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Mucilage from *Basella rubra* Linn. stems as a release modifier in sustained release tablet formulation

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Abstract
Medicines are beyond reach for the majority of the developing countries' population due to pharmaceutical firms' reliance on expensive raw ingredients despite abundant natural resources. This study provides a natural source of polymer that delays drug release as alternative to synthetic ones used in most tablet preparations. Mucilage from the stems of Basella rubra, locally known as *Alugbati* was employed as polymer in Metformin HCl sustained matrix tablets. Wet granulation was used to develop the tablets incorporating three increasing concentrations of mucilage. The formulated tablets were subjected to USP standards and only those that conform advanced to polymer swelling behavior and *in vitro* drug release. The matrix tablets passed all USP standards. The mucilage caused an abrupt increase in swelling and was able to sustain drug release for Formulations 1, 2 and 3. Based on one way ANOVA and Similarity Factor Test (f2), Formulation 3 was comparable to the commercially available Metformin HCl tablets with $p>0.05$ and f2 of 49.9% indicating no significant difference in release profiles. It was found that higher mucilage concentration showed an increased potential in sustaining drug release.

Keywords: Metformin, mucilage, sustained release tablets, Philippines

Introduction
Mucilages, which are typically polysaccharides that include hydrophilic molecules that may interact with water to generate viscous solutions or gels, are important sustaining agents in matrix tablets [1]. The medicine delivered from this gel is diffusion regulated, and it will be sustained throughout time [2].
According to the British Pharmacopeia, sustained release preparation of Metformin HCl will help decrease the frequency of administration thereby reducing or avoiding side effects and subsequently lead to an improvement in medication compliance which is valuable for patients suffering from chronic illnesses such as Diabetes Mellitus (DM).
Numerous studies regarding the pharmacological potential of *Basella rubra* have been conducted [3-8]. But, to date, there are no studies conducted on *Basella rubra* as a release modifying polymer in sustained release formulations.
In culinary practices in the Philippines, the leaves of *Basella rubra* are used as an edible substitute for okra and spinach in soups and stews while the stems are discarded as waste materials. This study attempts to utilize the discarded stems to evaluate this mucilaginous vegetable as an alternative excipient to expensive imported synthetic materials used in Metformin HCl sustained release preparations available in the market.
The main objective of this study is to investigate the potential of the mucilage from the stems of *Basella rubra* as release modifying polymer in Metformin HCl matrix tablets by comparing drug release profiles with commercially available Metformin HCl sustained and immediated release tablets.

Materials and Methods
Materials: Metformin hydrochloride, USP was obtained from CN Lab Canada, Asian Group (Shaanxi, China). Dibasic Calcium Phosphate was procured from Yana Chemodities (Cebu City, Cebu). Ruthenium Red was purchased from Bioworld Chemicals (Ohio, USA). All inactive ingredients (talc, magnesium stearate) used were of pharmaceutical grade while all

reagents (acetone, monobasic potassium phosphate, sodium hydroxide, hydrochloric acid) were of analytical (AR) grade.

Methods

Collection of Plant Sample

Basella rubra stems were obtained from a local market in Cebu City and certified by the University of San Carlos' Department of Biology. The stems were then cleaned with water to remove dirt and debris before being air dried to remove any clinging moisture.

Extraction of Mucilage

Kaleemullah *et al*.'s approach was adapted. AL. with minimal modifications. Three hundred (300) grams of plant material were crushed in a mortar and pestle and steeped in 2.25 litres of distilled water for 24 hours before boiling for 30 minutes and standing for 1 hour to release all mucilage into the water. To remove the marc from the solution, the material was squeezed from an eight fold muslin cloth [9].

Isolation of Mucilage

Following extraction, three times the amount of the filtrate was added to the filtrate to precipitate the mucilage. The mucilage was separated and distributed on glass plates before drying in an oven at 45 degrees Celsius. It was collected, crushed, and passed through a #80 sieve before being computed for % yield and stored in a desiccator for future use [9].

The isolated mucilage was calculated for percentage yield using the following formula:

$$Percentage\ Yield = \frac{Weight\ of\ isolated\ mucilage}{Weight\ of\ original\ sample}\ x\ 100$$

Confirmatory Test for Isolated Mucilage

Ruthenium Test: A little amount of dried mucilage powder was tested by mounting it on a slide with ruthenium red solution and examining it under a microscope. The presence of mucilage was suggested by the pink color seen [10].

