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Drug Discovery

Formulation and in vitro evaluation of gastroretentive accordion poly pill containing captopril and glibenclamide

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ABSTRACT

Background: The study aims to create a new oral dosage form for patients with hypertension and diabetes, focusing on a sustained gastroretentive formulation. This dosage form will be easier to take, less frequent, and increase patient compliance, enhancing the effectiveness of glibenclamide and captopril, which are commonly used as hypoglycemic and anti-hypertensive agents. *Materials and Method:* This research study focuses on using the solvent casting process to develop and assess accordion pill films. The films are intended to offer a revolutionary polypill gastro-retentive method and contain two key medications, glibenclamide and captopril. Different materials and processes were used to prepare different formulations, and the solvent casting method was used to formulate the films. The in vitro study assessed the accordion pill films' physical properties, drug release, and swelling behavior. It showed that these films could be used as gastro-retentive methods to distribute captopril and glibenclamide, which could enhance treatment regimens for cardiovascular disease and diabetes. *Results:* The results indicated that the drug content was high and that the materials were used consistently throughout the whole film. While all of the formulations had acceptable testing characteristics, The study analyzed drug release percentages over 13 hours, revealing that most formulations released 85% of the drug after 10 to 11 hours, with F6 and F7 being the best, with the highest release within 10 to 12 hours. It is demonstrated that all formulations followed fickian release and first-order kinetics. *Conclusion:* A viable poly pill gastro-retentive method is presented by the formulation and in vitro evaluation of an accordion pill that combines glibenclamide and captopril utilizing the solvent casting process. Patients with diabetes and cardiovascular disease may benefit from more effective treatment plans thanks to the accordion pill films' extended stomach retention and regulated drug release capabilities. Validating the efficacy and safety of

this innovative drug delivery method will require more investigation and development, including in-vivo investigations.

Keywords: Hypertension, Diabetes, Accordion pills, Gastro retentive formulation, poly pill

1. INTRODUCTION

Oral administration of drugs often presents challenges such as poor solubility, limited therapeutic windows, and small absorption windows. These issues can lead to adverse effects in older patients and make oral delivery difficult, especially for chronic conditions. Improving the pharmacokinetics of drugs with a narrow therapeutic index and effective oral delivery of low-soluble pills could significantly increase the safety and efficacy of treatments (Gabor et al., 2010; Rajput & Sailaja, 2023). Gastric retaining drug delivery systems offer a promising approach for oral medication administration, allowing longer and continuous absorption in the upper gastrointestinal tract under controlled conditions and reducing factors such as pH, microbial fauna, and enzyme activity. Gastro retentive formulations can enhance medication dissolution in the gastrointestinal system and GI tract, preventing drug precipitation and increasing the absorption phase (Davis, 2005).

Oral drug delivery systems offer benefits like high patient compliance, affordability, and ease of administration, but face challenges like gastrointestinal tract heterogeneity, pH, gastric retention period, surface area, and enzyme activity, limiting bioavailability (Mustafa et al., 2023). Intec Pharma's Accordion Pill (AP) is a unique oral delivery system for medications with limited absorption windows or low solubility, offering fixed-dose combinations and multiple drug release characteristics in a single capsule (Navon, 2019). The Accordion Pill is a gastro-retentive formulation made of biodegradable polymeric films used in pharmaceuticals. It remains in the gastrointestinal tract for up to 12 hours when taken with calories and is expelled from the stomach and completely digested. It is used with drugs from classes III and IV with fewer absorption windows (Navon, 2019). The accordion pill, when taken in the stomach, dissolves and remains in the stomach for up to 12 hours, enhancing efficacy and safety while reducing daily dosage frequency.

This ensures a continuous and prolonged absorption of the medication in this specific area. The Accordion Pill-Zaleplon (AP-ZP) aims to prevent "next day" side effects, promote rapid onset, and ensure adequate sleep maintenance. The Accordion Pill is made of undulating, multilayered biodegradable polymeric films that fit into a standard-sized capsule. AP has been tested in clinical trials, preclinical studies, and clinical trials to assess its safety, effectiveness, and safety in healthy individuals and patients (Chudiwal et al., 2017). A poly pill is a fixed-dose combination pill with various ingredients designed to simultaneously reduce various cardiovascular risk factors. The poly pill method, if widely used, could prevent heart attacks and strokes in people 55 and older, making it tolerably safe and more effective than other interventions in the Western world (Wald and Law, 2003). The usual adverse effects are nausea and vomiting7. Headache and the proper assessment of the unfolding of the film are not safe for repetitive evaluation in human volunteers (Kagan et al., 2006).

Dose dumping, substandard IV vivo-in vitro correlation, required supplementary patient counseling and education, can be very expensive, and non-uniform drug loading were the only adverse effects noticed of accordion capsules (Abdul and Poddar, 2004; Subramani et al., 2021). The most significant modifiable risk factor for global all-cause morbidity and death is systemic arterial hypertension, which is also linked to a greater chance of cardiovascular disease (CVD). Dietary modifications and increased physical exercise can help lower blood pressure prevent hypertension and its consequences for cardiovascular disease. By blocking the conversion of angiotensin-1 to angiotensin-2, the angiotensin-converting enzyme inhibitor captopril reduces blood pressure and has antihypertensive effects that peak 60–90 minutes after delivery.

