IJBPAS, May, 2026, 15(5): 2063-2075

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DEVELOPMENT, OPTIMIZATION AND CHARACTERIZATION OF MOUTH DISSOLVING FILM OF GLIPIZIDE FOR THE TREATMENT OF DIABETES MELLITUS

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Received 25th Feb. 2025; Revised 24th April 2025; Accepted 21st June 2025; Available online 1st May 2026

https://doi.org/10.31032/IJBPAS/2026/15.5.10106

ABSTRACT

Glipizide, a BCS Class II antidiabetic drug, exhibits poor solubility and limited oral bioavailability, making it challenging to dissolve. Its rapid absorption requirement makes it suitable for Rapid Release Drug Delivery Systems. The purpose of this work was to utilize the solvent casting method to design and improve fast-dissolving oral films, guided by a 3^2 factorial design. The consequences of polymer composition and superdisintegrants on film appearance, disintegration time, and in vitro drug release were investigated. Solid dispersion demonstrated improved miscibility and faster drug release compared to the pure drug. The optimised formulation (F5) demonstrated a 93.0 % drug release and a disintegration time of 21 seconds. The films quality was validated by assessments of their physical attributes, folding durability, drug content homogeneity, surface pH, and thickness homogeneity. These findings indicate that Glipizide mouth-dissolving films formulated with HPMC K100 and sodium starch glycolate enhance bioavailability and therapeutic efficacy.

Keywords: Fast dissolving oral film, Glipizide, 3^2 Factorial design, Diabetes Mellitus, bioavailability, first pass metabolism

INTRODUCTION

The costliest approach is oral administration. Several cutting-edge oral delivery methodologies have recently been developed to improve patient compliance and get around the physicochemical and pharmacokinetic problems associated with pharmaceuticals. These embrace computer-assisted three-dimensional printing (3DP) for tablet manufacturing and electrostatic drug coating and deposition **[1]**.

Other names for oral fast-dissolving films (FDF) include mouth-dissolving films (MDF), oral strips, and orodispersible films (ODF). when the saliva carrying the dissolved or dispersed medication is ingested, the drug is typically immersed normally certain medication are immersed directly through the mouth, throat, and esophagus, as saliva travels inside the stomach, possibly producing an immediate impact. Compared to other dose forms, such as tablets, this leads to a much better bioavailability and faster drug concentrations in the plasma **[2, 3]**.

In order to achieve the required qualities and properties, the polymer concentration for ODF manufacture can be raised to 60 to 65 percent weight per weight, although it is typically about 45 percent weight per weight of dried thin strips. In 2011, B *et al*. published the American Standard of Testing and Materials 2022 **[4]**.

Glipizide was used as a model pharmacological candidate in the current work to create an oral dissolving film. Glipizide functions by partially blocking potassium channels inside the pancreatic islets of Langerhans beta cells. The cell depolarises when voltage-gated calcium channels open as a result of blocked potassium channels. Insulin is produced by beta cells in response to the subsequent calcium influx. Clinically speaking, glipizide is an anti-diabetic sulfonylurea drug. To treat type 2 diabetes mellitus, it is taken orally. Glipizde is easily absorbed through the digestive system, and with just one dose, plasma concentrations reach their maximum one to three hours later. It has a two to four hour half-life and is closely associated with plasma proteins. The liver is where it is mostly metabolised, and the urine is where it is mostly removed as inactive metabolites **[5]**.

Oral film that dissolves quickly provide the new technological platforms for all medications in BCS class 2. Previously seen primarily in older persons, type 2 diabetes is now more prevalent in youngsters as a result of childhood obesity and overweight. Although type 2 diabetes is more likely to

strike older adults, it can strike children as well. Type 2 diabetes rates are rising in tandem with juvenile obesity rates. According to the Centers for Disease Control and Prevention (CDC), over 30% of American children and adolescents between the ages of 2 and 19 suffer from obesity. More than 75% of kids with type 2 diabetes have a close relative who also has the disease because of shared lifestyle choices or genetic predispositions. There is a higher chance if you have a parent or sibling who has type 2 diabetes. Glipizide is classified as a biopharmaceutical under system II and is essentially insoluble in water. Therefore, glipizide dissolution is a rate-limiting factor. To increase glipizide's bioavailability and rate of dissolution, its solubility must be improved. Glipizide's uniform bioavailability, suitability for both juvenile and elderly patients, and avoidance of first-pass metabolism all contribute to improved patient compliance. The advancement of a fast-dissolving oral film is necessary to increase absorption and decrease systemic and local side effects **[6]**.

