Evaluation of Mangifera indica gum as a sustained release polymer in Glibenclamide matrix tablet

Akshay Dwivedi*[1], Saurav Ghoshal[1], Manoj kumar Mishra[1],Sagar Bansal [1], Dheeraj Dubey[2]

[1]*Shambhunath Institue of Pharmacy, jhalwa, Prayagraj, Uttar Pradesh -211012, India*

[2]*School of Pharmacy, Shri Venkateshwara University, Gajraula, Uttar Pradesh- 244236, India*

Shambhunath Institue of Pharmacy, jhalwa, Prayagraj, Uttar Pradesh -211012, India

Corresponding Author: Akshay Dwivedi

akshaydwivedi1857@gmail.com

Abstract

Oral drug delivery is considered to be the most suitable drug delivery system (DDS) for the systemic circulation. Oral drug release system gained interest in the field of pharmaceuticals because of various advantages, i.e. proper therapeutic response, easy in dose administration, patient compliance etc. After oral delivery of a drug, the drug should be retained in the stomach and release the drug in a well-ordered way, so that the delivery of drug is continuous at its absorption sites in GIT (gastro intestinal tract). Floating drug delivery systems (FDDS) or hydro dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric matters, the drug is released gradually at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. The aim of the present research work was to formulate and evaluates the floating tablet of glibenclamide. The floating tablet of highly water soluble anti-diabetic drug, glibenclamide (GL) was prepared using *Mangifera indica* gum as the polymer by employing solvent evaporation method.

Keywords: drug delivery system, floating, floating tablets, glibenclamide, *Mangifera indica* gum.

Introduction

Orally administered drugs are most popular. Many methods have been used to create a drug reservoir that releases a large quantity of medication at a specified period. However, this method has several physiological issues, such as stomach emptying time (8-12hrs) and intestinal drug absorption window.[1] These difficulties led the researchers to create a DDS that exerts its pharmacological activity in the GIT for a long duration. Challenges are to establish a DDS that maintains its therapeutically active plasma concentration of drug for a long time by minimizing dose criteria and minimizing plasma concentration fluctuations by the drug's pharmacological outcome in a systemic and controlled manner. Oral DDS is best for systemic circulation. Oral drug release systems' advantages—proper therapeutic response, convenient dosage administration, patient compliance—attracted pharmaceutical companies. After oral administration, a medication should be retained in the stomach and released in a well-ordered manner to provide continuous drug delivery at GIT absorption sites [2]. Short GRT and random short GET prevented drug release at the absorption site in this system. The designed dosage form must extend GRT to provide an oral targeted drug delivery system. Over the last few decades, many GRDDS have been designed, including elevated density systems that retain in the lower part of the stomach [3,4], lower density systems that cause buoyancy in gastric-juice [5, 6, 7], muco-adhesive systems that bio-adhere to stomach mucosa [8], extendible, unfold able, or swell able systems that restrict emptying dosage forms through the pyloric sphincter [9], super- porous hydrogel system [10], magnetic system, etc. The present work outlines Gastro-retentive techniques that are now leading site-specific OCRDDS procedures. The modern drug-delivery system is extremely well built to transport a therapeutic amount of medication to the intended spot in the body.

Diabetes mellitus (DM) is a collection of metabolic illnesses that are characterized by hyperglycemia. Hyperglycemia is related with the abnormalities in the metabolism of glucose, fat, and protein, and these abnormalities are caused by errors in insulin production, insulin action, or both. Due to a lack of insulin action, the glucose that should have been transferred from the plasma into the cells is unable to do so. This predicament is sometimes referred to as "starvation in the midst of plenty." In this context, it promotes the breakdown of fat by stimulating gluconeogenesis, glucogenolysis, and lipolysis, which results in the production of ketone bodies, glycosuria, and polyuria. Multiple health consequences, including micro vascular, macro vascular, and foot ulcers, can be seen as a result of this condition, and they can contribute significantly to an increase in morbidity and mortality.

