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Formulation and Evaluation of Metformin Using Fenugreek Seed Mucilage Used as a Natural Polymer

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Abstract: ***The major goal of this study was to develop and test metformin sustained release tablets employing fenugreek seed mucilage (FSM) as a new binder, as opposed to standard polymers such as xanthan gum and HPMC. The study shows how FSM provides sustained medication release while keeping metformin physicochemical characteristics. The sustained-release matrix tablets were made on a laboratory scale utilizing the wet granulation process. 5 batches were created, each with varying quantities of fenugreek seed mucilage, xanthan gum, and HPMC. To examine the tablet's physical properties and consistency, different criteria such as thickness, hardness, weight variation, and content homogeneity were measured. FTIR tests were performed to determine the compatibility of metformin and the polymers employed. The results showed no incompatibility, indicating that the novel excipient, FSM was not affecting the drug's physicochemical qualities. The in-vitro drug dissolution investigation was conducted utilizing a USP type-II paddle apparatus to quantify the drug release rate from dosage forms and to assess thepolymers' efficacy in retarding drug release. The study discovered that raising the concentration ofthe matrix ingredient reduced the medication release rate. Among the formulations, the combination of FSM with HPMC (MS1) resulted in 95% drug release, FSM with xanthan gum achieved 96% drug release, and the MS4 formulation had the greatest drug release rate. Finally, the study showed that fenugreek seed mucilage and xanthan gum effectively develop metformin continuous-release matrix tablets. Lower concentrations of these polymers were more suited and effective, resulting in sustained drug release. This study demonstrates the potential of fenugreek seed mucilage as a novel and effective binder in sustained-release formulations.***

Keywords: Physicochemical Qualities, FSM, HPMC (MS1), USP, FTIR

I. INTRODUCTION

Diabetes is a disorder that happens when the body's glucose levels, often known as blood sugar, become too high. Glucose is necessary because it is the body's major source of energy. While the body may generate glucose, it is also derived from our food. Insulin, a pancreatic hormone, helps glucose enter the body's cells and be used for energy.

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Individuals with diabetes have either insufficient insulin production, no insulin production at all, or ineffective insulin utilization. As a result, glucose stays in the bloodstream rather than being delivered to cells. Diabetes raises the risk of complications that can affect several sections of the body, including the Eyes, kidneys, nerves, and heart. There is also a link between diabetes and some cancers. However, taking proactive measures to prevent or control diabetes can help lower the risk of certain health consequences (American Diabetes Association, 2022). Some types are given below.

1. **Diabetes:** This condition is characterized by improper insulin utilization by the cells in your body. The amount of insulin that the pancreas can make is insufficient to maintain blood sugar levels within acceptable limits. Diabetes type 2 is the most prevalent kind of the disease. If you have risk factors for type 2 diabetes, such as being overweight or obese and having a family history of the condition, your chances of developing the disease are higher. Diabetes type 2 can strike at any age, even in early childhood.

Understanding your risk factors and making healthy lifestyle choices, such as not gaining weight or decreasing it, can help postpone or avoid type 2 diabetes. Although the pancreas is capable of producing insulin, not enough of it is produced to vanish once the kid is born. On the other hand, type 2 diabetes is more likely to strike you later in life if you have gestational diabetes. Type 2 diabetes can occasionally be identified as diabetes during pregnancy.

2. **Prediabetes:** it is a condition in which a person's blood sugar levels are above normal but not high enough to be classified as having type 2 diabetes.
3. **Other Types of Diabetes:** A less common type of diabetes, called monogenic diabetes, is causedby a change in a single gene. Diabetes can also come from having surgery to remove the pancreas, or from damage to the pancreas due to conditions such as cystic fibrosis NIH external link or Pancreatitis. Several terms have been used to describe oral dosage forms that exhibit modified release properties; which include delayed release, sustained release, and controlled release. Each drug delivery system is focused on eliminating cyclic changes in plasma drug concentration observed after the administration of conventional delivery systems. Modified-release dosage forms are designed to rapidly achieve plasma drug levels that remain constant within the therapeutic range of the drug for a significant period or to achieve plasma concentrations of a slow-release drug that remain within the therapeutic range for extended periods of time.

