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Research Article

The *in vitro* equivalence study of polymorph-modified glimepiride tablets compared to Amaryl®

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Abstract

Glimepiride (GMP) is an oral antidiabetic drug classified as BCS class II, demonstrating extremely limited solubility, with a solubility level below 0.00384 mg/mL. Some generic drug manufacturers producing GMP (copy product) tablets encountered bioavailability issues due to poor dissolution, which did not meet the requirements. Therefore, measures were taken to enhance solubility through the modification of polymorphs. It is known that GMP exists in two polymorphic forms, namely Form I and an alternative Form II, which exhibits higher solubility in water. This study aims to produce and characterize the polymorph-modified GMP compared to non-modified GMP, develop an optimal formulation for polymorph-modified GMP tablets that adhere to pharmaceutical requirements as a representative copy drug model, and determine its similarity factor to Amaryl® as the innovator. The research methodology involved initiating the study by examining the polymorph transformation of GMP through the utilization of techniques such as neat grinding, solvent drop grinding, and solvent evaporation. The resulting samples were characterized using DSC, PXRD, and SEM analysis. The performance assessment encompassed the evaluation of flow properties, compressibility index, solubility, and dissolution rate compared to the non-modified GMP. Based on the characterization results, the best polymorph-modified GMP sample was used to produce a tablet formulation containing 4 mg of GMP using the direct compression method as a copy tablet model. In vitro equivalence testing was performed using a comparative dissolution test on the polymorph-modified GMP tablet compared to its innovator, Amaryl® 4 mg, in three different dissolution media, followed by determining the equivalence status using the similarity factor (f2) calculation. Based on the screening results of polymorph transformation, it was determined that the polymorph-modified GMP, using all three techniques, did not undergo a transition from Form I to Form II. Instead, it underwent amorphization, primarily observed in the solvent evaporation technique. Tablets containing polymorph-modified GMP using the solvent evaporation technique were able to enhance the *in vitro* dissolution rate profile compared to non-modified GMP tablets. The f2 values for the comparative *in vitro* dissolution test in acetate buffer pH 4.5 and phosphate buffer pH 6.8 were 60.15 ± 0.27 and 88 ± 0.35, respectively within acceptance criteria of 50–100. However, in KCl/HCl buffer pH 1.2, the f2 value was 45.15 ± 0.23. It was concluded that the polymorph-modified GMP tablet was not similar to its innovator, Amaryl®.

Keywords

Amorphization, comparative *in vitro* dissolution test, dissolution, glimepiride, polymorph modification, solubility

Introduction

Glimepiride (GMP) is a third-generation sulfonylurea antidiabetic drug known for its ability to effectively lower blood glucose levels. Glimepiride (GMP) possesses several notable advantages over other sulfonylureas, including its low dosage requirement, rapid onset of action, prolonged duration of effect, and minimal propensity for inducing hypoglycemia. These characteristics make GMP a preferred choice for the treatment of diabetes, as it provides effective glycemic control with a reduced risk of low blood sugar episodes (Ammar et al. 2006, 2007). However, GMP belongs to BCS class II, which is characterized by slow gastrointestinal absorption due to its poor solubility in water and high hydrophobicity. The solubility of GMP is significantly influenced by pH, with extremely limited solubility observed in water (<0.00384 mg/mL at 37 °C) and a slight increase in alkaline pH media (up to 0.02 mg/mL) (Frick et al. 1998; Kiran et al. 2009; Massi-Benedetti 2003). The distinctive characteristics of GMP present significant challenges for generic drug manufacturers who aim to produce copy products, particularly in achieving optimal bioavailability. The main obstacle lies in the inadequate dissolution of GMP, failing to meet the necessary (Gill et al. 2010; Singh et al. 2009). Consequently, it becomes imperative to undertake endeavors focused on enhancing the solubility of GMP, thereby improving its bioavailability and dissolution properties.

One approach to enhance the solubility and dissolution rate of GMP is through polymorph modification. It is known that GMP exists in two polymorphic forms, namely Form I and Form II, with Form II demonstrating higher solubility in water. This was investigated in a polymorph modification study where GMP Form II was obtained from Form I using the recrystallization method in an ethanol/water system (Bonfilio et al. 2011).

Polymorphism refers to the ability of a substance to exist in different energy states under varying pressure and temperature conditions while maintaining the same chemical properties or the ability of a substance to exist in two or more crystalline phases with differences in molecular arrangement and/or conformation within their crystal lattice. Understanding polymorphism is crucial in pharmaceutical manufacturing as each polymorph exhibits distinct physical properties such as solubility, density, and melting point (Endo et al. 2003).

There are two types of polymorphs: stable and metastable forms. In the metastable form, the drug's solubility increases, resulting in higher concentrations during the dissolution process, which then decreases to the normal solubility level in the stable form. A substance exhibits polymorphism when it can crystallize into different crystal systems due to temperature, pressure, and storage conditions (Bonfilio et al. 2011).

The process of transformation from one polymorph to another is a phase transition that can occur during both storage and production processes. If the phase transition is reversible, then both polymorphs are considered enantiotropic, characterized by the occurrence of a transformation temperature (Tt) to the other form, followed by a melting temperature (TL). If the phase transition is irreversible, then both polymorphs are considered monotropic, characterized by the initial melting of the starting form (TL), followed by a transformation (Tt) to another form. Based on research findings, GMP has been proven to exhibit two polymorphic forms, namely Form I and Form II, with a monotropic (irreversible) behavior. It begins with the melting of GMP Form I at 201.2 °C, followed by a polymorphic transformation into GMP Form II, indicated by recrystallization, and ends with the melting of GMP Form II at 219.1 °C (Zhang et al. 2013).

Polymorph modification involves altering the crystal form of a solid active pharmaceutical ingredient under specific temperature and pressure conditions to a metastable form, aiming to modify its physicochemical properties such as bulk density, melting point, optical and mechanical properties, solubility, and dissolution rate (Qiao et al. 2011). The different polymorphic forms of an active pharmaceutical ingredient exhibit distinct physicochemical properties. These polymorphic variations result in differences in drug solubility in aqueous or gastrointestinal fluids, consequently affecting dissolution rate and bioavailability (Gozali et al. 2014).

