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Nanocrystallization of Griseofulvin Prior to Its Tablet Formulation Improves the Drug Delivery

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ABSTRACT

Background: Griseofulvin belongs to Class II in the Biopharmaceutics Classification System. This study aimed at improving the delivery of this antifungal agent by nanocrystallizing the drug powder before the tablet formulation.

Methods: Two forms of griseofulvin nanocrystals (GRF3 and GRF2) were prepared with and without the inclusion of polysorbate 80 respectively. The two forms of the nanocrystals and the unprocessed drug (GRF1) were separately used to formulate griseofulvin tablets. Each form of the drug was formulated using two different binder concentrations (3% and 6% $^{w}/_{w}$ acacia gum) employing the wet granulation method. Physical and release properties of the tablets were determined using the compendial and the non-compendial methods.

Results: The mean weight of the formulated tablets ranged from 0.31 – 0.37 g. Formulation GRF2 with 6% $^{w}/_{w}$ binder concentration had the highest crushing strength of 8 kgF, GRF1 with 6% $^{w}/_{w}$ binder concentration had the lowest friability of 0.15% while GRF3 with 3% $^{w}/_{w}$ binder concentration had the shortest disintegration time of 9.25 min. There was no significant difference between the percent drug release from GRF3 tablets containing 3% $^{w}/_{w}$ binder concentration and those containing 6% $^{w}/_{w}$ concentration (cumulative drug release being 83% and 80% in 60 minutes).

Conclusion: Nanocrystallization of griseofulvin modulated with the inclusion of Polysorbate 80 enhances the delivery of the drug but higher binder concentration is required to ensure good tablet strength.

Keywords: Drug delivery, griseofulvin, nanocrystallization.

1. INTRODUCTION

Poor aqueous solubility, its associated low oral bioavailability and general drug delivery problems are becoming a major challenge [1]. Griseofulvin is classified as a Class II drug based on the Biopharmaceutics Classification System (BCS), and its absorption is inhibited by the dissolution rate-limiting profile [2]. There are different technologies available for solving the problem of poor aqueous solubility and dissolution of class II drugs. These include physicochemical techniques such as chemical modification, salt formation, amorphization and particle size reduction. The issue can also be addressed using different formulation development strategies such as solid dispersion, molecular complexation and lipid-based formulations [3]. Nanocrystal formation is a pharmaceutical technology that is also used to improve the bioavailability of poorly soluble drugs [4, 5]. It involves generating crystals of particle size about 100 nm. The minimized size causes an increase in the surface area, increase in solubility and also a proportionate increase in the bioavailability of poorly soluble drugs [6]. Nanocrystal formation can be through a top-down or bottom-up approach [7]. In the top-down processes, the formulation of nanoparticles starts from bulk materials, and it uses mechanical forces to reduce particle size. Milling and high-pressure homogenization are under the top-down category. In contrast, bottom-up processes involve crystal formation from solutions or liquid systems. Herein, molecular or atomic levels are the basic units that create the nanoparticles. Antisolvent precipitation and supercritical fluid techniques are under the bottom-up category [8]. Previous work of Olorunsola *et al*. [2] reported the generation of griseofulvin nanocrystals by antisolvent

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precipitation with and without Polysorbate 80. The nanocrystallization without the inclusion of Polysorbate 80 produced nanocrystals with Z-average of 77.8 nm attaining a 1.72-fold increase in aqueous solubility while nanocrystallization with the inclusion of the surfactant produced nanocrystals with Z-average of 44.70 nm attaining a 4.14-fold increase in aqueous solubility. In the work of Femi-Oyewo and Spring [9], it was reported that crystal fabrication facilitates drug processability and improves the product performance. Hence, the present work was designed to enhance the delivery of griseofulvin by formulating tablets using nanocrystals generated without polysorbate 80 and also using those generated with the surfactant. Surface active agents are known to be characterized by modulation of interfacial properties [10 - 12]. This character confers on them the ability to influence drug delivery.

