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DESIGN AND DEVELOPMENT OF MODIFIED RELEASE DOSAGE FORM OF BCS CLASS-III DRUG BY NOVEL PASTILLATION TECHNIQUE

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Keywords:

Pastillation, Pastilles of metformin hydrochloride, Solid lipid, Pore former, Contact angle

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ABSTRACT: The primary goal of this study was to evaluate solid lipids as an alternative to polymers in the formulation of oral modified-release pastilles. Lipids have been used in pharmaceuticals since ancient times for a variety of purposes. They are used as polymer substitutes in the development of dosage forms. The solvent-free technique of pastillation uses lipids to formulate a modified-release oral dosage form explored in this research study. The melt solidification apparatus was developed at the laboratory scale to formulate hemispherical-shaped pastilles using solid lipid stearic acid; the apparatus was optimized by applying a 2^3-factorial design in Minitab. Three factors (X1 needle gage, X2 dropping height, and X3 base plate temperature) were considered and studied at 2-level.Optimized conditions were found to be ideal dropping height of 1 cm, a needle gauge of 20 G, and a cooling plate temperature of 4°C. Pastilles were characterized for drug content uniformity, 94 ± 1.64% to 98.8 ±1.03%; drug release of the F8 batch showed 99.98% ± 1.09 drug release at 12 hr; an angle of contact greater than 95° ±0.45 was considered optimal for hemispherical-shaped pastilles with good flow and uniform size weight, which sustained drug release for 12 hr. These pastilles were then filled into "0" sized capsules and sachets. Compared to melt extrusion and freeze pillarization, the pastillation method is more convenient for formulating lipid-based dosage forms. Large-scale manufacturing is possible as the equipment for pastillation, the "Rotoformer," has already been established in the chemical and agrochemical industries.

INTRODUCTION: Diabetes mellitus is a chronic illness. It is of two types: type 1 and type 2. Out of them, type 2 diabetes is a long-lasting, progressive condition marked by inadequate insulin release and increased insulin resistance. Many cardiovascular issues can be overcome with good and effective glycemic control, as is widely recognized. The drug metformin hydrochloride is a type of biguanide oral hypoglycemic drug that is commonly used for the management of type II diabetes.

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It's a common illness with abnormalities in insulin production and its mode of action [1]. This drug is hydrophilic and has a short biological half-life, i.e., 1.5 to 4.5 hrs, with a slow, imperfect absorption rate via the oral route in the gastrointestinal tract. It shows 50% to 60% overall bioavailability [2]. Its dose optimization is challenging due to frequent dosing schedules and the possibility of gastrointestinal side effects.

Therefore, it is reasonable to believe that a metformin formulation with sustained release is necessary to increase patient compliance and lengthen the drug's duration of action [3]. For extending the release of medications, waxes have been extensively researched [4]. Different processing techniques, including melt granulation, wet granulation, direct compression, and extrusion

spheronization, are employed to create a wax matrix system [5]. The most efficient and effective dosage form is an oral controlled-release medication. Such systems' drug release mechanism ensures essentially constant drug levels at the site of action, which results in minimal peak-to-valley changes, lower medication doses, fewer dosing intervals, fewer side effects, and ultimately higher patient adherence to therapy [6].

The sustained release provides a distinctive form of drug release with sustained therapeutic action by holding the drug concentration steady in the therapeutic window for an extended period [7]. A controlled-release multiparticulate method traps the drug in several tiny drug depots. These particles range in size from nano to micro; it depends on the end product formed. These are known as pellets, microparticles, nanoparticles, microcapsules, *etc*. Also, these are often delivered in a unit dose by being compressed in tablet form, filled in a hard gelatin capsule, or packed in a sachet if the dose is large [8].

A two-by-three factorial design can be used to investigate the effect of two independent variables on a single dependable variable. Each unreliable variable has to be checked at two levels in the factorial design, and other unreliable variables have three levels [9]. Hypotheses are used to express research problems.

They are stated for them to be empirically tested. There are numerous methods for testing hypotheses. There are as many research designs as there are possibilities. Designs are meticulously planned to produce reliable and valid answers to the hypothesis. The research findings are determined by how observations and inferences are made.

The reliability of our observations and inferences is determined by how well we plan the research design. The number of independent variables, levels of each independent variable, and the types of independent variables all influence research design planning [10]. The factorial design is used when multiple independent variables have multiple levels. Factorial designs might have two, three, or four factors. When two or more variables or factors are utilized in a factorial design, all possible combinations of chosen values for each variable are utilized. In a factorial design, the chosen values of two or more independent variables are changed in all feasible ways, and the independent and interactive effects on the dependent variable may be analyzed. According to the definition, a factorial design is a way by which two or many unreliable variables can be manipulated in all probable combinations.

The experimenter can use a factorial design to study the independent and interactive effects of two or more independent variables [11]. Factorial design terms include: Factors are the broad term for the independent variable that the investigator manipulates in the experiment, or that is manipulated through selection.

Suppose the simplest effect of a factor in the dependent variable is the average of the effect of the factor alone over the level of other factors. In that case, that is considered the main effect. In some cases, concluding the main impacts of two independent variables without considering their interaction effect can be deceptive [12]. If the effect of one unreliable variable is dependent on the value of another independent variable, this is referred to as an interaction. An interaction is a fluctuation in the mean for various values of one component over various levels of the other factor [13].

MATERIALS AND METHODS:

Materials: A free sample of metformin hydrochloride was gifted by Wokhardt in Aurangabad, India. The solid lipids stearic acid, PEG 4000, Poloxamer 407, and PEG 6000 were purchased from vendor DSA Nashik, India. All other chemicals are of analytical grade and were utilized as received from the supplier. The gelatin capsule shell was procured from DSA, Nashik, India.