In this study, a screening of polymorph transformation of GMP was conducted using the techniques of neat grinding, solvent drop grinding, and solvent evaporation. The samples were thermally characterized using DSC, analyzed for their diffraction patterns using PXRD, and their crystal habits were examined using SEM. Performance evaluation included flow properties, compressibility index, solubility, and dissolution rate, which were compared to non-modified GMP. Based on the characterization results, the best polymorph-modified GMP sample was used to formulate tablets containing 4 mg of GMP using the direct compression method as a copy tablet model. To ensure the quality of the copy product and demonstrate its equivalence to the innovator, a comparative *in vitro* dissolution test was performed as a preliminary assessment for the *in vivo* bioequivalence study, as GMP is one of the generic drugs that require bioequivalence testing mandated by BPOM (Badan Pengawas Obat dan Makanan 2022b, 2022a).

This study aims to produce and characterize the polymorph-modified GMP compared to non-modified GMP, develop an optimal formulation for polymorph-modified GMP tablets that adhere to pharmaceutical requirements as a representative copy drug model, and determine its similarity factor to Amaryl® as the innovator through a comparative *in vitro* dissolution test as a preliminary assessment for the *in vivo* bioequivalence study.

Methods

The polymorph transformation screening of GMP

The polymorph transformation screening of GMP entails the utilization of distinct methodologies, including neat grinding (NG), solvent drop grinding (SDG), and solvent

evaporation (SE). The neat grinding procedure involves the grinding of 50 grams of GMP powder using a mortar and pestle for a duration of 30 minutes. In the solvent drop grinding technique, a similar amount of GMP powder, 50 grams, is subjected to grinding using a mortar and pestle for 10 minutes while simultaneously being dripped with acetone p.a. As for the solvent evaporation technique, 100 grams of GMP powder is dissolved in 100 ml of acetone p.a, stirred for 30 minutes until complete dissolution is achieved, and subsequently evaporated at ambient temperature to induce the recrystallization of GMP (Qiao et al. 2011).

The modified polymorph characterization and evaluation of GMP

The modified polymorph characterization of GMP involves the utilization of various analytical techniques, namely differential scanning calorimetry (DSC, STA PT1600, Linseis Thermal Analisis, Germany), powder X-Ray diffraction (PXRD, Bruker D8 Advance, USA), and scanning electron microscope (SEM, JEOL JSM-6360LA, Japan). Additionally, the performance evaluation encompasses the assessment of flow properties, compressibility index, solubility, and dissolution rate, which are compared with those of unmodified GMP.

The modified polymorph characterization of GMP

The thermal characterization involves the placement of a sample weighing 5–20 mg onto an aluminum crucible in the DSC instrument, with a temperature range of 30–300 °C and a heating rate of 10 °C per minute. The pattern of diffraction is characterized by placing a sample weighing 100–200 mg onto the sample holder in the PXRD instrument, within the angular range of 2θ 5–65°, using CuKα radiation (Kα1 = 1.54060 nm, Kα2 = 1.54439 nm) with a voltage of 40 kV and a generator current of 35 mA. The crystal habit characterization involves placing a sample weighing 1–5 mg onto the sample holder, coating it with gold-palladium using an auto fine coater in the specimen chamber of the SEM instrument, and observing it on a computer for capturing suitable magnified images.

The modified polymorph evaluation of GMP

The assessment of flow properties entails the utilization of a flow tester to measure both the flow rate and the angle of repose. The flow rate is determined by dividing 100 grams of powder by the duration it takes for it to traverse through a funnel, expressed in grams per second (g/second). A desirable powder flow is indicated when the time required for the passage of 100 grams of powder is under 10 seconds. On the other hand, the angle of repose is ascertained by measuring the angle formed by the inclined slope of the flowing powder heap as it descends from the funnel onto a flat surface. The angle of repose serves as an indicator, with values falling within the range of $\alpha = 25°–30°$ signifying a state of very easy flow, $\alpha = 30°–38°$ representing easy flow, and $\alpha > 38°$ indicating poor flow characteristics.

The compressibility percentage represents the ability of the powder to be compressed into tablet formulations. A lower compressibility percentage indicates excellent flow properties of the powder. Determining the compressibility percentage begins with the determination of bulk density, including tapped bulk density and bulk density, using a tab densitometer. The bulk density is determined by measuring the volume of 50 grams of powder poured into a 250 mL measuring glass without tapping and recording the volume. The tapped bulk density is measured using the same method as bulk density but with 10 and 500 taps. The compressibility percentage of the powder is determined from the measurements of bulk density and tapped bulk density using the following equation:

$$\%C = \frac{Tapped\ Bulk\ Density - Bulk\ Density}{Tapped\ Bulk\ Density} \times 100 \quad \textbf{(Equation 1)}$$

Interpretation of the results is as follows: %C = 5–15% indicates excellent flow, %C = 16–25% signifies good flow, and %C ≥ 26% represents poor flow.

The solubility testing was conducted by weighing an excess amount of powder (10 mg) and then placing it into a 10 mL vial. Each sample was dissolved in a pH 7.4 phosphate buffer solution until a saturated solution was formed. The vials were placed in an orbital shaker set at a speed of 50 rpm and conditioned at body temperature (37±0.5 °C). Stirring was performed for 24 hours to achieve equilibrium. The solution samples were filtered, and their concentrations were determined using an ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 228 nm.

The intrinsic dissolution rate testing was performed by weighing 200 mg of powder, which was then formed into pellets and mounted onto a holder. The pellets were immersed in a dissolution medium containing 250 ml of pH 7.4 phosphate buffer temperature of 37±0.5 °C. Ensure the absence of any air bubbles beneath the pellets before they were promptly positioned on a rotating apparatus, which operated at a constant speed of 100 rpm. The vertical distance between the surface of the pellets and the bottom of the dissolution vessel was meticulously maintained at a precise measurement of 2 cm. At predetermined time intervals of 5, 10, 20, 30, 45, and 60 minutes, precise aliquots of 10 mL were methodically withdrawn from the solution. To maintain consistency, each withdrawn aliquot was meticulously replaced with an equal volume (10 mL) of fresh dissolution medium, maintained at the same temperature as the experiment. Subsequently, the aliquots were subjected to a meticulous filtration process to remove any particulate matter, followed by the precise determination of their concentrations using a highly reliable ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan), operating at a specific wavelength of 228 nm.

The modified polymorph formulation and evaluation of GMP tablet

Based on the characterization results, the best formulation for the modified polymorph of GMP was selected for the tablet

formulation. Two formulations were prepared: the modified polymorph GMP tablet (MP) and the unmodified GMP tablet (NM), using the direct compression method with a tablet strength of 4 mg per 200 mg tablet weight (Table 1).