Captopril is an antihypertensive drug with a melting point of 105–108 °C. It is used to treat hypertension and congestive heart failure (Lee et al., 2003). Glibenclamide is a modern, effective hypoglycemic medication for NIDDM. It is a sulfonyl urea derivative with a melting point of 169–170 °C and is soluble in ethanol, methanol, alkali, and diethyl ether. Glibenclamide, a potent second-generation oral hypoglycemic medication, is effective in managing type II diabetes mellitus, a mild-to-moderate-severity condition (Iqbal et al., 2012). Glibenclamide boosts insulin secretion from the pancreas by interacting with beta-cell receptors or ATP-sensitive potassium channels and may also enhance the sensitivity of existing insulin receptors (Fujimura et al., 1986).

In the current study, research will be done on the design and formulation of accordion pills containing three actives: Captopril, low-dose aspirin, and glibenclamide, for patients with cardiovascular problems, hypertension, and diabetes, employing the “Solvent

Casting Method" to increase patient adherence, improve bioavailability, and decrease the number of medications by targeting multiple diseased patients using a single dosage form. A patient with cardiovascular problems and a concomitant disease of diabetes will only need such an accordion pill once daily for therapeutic effect.

2. MATERIALS AND METHODS

Materials

Captopril (M.W. 217.29) was gifted to us by Mylan Pharmaceuticals, and polymers, including HPMC (M.W. 10000-1500000), Na-alginate (M.W. 32,000-400,000), Sodium lauryl sulfate (SLS) (M.W. 288.38), and ethyl cellulose (M.W. 454.513), were purchased by Lahore Pharmacy College from a pharmaceutical company, and solvents, including ethanol (M.W. 46.08), and all materials, including Glibenclamide (M.W. 494.004), were obtained from SIGMA-ALDRICH, Germany. All the compounds and materials were used as they were given to us and were of the same grade.

Methods

Methods for manufacturing accordion pills are divided into two stages.
Preparation of the film
Encapsulation

Preparation of Film

The process of creating biodegradable film for accordion pills involves various techniques such as an analytical weighing balance, tablet press, Monsanto hardness tester, FTIR, Roche friabilator, disintegration apparatus, UV visible, and vernier caliper.

Solvent Casting Method

The preparation of the film starts with the preparation of the suspension or solution that contains polymers (along with API). The polymer is suspended and dissolved in water or other organic solvents (Waterman, 2007). This solution can be heated, or its pH can be adjusted. Finally, the polymer solution is cast in a petri dish or other suitable mold (Kong et al., 2015). Drying is performed to remove the solvent. Lamination produces a layered structure (Waterman, 2007).

Encapsulation

The overall process of pill production includes the formation of a film, the assembly of the film (lamination), folding, and encapsulation (Table 1). The solvent casting process is used to make the film, and all of the materials are precisely weighed. In the first step, polymer and solvent are combined to form a solution, and heat is applied to help the polymer dissolve in the solvent. It is then homogenized. Now cast it onto the Petri dish, which can produce a film of the desired shape and thickness. The thickness of the film is determined by measuring the volume of solution. To desiccate the film, the solvent is then allowed to evaporate in the oven. The temperature of the oven is set below 60 degrees Celsius. The drying takes place over 12 to 24 hours to produce a film with good properties. When the solution has evaporated, the dried film can be delaminated.

Three layers of film, containing different polymers and active ingredients, are assembled using an adhering agent like ethanol or salt solution. Techniques include welding, heat curing, fusion, melting, pressing, or cutting the film separately for easy assembly (Prakoso et al., 2023). After assembling the films, both outer layers are treated with an anti-adhering agent (a powder coating) to prevent adhesion to the folding device (Prakoso et al., 2023). The laminated film is folded into a suitable capsule shape using a folding apparatus. This process involves pressing the film against a press, creating an accordion shape. Secondary presses can be applied to achieve smaller foldings. The final step is encapsulation, where the folded film is inserted into the capsule base and the cap is fitted, forming the final dosage form (Prakoso et al., 2023).

Table 1 Formulation table of Accordion Pill

Use	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	Captopril	50	50	50	50	50	50	50	50	50
Drug	Glibenclamide	10	10	10	10	10	10	10	10	10
Synthetic Polymer	HPMC	75	100	50	100	-	-	50	100	50
Natural Polymer-1	Ethyl cellulose	-	-	50	100	50	100	-	-	50
Natural polymer-2	Sodium Alginate	-	-	-	-	50	100	50	100	50
Surfactant	Sodium Lauryl Sulfate (SLS)	5	5	5mg	5	5	5	5	5	5
Adhesive	Acrylic	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Solvent	Water: Ethanol (1:1)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Characterization

The characterization of the formulation consists of the following tests:

Pre-formulation Studies

Organoleptic studies

Evaluation is done using the senses. It contains the active pharmaceutical ingredient's flavor, color, and macroscopic appearance (Huang et al., 2001).

Solubility studies

For determining solubility, the shake-flask method was employed. The solubility was assessed using various buffers and solvents (Kiran and Gopinath, 2023).

Calibration curve

A calibration curve is used to find an unknown sample's concentration. To determine the captopril calibration curve, a 100-ml standard stock solution is prepared. To get the final concentration of 0, 0.5, 1, 1.5, 2, and 2.5 µg/ml, pipette out 1, 3, 5, 7, and 10 ml of the previously mentioned solution and dilute it with distilled water. These dilutions' absorption is measured at 265 nm. The absorbance and concentration are shown on the calibration curve (Kagan and Hoffman, 2008). A calibration curve is used to find an unknown sample's concentration. To determine the glibenclamide calibration curve, a 100-ml standard stock solution is prepared. To get the final concentration of 10, 20, 30, 40, and 50 µg/ml, pipette out 1, 3, 5, 7, and 10 ml of the previously mentioned solution and dilute it with distilled water. These dilutions' absorption is measured at 229nm. The absorbance and concentration are shown on the calibration curve (Kagan and Hoffman, 2008).