Method:

Fabrication of Melt Solidification Apparatus for Pastilles Preparation: Laboratory scale assembled device was fabricated by using a glass syringe with plunger, hypodermic metal needle (20 G), heating jacket, automatic temperature controller, stand with holder, ice plate **Fig. 1.**

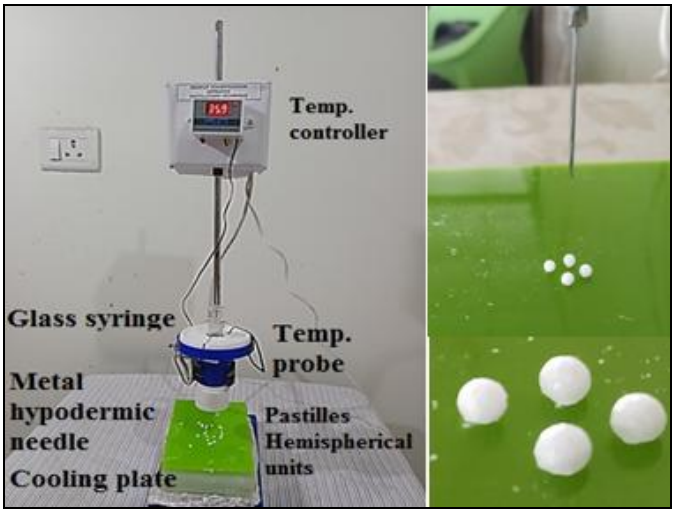

FIG. 1: LABSCALE MELT SOLIDIFICATION APPARATUS

Working Mechanism: A melted mixture of drugs, excipients, and solid lipids was put into the glass syringe. The he dating coil installed in the jacket on the outside of the glass syringe was connected to power using an automatic temperature regulator transformer. Depending on the substance's melting point, water jackets are used for substances that have a low melting point. The jacket is filled with oil, liquid paraffin, or another appropriate liquid for thermos table compounds with high melting points. The advantage of a liquid jacket is that it disperses heat uniformly and keeps the lipid molten for a longer time. The base plate where the created pastilles are collected must rest on an ice cube to get rapid solidification of the liquid drop. Size adjustments for pastilles can be made by adjusting the pressure applied to the plunger on the molten mass. For the screening trial, several parameters were changed to create placebo pastilles, such as the size of the needle (20G or 14G), the height difference from the needle tip to the cooling base plate (1–3 cm), the base plate with cooling, and the temperature of the plate (4, 10, and 25°C).

Optimization of Melt Solidification Apparatus: The 2^3 factorial designs were used to optimize the melt solidification apparatus to the formulation of the pastilles and placebo batches prepared with stearic acid by considering three operating variables (X1, X2, X3).

The effects of the three variables (X1: needle gauge size, X2: height difference to fall drop of molten mass on the cooling plate, and X3: difference in temperature between the cooling plate and lipid melt) were each examined at two levels **Table 1**. Pastilles' angle of contact (Y1) was a dependable variable or response variable, and the impact of each of these parameters was analyzed using MINITAB 18 Pro software.

TABLE 1: CONDITIONS FOR AN EXPERIMENT USING A FACTORIAL DESIGN

Code	Factor	Level	
		(-)	(+)
X1	Needle gauge size	16 G	20G
X2	Height difference to fall drop on cooling plate	1 cm	3 cm
X3	Temp. difference of plate	4°C	25°C

The operational and response variables are displayed in **Table 2**. Following the aforesaid investigations and trials, the optimal operating parameters were taken into consideration for the subsequent batch preparation based on their flow behavior as described in **Table 2**.

TABLE 2: MAKING THE PASTILLES USING STEARIC ACID USING A 2^3-FACTORIAL DESIGN

Batches	Factors				
	X_1 (Needle gauge size)	X2 (Height difference to fall drop on cooling plate)	X3 (Temp. difference of plate)	Average Angle of contact(Y1)	Flow
F1	16G	1cm	4°C	120°	Good
F2	16G	1cm	25°C	100°	Fair
F3	16G	3cm	4°C	110°	Good
F4	16G	3cm	25°C	70°	Poor
F5	20G	1cm	4°C	121°	Good
F6	20G	1cm	25°C	110°	Good
F7	20G	3cm	4°C	90°	Poor
F8	20G	3cm	25°C	80°	Poor

Determination of Angle of Contact: Pictures taken with the pastilles' horizontal side in contact with the cooling plate will show how the pastilles flow and change in size and shape as a function of the contact angle.

After that, Adobe Photoshop was used to adjust and proportionally enlarge the photographic image. The equation was used to calculate and analytically validate the pastilles' angle of contact with the cooling plate.

$$\theta = 2 \tan^{-1} 2h/d \quad \ldots\ldots\ldots\ldots (1)$$

Here,

h: Height of drop form the surface of cooling plate and *d*: Diameter of drop.

These variables are extracted from the image in order to determine the contact angle. Contact angles of each batch are recorded in **Table 2**, and flow behavior with respect to contact angle is given in **Table 4**.

Preparation of Pastilles with Stearic Acid: Formulation composition was taken as per **Table 3**.

Step I: Metformin hydrochloride is first melted in an oil bath at a temperature of 210–220°C.

Step II: Stearic acid, PEG 4000, and PEG 6000 were solid lipids, and Poloxamer 407 pore formers were heated individually in porcelain dishes at temperatures between 70 and 100 °C in an oil bath. This process guarantees that the drug is distributed uniformly throughout the matrix.

Step III: The heated glass syringe was then filled with this molten liquid (using the melt-solidification apparatus).

Step IV: Drops from a metal hypodermic needle of a certain size were allowed to fall to the cold plate drop-by-drop (with plunger pressure regulation controlled manually), and pastilles of hemispherical shape were created **Fig. 1**.