2. MATERIALS AND METHODS

2.1. Materials

The materials used include dimethylformamide (Guangdong Guanghua Sci-Tech Co. Ltd, China), distilled water prepared in Pharmaceutics Laboratory of University of Uyo, Polysorbate 80 (BDH Chemicals, England), griseofulvin powder (Thosco, Thode and Scobel, Hamburg, Germany), acacia gum (BDH Chemicals, England), starch (BDH Chemicals, England), lactose (BDH Chemicals, England), talc (BDH Chemicals, England) and magnesium stearate (BDH Chemicals, England).

2.2 Methods

2.2.1. Preparation of Nanocrystals

Griseofulvin nanocrystallization processes with and without inclusion of a surfactant were carried out using the antisolvent precipitation technique described in the previous work of Olorunsola *et al*. [2]. To prepare nanocrystals without the use of a surfactant, a 10 g quantity of griseofulvin powder was weighed and transferred into a 250 mL capacity beaker followed by the addition of 100 mL dimethylformamide. The beaker was placed on a magnetic stirrer; and homogenization of the drug and the solvent was done at 500 rpm for 45 min. The homogenized product was transferred into a bigger container followed by the addition of 500 mL water for precipitation. The entire content was transferred into a separating flask and the system was allowed to stand for an hour to allow proper separation. The precipitate was gently separated from the supernatant, air-dried for 3 h and then dried in an oven at 60 ^{o}C for 8 h to form griseofulvin crystals. The process was repeated one more time so as to get adequate quantity of the crystals. For the nanocrystals preparation using a surfactant, the entire process described above was repeated, the only difference being the addition of 5 g Polysorbate 80 to the 10 g griseofulvin before adding the solvent [2, 13].

2.2.2. Formulation of Griseofulvin Granules

Acacia gum at concentrations of 3% $^{w}/_{w}$ and 6% $^{w}/_{w}$ was used as the binder for the preparation of 6 batches of griseofulvin granules, the batch size being 50 tablets (Table 1). Pure drug, nanocrystals generated without a surfactant and nanocrystals generated with a surfactant were used for the granule formulation. The granules were prepared by wet granulation method based on the Tablet Formula in Table 1 such that 360 mg tablet would contain 250 mg griseofulvin, varying concentration of the binder and then other excipients. The required quantities of the ingredients (griseofulvin, starch and lactose) were weighed accurately and mixed thoroughly in a mortar. Granulation was done for each batch of granules by adding the required amount of acacia gum as binder solution. The wet mass was passed through a 2 mm stainless steel sieve and the granules were dried in the conventional air oven at 60 ℃ for 2 h. The dried granules were then passed through a 1 mm stainless steel sieve and stored for evaluations [14].

Table 1: Formula of griseofulvin tablets

	Batches					
Ingredients	GRF1a	GRF1b	GRF2a	GRF2b	GRF3a	GRF3b
Griseofulvin (%)	69.4	69.4	69.4	69.4	69.4	69.4
Starch (%)	10.0	10.0	10.0	10.0	10.0	10.0
Acacia (%)	3.0	6.0	3.0	6.0	3.0	6.0
Lactose (%)	15.6	12.6	15.6	12.6	15.6	12.6
Talc (%)	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5

GRF1a – Formulation of pure griseofulvin drug with 3% $^{w}/_{w}$ acacia gum
GRF1b – Formulation of pure griseofulvin drug with 6% $^{w}/_{w}$ acacia gum
GRF2a – Formulation of griseofulvin nanocrystals with 3% $^{w}/_{w}$ acacia gum
GRF2b – Formulation of griseofulvin nanocrystals with 6% $^{w}/_{w}$ acacia gum
GRF3a – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 3% $^{w}/_{w}$ acacia gum
GRF3b – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 6% $^{w}/_{w}$ acacia gum

2.2.3 Characterization of Granules

2.2.3.1 Angle of repose

A 10 g sample was taken from granules using an electronic weighing balance. It was poured inside a funnel of orifice diameter 0.75 cm clamped to a retort stand at a height of 10 cm from the table surface. The sample was allowed to flow freely and the angle of repose, Θ was calculated using Equation 1. The determination was done three times.