Melting point

A melting point test is performed to verify the identity and check the purity of the drug sample. The test is performed using a melting-point apparatus. The melting point apparatus is supplied with a silicon oil bath with a heater for heating the bath. The apparatus has an arrangement to hold the capillary tube in which the sample is to be placed. When the drug sample was melted upon heating, the point where the sample powder melted was noted (Huang et al., 2001).

pka determination

A common method for determining pka is potentiometric titration, which employs a pH electrode to observe the reaction. The equivalency point, or volume at which the slope is highest or the inflection point occurs, is used to compute the pKa value based on a change in the titration curve's form. Lower pKa values are indicative of stronger acids.

Stability studies

The required amount of drugs and excipient samples were weighed for the purpose of analysis, and they were then exposed to different humidity and temperature values in a stability chamber for up to 12 weeks. After that, the samples were taken out at one, two, and three-month intervals and examined for interactions between them (Mahajan et al., 2011).

Post Formulation Studies

Thickness

Three films of each formulation were taken, and the film thickness was measured using a micrometer screw gauge at three different places, and the mean value was calculated (Janczura et al., 2022).

Determination of drug content

A precisely measured 2.2 cm diameter piece of film was obtained, and it was dissolved in 100 ml of 0.1 N HCl solution in a 100 ml volumetric flask. It was then stored for 24 hours, stirring every now and then. The entire mixture was then sonicated. Appropriate dilutions were prepared using a 0.1 N HCl solution following sonication and filtering. At 212 nm, the produced solutions were examined using a UV-visible spectrophotometer (Sri et al., 2012).

Folding Endurance

Three films of each formulation of size 2.5×2.5 cm were cut by using a sharp blade. Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance (Keshavarao et al., 2011).

Surface pH of Films

For the determination of surface pH, three films of each formulation were allowed to swell for 2 hours on the surface of an agar plate. The surface pH was measured using a pH meter. An electrode of the pH meter is placed on the surface of the swollen patch, allowing it to equilibrate for 1 minute (Waterman, 2007).

Percent Swelling

(%) Following the determination of the initial weight and diameter of the film, the samples were left to swell on the agar plate surface, which was kept in an incubator with a temperature control of 37±0.2ºC. Three alternative time periods (1–5 h) were used to determine the weight of the videos (n = 3). The following equation was used to get the percentage swelling, or S:

$$\% \text{ Swelling} = (X\ t – Xo/Xo) \times 100,$$

where Xo is the original weight of the film at time zero and Xt is the weight of the swollen film after time (Bhattarai and Gupta, 2015).

Fourier transform infrared spectroscopy

FTIR will be conducted to check the compatibility between the ingredients. A spectral 100 FTIR ATR spectroscopy was used to create the spectra corresponding to the API, excipients, and 1:1 percent by weight physical mixes of API and excipient.

In vitro drug release studies

Dissolution tests were conducted for each formulation using a USP dissolving apparatus set at 37±0.5ºC and a 50rpm constant. The dissolve medium used for the research was 900 ml of 0.1N HCl. To prevent the proper dosage form from adhering to the vessel's bottom, the appropriate sample holder was utilized. A cylinder of 5 cm in diameter and 4 cm in height was utilized; it was intended to be larger than the dosage form. To maintain sink conditions, a certain quantity of samples was typically obtained every hour and replaced with new medium. For every test, a sample of film containing the drugs was used (Tanaka et al., 2005). At appropriate intervals, an aliquot of the sample was taken out, and the volumes were replaced with new dissolving liquid. At 212 nm, the material underwent spectrophotometric analysis (Mahajan et al., 2011).

Release kinetics

Several kinetic models, including the first-order, zero-order, Higuchi model, and Korsmeyer Peppas model, were taken into consideration in order to assess drug kinetics. The drug release mechanism and formulation type—controlled release or sustained release—were confirmed with these models. For this decision, the values of R2 and n have been used (Tanaka et al., 2005; Waterman, 2007).

3. RESULTS AND DISCUSSION

Various official and unofficial tests were used to evaluate the manufactured accordion pills.

Pre-Formulation Studies

Organoleptic studies

In organoleptic studies, it was found that captopril powder's texture was crystalline with a white color, while its taste was bitter and salty. The odor was found to be slightly sulfurous. The organoleptic studies of glibenclamide revealed that it is a white crystalline solid in its texture. Upon smelling it, it was odorless, and the taste was metallic.

Solubility studies

Captopril is soluble in water and in ethanol. Whereas glibenclamide is insoluble in water and soluble in ethanol, it has solubility in three different ratios: 330 parts alcohol, 36 parts chloroform, and 250 parts methanol. It combines alkali hydroxides to create salts that are soluble in water. Similar to tolbutamide, glibenclamide is a weak acid with a dissociation constant of 5.3±0.1. This is demonstrated by the fact that both compounds exhibit the same dissociation at half-neutralization in solvent mixes such as methanol and water or methyl cellulose and water.