Glibenclamide, also known as glyburide, is an oral ant diabetic medication used to treat type 2 diabetes. It belongs to a class of drugs called sulfonylureas, which stimulate the release of insulin from the pancreas and help lower blood sugar levels. Glibenclamide works by binding to specific receptors on the beta cells of the pancreas. This stimulates the release of insulin, which helps the body utilize glucose effectively and lowers blood sugar levels. Glibenclamide is primarily used for the management of type 2 diabetes, particularly when diet and exercise alone are insufficient in controlling blood glucose levels. The medication is taken orally in tablet form. The dosage and frequency of administration are determined by a healthcare professional and depend on

Individual needs, blood glucose levels, and other factors. One of the potential side effects of glibenclamide is hypoglycemia, or low blood sugar. It is important to closely monitor blood glucose levels and be aware of the symptoms of hypoglycemia, such as shakiness, sweating, dizziness, and confusion. If hypoglycemia occurs, consuming a source of glucose (like fruit juice or candy) is necessary to raise blood sugar levels. Along with hypoglycemia, glibenclamide can cause other side effects such as nausea, stomach upset, weight gain, skin rash, and allergic reactions. It may also rarely lead to more serious adverse effects like liver problems or blood disorders, **Figure 1**.

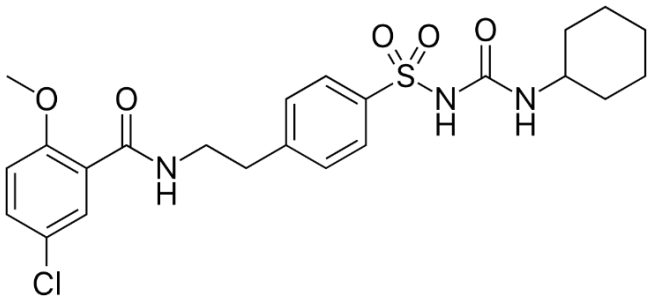

Figure 1: Structure of Glibenclamide

Materials

Glibenclamide was purchased from the Sun pharmaceutical industries LTD. Tandalja, Vadodara-INDIA, Eudragit and tween 80 from Central Drug House Pvt. Ltd., New Delhi, Hydroxyl propyl methyl cellulose (HPMC), Dichloro methane and Hydrochloric Acid from Loba chemie Pvt. Ltd. Mumbai and solvent was used as analytical grade and purchased from Research Lab Fine Chem Industries, Mumbai.

Method

Preformulation study of Drug

Determination of the physicochemical properties is the important steps are the Preformulation studies before incorporating of the drug in its formulation. The properties of drug greatly affect the various parameters like method of preparation, compatibility study and pharmaco-kinetic parameters of the formulation. For the safety, effective and the stable formulation the pre-formulation studies is necessary. The selected drug glibenclamide was identified by various methods like organoleptic properties, Melting Point Determination, Solubility, Partition-coefficient, UV-Spectrophotometric Study, FTIR Study.

Identification of drug and excipient

Appearance

The appearance is determined by the visible inspection of drug and excipient.

Melting points determination

The MP of drug, glibenclamide and other excipient was observed by the capillary MP apparatus. The melting point is the temperature at which a solid melts and becomes a liquid. In a typical procedure capillary tube was filled with tiny amount of drug from one end and another end blocked by heat and the drug loaded capillary inserted in one hole and thermometer inserted in another hole of the melting point apparatus and the melting temperature was determined.

Solubility

Solubility of the pure glibenclamide was determined with respect to these solvents system i.e. ethanol (95%), dichloromethane (DCM), 0.1 N HCl, acetone, diethyl ether etc.

Apparent partition coefficient study

Before, equal volumes of different solvents, such as 0.1N HCl as an aqueous phase and n-octanol as a non-aqueous phase, were previously saturated with each other by shaking together in a shaker for 3 hours. Then, the two phases were allowed to separate overnight after being shaken together for 3 hours. After waiting for twenty-four hours, the phases were separated, and then a known quantity of the medicine was dissolved in the aqueous phase that was left behind. At a temperature of 370.5 degrees Celsius, the two phases were combined once again in the separating funnel and shaken for a total of four hours. After four hours, the separating funnels were set aside in a separate location for another night in order to complete the solvents' mutual separation. After performing the necessary dilutions, spectrophotometry was used to quantify the drug concentration that was present in the aqueous phase. The outcomes after being worked through using Equation [11].