Physicochemical Analysis of Isolated Mucilage

The physicochemical analysis methods were somewhat modified from Joshi, 2015. The physical properties of the collected mucilage were assessed, including appearance, odor, solubility, pH, and viscosity [11].

Solubility of mucilage: One part dry mucilage powder was shaken with several solvents (water, hydrochloric acid, phosphate buffer) to test solubility.

pH and Viscosity of mucilage: These were performed by shaking a 1% w/v sample dispersion in water for 5 minutes. A digital pH meter and an Ostwald viscometer were used to determine the pH and viscosity, respectively.

Preparation of Metformin HCl Sustained Release Granules

This approach was modified and adapted from Singh *et al*. (2009). Metformin HCl formulations were made using the wet granulation technique in three different concentrations of Basella rubra mucilage: 1%, 8%, and 15%. Metformin HCl was dry mixed with the appropriate amount of mucilage and filler (dibasic calcium phosphate) then granulated with the appropriate amount of distilled water. The moist bulk was filtered using a no. 16 mesh screen. The wet granules were then dried for 3 hours at 50°C to remove the solvent. Dried granules were run through a Mesh No 20 to resize them. Granules were tested for flow qualities prior to compression [12].

Evaluation of Flow Properties of Metformin HCl Sustained Release Granules

The Metformin HCl sustained release granules were evaluated for the flow properties which include Angle of Repose, Hausner's ratio, and Carr's Compressibility index [13].

Angle of Repose: The funnel technique was used to calculate the angle of repose. Granules were permitted to freely flow through the funnel and onto the surface. Using the equation, the diameter of the granular cone was measured and the angle of repose was computed [13]. An angle of repose 46 and above indicates poor flow properties [13].

$$tan\ \theta = \frac{h}{r}$$

Where, $tan\ \theta$ – angle of repose, h – height of the cone, r – radius of the cone base

Hausner's Ratio: The Hausner's index was calculated by dividing the tapped density by the bulk density of the granules [13]. A Hausner's ratio of 1.45 and above indicates poor flow character [21].

$$Hausner's\ Ratio = \frac{Dt}{Db}$$

Where Dt - tapped density, Db - bulk density

Carr's Compressibility Index: The Carr's index, which defines the granules' compressibility, was calculated by dividing the difference between the tapped and bulk densities by the tapped density. The ratio was given as a percentage [13]. A Carr's index of 26 and above indicates poor compressibility [14].

$$Carr's\ index = \frac{Dt - Db}{Dt}\ x\ 100$$

Where, Dt - tapped density and Db - bulk density

NOTE: The bulk and tapped densities were obtained by weighing 10 g of the material into a 100 mL measuring cylinder and reading the volume without disturbing the cylinder to yield the bulk volume of the powder. Tapped density was determined by tapping the cylinder 100 times using a bulk density device until no powder remained on the surface [13].

Preparation of Metformin HCl Sustained Release Matrix Tablets

Following the assessment, the dried granules were combined with magnesium stearate as a lubricant and talc as a glidant (the lubricant and glidant ratio is 1:2) and crushed in a tableting machine using 8-mm biconvex punches and

dies. The matrix tablets were prepared once, and the tablets were split for the three trials.

Table 1: Formulation of Metformin HCl Sustained Release Matrix Tablets

Ingredients	FORMULATION CODE		
	F1 (1%)	F2 (8%)	F3 (15%)
Metformin HCl	500	500	500
Basella rubra Mucilage	10	80	150
Dibasic Calcium phosphate	475	405	335
Magnesium stearate	5	5	5
Talc	10	10	10
Total Weight	1000	1000	1000

Note: All ingredients are in milligrams

Evaluation of Metformin HCl Sustained Release Matrix Tablets

The general appearance and thickness of the developed tablets were assessed.

General appearance: The morphological characterisation of the tablets, including form, color, odor presence or absence, and surface roughness, was determined.

Thickness: Five tablets were chosen at random from each formulation, and their thickness was measured individually using a vernier caliper and represented in millimeters. This experiment was carried out in triplicate [13, 15].