It is difficult to incorporate glipizide into formulations due to their poor water solubility profile. These limitations also compel formulations to use alkalising excipients. There is some published research on the use of PEG-6000 to improve the solubility of glipizide **[7]**.

In order to enhance the solubility of Glipizide, the investigation's goals were to use PEG 6000 to make a solid dispersion. This study specifically sought to ascertain how PEG-6000 changed Glipizide's solubility. After solid integrated Glipizide mouth dissolving films have been further developed and tested in vitro, a suitable formulation of the film will be created using the factorial design technique **[8]**.

MATERIAL AND METHOD

Material

Glipizide Supra Chemicals Pvt Ltd, Mumbai, is a drug candidate. The materials utilized in this investigation—hydroxypropyl methyl-cellulose, SSG, polyethylene glycol, citric acid mg, and PEG-6000 mg—were acquired from Research-Lab Fine Chem Industries in Mumbai.

Method

Experimental Design

Several Trials were carried out before the design's implementation to ascertain the formulation parameters and environmental factors that caused the procedure to produce fast dissolving films (FDFs). A 3^2-factorial design was employed to optimize the formulation using Design-Expert® Software, which permits evaluation by nine experiments

to minimize the number of tests.The concentrations of superdisintegrant (SSG; X2) and film-forming polymer (HPMC; X1) were optimised using a factorial design. To assess the effects of these formulation variables on rapid dissolving oral films disintegration (Y1), drug release (Y2), and the optimised formula, a two-factor, three-level (32), full factorial design was performed **[9, 10]**.

Formulation of solid dispersion

Various drug and PEG 6000 ratios were used in the melting, solvent evaporation, and kneading processes to create solid dispersion (SD) **[8]**. To make a physical mixture (PM) in the following ratios, glipizide and PEG-6000 were thoroughly mixed in a glass mortar and pestle for five minutes: 1:1, 1:2, 1:3, 1:4, and 1:5. After that, the mixture spent a whole day in a desiccator. A bath of water was used to melt a physical mixture by gradually increasing the temperature until the melting was complete. The molten substance quickly cooled while being constantly stirred with a glass rod. Before being run through sieve number 100, the resulting solid dispersion was crushed for two minutes in a mortar. The generated dispersions were desiccator maintained and used for further study in glass vials.

Table 1: Factors

Independent variables	Conc.of HPMC K 100 M	Conc.Of SSG
Dependent variables	*In vitro* (DT)	% drug release

Table 2: Level

Name	-1	0	+1
HPMC K-100 M (X1)	200	300	400
SSG (X2)	12.42	18.63	24.84

EVALUATION OF GLIPIZIDE SOLID DISPERSION

solubility

A significant qualityt of solid dispersion that was mixed with the solvent (water and phosphate buffer at pH 6.8) and left it for 48 hours at room temperature, sometimes shaking, in order to test for solubility. Using a Shimadzu UV double-beam spectrophotometer, was collected and examined. Dilute the sample if needed. (by a factor of 100 or 1000)

Drug Content

To determine the amount of drug included in SDs were dissolved in 100ml of phosphate buffer (pH6.5) additional filtration, dilution, and spectrophotometric measurement of the absorbances were performed on the solution at the pre-set λ max 275 nm (UV visible spectrophotometer).

Percentage Drug Release

To calculate the percentage of drug release, the USP Apparatus 2 (Paddle) is utilized. Each

vessel received a solid dispersion containing 900 millilitres of phosphate buffer with a pH of 6.8 and 2.5 milligrams of Glipizide. Every sample was kept in a basket and rotated at a speed of 50 rpm while being kept at 37 °C. After a predetermined amount of time, a 10 ml sample is removed, and its percentage of medication release determined UV spectroscopy in conjunction with the appropriate dilution.

Fourier Transform Infra-Red Analysis (FT-IR)

Using an FTIR spectrophotometer, the glipizide solid dispersion's FTIR spectra were capctured. Dry air purging was used to run the device, and scans were performed at a resolution of 4 cm1 spanning the 4000-400 cm1 range.