Table 1. GMP tablet formulation.

Material	Formula	
	FI	FII
GMP NM	4 mg	-
GMP PM	-	4 mg
Amprotab	10%	10%
Magnesium stearate	2%	2%
Talc	1%	1%
Avicel PH102 ad	200 mg	200 mg

Information: FI = GMP NM Tablet (non-modification); FII = GMP PM Tablet (polimorf modification).

The evaluation of compacted mass encompasses several aspects, including flow properties, moisture content, compression ratio, and compressibility index. Additionally, tablet evaluation involves organoleptic assessment, size uniformity, hardness, friability, disintegration time, content uniformity, drug release rate determination, and dissolution testing.

Evaluation of compacted mass

The evaluation of mass compaction includes the characterization of flow properties, determination of moisture content, calculation of compression ratio, and assessment of compressibility index.

Flow properties analysis entails the utilization of a flow tester to measure the flow rate and determine the angle of repose. The flow rate is calculated by dividing the mass of the compacted material (100 grams) by the time it takes to pass through a funnel (g/second). An optimal flow rate is indicated when the time required for the flow of 100 grams is less than 10 seconds. The angle of repose is determined by measuring the angle formed between the slope of the flowing powder heap from the funnel and a flat surface. The angle of repose is interpreted as follows: $\alpha = 25° - 30°$ represents very easy flow, $\alpha = 30° - 38°$ signifies easy flow, and $\alpha > 38°$ denotes poor flow.

Moisture content determination involves the use of 10 grams of the compacted mass, which is placed in a moisture analyzer and heated until a stable reading is obtained. The moisture content of the compacted mass is considered acceptable when it falls within the range of 1–3%.

The compression ratio (**Cr**) is calculated by subtracting the volume of the compacted mass before compression from the volume after compression and then dividing it by the initial volume. It is considered satisfactory when the Cr value is less than 20%.

$$Cr = \frac{V0 - V500}{V0} \times 100\% \qquad \textbf{(Equation 2)}$$

In the equation, V0 represents the volume before compression (mL), and V500 corresponds to the volume after 500 taps (mL).

The compressibility percentage indicates the ability of the compacted mass to be compressed into tablet dosage forms. A lower compressibility percentage suggests excellent flow properties of the compacted mass. The determination of compressibility percentage begins with the measurement of bulk density, including bulk density before compression and bulk density after compression, using a tab densitometer. The bulk density before compression is determined by measuring the volume of a 50-gram sample poured into a 250 mL measuring glass without tapping and recording the volume. On the other hand, the bulk density after compression is measured using the same method as the bulk density before compression, but with 10 and 500 taps applied. The compressibility percentage of the powder is determined based on the measurements of bulk density before compression and bulk density after compression using the following equation:

$$\%C = \frac{Tapped\ Bulk\ Density - Bulk\ Density}{Tapped\ Bulk\ Density} \times 100 \qquad \textbf{(Equation 3)}$$

Interpretation of the results is as follows: %C = 5–15% indicates excellent flow, %C = 16–25% signifies good flow, and %C ≥ 26% represents poor flow.

Tablet evaluation

The observation of tablet physical properties includes organoleptic assessment of their shape, color, odor, and taste.

The testing of size uniformity involves measuring the thickness and diameter of 20 randomly selected tablets using a caliper. The tablet diameter should not exceed 3 times the thickness and should not be less than 1 and 1/3 times the tablet thickness.

Tablet hardness testing is conducted using a hardness tester. Twenty tablets are randomly selected and their hardness is measured based on the surface area of the tablet using a specified load expressed in kg/cm². The average hardness and standard deviation of the tablets are determined. Large tablets typically have a hardness ranging from 7–10 kg/cm², while small tablets have a hardness of around 4 kg/cm².

The friability (tendency to break or crumble) and fricsibility (tendency to abrade or rub off) testing are performed using a friability abrasion tester. A random selection of forty tablets is individually cleaned with a gentle brush and collectively weighed before the test (measurement a). Subsequently, the tablets are placed in the testing apparatus and subjected to 100 rotations. Following the test, the tablets are removed, cleaned once again, and the collective weight of the tablets is measured (measurement b). Tablets demonstrating desirable friability and fricsibility exhibit values below 1%, which are calculated utilizing the following equation:

$$f = \frac{a - b}{a} \times 100\% \qquad \textbf{(Equation 4)}$$

The disintegration time of the tablets is determined using a disintegration tester. Randomly selected tablets are individually placed in tubes containing 500 mL of 0.1 N HCl solution within a temperature range of 36 °C to 38 °C. The apparatus is activated, and the basket is set to move up and down at a frequency of 30 cycles per minute. The disintegration time is measured from the moment the apparatus is started until no residual tablet fragments are observed on the mesh. For uncoated tablets, the cumulative disintegration time of all six tablets should not exceed 15 minutes.

Uniformity of content testing is performed to ensure the consistency of the active ingredient content in each tablet. A total of thirty tablets, randomly selected, are analyzed for GMP content by measuring ten individual tablets using an ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 228 nm. If any tablet exhibits a GMP content outside the range of 85–115%, an additional twenty tablets are analyzed. Unless otherwise stated in the monograph, the content uniformity criteria are considered met if the GMP content falls within 85.0%–115.0% of the labeled value, with a relative standard deviation not exceeding 6.0%.

The quantification of GMP content in the tablets involves the grinding of ten tablets. Approximately 100 mg of the resulting powder is precisely weighed and then dissolved in methanol p.a. within a 50 mL volumetric flask then filtered. The GMP content within the tablets is subsequently analyzed utilizing an ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 228 nm. The GMP content is considered compliant if it falls within the range of 90% to 110% of the labeled value.

In vitro dissolution testing of the tablets is performed using a type II dissolution tester (paddle method). Six tablets are randomly selected and placed into 900 mL of pH 7.4 phosphate buffer solution at a temperature of 37.0 ± 0.5 °C, with a stirring speed of 50 rpm. Aliquots of 10 mL are withdrawn at specific time intervals of 2, 5, 8, 10, 15, 20, 30, 40, 50, and 60 minutes. Each withdrawal is replaced with an equal volume (10 mL) of fresh dissolution medium at the same temperature. The aliquots are filtered, and their concentrations are determined using an ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 228 nm.