Partition $Coefficient$**= concentration of organic phase/ concentration of aqueous phase**

UV-Spectrophotometric Study for determination of λ-max

The purpose of the UV-spectrophotometric investigation that was carried out was to ascertain the maximum absorbance value (max) of glibenclamide in 0.1N hydrochloric acid and distilled water. After dissolving 10 milligrams of the medication in a 10 milliliter volumetric flask with 10 milliliters of 0.1 percent hydrochloric acid, a standard stock solution of glibenclamide was created. This produced a solution with a concentration of one thousand micrograms per milliliter of standard glibenclamide. The normal stock solution was pipetted out one milliliter at a time into a volumetric flask holding ten milliliters, and then the volume was brought up to ten milliliters by adding 0.1 N hydrochloric acid in order to achieve a concentration of one hundred micrograms per milliliter. The maximum wavelength, or max, was determined by scanning the product, which was a solution, in the range of 200 nm to 400 nm with a UV-Visible spectrophotometer (made by Shimadzu in Japan with model number UV-1800).) [12].

Preparation of calibration curve of pure glibenclamide

Standard curves of Glibenclamide were prepared in solvent systems 0.1N HCl. For the preparation of calibration curve of pure Glibenclamide, a series of dilutions were made in the

manner of 0, 2, 4, 6, 8, 10µg/ml by preparing primary stock solution of 1mg/ml using respective solvent. Fr0m this stock solution 0.5 ml solution was withdrawn and diluted to 25 ml using respective solvent to get the conc. of 20 µg/ml (secondary stock solution). Afterward, from the secondary stock solution the different aliquots of 1ml, 2ml, 3ml, 4ml, and 5ml were withdrawn and diluted to 10 ml in different sample tube to get the final conc. of 2, 4, 6, 8, and 10 µg/ml. After preparation of these dilutions, the absorbance of each dilution was taken at their corresponding λmax scanned previously in 0.1N HCl. The calibration curves between absorbance against concentration were plotted in the solvent system. The regression equations of the standard curves of drug solutions were obtained and used for the quantitative determination of Glibenclamide in the experimental samples.

FTIR Study

The FTIR spectra of glibenclamide drug and other excipient were recorded by Fourier Transform Infra-red spectrometer (Bruker Alpha, Germany) in the frequency range of 4000-400 cm-1. The characteristic absorption peaks of glibenclamide, hydroxyl Propyl methyl cellulose and Eudragit, were obtained at different wave numbers. The main purpose of the FT-IR analysis is to determine the chemical functional groups present in the drug and other excipient [13].

Method of preparation of floating matrix tablet

Formulation is a multi-purpose word. In its most fundamental definition, it refers to the process of putting diverse components together using the appropriate sorts of connections or structures in order to fulfill the requirements of a formula. Direct compression was used to make floating tablets of glibenclamide. Different grades of HPMC K100 M, *Mangifera indica* gum were used, and the concentration of each of these ingredients varied. The weight of the tablets was altered such that each one would contain exactly 600 milligrams of glibenclamide. All of the powders were put through sieve with a #80 p0re size. A thorough mixing of the required amount of the medication and the polymers was performed. In the end, talc and two percent of magnesium istearate were used as the glident and the lubricant , irrespectively. Using a tablet compression machine, the mixture was immediately compressed, sometimes known as "punched." The weight of each pill was brought up to 800 milligrams. The formulas for the various batches are shown in table 6, which may be found here. Both *Mangifera indica* are natural polymers, were included into the formulations in varied concentrations. [14].