TABLE 3: FORMULATION COMPOSITION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASE PASTILLES

Batch	mg/batch					
	Met form in Hydrochloride (mg)	Stearic acid (mg)	PEG 4000 (mg)	PEG6000 (mg)	Poloxamer 407 (mg)	Colloidal silicon dioxide (mg)
F1	500	-	2000	-	-	75
F2	500	2000	-	-	-	-
F3	500	2000	300	-	-	-
F4	500	1500		75	-	-
F5	500	1750	-	150	-	-
F6	500	2000	-	300	-	-
F7	500	1500	-	-	75	-
F8	500	1750	-	-	150	-
F9	500	2000	-	-	300	-

TABLE 4: ANGLE OF CONTACT AND RESPECTIVE FLOW BEHAVIOR

Contact angle	Flow behavior
66-85º	Poor
85-105º	Fair
105-120º	Good

Analytical Method: The linearity of metformin hydrochloride in the water, basic pH 6.8 buffer, and acidic pH 1.2 buffer was determined by taking a concentration range of 2–12 g/mL. UV-VIS spectrophotometry was used to examine these solutions (Jasco UV 7300). In all liquids, metformin hydrochloride has a peak at 233 nm. A drug concentration vs. absorbance graph was used to plot the standard curve. In MS Excel, the regression equation and r2 were calculated.

Determination of Angle of Contact: Pictures taken with the pastilles' horizontal side in contact with the cooling plate will show how the pastilles flow and change in size and shape as a function of the contact angle. After that, Adobe Photoshop was used to adjust and proportionally enlarge the photographic image. Equation (1) was used to calculate and analytically validate the pastilles' angle of contact with the cooling plate.

Drug Content Uniformity: To estimate the amount of drug in a pastille containing 500 mg of metformin hydrochloride, the pastille was triturated and diluted in 20 ml of distilled water in 100 ml volumetric flasks. After being sonicated for 10 minutes, the residual volume was allowed to cool at

ambient temperature before being taken to the necessary level by distilled water. The 10 ml of the aforementioned solution were adequately diluted with distilled water, filtered through a 0.45 nylon filter, and then exposed to UV spectrophotometric examination at 233.5 nm to measure the drug present.

For the purpose of calculating the percent drug content, a standard drug solution was made in the same way as previously stated.

$$X = Y \pm C / M \ldots\ldots\ldots\ldots\ldots (2)$$

The following equation was used to compute the % drug content from the concentration:

Percent drug content = (Drug concentration in sample solution) / (Equivalent concentration of standard drug) × 100……(3)

Friability Test: The Roche friabilator's drum held a sample of 2000 mg pastilles that had been precisely weighed. For four minutes, the fiber rotating drum was set to 25 rpm. Pastille removal, dedusting, and precise weighing were performed. The following relationship was used to compute the friability weight losses of the tested pastilles:

$$\%F = (Wo\text{-}Wf) / Wo \times 100 \ldots\ldots\ldots..(4)$$

Here, Wo: weight of pastilles before test. Wf: weight of pastilles after test.

Crushing Strength: The significance of determining the crushing strength of pastilles is to know the fracture pattern for this pastilles, which was evaluated by applying punch pressure with respect to force. A texture analyzer instrument was used to conduct this test. The crushing strength of the optimized batch F8 was evaluated first before exposure to the dissolution medium and then again after exposure to the dissolution test by use of a texture analyzer (the CT3 Texture Analyzer of Brookfield) with the operating condition set at a 3 kg load cell. A single pastille sample was centered between a 25.3 mm diameter and 35 mm long acrylic bar as the upper punch descended at a steady speed of 0.3 mm/s. Here, N: is force Vs. Time (S) is graphs were captured using software (TexturePro CT) Study of surface morphology by scanning electron microscopy. The surface morphological study of pastilles done by using scanning electron microscope (JSM-6390LV, JEOL Instrument).

Fourier Transforms Infrared Spectroscopy (FTIR) Spectroscopy: FTIR data can be used to identify and verify unknown components or known materials using reference data, to evaluate the quality or dependability of a sample being tested, and to count the number of constituents in a combination. The samples were placed using the attenuated total reflection (ATR) technique, which allows for direct FTIR sample measurement. The ATR method scans between wave numbers 400 and 4000 cm^{-1} with an FTIR spectrophotometer (FTIR 4600 Jasco) and the sample is placed over the high-refractive –index prism to measure the infrared spectrum by an infrared beam of light. The obtained FTIR spectra were compared to references for a functional group peak.

Differential Scanning Calorimetric (DSC) Analysis: A differential scanning calorimeter (the Mettler DSC 1-star system) equipped with a liquid nitrogen sub-ambient accessory was used to perform differential scanning calorimetric (DSC) measurements on the optimized batch F8 with stearic acid. The apparatus's nitrogen purge gas flow rate was 100 ml/min. Samples ranging from 3 to 10 mg were weighed in an aluminum pan that was exposed to heat at a rate of 10°C/min from 30 to 300°C.

Drug Release Study: A dissolution medium of acidic buffer pH 1.2 containing 900 ml was utilized for the first two hours, with operating settings of 50 rpm and 37±0.5°C temperature. Using the dissolving test apparatus USP II, the test was conducted for an additional 12 hours after the medium had been replaced after two hours with a pH 6.8 phosphate buffer (make Electrolab TDT 8 L). At each time interval, 5 ml of the material was pipette-removed in aliquots and then replaced with that of the sample medium to keep the sink condition of the dissolution medium. The sample was tested with a UV spectrophotometer at 233.5 nm, and the absorbance was calculated.

Release Kinetics: The cumulative drug release data was fitted to models to evaluate the drug release kinetics and mechanism.

Stability Study: In accordance with ICH regulations, the HDPE bottles were used to store stearic acid-containing pastilles of the F8 batch.

They were sealed and kept in a stability chamber at 40°C for three months with a relative humidity of 75%. Drug release test analysis was performed on the samples that were taken out 1, 2, and 3 months later.

RESULT AND DISCUSSION:

Excipients Selection: Stearic acid, a solid lipid with a melting point of 70°C was selected as a matrix-forming agent for sustained release due to its hydrophobic properties. As pore formers and rate modifiers for the prolonged release of drugs from the hydrophobic matrix, PEG 4000, PEG 6000, and Poloxamer 407 have been employed. In some batches, colloidal silicon dioxide is added to increase melt viscosity.