Quality Control Tests of Metformin HCl Sustained Release Matrix Tablets

Quality control tests were carried out which include hardness, friability, weight variation, and content uniformity as per USP standards. This was the critical part since only those tablets which conform to the standards will proceed to dissolution testing. The following evaluation tests were carried out on formulated tablets and commercially prepared immediate and sustained release tablets [14]. These tests were conducted in triplicate which included:

Hardness: Five tablets were randomly picked and the hardness of the tablets will be determined using Monsanto hardness tester. This test was conducted in triplicate [13].
(USP LIMIT: normal tablet hardness ranges from 4-6 kilogram)

Friability Test: For this objective, a Roche friabilator was employed. A pre-weighed sample of ten tablets was placed in the friabilator, which was set to 25 revolutions per minute. The tablets were removed, dusted, and reweighed every 100 rotations [13, 15].
(USP LIMIT: Compressed tablets should not lose more than 1% of their weight)
The % friability was calculated by the formula:

$$Percent\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight}\ x\ 100$$

Note: The test only ran once. After tumbling, obviously cracked, cleaved, or broken tablets indicated that the tablets failed the test (USP 29 – NF 24).

Weight Variation: Twenty tablets from each batch were individually weighed using an analytical balance, and the average was computed [13].
(USP LIMIT: Not more than two tablets deviate from the average weight ± 5%)

Content Uniformity: Five tablets were weighed, then crushed into fine powder in a mortar. A properly weighed amount of the powder, corresponding to the average weight of five tablets, was put into a 200 ml volumetric flask containing pH 6.8 Phosphate buffer solution, and the volume was made up to the required volume. Ten (10) ml of this solution was collected and mechanically shaken for 30 minutes in a centrifuge at 3000 rpm. It was then filtered via Whatman filter paper #2. One (1) mL of the resulting solution was obtained and diluted to ten (10) mL of pH 6.8 Phosphate buffer as the blank. Using the Genesys10S UV-Vis Spectrophotometer, a sample was compared to a blank. The drug content was determined from the standard curve of Metformin HCl [13, 16, 17]. Percent uniformity in content was calculated using the formula from the Metformin HCl monograph in USP 38 and NF 33 [14].
(USP LIMIT: Content should fall within the range 90.0% - 110.0%.

$$\%\ Content = \frac{Au}{As}\ x\ \frac{Cs}{Cu}$$

Where Au – absorbance of sample solution, As – absorbance of standard solution, Cs – concentration of Metformin HCl in the standard solution in ug/mL; and Cu – concentration of Metformin HCl in the sample solution in ug/mL

Preparation of Phosphate Buffer

6.8 g of monobasic potassium phosphate was dissolved in 1000 mL of water and adjusted to a pH of 6.8 .± 0.1 using 0.2 N Sodium Hydroxide [15].

Standard Curve of Metformin HCl

100 mg of pure Metformin HCl was dissolved in 1000 ml of Phosphate buffer pH 6.8 to make a stock solution. Various working standards, such as 10g/ml, 20g/ml, 30g/ml, 40g/ml, 50g/ml, and 60g/ml, were prepared using suitable dilutions. As a blank, phosphate buffer was employed. The absorbance of the solutions was measured at 233 nm [19].

Swelling Behavior of Metformin HCl Sustained Release Matrix Tablets

The swelling index of tablets from the three formulations was used to express the amount of swelling. To investigate the swelling behavior, one tablet from each formulation was placed in a petri dish containing 20 mL of pH 6.8 phosphate buffer. After 1 hour, the tablet was removed, wrapped in tissue paper, and weighed. The technique was repeated every hour until the 12-hour mark was reached [20]. The swelling index of tablets was calculated using the formula:

$$Swelling\ Index = \frac{S}{R} x\ 100$$

Where, S - weight of tablet at time t; R - initial weight of the tablet

In vitro Drug Release Study

The USP Type II Dissolution Apparatus was used for the *in vitro* release investigations. For comparison, this test was performed on the designed Metformin HCl sustained release matrix tablets as well as the commercially available Metformin HCl immediate and sustained release preparations. The dissolve media was phosphate buffer (pH 6.8), which was maintained at 37.0 ± 0.5°C and 100 rpm in accordance with FDA, USP, and NF standards.. At 2-hour intervals, an aliquot of 5 mL sample was taken and replaced with another 5 mL of new dissolving media using a pipette until the medication was entirely released. The cumulative proportion of medication released was determined from the standard curve and plotted with time using a UV-Visible spectrophotometer to measure absorbance at 232 nm[15].

$$Concentration\ of\ drug\ (ug/mL) = (slope\ x\ absorbance) \pm intercept$$

$$Amount\ of\ drug\ (mg) = \left(\frac{concentration\ x\ bath\ volume\ x\ dilution\ factor}{1000}\right)$$

$$\%\ Drug\ release = \frac{Amount\ of\ Drug}{Label\ claim} * 100$$

Drug Release Analysis

Dissolution profiles of test and reference products should be compared using the similarity factor (f2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error that measures the degree of similarity (%) between the two curves. When the f2 value of two dissolution profiles is 50 or more, they are deemed comparable [21-23]. The similarity factor was calculated using the formula:

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

Where n - number of time points; Rj - dissolution of reference at time t; and Tj - dissolution of test sample at time t.