$\Theta = Tan^{-1}\left(\frac{2h}{D}\right)$ ..... (1)

Where h = height of heap and D is the diameter.

2.2.3.2. Bulk and tapped densities

A 10 g sample of granules was taken using an electronic weighing balance and carefully poured into a dried 50 mL measuring cylinder. The volume occupied by the granules was taken as the bulk volume. The cylinder containing the granules was mechanically tapped 100 times on a flat surface after which the tapped volume was taken. The bulk density (BD) and tapped density (TD) were calculated as the ratio of the mass to the corresponding volume. This determination was done three times for each batch and the mean and standard error of mean were calculated.

2.2.3.3. Hausner's ratio and Carr's index

The Hausner's ratio (HR) and Carr's index (CI) were calculated using the equations as provided by Hausner and Carr respectively [15].

$HR = \frac{TD}{BD}$ ..... (2)

$CI = \frac{TD-BD}{TD}$ X 100% ..... (3)

2.2.4 Preparation of Tablets

The granules were mixed properly to ensure an even distribution of the fine particles with the coarse ones. An amount of magnesium stearate equivalent to 0.5% of the granules weight and an amount of talc equivalent to 1.5% of the granules weight were added and gently mixed with the granules. The granules were compressed into tablets at a constant compression force of 15 kN using a tableting press fitted with 8.00 mm convex faced punches (Cadmach Ahmedabad, India).

2.2.5 Evaluation of Tablets Quality

2.2.5.1 Uniformity of weight

Twenty tablets were selected randomly from each batch and weighed individually using the analytical balance (OHAUS, United States). The average weight was determined as total weight divided by 20 and the standard error of mean was calculated for each batch.

2.2.5.2. Crushing strength

The crushing strength of tablets was determined using tablet hardness tester (Mosanto hardness tester). Determination was done for five tablets randomly selected from each batch to get the mean crushing strength. The standard error of mean was also calculated.

2.2.5.3 Friability

Ten tablets from each batch were obtained, dusted, weighed and placed in drum of a Roche friabilator. The tablets were tumbled for 4 minutes at a speed of 25 revolutions per minute. The tablets were then removed, dusted and weighed again. The friability of the tablets was expressed as a percent loss in weight.

2.2.5.4 Disintegration time

The disintegration time of the tablets was determined using disintegration tester. Distilled water thermostatically maintained at 37 ºC was used as the disintegration medium. One tablet was placed in each of the five tubes and the disintegration machine was set to operate at thirty cycles per minute. The time for each of the five tablets to completely disintegrate and pass through the mesh gauze disc was determined using a stop clock (Michael Kors, Germany). The mean was taken as the disintegration time of the tablets.

2.2.5.5 In vitro drug release study

The Beer-Lambert's plot for griseofulvin was first constructed using dimethylformamide in which the drug is soluble. Exactly 0.01 g of pure drug (griseofulvin), was added to 10 mL of dimethylformamide. Aliquots of 1

µg/mL, 5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL and 25 µg/mL were made by serial dilution method and their absorbance were read in a UV-spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai instrument Co., China) at a wavelength of 273 nm. Graph of absorbance versus concentration was plotted to obtain the calibration curve of griseofulvin in dimethylformamide. Drug release study was carried out using the United States Pharmacopoeia (USP) basket method. The dissolution study was carried out with RCZ-6C3 dissolution apparatus at 100 rpm in 900 mL dissolution medium of 0.1 N HCl maintained at 37 ± 0.5 ^{0}C. Aliquots (10 mL) were withdrawn at times 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes and 60 minutes, and replaced with an equivalent 10 mL of fresh dissolution medium maintained at the same temperature. The samples were filtered through a Whatman filter paper no.2 and then assayed using a UV-spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai Instrument Co., China) at a wavelength of 273 nm. The cumulative percentage drug release was calculated and a graph of cumulative percentage drug release against time was plotted.

2.3. Statistical Analysis

Data were analyzed by applying one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test using GraphPad Instat-3 software.