Table 1: Composition of different variables used this formulation

Ingredients	F1	F 2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	600	600	600	600	600	600	600	600	600	600
HPMC K100 M	40	40	40	50	50	50	40	30	40	40
Mangifera Indica gum	40	50	40	40	30	40	30	20	30	40

Sod. bicarbonate Nate	40	40	40	40	30	50	30	30	30	30
Citric Acid	25	25	25	25	15	15	15	15	15	15
Magnesium Stearate	16	16	16	16	16	16	16	16	16	16
Talc	16	16	16	16	16	16	16	16	16	16
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight	800	800	800	800	800	800	800	800	800	800

All quantities are in mg, all the batches contained 2% w/w talc and 2% w/w magnesium stearate and each tablet contains uniform weight of 800 mg.

Pre-compression Evaluati0n Parameters

Prepared floating tablet were evaluated for their many micrometric properties such as like-

Bulk density

In order to calculate the mass per unit volume of the floating tablet, a batch of the particles was transferred to a graduated cylinder containing 10 milliliters. After that, we repeated the process three times at intervals of two seconds, each time dropping the cylinder from a height of one inch onto a hard surface. After that, the volume of the powder was measured, and the bulk density was determined by dividing the weight, which was measured in grams, by the volume, which was measured in centimeters three. The tap density is determined by applying the traditional tapping method using a 10 mL measuring cylinder and reducing the number of tapings to 100. This method was described in detail in Shariff et al., 2007. The ratio of the weight of the untapped floating tablet to their total volume was used to calculate the bulk density of the matrix tablet, which was then expressed as a percentage [15].

Bulk density = M/V

Where M = Weight of matrix tablet sample, V = Apparent volume of matrix tablet

Tapped density

The mechanical tapping of a graduated measuring cylinder that contained the floating tablet was used to determine the tapped density, and the calculation was made. It is the ratio of the volume of the microsphere when it was first tapped to the volume of the microsphere after it was tapped.

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$$\text{Tapped density} = \frac{wt.of\ matrix\ tablet}{final\ tapped\ volume\ of\ the\ matrix\ tablet}$$

Compressibility index

The compressibility index is a tendency of matrix tablet to be compressed. It's calculated by this formula**.**

$$\mathbf{CI}=\frac{\boldsymbol{TD-BD}}{\boldsymbol{TD}}\times\mathbf{100}$$

Where - TD =Tapped Density, BD = Bulk Density

ANGLE OF REPOSE

For the purpose of this investigation, a glass funnel having an interior diameter of 35 mm was utilized. A graph paper is laid out on a flat surface, and the tip of the funnel is positioned at a specific height (h) above the paper.

This quality was determined by measuring the greatest angle that could possibly exist between the surface of the microsphere pile and the horizontal plane; this was accomplished by keeping the funnel in the same position during the evaluation [16].

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height of the conical pile of particles and radius of the base of the pile respectively.

Drug polymer compatibility study

Drug-polymer interaction studies were carried out by using FTIR and XRD analysis.

FTIR Study

For finding drug polymer we performed FTIR for both formulations blank and drug-loaded in a frequency range of 4000-400cm^{1}.

Morphological characterization

The scanning electron microscope was utilized to investigate the dimensions of the glibenclamide-loaded matrix tablet. In order to prepare the samples, each sample was first mounted onto a metal stub using adhesive tape on both sides of the stub. A high vacuum evaporator was used for the process of carbon coating. After then, the activity of scanning and capturing pictures was finished. **[17]**.

***IN-vitro* drug release study**

The USP dissolving Test Apparatus Type 1 (Basket Type) performed in vitro drug release investigations at 100 rpm in 900 ml of dissolving media at 37°C±0.5°C. The study employed 100mg of weighted floating pill. Dissolution was in 0.1N HCl. After 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours, 5ml of sample was removed from dissolving media and replaced with 5ml

of fresh medium. The material was processed through W.F.P. and UV-spectrophotometric allyassessed at 233 nm. **[18]**.

Result and discussion

Melting point Determination

The melting point of MH and other excipient was determined by using capillary method through MP apparatus. The observation was done in triplicate.