FORMULATION OF FAST DISSOLVING ORAL FILMS

Using the, method of solvent evaporation. the quickly disintegrating films were created. HPMC K 100 M was the hydrocolloid that was utilized to make the films. The specified volume of water was used to dissolve a precisely weighted amount of hydrocolloid using a magnetic stirrer, a determined amount of propylene glycol was added to the previously prepared solution as a plasticizer and dissolved. Two milliliters of the appropriate solvent were used to individually dissolve a weighed quantity of Glipizide SD. The Glipizide solid dispersion solution was completely combined with a pre-made hydeocolloid and plasticizer solution. To eliminate air bubbles, the previously described solution is left for ten minutes or, if required, may be the sonication was held. After that, the film was placed on a petri plate and left to dry for the entire night. The film was then meticulously taken out and cut to the necessary 2 cm by 2 cm size.

Table 3: Mouth-dissolving film formula modification using full factorial design

Formulation ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide (mg)	40	40	40	40	40	40	40	40	40
HPMC K100M (mg)	441.421	400	200	200	400	300	158.579	300	300
SSG (mg)	18.63	12.42	12.42	24.84	24.84	18.63	18.63	27.412	9.847
PEG 400 (ml)	1	1	1	1	1	1	1	1	1
PEG 6000(mg)	200	200	200	200	200	200	200	200	200
Citric acid (mg)	50	50	50	50	50	50	50	50	50
Water Upto	30	30	30	30	30	30	30	30	30

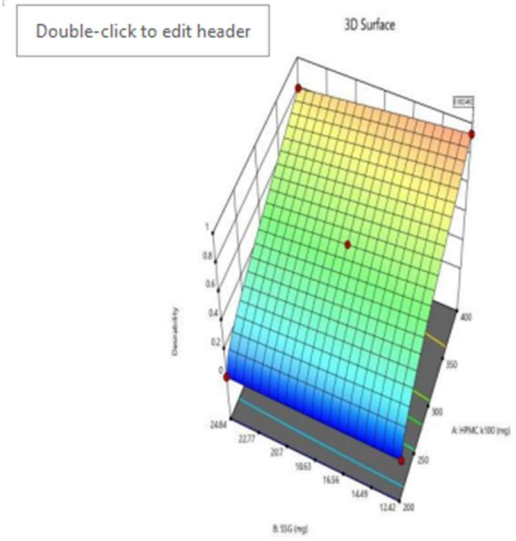


Figure 1: 3D graph of desirability

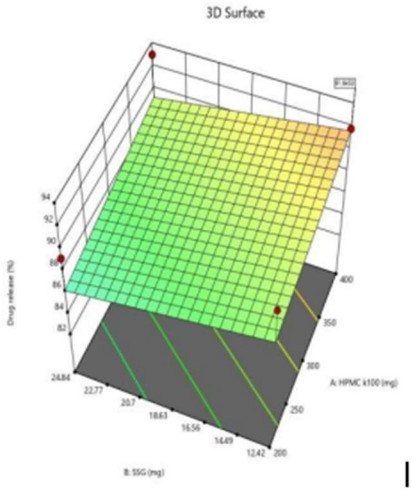


Figure 2: 3D Response surface plot showing effect of polymer conc. On drug release