3. RESULTS AND DISCUSSION

3.1. Flow properties of granules

The flow properties of the granules are shown in Table 2.

Table 2: Flow properties o granules

Batches	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)
GRF1a	22.57 ± 0. 89	0.56 ± 0.02	0.63 ± 0.01	1.13	11
GRF1b	22.26 ± 1.32	0.59 ± 0.01	0.71 ± 0.02	1.20	17
GRF2a	22.53 ± 2.11	0.45 ± 0.01	0.50 ± 0.00	1.11	10
GRF2b	22.48 ±1.38	0.50 ± 0.02	0.63 ± 0.02	1.26	21
GRF3a	27.02 ± 2.32	0.56 ± 0.02	0.63 ± 0.01	1.13	11
GRF3b	31.43 ± 1.31	0.40 ± 0.01	0.59 ± 0.02	1.48	32

GRF1a – Formulation of pure griseofulvin drug with 3% $^w/_w$ acacia gum
GRF1b – Formulation of pure griseofulvin drug with 6% $^w/_w$ acacia gum
GRF2a – Formulation of griseofulvin nanocrystals with 3% $^w/_w$ acacia gum
GRF2b – Formulation of griseofulvin nanocrystals with 6% $^w/_w$ acacia gum
GRF3a – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 3% $^w/_w$ acacia gum
GRF3b – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 6% $^w/_w$ acacia gum

All the batches, with the exception of GRF3b, have angle of repose less than 30°. Since angle of repose not above 30° signifies a good flow [16], all the batches apart from GRF3b can be considered to have good flow. Angle of repose is usually used as an indirect method of qualifying granule flowability because of its dependence on and its relationship with interparticle cohesion. Different angles of repose could be obtained for the same powder owing to difference in handling prior to measurement. Hence, angle of repose is not an absolute measure of granule flow. The Hausner's ratio and Carr's index for all the batches vary the same way since both parameters are based on the bulk and tapped densities. The two indices are measures of the propensity of the granule to be compressed, and are used for predicting flow. They are indirect measures of bulk density, size and shape, moisture content, and cohesiveness of materials as all these parameters can influence compressibility. Hausner's ratio below 1.19 and Carr's index below 16% correspond to good flow; Hausner's ratio of 1.19-1.25 and Carr's index of 16-20% correspond to a fair flow; Hausner's ratio of 1.26-1.34 and Carr's index of 21-25% correspond to a passable flow while Hausner's ratio above 1.34 and Carr's index above 25% correspond to a poor flow [16]. Hence, GRF1a, GRF2a and GRF3a are characterized by good flow while the other three are not.

3.2. Physical properties of tablets

The physical properties of the formulated tablets are shown in Table 3. The mean weight ranged from 0.34 - 0.36 g for the pure drug (griseofulvin), 0.31- 0.37 g for nanocrystals generated without surfactant and 0.34 - 0.36 g for nanocrystals generated with surfactant (polysorbate 80). The hardness of formulated tablets ranged from 5.00 – 7.50 kgF for pure drug (griseofulvin), 5.00 – 8.00 kgF for nanocrystals generated without surfactant (polysorbate 80), and 1.50 – 2.00 kgF for nanocrystals generated with surfactant (Polysorbate 80). The friability reduced from 0.45 to 0.15% on increasing the binder concentration from 3 to 6% for pure drug; reduced from 0.31 to 0.16% for nanocrystals generated without surfactant (polysorbate 80) and from 0.72 to 0.59% for nanocrystals generated with surfactant. Disintegration time was in the order GRF3 < GRF2 < GRF1; and higher concentration of the binder produced tablets with longer disintegration time in all the cases.