Comparative *in vitro* dissolution tests

Comparative *in vitro* dissolution tests were conducted on 12 tablets each of GMP MP and Amaryl®. The dissolution studies were performed using 900 mL of three different dissolution media: KCl/HCl buffer pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8, all maintained at a temperature of 37.0 ± 0.5 °C. The USP type II dissolution apparatus with an agitation speed of 50 rpm was utilized. Samples of 10 mL were withdrawn at 10, 15, 30, 45, and 60 minutes and the contents of the active ingredient were analyzed using an ultraviolet-visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 228 nm.

The results of the comparative *in vitro* dissolution test were expressed in terms of the similarity factor (f2), calculated using the following equation:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right] \times 100\right\} \quad \textbf{(Equation 5)}$$

F2 represents the similarity factor, Rt denotes the cumulative drug amount dissolved at each sampling time from the reference product, and Tt represents the cumulative drug amount dissolved at each sampling time from the test product (Badan Pengawas Obat dan Makanan 2022b; Satrialdi et al. 2011). A product is considered equivalent or exhibits a similar dissolution profile to the innovator product when the similarity factor falls within the range of 50 to 100.

Results and discussion

The characterization and performance evaluation of modified polymorphs of GMP

The characterization and performance evaluation of the modified polymorphs of GMP was carried out through the transformation of GMP form I into form II using the techniques of neat grinding, solvent drop grinding, and solvent evaporation. The resulting modified polymorphs were subjected to characterization techniques including powder X-Ray diffraction (PXRD) for assessing diffraction patterns, differential scanning calorimetry (DSC) for analyzing thermal profiles, and scanning electron microscopy (SEM) for examining crystal habits. These characterization results were compared with existing literature data to confirm the polymorphic form of GMP. It is noteworthy that GMP exhibits two distinct polymorphic forms, namely form I and form II, with form II demonstrating higher solubility in water compared to form I (Bonfilio et al. 2011).

Fig. 1 presents the PXRD diffractograms of GMP Form I and Form II obtained from the literature (Bonfilio et al. 2011).

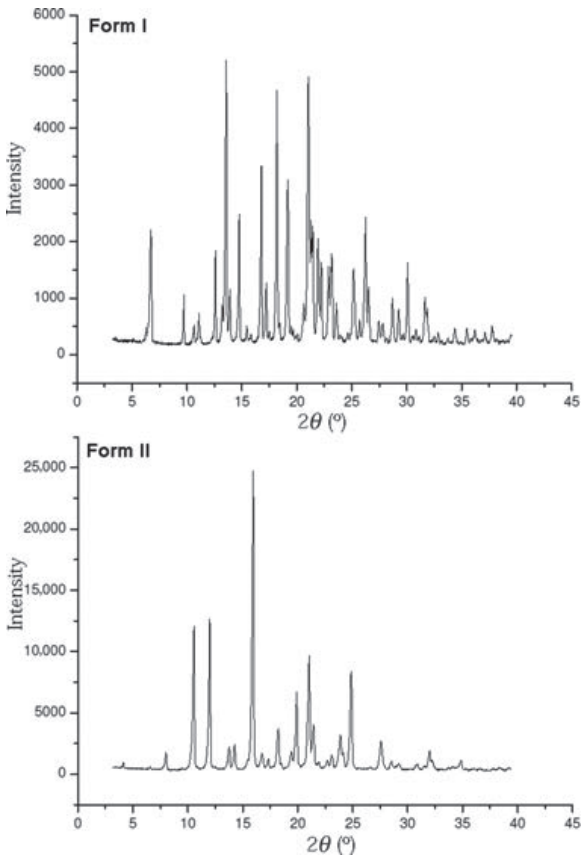

Figure 1. PXRD Difractogram of Forms I and II of GMP (Bonfilio et al. 2011).

Fig. 2 illustrates that in this study, GMP exists in form I (Bonfilio et al. 2011). The X-ray diffraction (XRD) patterns of the modified polymorphs of GMP obtained through neat grinding, solvent drop grinding, and solvent evaporation techniques are relatively similar to those of the non-modified GMP. This can be identified by the presence of five highest intensity peaks that exhibit comparable 2θ values, as indicated in Table 2.

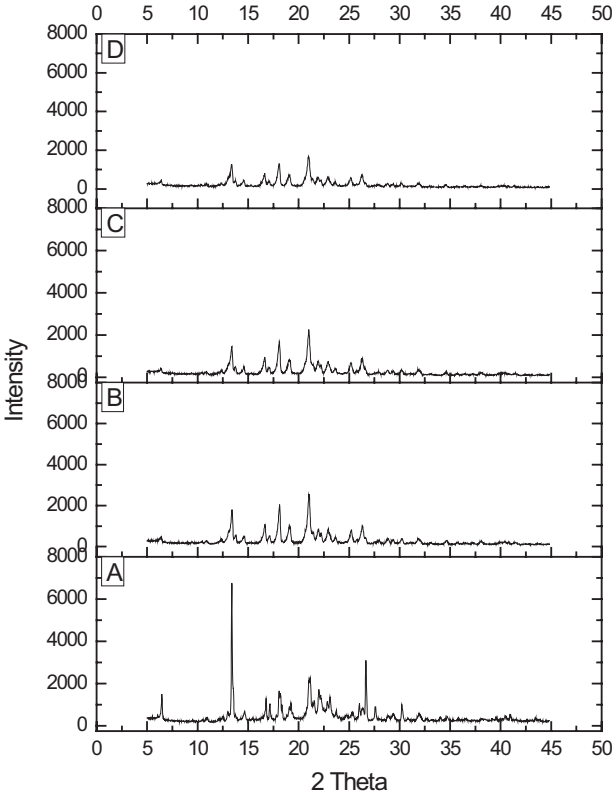

Figure 2. PXRD Difractogram of Non-modified GMP [**A**]; Modified GMP with Neat Grinding GMP [**B**]; Solvent Drop Grinding [**C**]; Solvent Evaporation [**D**].

Table 2. Data of Five Highest Intensity Peaks with The Most Prominent Interference In The PXRD Diffractogram of GMP.

GMP samples	2 theta (°)				
	6,36–6,46	13,38–13,40	18,08–18,20	20,98–21,14	26,28–26,66
Non modified	1498	6757	1544	2285	3102
Neat Grinding	437	1806	2052	2560	1024
Solvent Drop Grinding	493	1467	1697	2256	912
Solvent Evaporation	454	1267	1310	1689	734

The modified polymorphs of GMP obtained through all three techniques did not undergo polymorphic transformation but rather exhibited a decrease in peak intensity interference. This phenomenon is referred to as amorphization (Brittain 2011, 2012; Giron 2001).