Evaluation of Operating Condition on Pastilles Angle of Contact: To assess how quickly a melt drop would travel across the cooling plate surface, this was done by calculating the angle of contact of the pastilles. To evaluate the impact of several operating parameters on the contact angle, the 2^3 factorial design was used, with operating parameters including needle size, height from the cooling plate, and plate temperature. The results are summarized in **Table 2**. Stearic acid alone, *i.e.*, without any medication, was used in the trail screening study to optimize the operational parameters. The manufacturing of additional batches was then done using these optimized settings.

Impact of Needle Gauge size: Based on the contour plot of the angle of contact vs. needle gauge size and height difference from the cooling plate **Fig. 2A**, it was concluded that there was no impact of needle gauge size on the angle of contact of pastilles at a steady cooling plate temperature of 4°C and a variable height difference from the plate. Similarly, in the contour plot of angle of contact vs. needle size and cooling plate temperature **Fig. 2B**, it was observed that at steady height differences of 1 cm and low plate temperatures with 16G needle size, the angle of contact was higher. When the plate temperature is significantly lowered, the impact of the needle size is reduced. Therefore, the angle of contact was clearly demonstrated to be unaffected by needle size, and as a result, the shape of the generated pastilles was also unchanged. If there was an increase in needle orifice size from 20G to 16G, it was found that the pastilles size increased from 2.0 ± 0.2 to 3.5 ± 0.1 mm. Additionally, suppose the needle size is reduced further below the range mentioned above. In that case, the melt may have trouble exiting the needle, and if the needle size is increased above the range mentioned, larger pastilles may occur that cannot fit within the capsule.

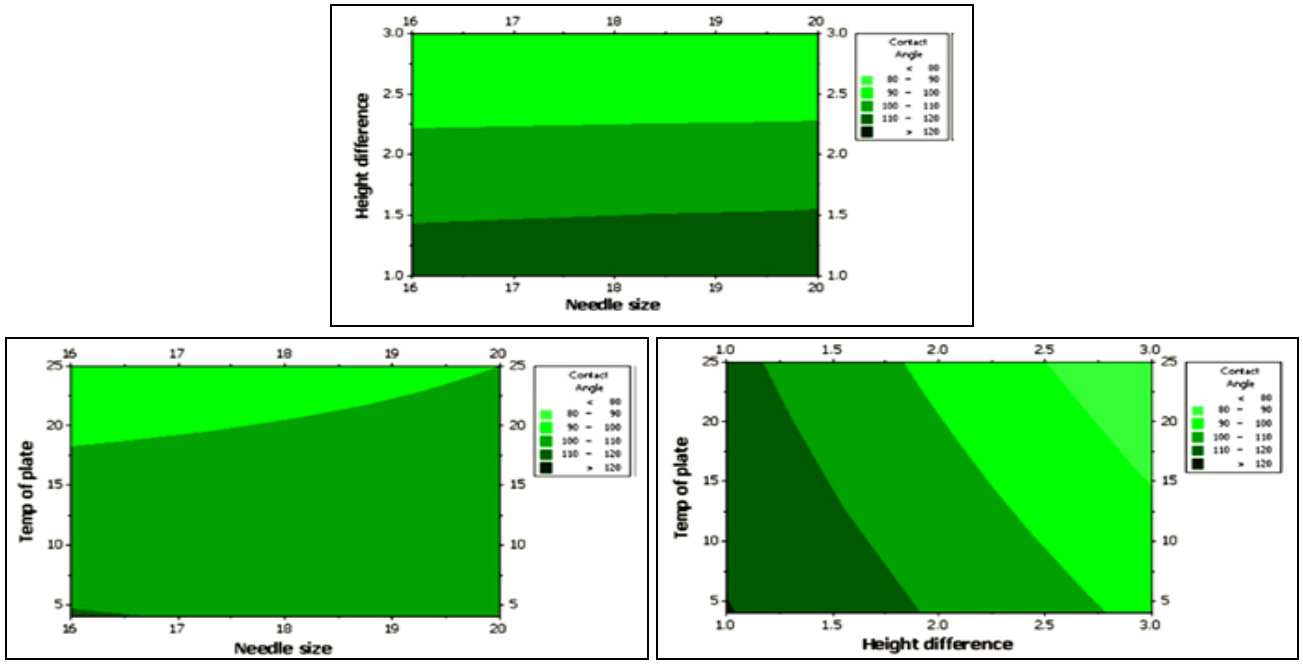

FIG. 2: (A) CONTOUR PLOT OF ANGLE OF CONTACT VS. NEEDLE GAUGE SIZE, HEIGHT DIFFERENCE, (B) CONTOUR PLOT OF ANGLE OF CONTACT VS. NEEDLE GAUGE SIZE, PLATE TEMPERATURE, (C) CONTOUR PLOT OF ANGLE OF CONTACT VS. TEMPERATURE OF PLATE AND HEIGHT DIFFERENCE

Keeping constant plate temperature (4°C) and needle gauge size, it was found that there is an inverse relationship between drooping height and contact angle. As the dropping height increased, the angle of contact significantly decreased **Fig. 2A**. From the contour plot of angle of contact vs. plate temperature and height difference of the needle **Fig. 2C**, it was concluded that, after a decrease in the drop's falling distance, the force due to the drop falling on the cold surface was less. This will lessen the spread of the drop, which rapidly freezes as its heat is transferred to the cool plate. The contour plots **Fig. 2A and C** indicate that a falling height of 1 cm was appropriate for making the pastilles with higher contact angles, regardless of the needle gauge size and plate temperature. It might not be able to reduce or increase the lowering height further.