Table 2: Melting point of *Glibenclamide* and excipient

Sr. No.	Drug/Excipient	Reference	Experimental value
1	***Glibenclamide***	223-226^{0}C	225.63 ± 0.9^{0}C
2	**Hydroxyl Propyl methyl cellulose**	192-200^{0}C Differ according to grade	195.87 ± 1.4^{0}C

Table 3: Solubility study

Drug/ Excipient	95%Alcohol	Ether	DCM	0.1NHCL	Acetone	Methylene chloride
Glibenclamide	Soluble	Insoluble	Soluble	Soluble	Insoluble	Insoluble
HPMC	Insoluble	Insoluble	Soluble	Soluble	-	-
Mangifera Indica gum	Soluble	-	Insoluble	Insoluble	Soluble	-

Apparent partition coefficient study

The partition coefficient of the pure *Glibenclamide* was determined by Shake Flask method and the study was performed for two different solvent system viz. 0.1N HCl as aqueous phase with n-octanol as an organic phase by using separating funnel (50 ml) .The partition coefficient values of *Glibenclamide* in different solvent systems are given below.

Table 4: Partition coefficient of *Glibenclamide* in different solvent

Solvent system	Partition coefficient, Mean ± SD, n = 3
0.1N HCl + n-Octanol	0.82 ± 0.07

UV-VIS spectrophotometer

Determination of λ_{max} of the pure drug

Visible Spectroscopy study of the pure drug was prepared in different solvents i.e. 0.1N HCl. The λ_{max}233.50nm of the pure drug was observed in the individual solvents and given in table 6.5 and the figure of spectrum given in Figure 2.

Table 5: λ_{max} of the *Glibenclamide* . in different solvent

Solvent system	λ_{max}
0.1 N HCL	233.50 nm

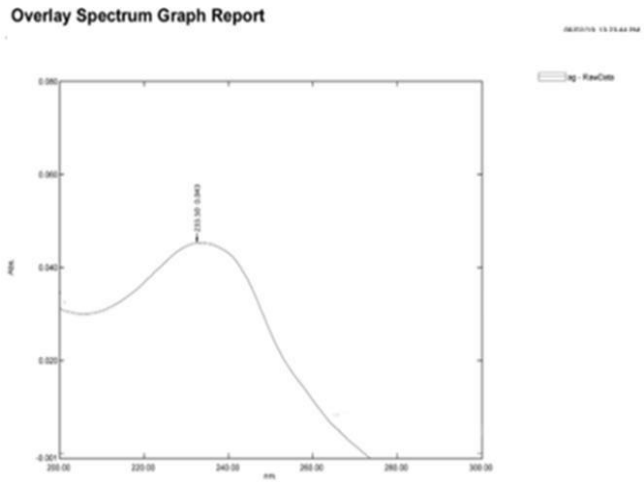

Figure 2: UV-Visible spectra of Glibenclamide in 0.1N

HCLPreparation of calibration curve of pure glibenclamide

The UV-visible spectroscopy study of the pure drug was prepared in 0.1N HCL the sharp peak observed at the λ_{max}233.5nm respectively. The Spectro-photometric analysis is generally based on this λ_{max} through the whole study. The regression coefficient of each calibration curve was calculated and found to be closer to the one which indicates the linear relationship between the drug concentration and the absorbance. Thus the regression equations were used for the quantitative estimation of *Glibenclamide*. The absorbance value and different concentration levels for these solvent systems are presented in the table-6.6 and the calibration curve in the Figure 3.

Table 6: Absorbance of GL in 0.1N HCl

SN.	Conc.(µg/ml)	Absorbance (λ_{max}– 233.5nm)
1.	0	0
2.	2	0.119
3.	4	0.235
4.	6	0.368
5.	8	0.505
6.	10	0.652