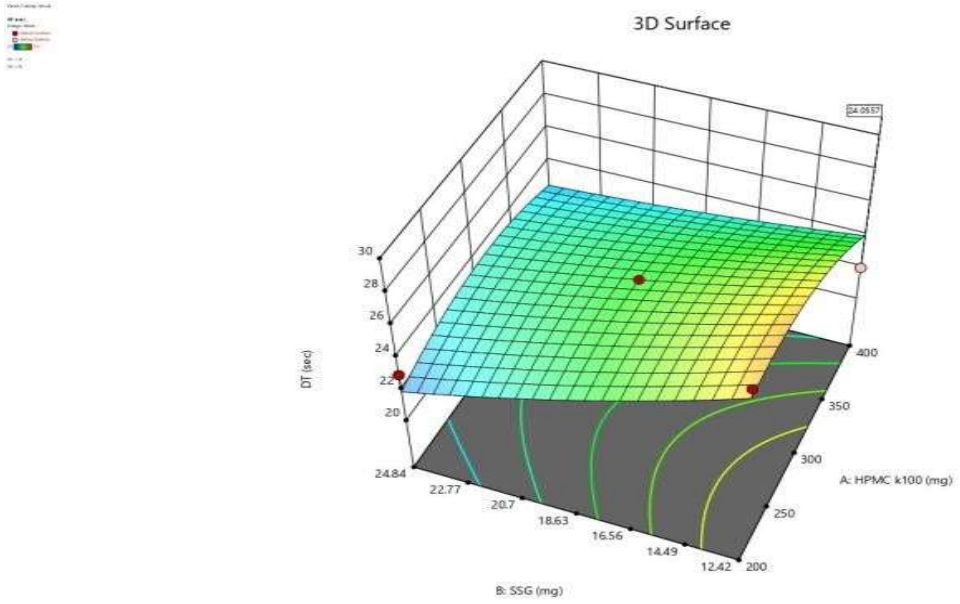


Figure 3: 3D Response surface plot showing effect of polymer conc . on drug release

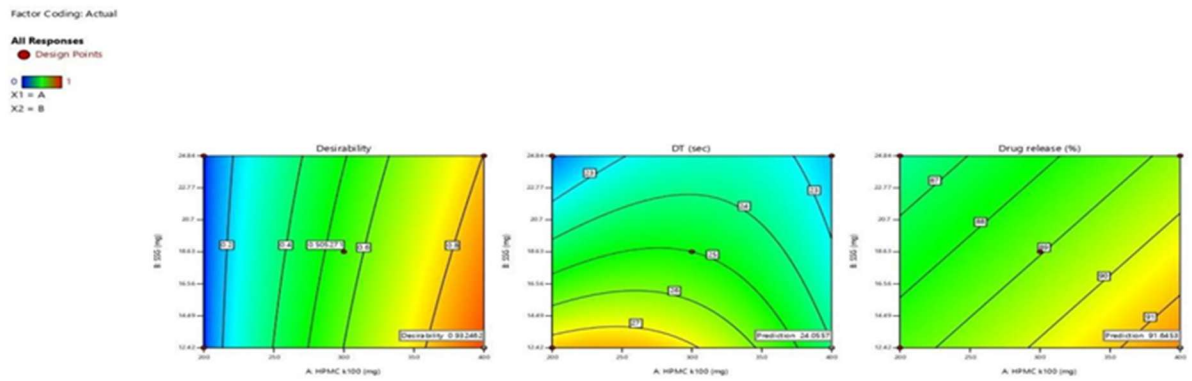


Figure 4: Response surface graph of the effect of concentration of HPMC and SSG on % drug release and disintegration time. A: Contour Plot of Desirability, B: Contour Plot of disintegration time, contour plot of % drug release

EVALUATION OF MOUTH-DISSOLVING FILM

Weight of film

Through the use of an analytical scale to weight oral fast-dissolving films, we were able to determine the average weight of each film. Movies need should weigh nearly the same. It helps to make sure that a film has the right amount of API and excipients.

Thickness

The micrometer screw gauge, the film's thickness was determined. Five separate places were used to assess the thickness in order to ensure consistency. Less than 5% of the film should be thick.

Weight Variation

Ten randomly selected films had their average weight determined. Weighing each film separately and comparing it to the average weight allowed us to calculate the variance.

Folding Endurance

Cutting and folding a film repeatedly until it disturbs is how folding endurance is measured. The number of times the film has being folded in the identical manner without disintegrate is known as the folding endurance value. The film proved to be resistant to 100-150 folds.

In Vitro Disintegration Time

The number of time (measured in seconds) that a film dissolves when it comes into contact with water or saliva is known as its disintegration time.

Petri Dish Method

The number of times it looks for the oral film to entirely dissolve was recognized when it was set on top of a petri dish loaded with two milliliters of distilled water.

In-Vitro Dissolution

The Glipizide fast-dissolving film's release rate was ascertained using the USP Dissolution Test Apparatus-II. 50 paddle

spins per minute and 37 °C were used for the 900ml Phosphate Buffer Solution PH 6.8 dissolving test. Aliquot Five milliliters of the solution were taken out of the dissolving device at five, ten, fifteen, twenty, twenty-five, and thirty-minute intervals. At the same time, five milliliters or an equivalent volume of fresh dissolving media were added. The Aliquot was passed through the filter paper made by Whatman. The filtered solution's absorbance was measured at 275 nanometers. The top of the revolving paddle and the surface of the dissolving media should be at least one centimeter apart when the aliquot is being removed from the vessel wall. The formula derived from the standard curve or the standard curve or the % drug release formula can be used to calculate the cumulative percent drug release.

