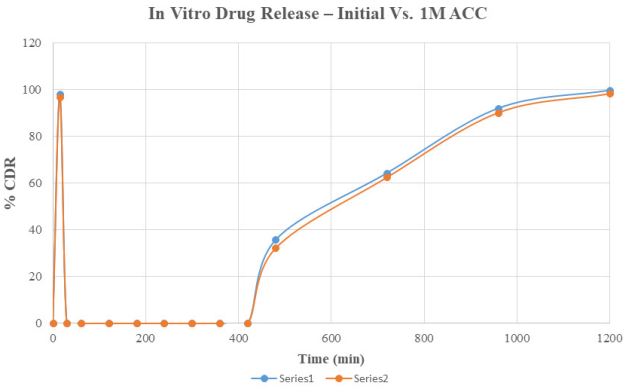

Fig. 9: *In-vitro* drug release of optimized pulsincap

dispersion or aggregation. All SD powders have better flow properties due to their smaller and less cohesive particles by using adequate polymer. For the creation of Pulsincap®, '000' size capsules were chosen, and two layers of the ideal coating— 10% w/v ethyl cellulose in methanol and 0.5% di-butyl phthalate were applied. The micro-meritic characteristics of tablet powder combinations IR and SR were characterized, showing good to excellent flow properties *via* wet granulation. Immediate release tablet hardness was maintained at 3 kg/cm^2 to control friability, kept below 1%. Disintegration time was 2 minutes for the immediate release tablet, and polymer concentrations were optimized based on *in-vitro* drug release. *In-vitro* dissolution studies performed on optimized Pulsincap®

and sample analyzed in the HPLC system and found satisfactory results like 97.7% drug release with RSD 1.3% (Acceptance limit %RSD should be ±2%).

For sustained release tablet optimization, a full factorial 3^2 design was employed, with HPMC K4M with HPMC K100M CR concentrations as independent variables. Nine formulations (B1–B9) were evaluated for %CDR, with a coefficient of correlation (r^2) of 0.78 to 0.86, indicating good model predictability. HPMC K4M positively influenced %CDR, while increasing HPMC K100M CR retarded release due to gel layer formation. Sustained release tablet hardness was kept constant at 4.5 kg/cm^2, with friability below 1%. Polymers for the erodible plug included HPMC K15M, guar gum, and aloe vera, with different ratios evaluated to achieve the desired lag time and %swelling. Finally, the accelerated stability study was performed on the optimized Pulsincap® formulation to establish shelf life and suitable storage conditions during transport and long-term storage.

Conclusion

In this study, solid dispersion (SD) techniques were employed using the phase-by-phase solubility method to enhance the solubility of glibenclamide. Solid dispersions prepared with polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol as carriers significantly improved the solubility and drug release dissolution rate compared to the pure glibenclamide API. The Pulsincap® formulation was developed for the treatment of diabetes. Compatibility between the drug and polymers was confirmed through hydrogen bonding studies conducted using FTIR spectrophotometry.

The final formulation, designed as a capsule dosage form, consisted of immediate-release (IR) and sustained-release (SR) mini tablets combined using aloe vera as a filler. *In-vitro* drug release studies were utilized to optimize the IR tablets, while the SR tablets were optimized using a full factorial 32 design to achieve the desired qualities, such as %cumulative drug release (CDR) at 1, 4, and 8 hours. The erodible plug was fine-tuned based on lag time and percentage swelling.

The optimal batch released the medication during the morning's peak serum concentration, potentially enhancing the effectiveness of diabetes therapy. All experimental result data met the acceptance criteria, confirming the success of the study.

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HOW TO CITE THIS ARTICLE: Desai S, Thakkar V, Gandhi T, Gandhi A, Parekh K, Joshi A. Fabrication and Optimization of Glibenclamide Drug Delivery System Using Pulsatile Approach for Hyperglycemia. Int. J. Pharm. Sci. Drug Res. 2024;16(6):922-930. **DOI:** 10.25004/IJPSDR.2024.160601