Calibration curve

Captopril and Glibenclamide showed a straight line when the drug concentration and absorbance were plotted on a graph as shown in Figure 1(a) and Figure 1(b), respectively. Values for concentration and absorbance of captopril and glimenclamide are shown in (Table 2).

Table 2 Values for concentration and absorbance of captopril and glibenclamide

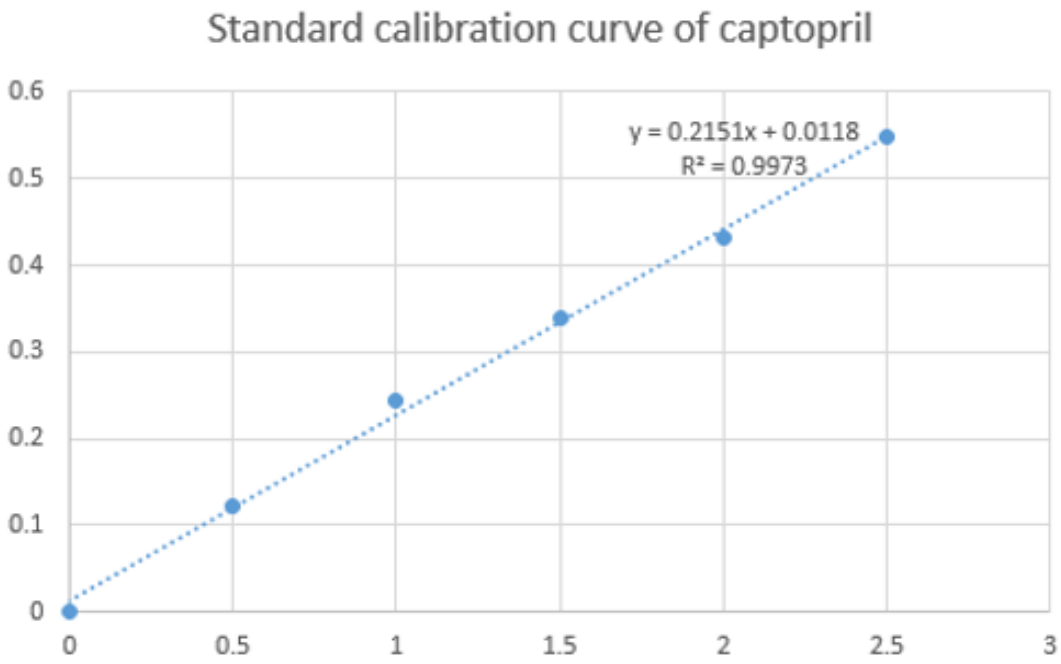
Captopril		**Glibenclamide**	
Concentration(µg/ml)	**Absorbance(λ)**	**Concentration(µg/ml)**	**Absorbance(λ)**
0	0	10	0.091
0.5	0.122	20	0.174
1	0.244	30	0.266
1.5	0.338	40	0.387
2	0.432	50	0.459
2.5	0.548	10	0.091
λ max	265 nm	λ max	229 nm

Melting Point

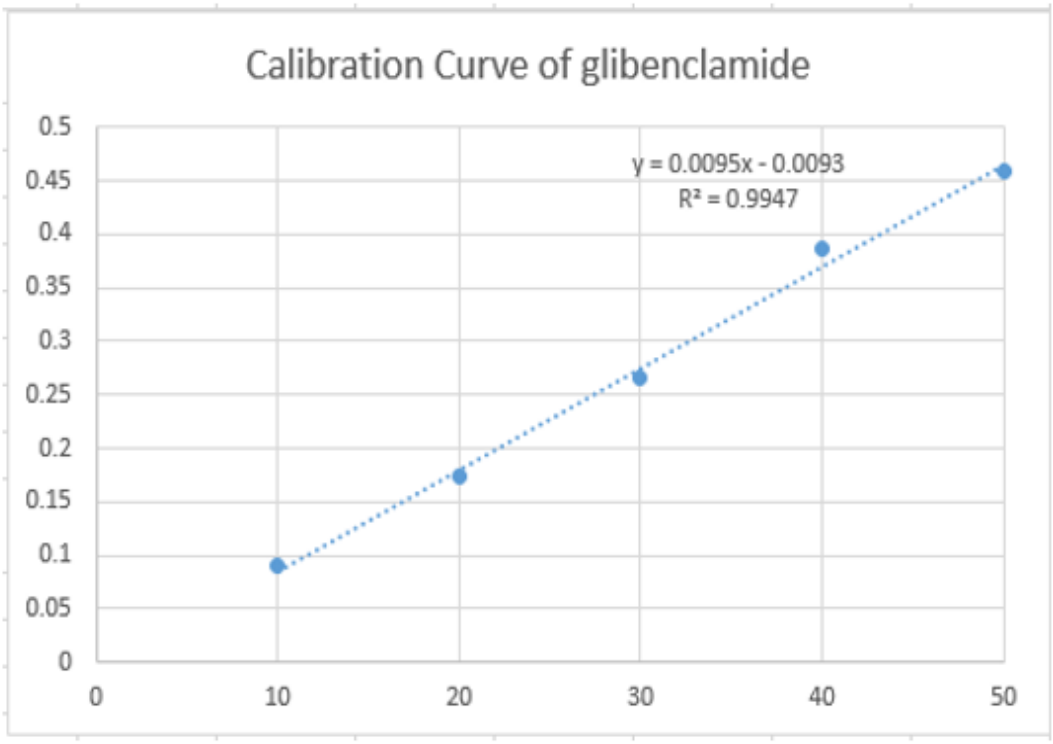
The melting point of captopril was found to be 107 °C. The melting point of Glibenclamide was found to be 170 °C.

pka determination

Captopril pKa was found to be 9.8. Whereas the Glibenclamide pKa value was found to be 5.11.