Drug Content Study

Operating a UV/visible spectrophotometer, the drug concentration of the oral strip, which had a surface area of 4 cm^2, was determined at 275 nm after it had been scattered in 10 ml of phosphate buffer at pH 6.8. Three tests were conducted on each formulation, and the average results were noted.

Stability Study

A formulation's success is largely dependent on how stable it is. A batch of ODF was kept for three months at the suggested relative humidity levels (40 °C/75 %) in order to evaluate this. The samples were first wrapped in aluminum foil and then in butter paper. Tensile strength, pH, drug content, moisture content, and drug release profile were among the variables examined in monthly samples.

RESULTS AND DISCUSSION

solubility

It was discovered that PEG 6000 was the most soluble version of glipizide. Glipizide's solubilities in phosphate buffer (6.8) and water were determined to be 2.876 mg and 3.567 mg, respectively. A 1:5 ratio of glipizide to PEG-6000 would be an excellent solid dispersion carrier, according to the solubility investigations, when assessed using a Shimadzu UV 2450 dual- beam spectrophotometer and the appropriate dilution when required.

Drug Content and Percentage Drug Release Study

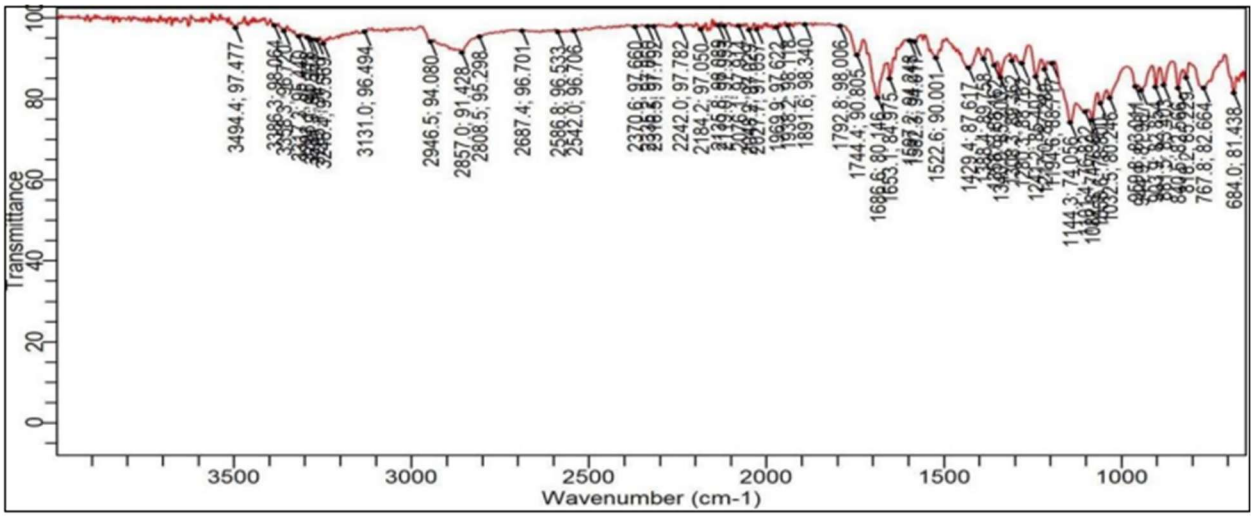
The highest percentage of TEL content and drug release, as determined by examination using UV spectroscopy, happened when the drug to polymer ratio was 1:5. The drug release curve and % Glipizide concentration for different polymer ratios are shown in **Figure 2**. All solid dispersions were prepared in PEG 6000 after it was determined that a 1:5 ratio of drug to PEG 6000 is an adequate

carrier based on studies on drug solubility, drug essence, and remedy release.

Compatibility Study of Solid Dispersion

FTIR SPECTROPHOTOMETRIC STUDY

Glipizide solid dispersion FTIR spectra be set down on an FTIR spectrophotometer. Dry air purging has been used to run the device, and scans were performed at a resolution of 4 cm1 spanning the 4000-400 cm1 range.