It was found that if the temperature of the cooling plate was low, the drop would cool quickly, preventing it from spreading on the plate, and the pastilles would form right away with a high contact angle. The drop takes too long to cool and solidify if the cooling plate's temperature is higher. Because of this, the angle of contact vs. temperature of the plate and needle gauge size and vs. plate temperature and height difference **Fig. 2B** and **C** indicate that, regardless of the height difference and needle gauge size, maintaining a low plate temperature (4°C) is necessary for the formation of pastilles with a greater contact angle. However, it was discovered that further temperature reduction may increase the angle of contact by minimizing the spreading duration. Rapid cooling may cause a further rise in the solidification rate, which could lead to porous pastilles. After examining the angle of contact using a photographic technique, it is suggested that any angle of contact greater than 90 degrees yields pastilles with the predicted spherical shape. The study finds that a higher angle of contact is preferable because it produces pastilles with a good flow quality and a hemispherical form.

The summary is in **Table 4**. The optimal settings to generate ideal pastilles with a suitable angle of contact were 1 cm height (distance from needle tip to base plate) and temperature of the cooling plate at 4°C, based on the results from the contour plots mentioned above. It was hypothesized that decreasing the height of the needle tip and cooling plate would have a less significant effect on drop strikes to the plate and that spreading time would decrease as a result of a lower temperature. Pastilles with a lower angle of contact may not have a spherical shape if the spreading period is longer. With an increase in pastilles with a sphere shape, these two characteristics help to enhance the contact angle. It was determined that pastilles of the necessary size created by a 20 G needle were simple to load into size "0" capsules. Pastilles contact angles are displayed in **Fig. 3**.

Determination of Angle of Contact: The angle of contact of the pastilles in each batch was calculated using equation (1) and summarized in **Table 5**. Angle of contact for optimized batch F8 was found to be 120°, which indicates pastilles with good flow behavior.

TABLE 5: RESULTS OF ANGLE OF CONTACT

Batches	Average Contact Angle	Flow
F1	105^o	Good
F2	90^o	Fair
F3	100^o	Fair
F4	90^o	Fair
F5	115^o	Good
F6	110^o	Good
F7	90^o	Fair
F8	120^o	Good
F9	95^o	Fair

Drug Content Uniformity in Pastilles: Uniform distribution of drug in the matrix, as evidenced by the drug content values for formulation batches F1 to F8 shown in **Table 6**. Additionally, it was noticed that the drug dose did not experience potential degradation because of the effect of high temperatures at the time of the formulation process.

TABLE 6: DRUG CONTENT UNIFORMITY TEST

Batch Code	Loaded amount of drug (mg) in pastilles (x)	Actual drug content (mg) in each tablet (y)	% Drug Content (y/x)*100
F1	500	498	99.6 ± 1.41
F2	500	480	96.0 ± 0.54
F3	500	490	98.0 ± 1.05
F4	500	470	94.0 ± 1.64
F5	500	485	97.0 ± 0.97

F6	500	480	96.0 ± 1.08
F7	500	498	99.6 ± 1.31
F8	500	494	98.8 ± 1.03

Dissolution Study of Pastilles: The dissolution tester for USP type II (paddle) (Electrolab TDT 8L) was used for the dissolution study. It was set at 37±0.5°C at 50 rpm, and the 900 ml phosphate buffer pH 6.8 dissolution medium was used for 2 hours, followed by 12 hours in pH 1.2 buffer. It was observed that the pastilles formulated with PEG 4000 (F1) showed immediate drug release within 50 min. This may be due to the highly hydrophilic nature of PEG 4000. **Fig. 3A, B, C**.

Effect of Composition of Dissolution Medium on Drug Release and Morphology of Pastilles: It was noticed that pastilles from the F2 batch were studied in a buffer medium with a pH of 6.8 for 2 hours, then the medium was replaced with a pH 1.2 buffer. It was observed that the drug was released completely within 8 hr **Fig. 3A**, but at that time, the pastilles became a swollen disc shape with very soft pulp that is easily deformed; the shape and size completely differ before and after exposure to the dissolution medium **Fig. 4A.** It happened because it is given in literature that stearic acid reacts with metal hydroxides present in phosphate buffer pH 6.8 and creates a water-soluble sodium salt of stearic acid. So there was incompatibility between static acid and phosphate buffer pH 6.8 but not with that of pH 1.2 buffer medium. According to the literature, mixing sodium buffer, i.e., Na_2HPO_4 and NaH_2PO_4, into the composition of pH 6.8 phosphate buffer overcomes the incompatibility of stearic acid with that of pH 6.8 buffer medium. A mixed sodium and pH 6.8 buffer medium was used for the dissolution study instead of pH 6.8 buffer alone. It was noticed that the release of drug from batch F2, i.e., only with stearic acid, was very slow, with only 23.24 percent of the drug released in 12 hours of study **Fig. 3A**. This was a surface-adsorbed drug that was only released, but because of the absence of a pore former and a highly hydrophobic lipid matrix, the dissolution medium cannot go inside the inner layer of pastilles to release the entrapped drug. It was concluded that the release of drugs could be controlled by diffusion as well as the dissolution of the drug into water-filled pores inside the matrix; hence, the drug release was improved by two approaches. The first approach involved incorporating PEG 4000 and PEG 6000 water-soluble agents into the lipid matrix to create pores and act as pore-forming agents. Another second approach involved the use of poloxamer 407, a surfactant and stabilizer that aids in the solubilization of hydrophobic molecules, allowing them to dissolve more quickly and completely in polar media.