Table 3: Physical properties of tablets

Batch	Mean Weight (g)	Hardness (kgF)	Friability (%)	Disintegration Time (min)
GRF1a	0.34±0.00	5.00±1.00	0.45	18.34±0.49
GRF1b	0.36±0.01	7.50±1.00	0.15	20.40±0.73
GRF2a	0.31±0.03	5.00±1.90	0.31	12.45±0.00
GRF2b	0.37±0.00	8.00±1.50	0.16	16.44±0.13
GRF3a	0.34±0.02	1.50±1.00	0.72	09.25±0.83
GRF3b	0.36±0.01	2.00±1.00	0.59	12.51±0.58

GRF1a – Formulation of pure griseofulvin drug with 3% $^{w}/_{w}$ acacia gum
GRF1b – Formulation of pure griseofulvin drug with 6% $^{w}/_{w}$ acacia gum
GRF2a – Formulation of griseofulvin nanocrystals with 3% $^{w}/_{w}$ acacia gum
GRF2b – Formulation of griseofulvin nanocrystals with 6% $^{w}/_{w}$ acacia gum
GRF3a – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 3% $^{w}/_{w}$ acacia gum
GRF3b – Formulation of griseofulvin nanocrystals/Polysorbate 80 with 6% $^{w}/_{w}$ acacia gum

Uniformity of weight is a pointer to good manufacturing practices and uniformity of the amount of active pharmaceutical ingredient (API) in the formulation. Tablets containing GRF1 and GRF3 had better weight uniformity compared to GRF2. The normal range of crushing strength is from 4-7 kgf. The study revealed that Batches GRF1a, GRF1b and GRF 2a passed the test for crushing strength while GRF2b, GRF3a and GRF3b failed the test. While Batch GRF2b is extremely strong due to the high concentration of the binder, Batches GRF3a and GRF3b are extremely weak because of the inclusion of surfactant [17]. This implies that nanocrystals produced with the inclusion of polysorbate 80 is characterized by low crushing strength. A friability of less than 1% is expected for a tablet to pass friability test. All the batches passed the friability test. Hence, the tablets are not susceptible to attrition [18].

3.3. Drug release properties of tablets

The performance of a drug is primarily influenced by the tablet disintegration and subsequently the drug dissolution. Disintegration time of tablets containing GRF1 showed that it took a longer time for the tablets to disintegrate compared to those of GRF2 and GRF 3 (Table 3). This shows that nanocrystallization of griseofulvin addresses the long disintegration time associated with griseofulvin tablet. The presence of the surfactant caused further decrease in the disintegration time. Incorporation of surfactants in binder solutions had been attributed to improved wetting of powders and decrease in disintegration time of tablets [19, 20]. The standard calibration curve of griseofulvin is shown in Figure 1 while the dissolution profile of tablets containing 3% binder concentration and that of tablets containing 6% binder concentration are shown in Figures 2 and 3 respectively.