Optimization of Formulation

Design experts used statistical technology to optimize the oral fast-dissolving films. Hydrocolloid HPMC produced a clear solution right away, in contrast to other HPMC E grades. The union created more flexible, translucent sheets compared to others polymers. Utilizing optimization approaches allows for a deeper understanding and the investigation of ranges for forming and processing in factors. By employing a rational approach to pick the right excipients and production methods for a particular product, a formulation can be methodically chosen.

Table 4: Batch -wise results of drug release and disintegration studies

Formulation code	Factor 1A HPMC K100 mg	Factor 2 B SSGmg	Response 1 DT (Sec)	Response 2 Drug release (%)
F1	441.421	18.63	24	88.27
F2	400	12.42	22	91.83
F3	200	12.42	28	91.83
F4	200	24.84	23	89.21
F5	400	24.84	21	93.0
F6	300	18.63	25	85.29
F7	158.587	18.63	22	82.62
F8	300	27.41	19	86.52
F9	300	9.84	29	92.38

EVALUATION ORAL FAST DISSOLVING FILMS

Weight, thickness, pH, folding durability, and content uniformity are among the physical characteristics of films that are displayed in Table 5. As shown in the table, the Glipizide solid dispersion may be successfully incorporated into oral rapid-dissolving films using the prepared films.

In Vitro Dispersion Studies

According to *In vitro* Glipizide decomposition, the study discovered that Glipizide was released from Glipizide-SD films more easily than from pure medications. This might imply that the drug was released in the films right away. But it doesn't tell you anything about how well a drug substance is absorbed. It is limited to demonstrating the efficacy of in vitro dispersion. Therefore, to find out more about the rate of API absorption, it could be wise to conduct pharmacokinetic studies of dietary supplements.

Drug Content Study

In a formulation with rapid drug release in phosphate buffer 6.8, glipizide has demonstrated good effectiveness. During the first three minutes, it was found that the simulated salivary fluid contained above 60%. As a result, it implies that buccal administration is suitable for a dose type that has immediate effects.

Stability Study

After six months of storage at 40°C/75% RH, the films were put through stability tests to see how stable they were in terms of their external look, folding resistance, drug content, and drug release properties. After 0 and 30 days, a sample was collected.

Table 5: Physical properties of mouth dissolving films

Formulation	Weight of film (mg)	Thickness (mg)	Folding Endurance	In vitro disintegration time (sec)	Surface PH
F1	119.43	0.45	144	24	6-7
F2	135.23	0.48	148	22	6- 7
F3	128.57	0.45	157	28	6- 7
F4	132.52	0.46	142	23	6- 7
F5	132.19	0.45	141	21	6- 7
F6	141.65	0.66	154	25	6- 7
F7	129.23	0.45	143	22	6- 7
F8	137.32	0.52	152	23	6-7
F9	136.42	0.56	145	29	6- 7

Table 6: Stability Study

Parameters	0 days	One month
Thickness	0.45	0.44
Folding indurance	141	140
In vitro disintegration time (sec)	21	21
I*n vitro* dissolution %	93.0	92.97