(a)



(b)

Figure 1(a): Calibration curve of captopril, (b): Calibration curve of Glibenclamide

Stability studies

Captopril was stable, and we could store the sample for 6 months at 50 °C with no decomposition. We could also place captopril in a methanol solution at 5 °C for up to 2 weeks. Glibenclamide is stable, and we can store the sample for 90 days at less than 40 °C.

Post Formulation Studies

Thickness

The thickness of the prepared films F1-F9 were found to be from 0.76mm-0.65mm as shown in table III, exceeding the official limit of 5 micrometer to 200 micrometer.

Drug content

When the drug content of the produced film formulations was analyzed, it was found that, in accordance with content uniformity tests, every formulation had almost the same amount of drugs. The results in the table 3 show that the drug content of all formulations F1–F9 was within the official limit of 85%–110%.

Folding Endurance

A manual measurement was made of the folding endurance. After being cut, a strip of film was examined for folding endurance until it broke at the same place. Table 3 lists how many times the film folded before breaking.

Surface pH

The surface pH of each film ranged from 6.24 to 6.77, falling within the acceptable buccal pH range. Table 3 shows the figures. The formulation's pH was nearly neutral, according to the findings, and it was safe to use.

Percent Swelling

The range of the swelling percentage was 18.36% to 46.24%. It was found to be higher for F5, i.e., 46.24%. The results are shown in (Table 3). A greater proportion of swelling indicates a higher and faster beginning of effect from the drug release.

Table 3 Result of Content Uniformity, Folding Endurance, Surface pH, Percent Swelling and Thickness of Accordion Poly Pills

Formulation code	Content uniformity	Folding endurance	Surface pH	Percent swelling	Thickness
F1	89%	287	6.77	18.36%	0.63mm
F2	91%	289	6.72	26.44%	0.76mm
F3	89%	267	6.68	23.35%	0.71mm
F4	90%	270	6.24	28.44%	0.62mm
F5	92%	272	6.34	46.24%	0.72mm
F6	91%	266	6.45	35.55%	0.64mm
F7	95%	278	6.68	30%	0.60mm
F8	94%	276	6.53	37.68%	0.63mm
F9	96%	260	6.52	35.44%	0.65mm

Fourier transform infrared spectroscopy

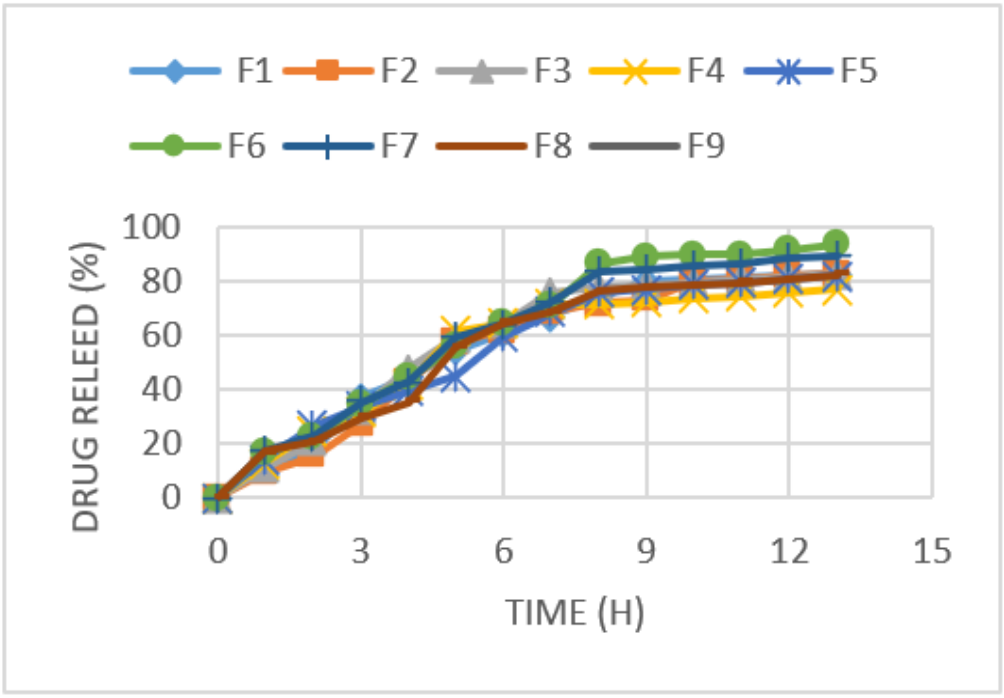
FTIR of Film of CAPTOPRIL

Captopril's FTIR spectra revealed distinctive bands at 3363 cm-1, which point to C-H stretching. At 2111 cm-1, a conspicuous peak was observed, signifying the SH stretch. A peak was seen at 1051 cm-1, suggesting C = O of amide, and at 1457 cm-1, confirming C = O of the COOH group. Captopril film FTIR. Peaks were displayed in the following ranges: 1457–1375 cm-1 for OH bending, 11126.5 cm-1 for C–O stretching, and 1051 cm-1 for CN stretching.