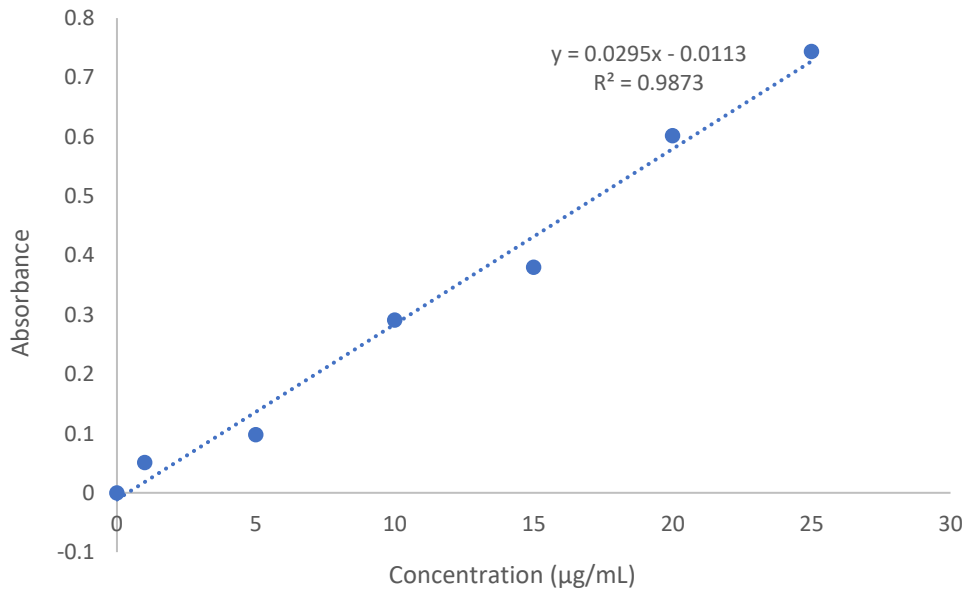

Figure 1: Griseofulvin standard curve

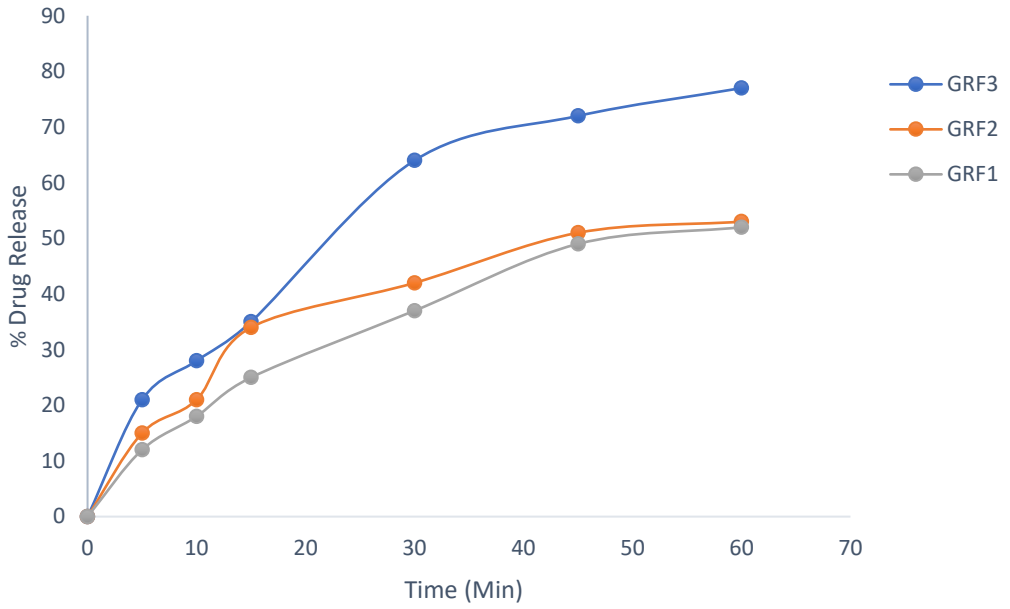

Figure 2: Dissolution profile of tablets containing 3% binder

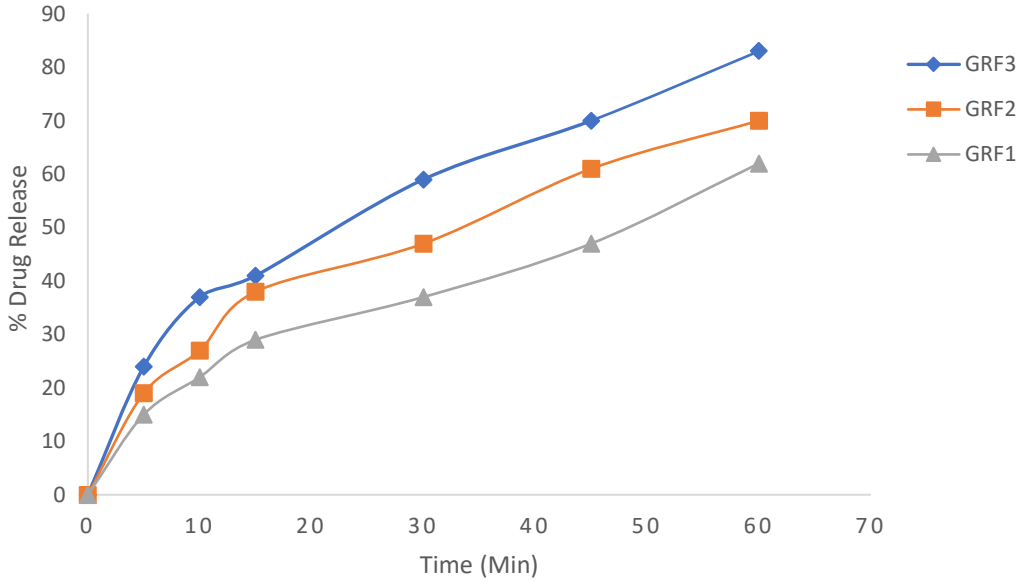

Figure 3: Dissolution profile of tablets containing 6% binder

From the dissolution result of tablets containing 3% $^{w}/_{w}$ binder concentration, drug release for nanocrystals was rapid compared to the pure drug. There was 42% drug release for the ordinary nanocrystals and 64% for nanocrystals with Polysorbate 80 eclipsing that of pure griseofulvin with 37% drug release in 30 minutes. At 60 minutes, there was drug release of 53% from tablets containing the ordinary nanocrystals, 77% for nanocrystals with Polysorbate 80 and 52% for pure drug showing that there was least drug release for the unprocessed drug and highest drug release for nanocrystals generated with inclusion of Polysorbate 80. For drug dissolution from tablets containing 6%$^{w}/_{w}$ binder concentration, drug release for nanocrystals was rapid compared to the unprocessed drugs. There was 47% drug release for ordinary nanocrystals and 59% for nanocrystals prepared with Polysorbate 80 eclipsing that of pure drug with 37% release in 30 minutes. The dissolution reached its peak of drug release of 70% for ordinary nanocrystals, 83% for nanocrystals prepared with Polysorbate 80 and 62% for pure drug in 60 minutes showing the least drug release to be from the unprocessed drug while the highest remains from the nanocrystals prepared with Polysorbate 80. Increase in disintegration and dissolution rates of tablets would occur in the presence of surfactants provided the system is significantly hydrophobic [19, 20]. Even though

the drug release from tablets containing 6% $^{w}/_{w}$ acacia gum concentration was not significantly different from the release from tablets containing 3% $^{w}/_{w}$ acacia gum at time 30 minutes for each form of the drug substance, the eventual release at time 60 minutes was higher for tablets containing 6% $^{w}/_{w}$ acacia gum. It implies that acacia gum as a binder initially inhibited drug release, but after some