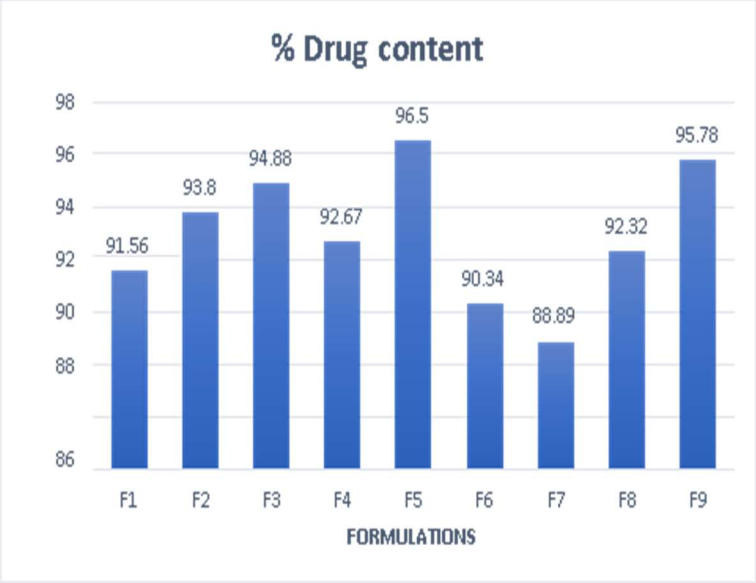


Figure 5: Bar chart of Drug content study

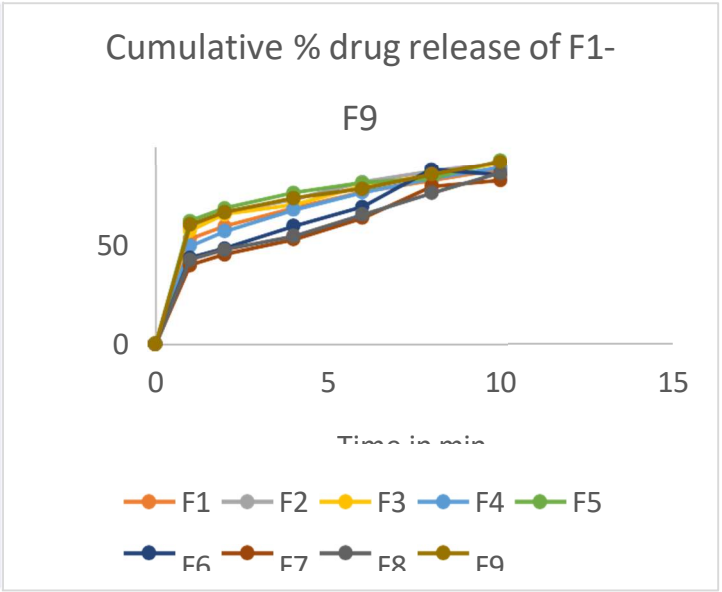


Figure 6: In - Vitro drug release study of F1-F9

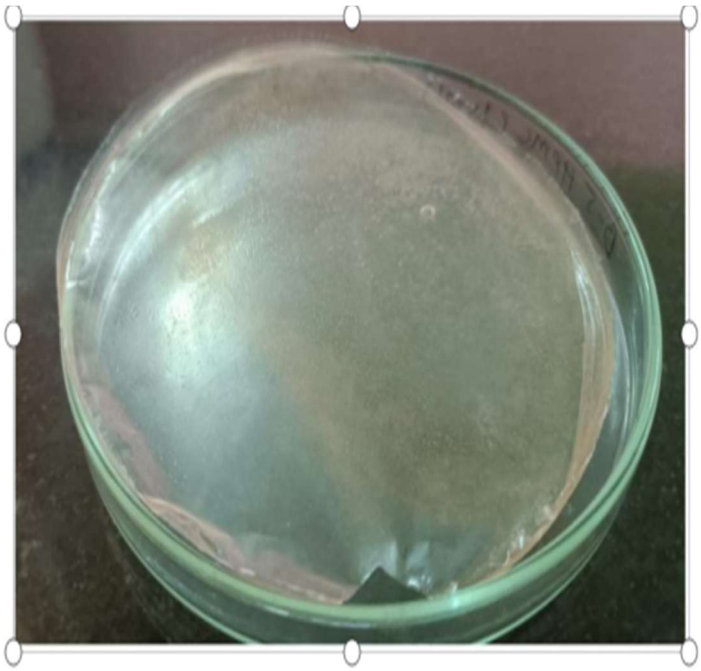


Figure 7: Mouth dissolving oral film

CONCLUSION

Developing an oral dissolving film with enhance Glipizide solubility was the goal of this investigation. IR studies have demonstrated the compatibility of glipizide with excipient. Glipizide solid dispersion was made using Glipizide-PEG 600. Solid dispersions with a drug-to-carrier ratio of 1: 5 are made using the melting method. Glipizide and PEG-6000 solid dispersions were shown to have a higher rate of drug release. The solvent casting technique have been accustomed to generate the films. A film-forming polymer called HPMC K 100M was used to quickly hydrate the film. Sodium starch glycolate was utilized as a super disintegrant to improve disintegration. The films thickness, folding endurance, in-vitro disintegration time, and dispersal characteristics were also examined. HPMC K100 M, which was created using a 3^2 complete factorial technique, was part of the formulation.

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