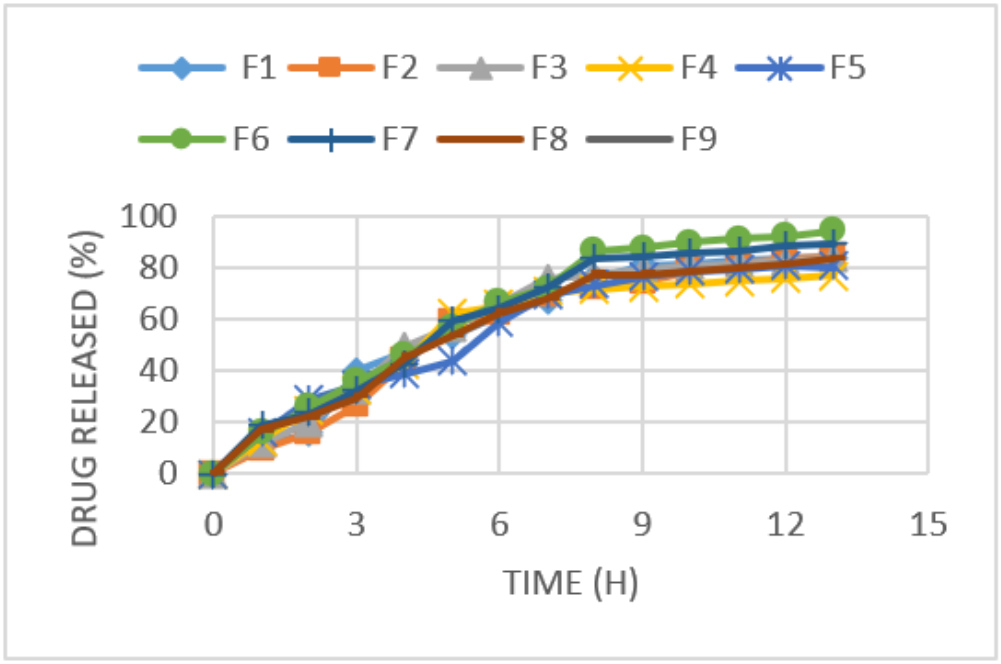
FTIR for film of Glibenclamide

Glibenclamide FTIR spectra showed an NH stretch at wave number 3365 cm^{-1}, an Ar-H (aromatic group) absorption peak at wave number 2875cm^{-1}, and C=O absorption peaks at 1351cm^{-1}.Glibenclamide film FTIR.

In Vitro Dissolution Studies



(a)



(b)

Figure 2(a): Percentage drug release over time for Captopril (b): Graph for drug dissolution studies for Glibenclamide

Dissolution studies of Captopril

The percentage of drug release from the film of Captopril was monitored for a specific number of hours. Within the kinetic analysis, the order of release for each formulation was ascertained using the drug release% vs. time graph plot. In 10 to 11 hours, 85% of the drug was released from the majority of the formulations examined in dissolution experiments. There is no drug release at time zero. At first, the drug release rate was slow. Within five hours, 50% of the drug was released from all formulations except F5. For F5, the majority of the drug was released six to seven hours earlier than expected. The maximum amount of the drug has been released by F1-F9 after 13 hours. The formulations F6 and F7 are regarded as the best since they demonstrated the maximum drug release in a time frame of 10 to 12 hours. The pattern of drug release for the captopril film is shown in (Figure 2a).

Dissolution studies of Glibenclamide

As shown in Table 4, the percentage of drug release in the film of Glibenclamide was monitored for a specific number of hours. Within the kinetic analysis, the order of release for each formulation was ascertained using the drug release% vs. time graph plot. In 10 to 11 hours, 85% of the drug was released from the majority of the formulations examined in dissolution experiments. No drug was released at time zero. At first, the drug was released quite slowly. Within five hours, 50% of the drug was released from all formulations except F5. For F5, the majority of the drug was released six to seven hours earlier than expected. The maximum amount of the drug has been released by F1-F9 after 13 hours. The formulations F6 and F7 are regarded as the best since they demonstrated the maximum drug release in a time frame of 10 to 12 hours. The pattern of drug release for the glibenclamide film is shown in (Figure 2b).

Release Kinetics

Release Kinetics of Captopril

One essential tool that helps in a better understanding and interpretation of the processes responsible for drug dissolution is the ability to relate drug dissolution data to a suitable, sensible representation. This capability also enables control over the release characteristics to meet specific therapeutic requirements. The in vitro dissolution rate pattern was computed or represented using various mathematical model factors. The value of r2, which helps in understanding the nature of accordion pill films containing captopril, is shown in the (Table 4). The values of r2 for zero-order and first-order kinetics, which are 0.7120 and 0.9596, respectively, show that the accordion pill films follow first-order kinetics. This is because the r2 value for first-order kinetics is closer to 1. In the Korsemeyer-Pappas model, the value of n was between 0.45 and 0.89, showing that all formulations followed first-order kinetics.

Release Kinetics of Glibenclamide

One essential tool that helps in a better understanding and interpretation of the processes responsible for drug dissolution is the ability to relate drug dissolution data to a suitable, sensible representation. This capability also enables control over the release characteristics to meet specific therapeutic requirements. The in vitro dissolution rate pattern was computed or represented using various mathematical model factors. The value of r2, which helps in understanding the nature of accordion pill films containing glibenclamide, is shown in the (Table 4). The values of r2 for zero-order and first-order kinetics, which are 0.7234 and 0.9601, respectively, show that the accordion pill films follow first-order kinetics. This is because the r2 value for first-order kinetics is closer to 1. In the Korsemeyer-Pappas model, the value of n was between 0.45 and 0.89, showing that all formulations followed first-order kinetics.