Fig. 3 depicts the DSC thermograms of GMP form I and form II. Both forms exhibit endothermic peaks above 200 °C, corresponding to their respective melting points. However, form II displays an additional exothermic peak around 140 °C, indicating a polymorphic transition from

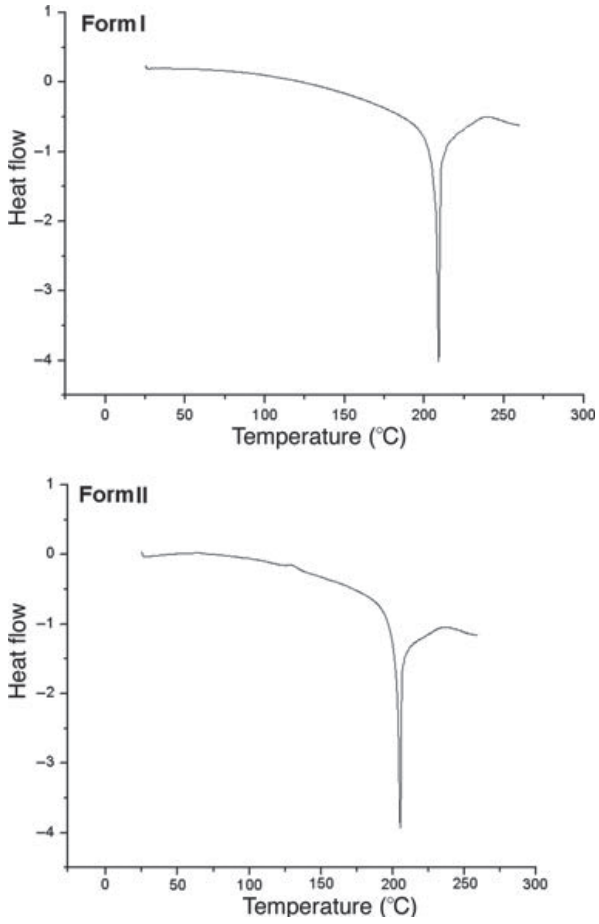

Figure 3. DSC Termogram of Forms I and II of GMP (Bonfilio et al. 2011).

form II to form I (Bonfilio et al. 2011). This indicates that GMP form II is metastable, whereas GMP form I is physically stable (Endo et al. 2003).

Fig. 4 illustrates that in this study, GMP exists in form I. The thermogram of DSC non-modified GMP shows an endothermic peak at 209.7 °C without an additional exothermic peak around 140 °C. The melting point of GMP in this study is concomitant with the literature (Bonfilio et al. 2011). The endothermic peak of a modified polymorph of GMP obtained through a neat grinding technique and solvent drop grinding is relatively similar to non-modified GMP. It is shown around 210.2 °C and 210.4 °C. However, the modified polymorph of GMP obtained through solvent evaporation exhibited a decrease in the endothermic peak at 203.3 °C. This phenomenon is referred to as amorphization. A solid exhibiting a high degree of crystallinity is typically characterized by a sharp and prominent endothermic peak in the DSC thermogram, indicating a high melting point. Conversely, an amorphous solid tends to display a lower melting point, often depicted by a gradual or less distinct endothermic peak in the DSC thermogram (Lee 2014).

The crystal habit of GMP form I, as depicted in Fig. 5, appears irregular and forms agglomerates or clusters. In contrast, GMP form II exhibits a morphology resembling rods or needles.

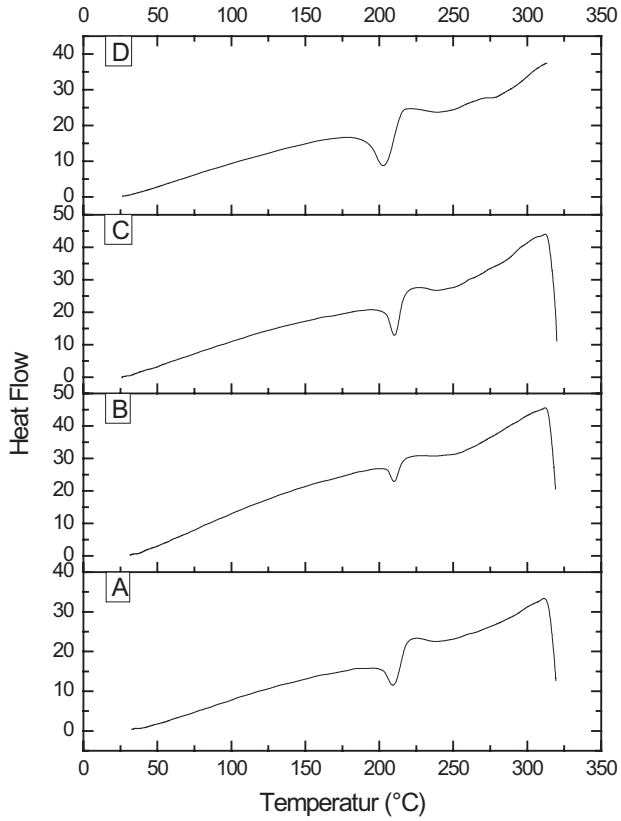

Figure 4. Termogram DSC of Non-modified GMP [**A**]; Modified GMP with Neat Grinding GMP [**B**]; Solvent Drop Grinding [**C**]; Solvent Evaporation [**D**]

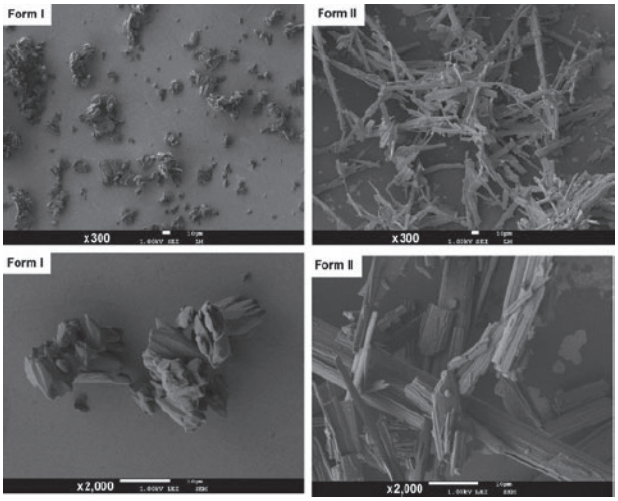

Figure 5. SEM morphology of forms I and II of GMP (Bonfilio et al. 2011).