Results and Discussion

Confirmatory Test of Mucilage

A color shift (from light yellow to pink) was detected under a compound microscope after Ruthenium red solution was applied to a tiny amount of dried mucilage powder, confirming the existence of mucilage.

Table 2: Physicochemical Analysis of Isolated Mucilage

Physicochemical Properties	Observation
Appearance	Powder
Color	Brown
Odor	Odorless
Solubility: Water Phosphate Buffer pH 6.8	Soluble but swells in water Sparingly soluble forming viscous solution
pH (n=5)	5.72 ± 0.023
Viscosity (n=5)	465.34 centipoise ± 6.872

Table 3: Flow Properties of Metformin HCl Tablet Matrix Granules

Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (º)
F-1	23.333 ± 1.15	20.667 ± 0.58	11.364 ± 1.97	1.129 ± 0.02	38.697 ± 2.50
F-2	30.333 ± 1.53	25.333 ± 3.06	16.657 ± 6.49	1.205 ± 0.10	35.537 ± 0.49
F-3	27.000 ± 1.00	24.333 ± 0.58	9.795 ± 3.89	1.110 ± 0.05	35.850 ± 2.56

USP Quality Control Tests

Furthermore, the matrix tablets were tested for thickness, hardness, friability, weight variation, and content uniformity in comparison to commercially available Glucophage® (Metformin HCl) immediate release and Glucophage® XR (Metformin HCl) sustained release tablets. All results from the quality control tests are tabulated in Table 4.

Table 4: Evaluation of Metformin HCl Sustained Release Matrix Tablets

Code	Thickness (mm)	Hardness (kg)	Friability (%)	Weight Variation (g)	Content Uniformity (%)
F-1	7.957 ± 0.011	13.327 ± 0.817	0.794 ± 0.122	1.004 ± 0.0004	99.876 ± 0.046
F-2	6.446 ± 0.008	4.633 ± 0.301	0.597 ± 0.113	1.131 ± 0.262	99.842 ± 0.101
F-3	6.445 ± 0.001	6.633 ± 0.284	0.242 ± 0.056	1.001 ± 0.009	99.836 ± 0.022
Glu-IR	5.552 ± 0.002	16.147 ± 0.401	0.046 ± 0.004	0.526 ± 0.0422	99.669 ± 0.074
Glu-SR	6.972 ± 0.012	9.787 ± 0.290	0.221 ± 0.020	1.039 ± 0.001	99.841 ± 0.076

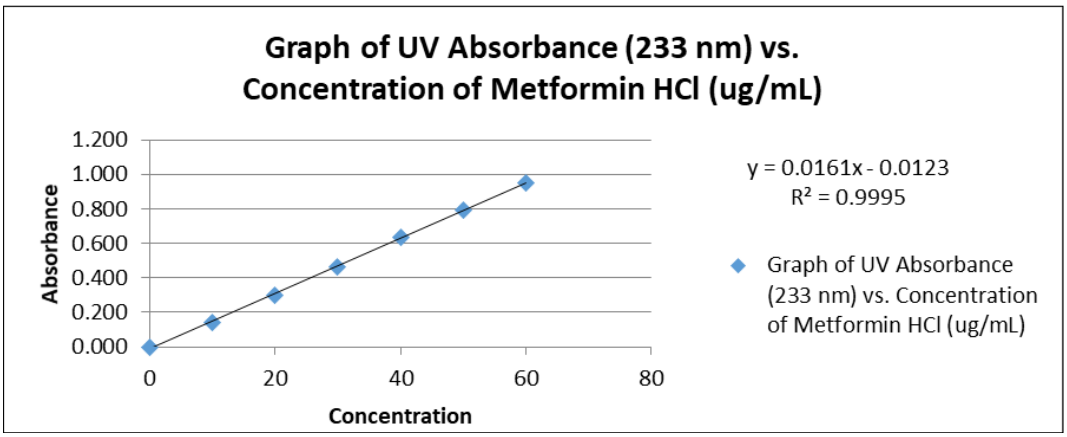

Fig 1: Metformin HCl Standard Curve

Swelling Behavior of Metformin HCl Sustained Release Matrix Tablets: As shown in Figure 4, all the formulations containing *Basella rubra* mucilage swell (F-1 being the highest, followed by F-3 then F-2) at the first hour. As time increases, the swelling behavior decreased.