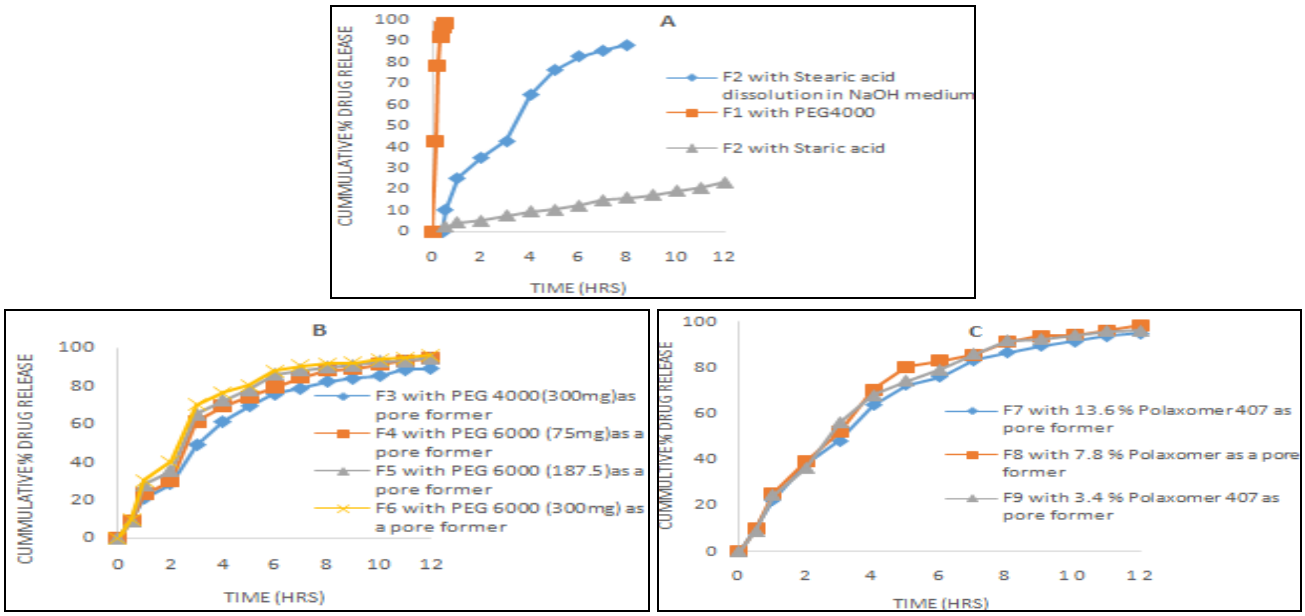

FIG. 3: (A) EFFECT OF MATRIX FORMING AGENTS AND DISSOLUTION MEDIUM ON DRUG RELEASE, (B), (C) DISSOLUTION STUDY SHOWS INFLUENCE OF PORE FORMER ON THE RELEASE OF DRUG

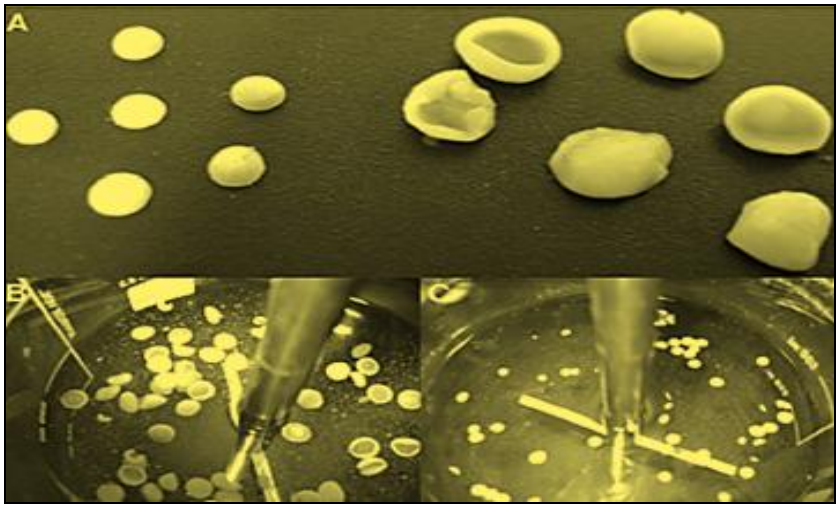

FIG. 4: (A) EFFECT OF PH 6.8 BUFFER MEDIUM ON PASTILLES BEFORE AND AFTER EXPOSURE (B) PASTILLES TEXTURE DURING DISSOLUTION STUDY IN BUFFER PH 6.8 MEDIUM (C) IN BUFFER PH 6.8 MIXED SODIUM PHOSPHATE MEDIUM

Effect of Pore Former as Release Rate Modifier: PEG 4000, PEG 6000, and Poloxamer 407 were used as pore-formers (F3–F9), and their dissolution profiles are shown in **Fig. 3 B and C**. After addition of pore former PEGs results in increased in drug release. During the dissolution study, it was noticed that both PEGs and drugs present on the surface of the pastilles that were starting to dissolve would allow aqueous medium to enter the core of the pastilles, and medium would reach inside the center of the pastilles because of the creation of pores. It was observed that PEG 6000 had a faster release rate than PEG 4000.

The substance's physical condition, molecular weight, and hydrophilicity may all contribute to this type of release rate. According to reports, the melting point of PEGs rises along with their molecular weight. PEGs that are solid will have larger holes because of their higher molecular weight. This is demonstrated by the fact that batch F-6 has a faster drug release rate than batch F3 because PEG 6000 has a higher molecular weight than PEG 4000, leading to comparably larger channels. Approximately 30% of the drug was generally released in the first two hours, and only in the case of F-6 was there a sustained release, with more than 90% of the drug released in the next twelve hours.

Additionally, because the drug and PEG present at the surface quickly dissolved, it was initially necessary to limit the rapid drug release. The mechanism of diffusion is entirely responsible for the remaining unreleased drug release from the pastilles. The drug release profiles of batches F7 and F9 were comparable to those of the F8 batch, with minor differences in the initial release. The poloxamer 407 was utilized as a different pore-forming agent in batches (F7, F8, and F9). It was observed that the dissolution profile of the F8 batch was 99.98% ± 1.09 % after 12 hours of investigation. The stabilizer poloxamer 407, based on surfactants, produces more pores with varying concentrations (F7, F8, and F9), and the dissolution medium enters the pastilles. The release rate varies about the amount of drug present in the matrix, depending on the amount of lipid (stearic acid) present. A batch that was optimized (F8) adhered to the first-order drug release kinetic model. It was discovered that n had a numerical value of 0.6782 and a correlation coefficient of 0.9404, confirming non-fickian transport.