Table 4 Drug release kinetics of Captopril and Glibenclamide

Captopril								
Formulation	**Zero order**		**First order**		**Higuchi**		**Korsemeyer**	
	K0	**R(Square)**	**K1**	**R(Square)**	**kH**	**R(Square)**	**kKP**	**n**
F1	8.076	0.8367	0.159	0.9814	24.484	0.9388	19.084	0.618
F2	7.921	0.8627	0.150	0.9745	23.918	0.9221	17.071	0.659
F3	8.138	0.7984	0.164	0.9792	24.750	0.9330	20.456	0.590
F4	7.605	0.7120	0.147	0.9596	23.285	0.9319	22.029	0.526

F5	7.741	0.8307	0.146	0.9779	23.495	0.9515	19.008	0.600
F6	8.870	0.8714	0.188	0.9746	26.821	0.9491	19.910	0.641
F7	8.525	0.8463	0.175	0.9775	25.832	0.9460	20.046	0.620
F8	7.925	0.8264	0.153	0.9845	24.064	0.9507	19.539	0.598
F9	7.953	0.8657	0.155	0.9746	23.921	0.9231	17.076	0.660
Glibenclamide								
Formulation	**Zero order**		**First order**		**Higuchi**		**Korsemeyer**	
	K0	**R(Square)**	**K1**	**R(Square)**	**kH**	**R(Square)**	**kKP**	**N**
F1	7.963	0.8480	0.154	0.9861	24.122	0.9417	18.482	0.626
F2	7.842	0.8640	0.148	0.9761	23.680	0.9228	16.868	0.660
F3	8.070	0.7898	0.162	0.9768	24.556	0.9299	20.490	0.586
F4	7.579	0.7234	0.146	0.9601	23.184	0.9315	21.568	0.534
F5	7.773	0.8467	0.146	0.9831	23.562	0.9509	18.453	0.615
F6	8.797	0.8756	0.183	0.9682	26.569	0.9395	19.152	0.654
F7	8.535	0.8431	0.176	0.9811	25.877	0.9497	20.334	0.614
F8	7.861	0.8305	0.150	0.9718	23.829	0.9321	18.577	0.618
F9	7.845	0.8644	0.149	0.9766	23.684	0.9230	16.870	0.668

4. DISCUSSION

As a unique poly pill gastro-retentive strategy, the formulation and in-vitro evaluation of an accordion pill containing glibenclamide and captopril show promising implications for improved treatment regimens in patients with diabetes and cardiovascular disease. This study benefited from the use of the solvent casting process for film formulation. Many medications can be combined onto a single film using solvent casting, creating a handy and patient-friendly dosing form. Furthermore, the exact management of film thickness, consistent drug dispersion, and drug-film-forming material compatibility are all made possible by this technology. Captopril and glibenclamide both showed acceptable drug release profiles, according to the findings of the in vitro test. The extended drug release of the accordion pill films demonstrated their gastro-retentive qualities.

This method of sustained drug release may increase therapeutic outcomes and minimize dosage frequency while also increasing efficacy and patient compliance. Moreover, the in-vitro evaluation's observation of floating behavior implies that the accordion pill films may remain in the stomach area for a considerable amount of time. This extended stomach retention may improve drug absorption and bioavailability, particularly for drugs that need to be absorbed in the upper gastrointestinal tract, such as captopril and glibenclamide. But it's crucial to take this study's shortcomings into account. The in-vitro assessment sheds light on drug release and floating behavior; nevertheless, more research is required to evaluate the accordion pill films' pharmacokinetic profile and in-vivo efficacy. It is also important to consider any possible drug interactions as well as stability problems that may exist between glibenclamide, captopril, and the film-forming substances.

5. CONCLUSION

The goal of the current effort is to create a gastroretentive accordion poly pill containing captopril and glibenclamide. The solvent-casting method was used to create accordion pill films containing glibenclamide and captopril. The prepared films showed satisfactory results in terms of content uniformity, high folding endurance, surface pH, and percent swelling. The thickness increased as the polymer content increased. According to a study of content homogeneity, the drug is dispersed consistently throughout the film. All of the formulations had acceptable testing properties. The study analyzed drug release percentages over 13 hours, revealing that most formulations released 85% of the drug after 10 to 11 hours, with F6 and F7 being the best, with the highest release within 10 to 12 hours.

According to the FTIR tests, it would appear that there is no possibility of interaction between the drugs and the polymers of other excipients used in the strips. The formulation and in vitro evaluation of an accordion pill combining glibenclamide and captopril using the solvent casting process are shown in this paper as a feasible gastro-retentive strategy. Patients with diabetes and cardiovascular

disease may benefit from more effective treatment plans thanks to the accordion pill films' extended stomach retention and regulated drug release capabilities. Validating the efficacy and safety of this innovative drug delivery method will require more investigation and development, including in-vivo investigations.

Informed consent
Not applicable

Ethical approval
Not applicable

Conflicts of interests
The authors declare that there are no conflicts of interests.

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Data and materials availability
All data associated with this study are present in the paper.