Fig. 6 illustrates that both the non-modified GMP and the modified polymorphs of GMP exhibit form I crystal habits, characterized by irregular agglomerates that interconnect due to their highly hydrophobic nature. However, in the morphology of GMP obtained through the solvent evaporation technique, a reduction in particle size is observed, which can have an impact on the solubility and dissolution rate of the compound.

Based on the comprehensive characterization using PXRD, DSC, and SEM techniques, it was observed

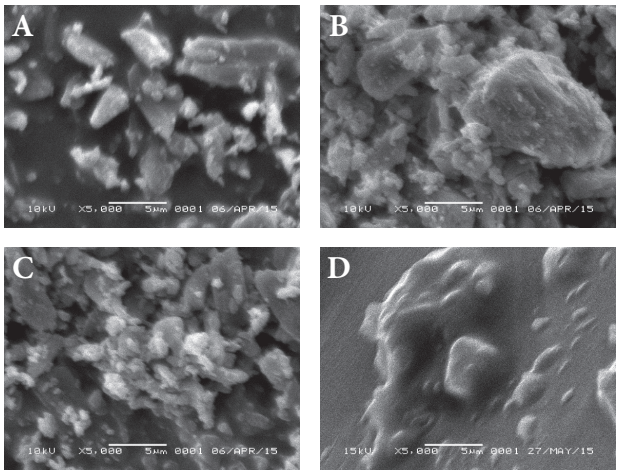

Figure 6. SEM morphology of non modified GMP [**A**]; modified GMP with neat grinding GMP [**B**]; solvent drop grinding [**C**]; solvent evaporation [**D**].

that the modified polymorphs of GMP obtained through the three different methods did not undergo a polymorphic transformation from form I to form II, but rather exhibited amorphization. Notably, the solvent evaporation technique showed the most prominent amorphous characteristics. These findings highlight the absence of polymorphic changes in GMP and the significant impact of amorphization on its physicochemical properties.

The subsequent performance evaluation aimed to identify the most effective technique for polymorph modification of GMP, specifically in terms of its physical and chemical performance. This evaluation encompassed various parameters, including flow properties, compressibility index, solubility, and dissolution rate, which were compared to those of the non-modified GMP. Notably, the results presented in Table 3 indicate that the modified polymorphs of GMP obtained through the solvent evaporation technique exhibited the most favorable physicochemical performance. The solvent evaporation technique involved the dissolution of GMP at the molecular level, followed by recrystallization, leading to the amorphization of the compound (Giron 2001). This amorphization process had significant implications for the flow properties, compressibility index, particle size, and ultimately the mechanical properties, solubility, and dissolution rate of GMP (Censi and Di Martino 2015). Overall, the solvent evaporation technique demonstrated superior performance in enhancing the physicochemical properties of GMP for tablet formulation.

Despite the absence of polymorphic transformation of GMP from form I to form II, the performance evaluation demonstrated enhanced physical and chemical properties, encompassing flow properties, compresibility index, solubility, and dissolution rate, particularly in the modified polymorphs of GMP obtained through the solvent evaporation technique. These findings serve as a foundation for the formulation of GMP into tablet dosage forms.

Table 3. The Results of The Performance Evaluation of Modified Polymorphs of GMP.

GMP samples	Flow Properties		Compressibility Index (%)	Solubility (mg/mL)	Dissolution Rate at 60 min (%)
	Flow rate (gram/second)	Angle of repose (°)			
Non-Modified	-	-	28.88 ± 1.76	0.0050 ± 0.0012	25.46 ± 0.103
Neat grinding	3.34 ± 0.51	28.37 ± 1.53	23.68 ± 1.82	0.0059 ± 0.0027	38.10 ± 0.135
Solvent drop grinding	3.10 ± 0.75	33.82 ± 1.67	26.24 ± 1.38	0.0056 ± 0.0025	34.43 ± 0.127
Solvent evaporation	1.20 ± 0.22	25.42 ± 1.16	14.55 ± 1.55	0.0096 ± 0.0032	56.93 ± 0.148

Information: (-) = unable flow.

Formulation and evaluation of modified polymorphs of GMP tablets

The formulation of these tablets employed simple excipients, including amprotab as a disintegrant, avicel PH 102 as a filler, magnesium stearate as a lubricant, and talc as a glidant. The objective was to compare the tablet characteristics of GMP-modified polymorphs against tablets containing non-modified GMP, through the evaluation of compaction properties and final product attributes.

Tables 4 and 5 present the results of the compaction evaluation and the assessment of the finished product (tablet) characteristics for both non-modified and modified polymorphs of GMP. The compaction evaluation comprises assessments of flow properties, moisture content, compression ratio, and compressibility index. The tablet evaluation encompasses organoleptic properties, size uniformity, hardness, friability, fricsibility, disintegration time, content uniformity, assay, and dissolution rate.

Table 4. The Results of The Compaction Evaluation.

Parameter	Formula		Criteria
	FI	FII	
Flow properties:			
Flow rate (gram/second)	15.13 ± 0.15	8.28 ± 0.18	≤ 10 gram/second
Angle of repose (°)	38.20 ± 0.37	23.07 ± 0.21	25–30°: Very easy flow 30–38°: Easy flow > 38°: Poor flow
Moisture content (%)	1.7 ± 0.59	1.5 ± 0.38	1–2
Compression ratio (%)	21.83 ± 0.72	18.75 ± 0.46	≤ 20%
Compressibility index (%)	29.10 ± 0.39	22.72 ± 0.27	5–15%: Very good flow 16–25%: Good flow 26%: Poor flow

Based on the evaluation of tablet bulk properties (Table 4), the tablets containing GMP with modified polymorphs meet the criteria for direct compression due to their favorable flow properties and compressibility compared to the tablets containing non-modified GMP. This can be attributed to the amorphization process that occurs during the modification of GMP polymorphs using the solvent evaporation technique, leading to the transformation of the GMP solid into a fine and lightweight form.

The evaluation results of the tablets (Table 5) containing modified polymorphic GMP and non-modified GMP met the specified criteria, although the non-modified GMP tablets exhibited lower performance, particularly in terms of content uniformity and drug content. This can be attributed to the fine and agglomerated nature of the non-modified GMP raw material, resulting in challenges

Table 5. The Results of Tablet Evaluation.