time with complete disintegration of the tablets, it promoted the drug dissolution and potentiated the effect of Polysorbate 80. Surface activity had been observed with some natural gums [21]. The nanocrystals, especially the form generated with the inclusion of Polysorbate 80, could be subjected to further development for commercial production and clinical use [22]. This is so because the known antifungal use of the drug [23, 24] can be optimized since the major limitation of the drug is the poor release.

4. CONCLUSION

Nanocrystallization does not cause a significant change in the strength of tablets formulated with the processed drug. However, inclusion of polysorbate 80 during nanocrystallization causes a decrease in the strength of tablets. On the other hand, nanocrystallization causes a decrease in the disintegration time; and the inclusion of a surfactant during nanocrystallization causes a further decrease. The use of nanosized particles of griseofulvin for tablet formulation improves the dissolution of the drug from the tablet; and the inclusion of Polysorbate 80 during the generation of the nanosized crystals of griseofulvin causes further improvement in the delivery of the drug from tablets. Further research is appropriate to determine how the tablet strength could be optimized while still upholding the benefit of improved delivery of griseofulvin using the nanocrystals generated with Polysorbate 80.

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Conflict of Interest

There is no conflict of interest associated with this publication.

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Authors' Contributions

This study was conceived by Emmanuel Olorunsola. The design was done by Emmanuel Olorunsola and Mbang Femi-Oyewo. Data collection with the analysis was done by Jennifer Ekuma while the interpretation of results was done by all the authors. The manuscript was written by Jennifer Ekuma and Emmanuel Olorunsola while its revision was done by Mbang Femi-Oyewo and Clifford Orakwe. All the authors gave approval for the version of the manuscript being published.

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