A. Reason for the Selection of FSM as a Natural Polymer

1. Fenugreek seed mucilage refers to the gelatinous substance that is naturally present in fenugreekseeds. It is a type of soluble fiber that forms a thick, sticky Material when the seeds are socked in water.
2. This mucilage is known for its ability to provide antimicrobial activity, these are biologically neutral in nature. Better water solubility.
3. Polymer have good film former properties, mucilage has biodegradable, economical and ecofriendly film former.
4. Fenugreek seed mucilage is used as a carrier in sustained release formulations. It found easily.
5. This polymer can also play different roles in various formulations like: emulsifying, hydrating, thickening, gelling and suspending agents.

II. MATERIALS

a) Metformin HCL
b) Fenugreek seed mucilage
c) Xanthun gum
d) HPMC
e) Magnesium
f) Talc
g) Isopropyle alcohol

III. METHODOLGY

- **Procurement of Chemical into Fenugreek Seed Mucilage:** - Prior to obtaining the chemicals needed to extract the mucilage from fenugreek seeds, determine which reagents are required, such as citric acid or ethanol. Select reliable vendors who offer premium chemicals, and confirm the compounds purity and requirements. Place orders in the necessary numbers, making sure they are stored properly and under the right circumstances (temperature control, for example).For the extraction procedure to be successful and safe, keep correct records of the chemicals and adhere to legal regulations.

A. Some Steps are Following

1. The seed of polymer were washed in water and dried into oven for sufficient temperature in oven, and powdered coarsely with grinder.
2. Coursed powder was soaked in distilled water for 10 hr, and then gum was filtered out from the bulk material by using muslin cloth.
3. The filtrate was precipitate with ethanol several times to compute the extraction process.
4. The gum was air dried at 60^0 C, crushed into powdered and collect extraction mucilage,
5. Then package into polythene container for further used.

B. Polymer Analysis and Pre-Formulation Studies

The powder blends of polymers were evaluated before formulations to assess the flow propertiesof the powder.

- **Bulk Density**

Required amount of powder m was transferred into the measuring cylinder, and apparent volumeV0 was measured, bulk density in g per ml is calculated by the formula.

$$\text{Bulk density} = m/V_0 .$$

Where m-mass of powder, V0 – apparent volume.

Tapped Density: After determination of bulk density the measuring cylinder V_a volume in ml was measured initially, later the same cylinder was set for 100 tappings on tapped density apparatus and measure the tapped volume finally V_b.

Calculate tapped density in g per ml by the formula.

$$\text{Tapped density} = V_a/V_b$$

Where V_a - initial volume, V_b - final tapped volume.

Carr's Index: It is an indirect method of measuring powder flow from bulk densities to measure bridge strength and stability. Carr's index of each formulation was calculated according to the equation.

Carr's index = (Tapped density - bulk density)/tapped density *100.

Hausner Ratio: It is essential to determine the compressibility strength of powder. It was calculated according to equation.

Hausner ratio = Tapped density/bulk density.

Angle of Repose: Accurately weighed quantity of powder was transferred into a funnel which was adjusted to a height of 2 cm in such a way that the tip of funnel touches apex of a pile of powder heap. Finally, the height and radius of powder cone were measured using the following equation.

$$\tan\theta = h/r ,$$

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

Where, θ = Angle of repose, h = Height of heap and r = radius

C. Compressibility Index

Compressibility index was determined by the following formula:

Compressibility Index= [Tapped density – Bulk density / Tapped density] x100

Hausner's ratio

Hausner's ratio was determined by the following formula:

Hausner's ratio = Tapped Density / Bulk Density

IV. ANALYTICAL METHODS

There are several methods used to estimate metformin in pharmaceutical preparation such as UV, FTIR, methods will be reported, among these FTIR is the most widely used method for the analysis of metformin. In this review an attempt has been made to compile all the analytical methods whichhas been recently used for the analysis of metformin.

A. UV Spectroscopy

The absorption maximum of the test solution was observed between 200- 400 nm region by using UV Visible Spectrophotometer. Metformin will received as gift sample in tablet form. Each film will coated tablet contains metformin HCl I.P. (1000 mg).

Methanol A.R grade will procured from Qualigens fine, Potassium di-hydrogen orthophosphate AR grade, sodium hydroxide AR grade. UV is spectrophotometer with 1 cm matched quartz cells will used for the measurement of the absorbances. electronic balance will be used for weighing the samples. metformin has l max at 234 nm in a water and methanol mixture (60:40). An acceptable response will be obtained upon detection of both drugs at 227 nm either individually or in combination.