Parameter	Formula		Criteria
	I	II	
Organoleptic	The tablets are round and flat, white in color, and odorless	The tablets are round and flat, white in color, and odorless	The tablets are round and flat, white in color, and odorless
Size Uniformity	(MC)	(MC)	None of the tablet diameters exceed three times the thickness, and none of the tablets have a diameter less than 1 1/3 times the thickness.
Diameter (cm)	0.795 ± 0.005	0.790 ± 0.003	
Thickness (cm)	0.450 ± 0.076	0.495 ± 0.022	
Hardness (kg/cm^2)	2.35 ± 0.91	4.25 ± 0.55	4–6 kg/cm^2
Friability (%)	0.75 ± 0.007	0.65 ± 0.005	< 1%
Fricsibility (%)	0.606 ± 0.003	0.404 ± 0.002	< 1%
Disintegration time (minutes)	5.145 ± 0.06	5.140 ± 0.04	< 10 min
Content Uniformity (%)	93.901 ± 3.927 (RSD = 4.182)	99.139 ± 2.072 (RSD = 2.09)	85.0%–115.0% (RSD ≤ 6)
Drug content (%)	92.975 ± 0.256	100.96 ± 0.314	90%–110%

Information: MC = meet the criteria.

in achieving homogeneity during the blending process with other excipients (Darusman et al. 2021).

Fig. 7 illustrates the dissolution profiles of the modified polymorphic GMP tablets, demonstrating a significant increase in the percentage of drug dissolved compared to the non-modified GMP tablets. The dissolution rate at 60 minutes for the modified polymorphic GMP tablets exhibited a substantial enhancement of 98.82 ± 0.86% compared to the non-modified GMP tablets, which displayed a dissolution rate of 56.35 ± 0.43%.

GMP exists in two polymorphic forms, namely form I and form II, with form II exhibiting higher solubility in water (Bonfilio et al. 2011). The polymorphic form of an active pharmaceutical ingredient (API) demonstrates distinct physicochemical properties such as density, solubility, optical properties, and mechanical behavior. These properties influence the mechanical properties or manufacturability, as well as the dissolution rate and bioavailability of the API (Zhang et al. 2013).

FII refers to a tablet formulation containing GMP with modified polymorphs obtained through the solvent evaporation technique. In the solvent evaporation process, GMP powder undergoes dissolution at the molecular level, followed by recrystallization at room temperature. This process leads to amorphization, which subsequently impacts the solubility and dissolution rate of the drug (Giron 2001; Gozali et al. 2014).

Comparative *in vitro* dissolution tests

Comparative *in vitro* dissolution testing was conducted on GMP modified polymorph tablets as a preliminary assessment for bioequivalence, comparing them to the reference innovator drug Amaryl® at a 4 mg dose. The dissolution testing was performed at three different pH levels (1.2, 4.5, and 6.8) to simulate gastrointestinal conditions. The similarity between the dissolution profiles of the test and reference products was evaluated using the similarity factor (f2), and the obtained values fell within the acceptable range of 50–100 (Badan Pengawas Obat dan Makanan 2022b).

The comparative *in vitro* dissolution profiles of the GMP-modified polymorph tablets and Amaryl® in different dissolution media were assessed through Figs 8–10. The f2 values for the KCl/HCl buffer pH 1.2 dissolution test did not meet the acceptance criteria of 50–100, with a value of 45.15 ± 0.23. This deviation can be attributed to the %CV exceeding 10% for each time point. However, for the dissolution tests conducted in acetate buffer pH 4.5 and phosphate buffer pH 6.8, the f2 values were within the acceptable range of 50–100, specifically 60.15 ± 0.27 and 88 ± 0.35, respectively. Consequently, it can be concluded that the GMP-modified polymorph tablets are dissimilar to the innovator product, Amaryl®. The requirements for comparative *in vitro* dissolution testing mandate that the test and reference products are considered similar if their f2 values fall within the range of 50–100 for the three pH conditions (pH 6.8, 4.5, and 1.2).

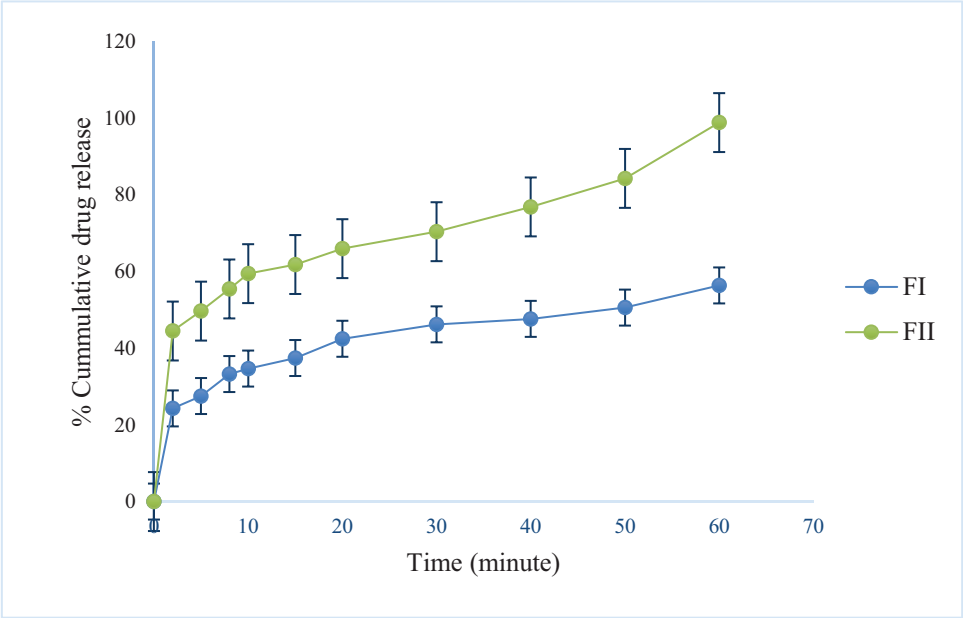

Figure 7. Dissolution profile comparison curve of non-modified GMP tablet [FI] and GMP-modified tablet polymorph (FII).