Scanning Electron Microscopy: The pastilles photo A shows that the pastilles of F-1 have a circular shape with a highly smooth and uniform texture **Fig. 5A.** Whereas pastille photo B at higher magnification shows a porous matrix with a higher degree of crystallinity **Fig. 5B**. Another image with a higher degree of magnification **Fig. 5B** depicts a porous matrix with a high degree of crystallinity. The main reasons for the faster release of drugs from the PEG-based matrix are the higher solubility and greater porosity of PEG in water. However, due to its quicker solidification rate and higher melt viscosity, pastilles of F-8 likewise exhibit a circular structure **Fig. 5C**, though they are

smaller in size than pastilles of F-1. High viscosity prevents the drop from spreading too widely since it solidifies more quickly and has less spreadability. In the zoomed-in view of F-8 **Fig. 5D**, pores were seen on the upper surface, likely created by the rapid solidification rate, preventing the melt from spreading properly.

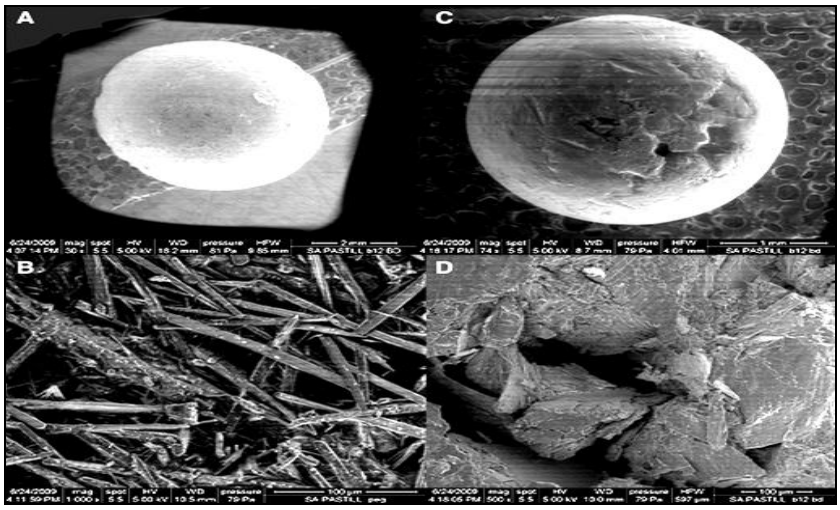

FIG. 5: SEM MORPHOLOGICAL ANALYSIS OF PASTILLES (A) PASTILLE OF F1-BATCH (B) PASTILLE OF F1-BATCH AT HIGHER ZOOMING (C) PASTILLE OF F8-BATCH (D) PASTILLE OF F8-BATCH AT HIGHER ZOOMING

Fourier Transforms Infrared Spectroscopy (FTIR) Spectroscopy: It was noted that the peak of the IR spectra of metformin hydrochloride **Fig. 6** had amine stretching at 3367.1 cm^{-1} -NH, NH deformation at 1622.8 cm^{-1}, and CNC deformation at 933.378 cm^{-1}. Stearic acid's IR spectra exhibited a peak at 2912.95, 2847.38 cm^{-1} for -CH2- Stretching vibrations, 1696.09 cm^{-1} for Alkanes, and 1731.76 cm^{-1} for C=O. Stretching of esters of more saturated acids, with a C=O (from carboxylic group) stretch of 1175.4 cm^{-1} and an O-H (from hydroxyl group) stretch of 1432.83 cm^{-1}.

When metformin hydrochloride and stearic acid were combined, the peaks didn't exhibit any discernible alterations in their structural characteristics.

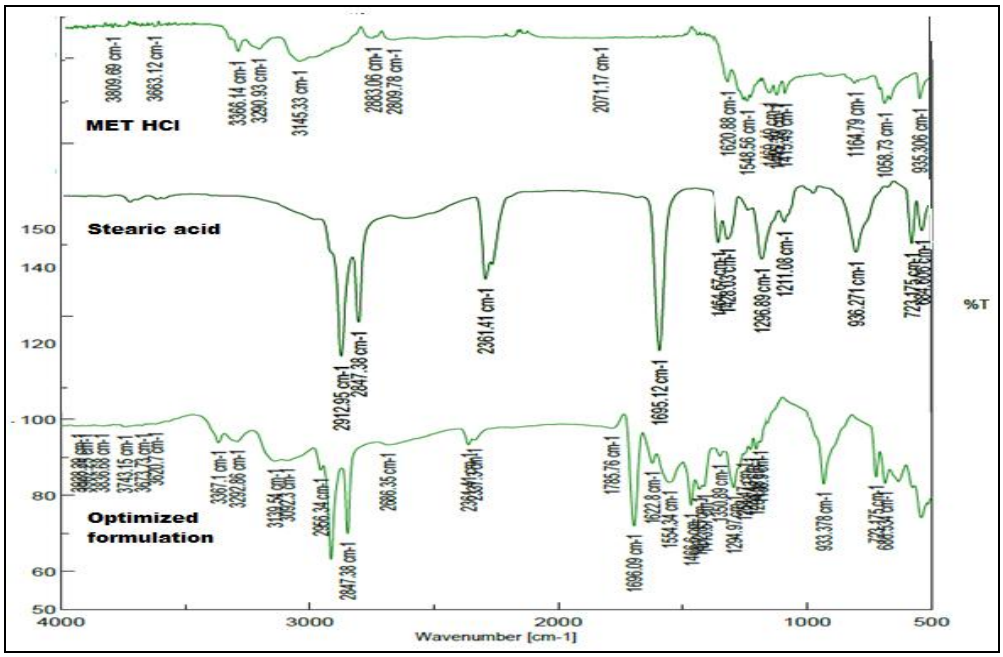

FIG. 6: FTIR OF METFORMIN HCL, STEARIC ACID AND OPTIMIZED FORMULATION. *MET HCl: Metformin Hydrocloride.