B. FT-IR

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the drug formulation to infrared absorption spectral analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

C. Preparation of Samples

i. *Preparation of Metformin-Fenugreek Seed Mucilage Granules:* Formulate granules by blending a predetermined amount of metformin with fenugreek seed mucilage and necessary excipients like HPMC, xanthun gum, Mg. stearate and IPA as per requirement using suitable wet granulation techniques.

ii. *Sample Preparation for FTIR Analysis:*

- Take a representative sample (batches) of the granules. Grind into very fine powder and prepare them for FTIR analysis.
- Typically, a small amount (few milligrams) is sufficient.

D. Data Analysis Interpretation of FTIR Spectrum: Analyse the FTIR spectrum obtained from the sample. Identify characteristic peaks corresponding to pure Metformin, fenugreek seed mucilage, and other excipients used.

V. FORMULATION

1. 500 mg of metformin HCl will be included in each matrix tablet, which will be made using the standard wet granulation procedure. The trial preparation of the tablets will serve as the basis for choosing the polymer combination in the formulation.
2. The active component in each formulation is 500 mg, making a tablet's total weight of 1000 mg. Each formula will be used to make a batch of five pills.
3. A 60-mesh sieve will be used to filter every ingredient. To guarantee total phase homogeneity, all ingredients—aside from the glidant and lubricant—will be properly mixed.
4. An isopropyl alcohol solution will be used for manual granulation. A 12-mesh sieve will be used to filter the moist materials, and the Wet masses will be run through a 12-mesh sieve, and the resulting wet granules will be air dried for 10 minutes before being dried for two hours at 45 to 50 degrees in a tray dryer.
5. After drying, the granules will be lubricated with magnesium stearate and sorted through a 16-mesh sieve. After that, compression will happen with a tablet punching machine. Granules flow and compressibility properties will be assessed before compression.

VI. POST FORMULATION STUDIES

Weight Variation: Ten tablets from each batch will be selected randomly and weighed on a digital balance (Shimadzu, Japan) individual weights will be compared with average weight. The percentage difference in the weight variation should be within the permissible limits.

A. Weight Variation = Individual wt. of tab. – Avg. wt. of Tab

i. *Thickness:* The thickness of all formulations will determine by the screw gauge. Standard deviation values indicate all formulations will be within the range.

ii. *Tablet Hardness:* The hardness of the tablets for shipping or breakage under conditions of storage, transportation, and handling depends on hardness which will be determined using Monsanto hardnesstester.

iii. *Friability:* The Friability of five tablets will be determined using a Roche friability. This device subjects tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets will placed in the friability and will be subjected to 100 revolutions dedusted and reweighed. The friability (F) is given by the formula:

$$\text{Friability (\%)} = \frac{(\text{Initial Weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

Where W0 is the weight of the tablets before the test. Wis the weight of the tablet after the test.

B. Content Uniformity

Five tablets will weigh accurately and be powdered, powder equivalent to 10 mg of the drug will be dissolved in phosphate buffer pH 6.8, filtered using a 0.2 um membrane filter. The drug content willbe measured by ultraviolet (UV)-spectrophotometer at 233 nm.

Determination of the Swelling Index: swelling index studies were conducted using the ankle dissolution apparatus, no rotation speeds were applied.

$$\text{Swelling index S(w)} = \frac{W_t - W_o}{W_o}$$

Where W_o is the initial weight of the dry tablet and W_t is the weight of the swollen tablet at a time t.

C. In-Vitro Dissolution Study

A USP dissolving equipment Type 2 (paddle) was used for an in vitro drug release investigation involving tablets. 900 mL of pH 6.8 phosphate buffer was used in the dissolution test, which was conducted at 37 ± 0.5°C and 50 rpm. A 5.0 mL sample of the solution was removed from the dissolving equipment and replaced with new dissolution media at different intervals. Following filtering, these samples were diluted to the proper concentration using pH 6.8 phosphate buffer at Jaipur National University's Methodology M. Pharm. (Pharmaceutics) School of Pharmaceutical Sciences.

A UV spectrophotometer (SHIMADZU UV-1700) was used to test the absorbances of these solutions at 234 nm. An equation developed from a standard curve was used to determine thecumulative percentage of medication release.