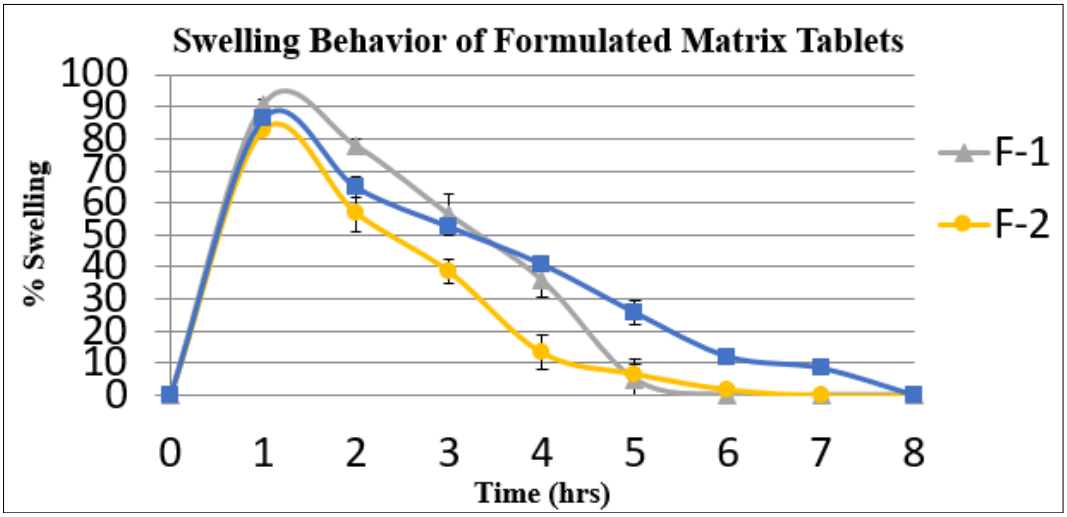

Fig 2: Swelling Behavior of Formulated Matrix Tablets

***In vitro* Drug Release Study**

Results from drug release study are shown in Figure 5. The commercially prepared Glucophage® (Metformin HCl) immediate release tablets achieved 100% drug release at 0.27 hours or 16 minutes. Furthermore, in order to compare the dissolution profile of constructed matrix tablets to that of Glucophage® XR (Metformin HCl) sustained release tablets, the dissolution data were processed for the computation of the similarity factor (f2). Because of the f2 value of 49.9-50, only F-3 was similar to Glucophage® XR (Metformin HCl).