Differential Scanning Calorimetric Analysis: One of the most commonly used methods for examining the crystalline and amorphous states of drugs in pastilles is DSC. This was accomplished by calculating the temperature and energy variations at the phase transition. The endothermic peak in **Fig. 7A, B** shows that metformin hydrochloride and stearic acid melted at around 233.27°C and 57.37°C, respectively. In optimized batch **Fig. 7C,** the endothermic peak of lipid repeated at nearly identical numerical values, and the less intensity peak of drug with nearly at same numerical values appeared may be due to the drug present on the surface of pastilles and the remaining drug was in complex with lipid; hence it confirmed the formation of complexation with no interaction between the drug and solid lipid material.

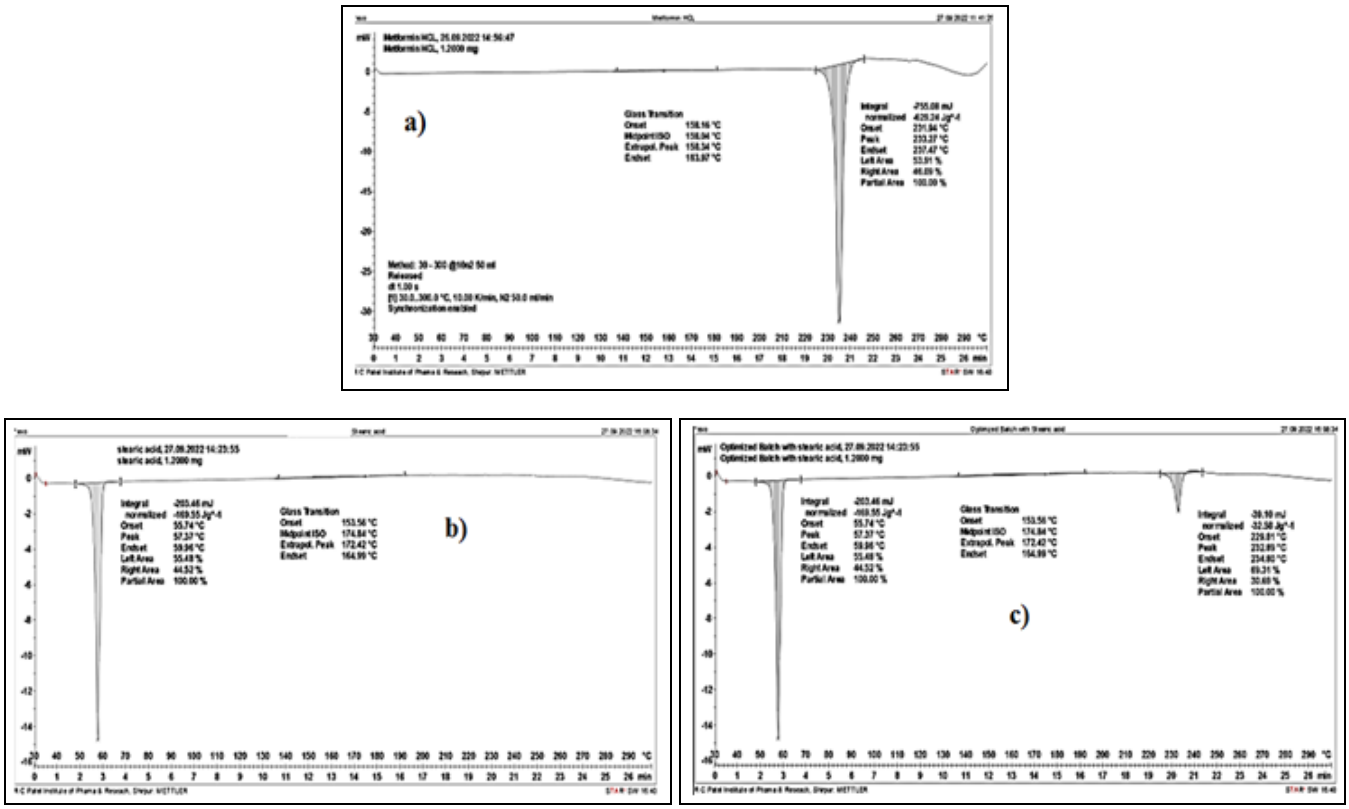

FIG. 7: (A) DSC THERMOGRAM OF METFORMIN HCL, (B) DSC THERMOGRAM OF STEARIC ACID, (C) DSC THERMOGRAM OF OPTIMIZED BATCH F8

Stability Study: After contrasting the initial samples' stability data with the samples kept in a controlled environment. The storage condition was shown to have no bearing on the physical characteristics and drug release profiles of the stored samples **Fig. 8**. No difference in the formulation's drug concentration (Initial 98.44 ± 1.02%, 1 Month 97.54± 0.58 %, 2 Month- 98.10±1.05 %, and 3 Month- 96.32± 0.80 %) was observed. This demonstrates that the preparation's lipid excipient is both physically stable and resistant to environmental changes.

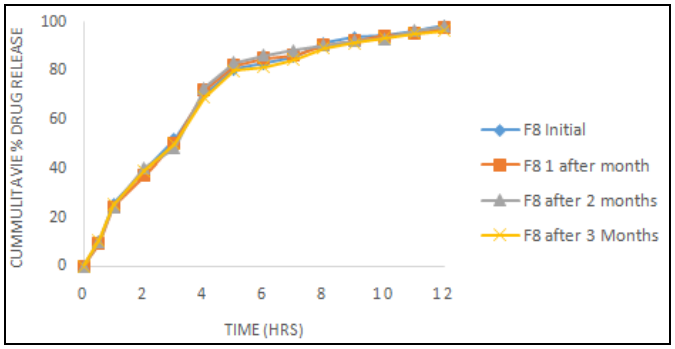

FIG. 8: DRUG RELEASE PROFILES OF THE F8 BATCH'S INITIAL AND STABILITY SAMPLES

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