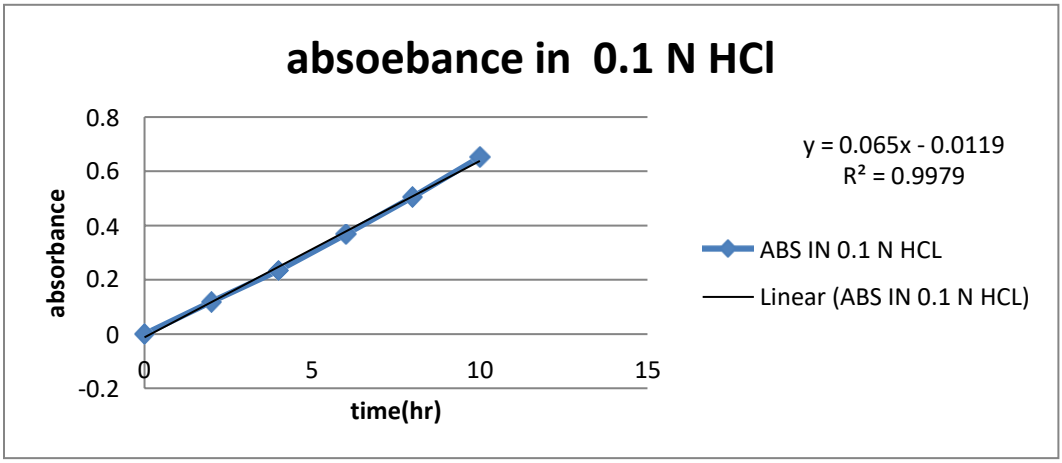

Figure 3: Calibration plot of GL in 0.1N HCl

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of pure *Glibenclamide* and another excipient like HPMC and Eudragit was taken and interpreted for the presence of some key structures and functional groups like C-H stretching, N-H stretching and bending, C-N etc. stretching these stretching confirms the structure of MH. The C-H, C-O, C=C, O-H etc. stretching confirms the structure of HPMC, and the C-H, C=O, O-H, C-O etc. that confirms the structure of eudragit S100.

The Figure of the FTIR spectrum is shown in the Fig- 6.3,6.4 & 6.5, and interpretation of spectrum is shown in the table- 6.7, which revealed the drug sample and excipient were pure and authenticate.

Table 7: Functional Group of drug and Excipient

Sr. No	Structures	Std. Range(Cm-1)	Observed value (Cm-1)
A.	***Glibenclamide***		
1.	N-H(stretching)	3500-3300	3365.04
2.	$N-(CH_3)_2$	2800-2600	3140.87
3.	C-N	1360-900	930.38
4.	C-H	3000-2700	3365.04
5.	N-H(bending)	1640-1550	1622.37
6.	N-H(deforming)	1550-1510	1543.62
B.	**HPMC**		
1.	C-H	3000-2700	2902.33
2.	C-O	1350-1050	1003.92
3.	O-H	3700-3200	3268.32
4.	C=O	1750-1680	1592.31
5.	C=C	1600-1400	1412.41
C.	**Magnifier India gum**		
1.	C-H	3000-2850	2952.59
2.	C=O	1750-1680	1730.55
3.	O-H	3600-3200	3469.48
4.	C-O	1300-1050	1154.8