D. Kinetic Analysis of Dissolution Data

The in vitro drug release data will be fitted into zero-order, first-order, and Higuchi by employing the method of least squares the mechanism of drug release will be compared for all the formulations.

$$Mt/M\infty = Ktn$$

$$Mt/M\infty = b+k2t1/2$$

In the Peppas equation, Mt/M∞ is the fraction of the drug released up to time t, K kinetic constant, and n is the release exponent indicative of the release mechanism. In Higuchi and zero-order release equations, k1, k2, and k3 are constants s. On the other hand, the Higuchi equation expresses a diffuse release mechanism.

VII. RESULT AND DISCUSSION

Table 1: The Results of the Micromeritic Properties of the Granules Are Presented

Formulation NO	Angle of Repose	Bulk Density	Tapped Density	Compressi on--ability Index	Hausner Ratio
F1	20.08	0.981	1.076	8.82(Good)	1.090 (Good)
F2	22.68	0.952	1.092	12.82(Good)	1.147(Good)
F3	23.64	0.969	1.089	11.01(Good)	1.123(Good)
F4	21.64	0.941	1.074	12.38(Good)	1.141(Good)
F5	23.26	0.982	1.090	9.90(Good)	1.109 (Good)

Table 2: Standard Calibration Curve of Metformin HCL

S.NO	Concentration (mcg/ml)	Absorbance
1	2	0.189
2	4	0.355
3	6	0.565
4	8	0.745
5	10	0.95

Appropriate volumes of aliquots from standard Metformin stock solution B were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with methanolto obtain concentrations of 2, 4, 6, 8, and 10µg/ml. The absorbance value of each solution against methanol as a blank was measured at 237 nm. From that absorbance value, the regression equation and correlation coefficient ($r^{2)}$ are determined and presented.

This is a redrawn figure that displays the calibration curve and the UV spectra of metformin. The calibration curve, which also includes the equation of the line and the R2 value, illustrates the relationship between concentration and absorbance, while the UV spectrum plot displays absorbance against wavelength.

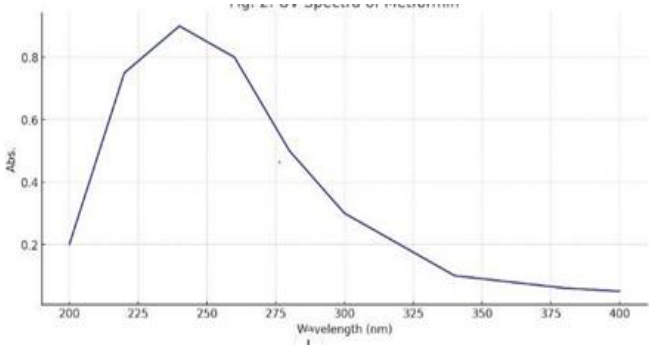


Fig. 1: UV Spectra of Metfoemin

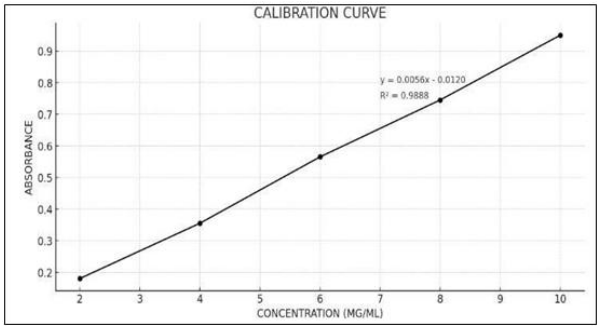
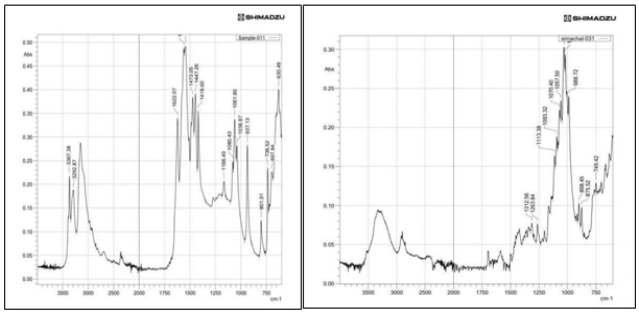
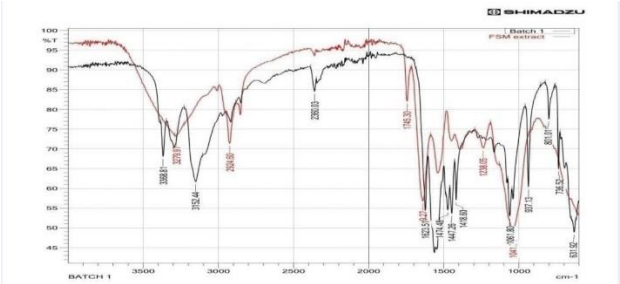