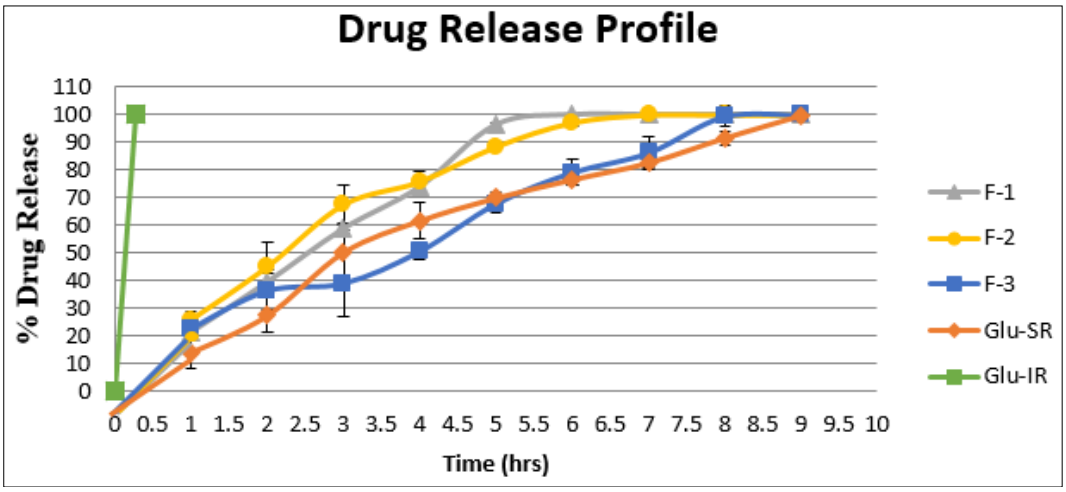

Fig 3: Drug Release Profile of Formulated and Commercially Available Tablets

Discussion

The mucilage from the stems of Basella rubra Linn. was used in this investigation. Metformin HCl was employed as a natural excipient to modulate the drug's release. The dried powdered mucilage was submitted to physicochemical examination. Basella rubra mucilage at 1% (w/v) demonstrated a less acidic and closer to neutral pH (5.72 ± 0.023), indicating that it may be less irritating to the gastrointestinal system and may be employed in various medicinal and food formulations [24]. The viscosity of 1% (w/v) Basella rubra mucilage measured using an Ostwald viscometer was 465.34 ± 6.872 centiPoise (cP). One of the characteristics that governs medication release is viscosity[5]. Many authors have researched matrix systems based on HPMC and determined that the higher the degree of viscosity of a polymer, the faster its side chains expand, generating a highly strong gel that reduces drug release rate [24, 25].

Before being compressed into tablets, the granules formed by wet granulation were submitted to several flow property tests to confirm that the granules have sufficient flowability and compressibility to produce excellent tablets. This is a critical metric to monitor since it impacts the dose's mass homogeneity [26]. Furthermore, the cohesiveness of granules, which tends to flow slowly through the funnel, may contribute to angle of repose, and vibrating the funnel contributes intrinsic variability in measuring procedure [1].

According to the findings of the study, all of the developed matrix tablets and commercially manufactured tablets showed no signs of capping, chipping, or lamination. Based on the weight variation study, all of the formulations and commercially manufactured tablets fit within the 5% variance in tablet weight allowed. This guarantees that the dose or quantity of medications is exact within formulas. The thickness parameter of tablets from different formulations indicated values that differed by less than 5%. This number is also important for keeping the medication quantity consistent and reproducible during manufacture. The percentage friability evaluation for all formulations falls within the satisfactory range of less than 1%. The friability data revealed that prepared tablets can survive stress and abrasion during shipping and storage. All formulations were determined to be good in terms of hardness, with Formulation-1 having the maximum hardness of the three. This is appropriate since oral pills typically have a hardness of 4 to 10 kg, although this can range from 10 to 20 kg for continuous release formulations. The content homogeneity among tablets in the formulation was determined to be good, with a content uniformity of roughly 99%.

Drug release mechanisms are complicated and include many steps, including the entry of the aqueous medium into the matrix, swelling of the matrix, solubility of the drug in the medium, diffusion of the drug through the gel layer, and erosion of the swollen matrix [27, 28]. The input of water into the matrix system controls drug release in systems containing biodegradable polymers, particularly hydrophilic systems. This water entry causes the polymer to expand or the matrix to erode [29]. Figure 4 shows that the swelling behavior of all three formulations decreases following a sudden rise. This sudden rise, known as the "burst effect," is observed when a high viscosity polymer is combined with a high solubility of Metformin HCl [30]. The burst effect was also seen in a study done by Ahad *et al*, in which Hibiscus rosasinensis mucilage was utilized as a hydrophilic polymer [31]. The medication progressively diffused out of the gel when the tablet inflated and became a gel. This explained the drug's prolonged release.

Conclusion

Through this research, it was found that higher concentration of *Basella rubra* mucilage showed an increased potential in sustaining drug release. Based on one way ANOVA, only Formulation 3 was comparable to the reference, Glucophage® XR (Metformin HCl) sustained release tablets which showed no significant difference ($p > 0.05$). All the other formulations were found to be statistically comparable with Glucophage® (Metformin HCl) immediate release. This was further confirmed when similarity factor (f2) was obtained. Formulation 3 showed comparable dissolution profile to that of the reference drug with f2 value of 49.9%.

Recommendations

The results of the study revealed that 15% *Basella rubra* mucilage incorporated in a tablet matrix successfully modified the release of the drug. The researcher thereby recommends conducting further studies on increased concentration of *Basella rubra* mucilage (20% and above). Also, future researchers can conduct stability studies to test if the formulated tablets will still conform to USP standards and sustain drug release.

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