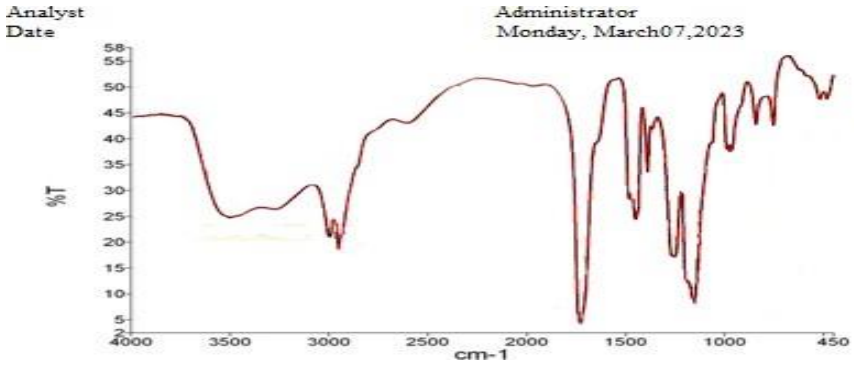

Figure 4: FTIR spectrum of *Magnifier India* gum

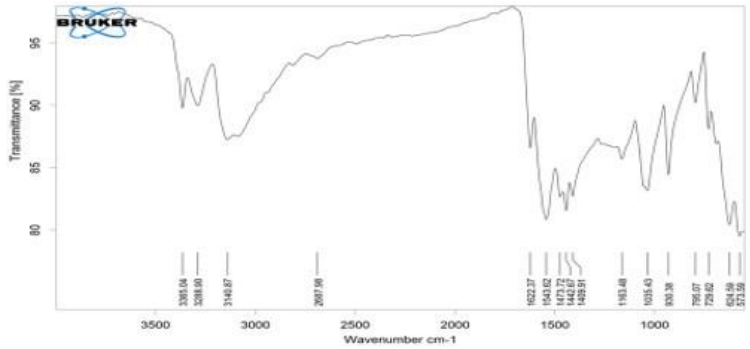

Figure 6: FTIR spectrum of the pure

Drug loading & drug entrapment

The formulation's drug loading was 11.10–17.04 and entrapment efficiency was 60.02–95.30. F3 had the highest drug loading and entrapment effectiveness of the five drug-loaded formulations. Due to drug saturation of the floating drug matrix tablet, the % drug loading and % entrapment efficiency declined with increasing drug loading beyond 150mg (F3), i.e. F4, F5.

Table 8: Drug loading and entrapment efficiency

Formulation	% Drug loading	% Entrapment efficiency
F1	14.30±0.54	83.49±1.33
F2	11.10±0.75	87.43±1.97
F3	17.04±0.43	95.30±0.49
F4	15.58±0.62	68.43±1.29
F5	13.31±0.47	60.02±1.65

Micrometrics properties

There was not a single micrometric property that fell outside of the permissible range. The formulations (F1, F2, F3, and F5) were found to have outstanding flow-ability, while the formulation F9 was found to have fair flow-ability. The compressibility index of the

formulations was found to range between 7.04 and 20.00 percent. The angle of repose of each of the formulations, which ranged from 18.147 to 27.47 percent, indicated that they all had outstanding flow properties. Table 6.11 presents the findings of the study.

Table 9: Micrometric properties

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Angle of repose (ɵ)
F1	0.75±0.01	0.86±0.01	12.79	18.147
F2	0.73±0.04	0.84±0.01	13.10	24.261
F3	0.66±0.02	0.71±0.02	7.04	21.80
F4	0.76±0.01	0.95±0.02	20.00	27.47
F5	0.71±0.03	0.81±0.01	12.35	25.91

Optimization of formulation

Formulation F3 was fund to be optimized based on % yield, bu0yancy, % drug loading, % entrapment efficiency and micrometric properties. Further studies i.e. FTIR study, SEM, and drug release were performed on optimized formulation (F3).

SEM (scanning electron microscopy)

The morphological characterization of optimized formulation (F3) was conducted by SEM analysis. The shape 0f floating matrix tablet was found to be spherical and had smooth surface. The agglomeration of floating tablet was not seen because of the rigid nature of floating tablet. The SEM photograph of floating matrix tablet is shown in Figure 7.