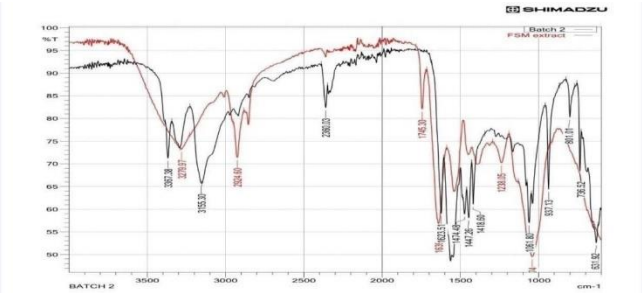
Fig. 2: FT-IR Studies



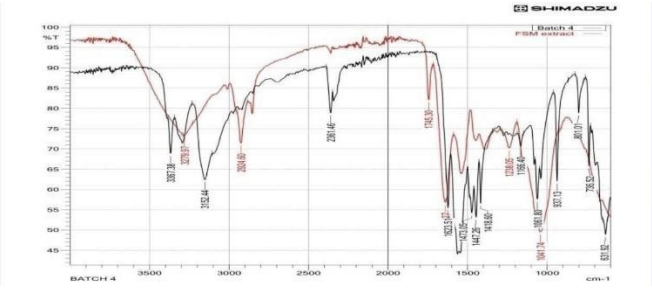
Infra Red Spectrum of Drug-Polymer Without FSM: FSM (Batch-0)



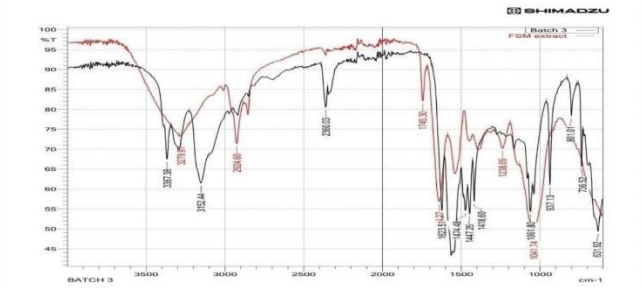
Infra Red Spectrum of Drug-Polymer with FSM: FSM (batch-1)



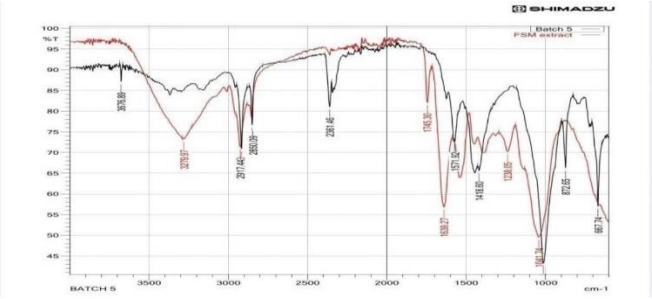
FSM (Batch-2)



FSM(Batch-4)



FSM (Batch-3)



FSM(Batch-5)

Table 3: Manufacturing Formula of Metformin Hydrochloride

Sr no	Ingredient	MS1	MS2	MS3	MS4	MS5
1	Metformin HCL	500	500	500	500	500
2	FSM	50	100	150	200	250
3	HPMC	100	150	200	--	--
4	Xanthan gum	--	--	--	100	150
5	Magnesium stearate	10	10	10	10	10
6	Talc	340	240	140	190	90
7	IPA	Q.S	Q.S	Q.S	Q.S	Q.S
	Total	1000	1000	1000	1000	1000

Table 4: The Result of the Physiochemical Properties of the Prepared Tablets Was Done as per the Procedure and Presented

Batch no.	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Content uniformity (%)
1	1007 ±5	4.42	6.59	0.271	99.7
2	1002 ±5	4.42	6.59	0.263	99.2
3	1000 ±5	4.41	6.80	0.291	99.6
4	1001 ±5	4.56	7.26	0.300	99.9
5	1001 ±5	4.33	6.33	0.285	99.1

Table 5: In Vitro Dissolution Profile of Metformin Sr Tablets in ph 6.8 Buffer Solution