REFERENCES

1. Abdul S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. J Control Release 2004; 97(3):393-405. doi: 10.1016/j.jconrel.2004.03.034
2. Bhattarai M, Gupta AK. Fast dissolving oral films: A novel trend to oral drug delivery system. Sunsari Tech Coll J 2015; 2:58-68. doi: 10.3126/stcj.v2i1.14802
3. Davis SS. Formulation strategies for absorption windows. Drug Discov Today 2005; 10(4):249-257. doi: 10.1016/S1359-6446(04)03351-3
4. Fujimura A, Kajiyama H, Ebihara A, Iwashita K, Nomura Y, Kawahara Y. Pharmacokinetics and pharmacodynamics of captopril in patients undergoing continuous ambulatory peritoneal dialysis. Nephron 1986; 44(4):324-328. doi: 10.1159/000184014
5. Gabor F, Fillafer C, Neutsch L, Ratzinger G, Wirth M. Improving oral delivery. Handb Exp Pharmacol 2010; (197):345-98. doi: 10.1007/978-3-642-00477-3_12
6. Huang Y, Cheng Y, Alexander K, Dollimore D. The thermal analysis study of the drug captopril. Thermochim Acta 2001; 367-368:43-58. doi: 10.1016/S0040-6031(00)00687-0
7. Iqbal SA, Jose S, Zaafarany I. Synthesis, Physico Chemical and Spectral Studies of Mercury Complex of Glibenclamide; An Oral Antidiabetic Drug. Orient J Chem 2012; 28(1):613-618.
8. Janczura M, Sip S, Cielecka-Piontek J. The Development of Innovative Dosage Forms of the Fixed-Dose Combination of Active Pharmaceutical Ingredients. Pharmaceutic 2022; 14(4): 834. doi: 10.3390/pharmaceutics14040834
9. Kagan L, Hoffman A. Selection of drug candidates for gastroretentive dosage forms: pharmacokinetics following continuous intragastric mode of administration in a rat model. Eur J Pharm Biopharm 2008; 69:238-246. doi: 10.1016/j.ejpb.2007.10.019
10. Kagan L, Lapidot N, Afargan M, Kirmayer D, Moor E, Mardor Y, Friedman M, Hoffman A. Gastroretentive Accordion Pill: Enhancement of riboflavin bioavailability in humans. J Control Release 2006; 113(3):208-15. doi: 10.1016/j.jconrel.2006.03.022
11. Keshavarao KP, Mudit D, Gunashekara K, Shahnawaz A, Mangla NS, Aja K. Formulation and evaluation of mouth dissolving film containing Rofecoxib. Int Res J Pharm 2011; 2 (3):273-278.
12. Kiran CVR, Gopinath C. Idiom of gastroretentive drug delivery systems: Comprehensive view on innovation technologies, patents and clinical trails. NeuroQuantology 2023; 21(6):1237-1253. doi: 10.48047/nq.2023.21.6.NQ23127
13. Kong I, Tshai KY, Hoque ME. Manufacturing of natural fibre-reinforced polymer composites by solvent casting method. NFRPC 2015; 331-349. doi: 10.1007/978-3-319-07944-8_16
14. Lee KJ, Kang A, Delfino JJ, West TG, Chetty D, Monkhouse DC, Yoo J. Evaluation of critical formulation factors in the development of a rapidly dispersing captopril oral dosage

form. Drug Dev Ind Pharm 2003; 29(9):967-79. doi: 10.1081/ddc-120025454

15. Mahajan A, Chhabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A review. Der Pharm Lett 2011; 3(1):152-165.
16. Mustafa MA, Rashid M, Ahmad S, Farooq H, Khan AM, Naeem S, Amin B, Ahmed F, Rafi Q, Tariq N. Effect of receptor and donor phase composition on permeation of pharmaceutical compound through model membrane. Drug Discovery 2023; 17: e27dd1943. doi: 10.54905/disssi.v17i40.e27dd1943
17. Navon N. The Accordion Pill®: unique oral delivery to enhance pharmacokinetics and therapeutic benefit of challenging drugs. Therv Deliv 2019; 10(7):433-442. doi: 10.4155/tde-2018-0067
18. Prakoso FAH, Indiarto R, Utama GL. Edible Film Casting Techniques and Materials and Their Utilization for Meat-Based Product Packaging. Polymers (Basel) 2023; 15(13):2800. doi: 10.3390/polym15132800
19. Rajput JS, Sailaja AK. Formulation and evaluation of curcumin loaded ethosomes as novel drug delivery system. Drug Discovery 2023; 17: e16dd1917. doi: 10.54905/disssi.v17i39.e16dd1917
20. Sri KV, Rohini P, Reddy GK. Montelukast sodium oral thin films: formulation and invitro evaluation. Asian J Pharm Clin Res 2012; 5(4):266-70.
21. Subramani M, Vekatashwaramurthy N, Sambathkumar R. A Novel Approach on Role of Polymers Used in Sustained Release Drug Delivery System—A Review. Saudi J Med Pharm Sci 2021; 7(4):170-178.
22. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, Higaki K, Kimura T. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): in vivo evaluation. J Control Release 2006; 112(1):51-6. doi: 10.1016/j.jconrel.2006.01.020
23. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326(7404):1419. doi: 10.1136/bmj.326.7404.1419
24. Waterman KC. A critical review of gastric retentive controlled drug delivery. Pharm Dev Technol 2007; 12(1):1-10. doi: 10.1080/10837450601168680