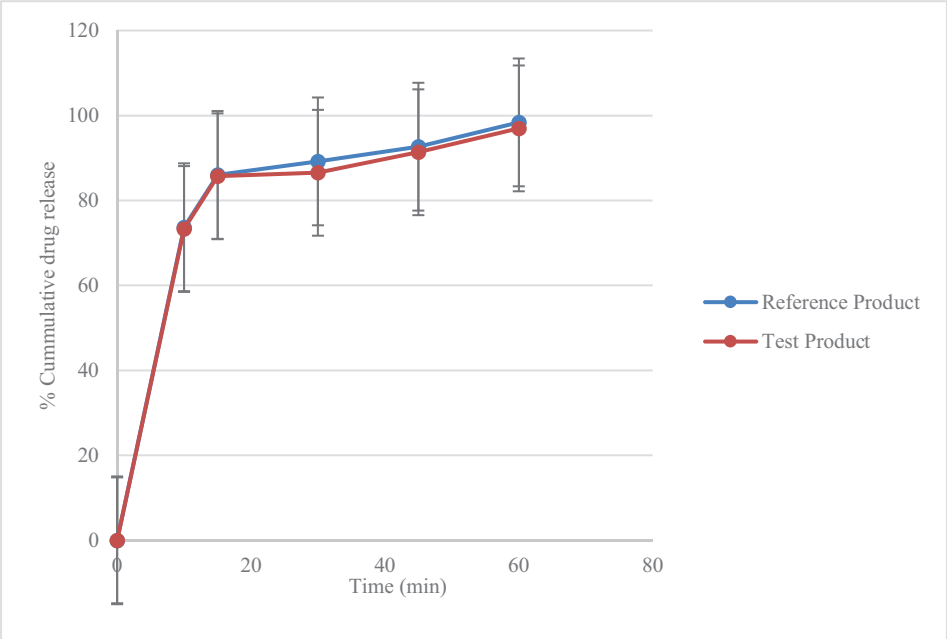

Figure 8. Dissolution profiles of the test and reference products in phosphate buffer pH 6.8.

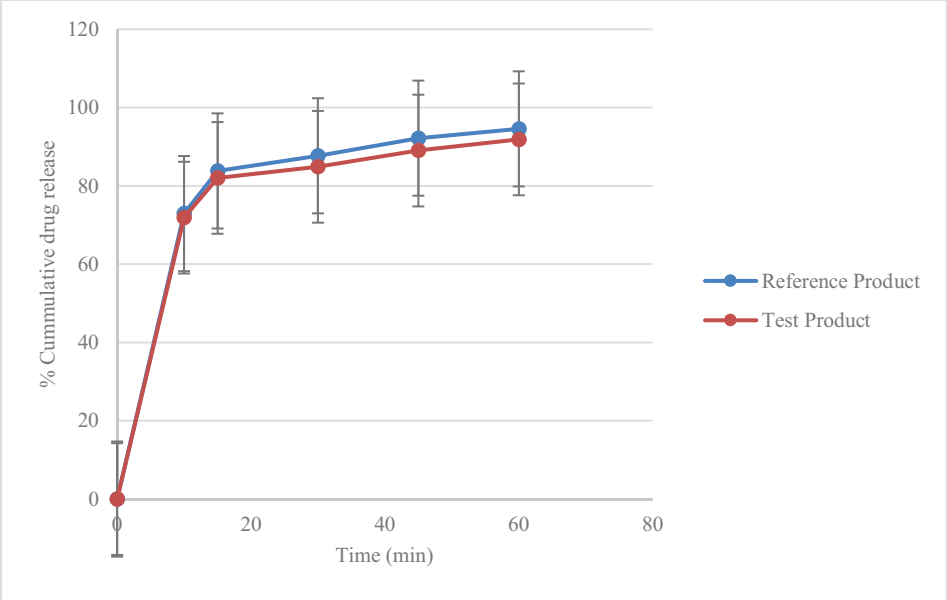

Figure 9. Dissolution profiles of the test and reference products in citrate buffer pH 4.5.

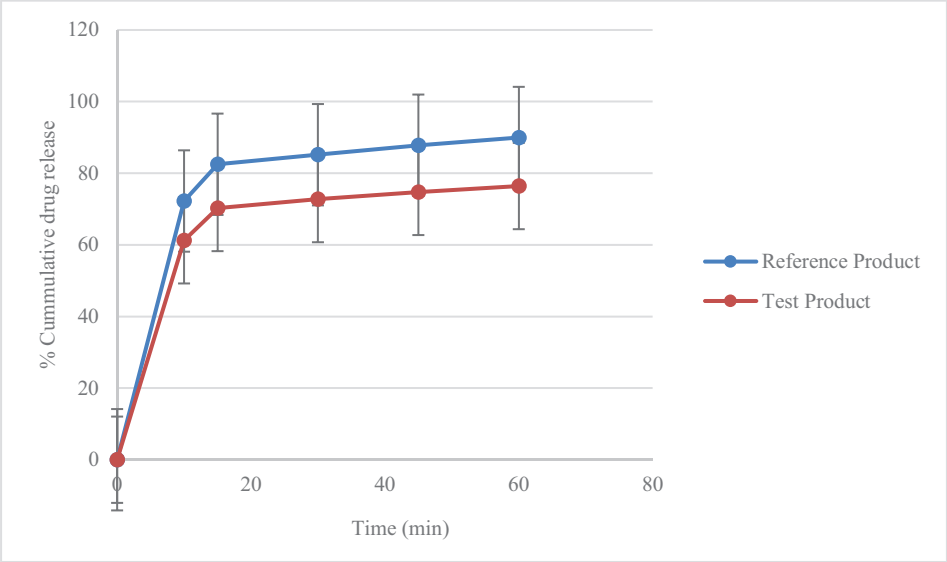

Figure 10. Dissolution profiles of the test and reference products in KCl/HCl buffer pH 1.2.

Considering GMP's pKa value of 6.2, it is established that GMP undergoes increased ionization at pH levels above its pKa (Darusman and Rahayu 2017). This enhanced ionization renders GMP more polar in nature, thereby leading to improved solubility and dissolution rate (Darusman and Siti M 2017). The modification of GMP's polymorphs aimed to enhance its solubility and dissolution rate without undergoing a transformation from form I to form II; rather, the amorphous state was achieved (Giron 2001). This elucidates the dissimilarity observed in the f2 value at pH 1.2.

Conclusion

The modified polymorph of GMP obtained through neat grinding, solvent drop grinding, and solvent evaporation techniques did not exhibit a polymorphic transformation from form I to form II, but rather experienced amorphization, particularly with the solvent evaporation technique. Tablets containing the modified polymorph of GMP achieved through solvent evaporation showed an enhanced *in vitro* dissolution profile compared to non-modified GMP tablets. The results of the comparative *in vitro* dissolution testing indicated that the modified polymorph GMP tablets were not similar to the innovator product, Amaryl®.

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