Time inmin	MS1	MS2	MS3	MS4	MS5
0	0	0	0	0	0
1	27.56	23.82	20.85	21.75	20.95
2	31.97	30.58	28.93	30.63	29.54
3	46.88	43.46	41.77	44.86	40.72
4	58.98	53.84	51.48	50.53	49.80
6	68.31	66.37	62.74	65.72	61.91
8	79.47	74.65	71.74	78.43	73.05
10	85.83	86.63	83.99	88.50	85.60
12	95.94	93.64	91.77	96.83	96.51

In vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 50 rpm. The percentage of drug release at the end of 30 min was found in the range of **90– 98 %.**

Table 6: In Vitro Release Kinetic Parameter of Metformin Hydrochloride SR Tablets

Sr. no.	Zero order		1st order		Higuchi		Korsmeyer-peppas		
	r2	K	r2	K	r2	K	N	r2	K
MS1	0.091	8.67	0.952	-0.28	0.99	25.91	0.636	0.989	23.619
MS2	0.913	8.72	0.931	-0.25	0.991	26.28	0.651	0.995	21.368
MS3	0.900	8.21	0.911	-0.13	0.986	26.16	0.707	0.997	19.102
MS4	0.905	8.10	0.923	-0.21	0.990	26.20	0.644	0.996	20.98
MS5	0.903	8.29	0.915	-0.19	0.985	26.19	0.662	0.998	19.676

VIII. DISCUSSION

Because the wet granulation procedure is simple and feasible, it was used in this investigation to prepare metformin hydrochloride tablets for sustained release. Several formulations were created by altering the amount of polymer in order to examine how different polymer concentrations affected the rates of medication release. The blended powder's physical examination revealed that it was suitable for tablet compression. The release profile of the optimized formula fitted best to the Korsmeyer-Peppas model with an R2 value of 0.995. The n value for the Korsmeyer-Peppas model was found to be more than 0.5. it follows non-Fickian transport. The result of dissolution studies as shown and indicates that formula MS1, MS2, and MS3, release 46.88, 43.46, 41.77 after 2 hr and 95.94, 93.64, 91.77 after 10 hr. of formulation containing (FSM + HPMC), MS4, MS5, release 44.86, 40.72 after 2 hr. and 96.83, 96.51 drug content release after 10 hr. respectively (FSM +XANTHUM GUM).

IX. CONCLUSION

In conclusion, fenugreek seed mucilage has proven to be an effective binder in the formulation of Metformin SR (sustained release) tablets. The study revealed that fenugreek seed mucilage provides adequate binding properties, ensuring the mechanical strength and integrityof the tablets. Moreover, it facilitates a sustained release profile of Metformin, which is beneficial for maintaining consistent therapeutic drug levels over an extended period, thereby enhancing patient compliance and potentially reducing the frequency of dosing. Fenugreek seed mucilage is used as the novel binder in the formulation MS_1, MS_2, MS_3, MS_4, and MS_5 at concentrations of 5%, 10%, 15%, 20%, and 25% respectively. HPMC is selected as a hydrophilic matrix former, creating a gel barrier upon contact with gastric fluids. This gel barrier controls the drug release rateby slowing down the diffusion of Metformin from the tablet. HPMC used in the formulation MS_1,MS_2, MS_3 at the concentration of the 10%, 15%, 20%. Xanthan Gum swells upon hydration, expanding the matrix and prolonging the drug release duration. Xanthan gum was used in the formulation MS_4, and MS_5 at the concentration of 10%, and 15%. The percentage Drug content of all tablets was found to be between 91.3% - 101.2% of metformin SR, which is within the limit. The formulations that show the maximum drug release are (FSM + HPMC) at 93.78% and (FSM + XANTHUM GUM) at 96.17%. According to the above results, release kinetics were shown to be improved as the concentration of HPMC increased. The percentage of drug release was also found to Have increased for these formulations, coming in at 95.94, 93.64, and 91.77, respectively. Additionally, the results showed that there are no changes in release kinetics as the concentration of xanthan gum increases. The percentage of drug release for these formulations was also determined to be the same at 96.83 and 96.51, respectively. As a result, the MS4 batch is chosen as the optimum batch after considering all the satisfying parameters.

DECLARATION STATEMENT

I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/ Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been funded by any organizations or agencies. This independence ensures that the research is conducted with objectivity and without any external influence.
- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Authors Contributions:** The authorship of this article is contributed solely.

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