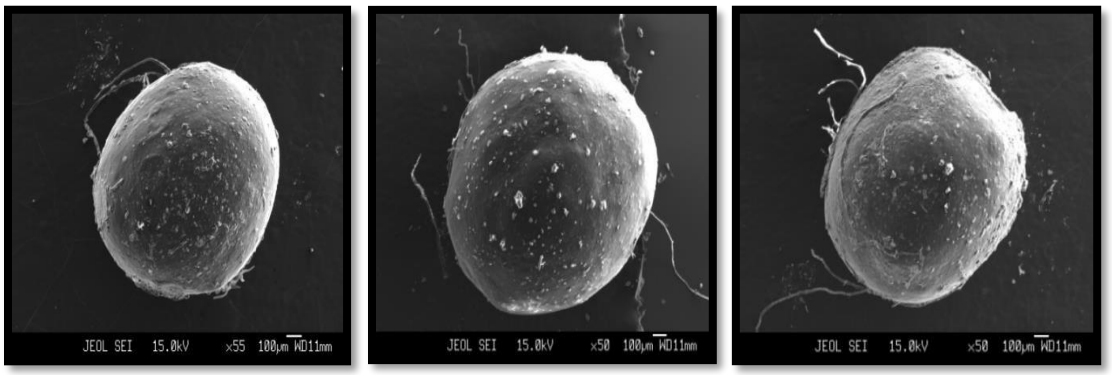

Figure 7: SEM of optimized drug loaded floating matrix tablet

IN-vitro drug release study

The *in-vitro* study of optimized formulations (F3) was performed by using USP Dissolution Test Apparatus Type 1 (Basket Type) in the 0.1N HCl. The percentage release of *Glibenclamide*. from optimized formulation was investigated for a period of 24 hours and sample was analyzed in triplicate. The result of the release study is shown in table- 6.12, and Figure- 6.15.

Table 10: *IN-virto* drug release study

S.N.	Time(hr)	Cumulative % drug release ± SD of formulation (F-8)
1	5	16.58±1.14
2	6	23.75±1.93
3	7	32.22±2.05
4	8	42.88±1.28
5	9	52.09±2.74
6	10	65.16±1.71
7	12	78.28±2.36

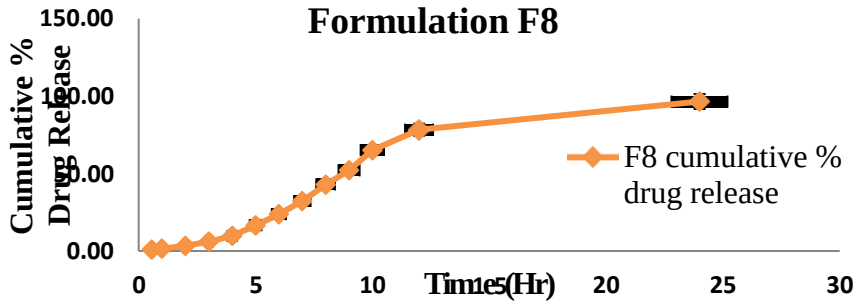

Figure 8: Drug release profile of optimized formulation (F3)

Conclusion

Utilizing direct compression techniques allowed for the effective formulation of an HPMC and *Mangifera indica* gum mix floating tablet that was filled with glibenclamide. It was discovered that increasing the quantity of medication resulted in a lower percentage of yield. It was discovered that formulation F3 had the highest percentage yield (84.4%). The percentage of buoyancy of formulation F3 was determined to be 80.67%, and it was discovered that the percentage of buoyancy could be altered by adjusting the ratio of polymer to medication. As the amount of drug to be loaded increased above 150 mg (F3), the formulation became saturated with the drug, which led to a drop in both the percentage of drug loading and the percentage of entrapment efficiency. It was determined that Formulation F3 was the most optimal in terms of yield percentage, buoyancy, percentage of drug loading, percentage of entrapment efficiency, and micrometric characteristics. The FTIR spectrum of the optimized formulation (F3) demonstrated that there was no chemical interaction that occurred throughout the process of formulating the floating tablet, and it was discovered that the medicine was compatible with the polymer. The crystalline structure of the medication was found to be present in the floating tablet by the presence of the strong peak of Glibenclamide that was also detected in the XRD spectrum of the optimized formulation (F3). A photomicrograph taken using a scanning electron

microscope (SEM) revealed optimized floating tablet (F3) that had a nearly spherical form and a rough surface that lacked any pores.

The floating tablet were able to release the medicine for up to 24 hours in the in-vitro release research, which was conducted in a fluid that was meant to replicate the contents of the stomach. The results of the investigation showed that 96% of the medication was liberated from the formulation (F3). The drug release kinetics of the F3 formulation were best accounted for by the korsmeyer-peppas model. This was due to the fact that the R2 value for the model was 0.971, which was significantly closer to 1 than the R2 value for any of the other models. The drug release mechanism was a super case-II transport, and the release exponent, n, was discovered to be 1.490, which was a value that was more than 1.

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Conflict of interest

Authors declare no conflict of interest

Ethics approval and consent to participate: Not applicable.

Human and animal rights: Not applicable.

Code availability: Not applicable.

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