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Research Article

# Comparison of the Use of Kinetic Model Plots and DD Solver Software to Evaluate the Drug Release from Griseofulvin Tablets

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## Abstract

Awareness of the release kinetics of active drugs is important in formulating drugs that have the desired delivery and in predicting the behaviour of the formulated drug in vivo. The study aims to determine the mechanism of drug release from griseofulvin tablets formulated with different surfactants using mathematical models and to compare the use of graphs and DD solver software in fitting dissolution profiles to kinetic models. The batches P1 -P3 were composed of the surfactant - PEG 4000 in different concentrations. A control batch without surfactant and a commercial brand (Mycoxyl 500) were used for comparison. Granule and tablet quality tests indicated quality formulations. Dissolution profiles showed that the surfactant improved drug release of griseofulvin and batches (batches P1 -P3) formulated with PEG 4000 had the best release profiles comparable with the commercial brand. The Excel Add-in DD solver and kinetic plots were used to determine the kinetic model of best fit. The Higuchi model was the best fit for batches P1 -P3. The first order and Hixon -Crowell also fit batches P2 and P3. The Korsmeyer's model showed that batches P1 -P3 exhibited anomalous diffusion. The tablets formulated with PEG were as good as the commercial brand and they had an anomalous diffusion of the drug from the tablet; meaning that drug diffused following Fickian law and also diffused through a swollen and porous matrix. Kinetic plots and the DD solver can be used for fitting dissolution profiles to kinetic models.

**Keywords:** Griseofulvin, Kinetics, Models, Surfactants, Polyethylene glycol (PEG) 4000, DD solver, Dissolution profile, mathematical models

## INTRODUCTION

Griseofulvin is drug used in the treatment of dermatophyte infections. It is used orally, for external fungal infections [1]. It binds tightly to keratin precursor cells making such skin cells resistant to further fungal attack [2]. It has a high lipid permeability and a poor aqueous solubility therefore belonging to the Biopharmaceutical Classification System (BCS) II. For a drug to be available in the body, it has to be released from its dosage form. Drug release is a process in which the active drug in a dosage form is released through diffusion or dissolution in the aqueous medium in the body [3]. Drug release could be immediate release – with no purpose of delaying drug absorption and availability, it could be delayed-release whereby there is an intended delay in the drug absorption. Extended-release dosage forms are formulated to make the drug available over a period of time, control release dosage forms regulate the quantity and time of the drug release, it could be pulsatile and extended [4]. Since a drug should solvate before absorption can take place, tablets must dissolve in the contents of the gastrointestinal tract before systemic absorption occurs [5]. Dissolution studies provide useful information on the release pattern of drugs and several mathematical kinetic models have been published to study the release kinetics of drugs [6]. Some mathematical models used in describing drug release are: Hixon-Crowell model, Higuchi model, first order kinetics and zero order kinetics, while Korsmeyer - Peppas model and the Weibull model have been used to interpret drug release mechanism [7]. These kinetic models describe the drug amount dissolved (C) from solid dosage form as a function of test time (t) or written as: C=f(t).

### Zero-order kinetics

This model describes a drug release rate which is independent of its concentration [6-8]. This type of dissolution usually happens in dosage forms that do not disaggregate, and it is usually slow [9]. Rate of drug release is usually constant and drug level in the blood remains constant throughout delivery [10].

$$Q_t = Q_0 + K_0 t$$

Qt=Drug amount dissolved in time (t), $Q_0$ = Starting amount of drug in the aqueous medium, $K_0$ = constant of zero order release which is written as concentration/time. A plot of cumulative amount of drug versus time will give a straight-line slope of $K_0$ and a zero intercept.

$$C = k_0 t$$

### First order kinetics

Here the drug release rate is dependent on the drug of interest's concentration. It can be shown by the equation:

$$^{DC}/_{dt} = -K_1 C$$

$K_1$ = First order rate constant expressed in time$^{-1}$ or per hour

$$\log Q_t = \log Q_0 - \frac{Kt}{2.303}$$

$Q_t$ = Amount of drug released in time (t), $Q_0$ = Initial amount of drug in aqueous medium, K = first order release constant. Plot of log cumulative % of drug remaining [log ($Q_0$ -$Q_t$)] versus time [t] will give a straight-line graph, a slope of k/2.303 and intercept at t=0 of log $Q_0$.

**Higuchi model**

It explains that the portion of released drug is directly related to square root of time. Here drug can be released by diffusion and dissolution. The fundamental Higuchi equation is:

$$Q = A\sqrt{D(2C_o - C_s)\,C_s t}$$

Q = Cumulative drug amount released in (t) time per unit area, A = Area, Co = Initial drug concentration, Cs = drug solubility, D= diffusion coefficient.

In a situation whereby the drug concentration in the formulation is lower than its solubility, the release occurs through a porous system and it can be expressed thus:

$$Q = \sqrt{(D\delta/\tau)(2C - \delta C_s)\,C_s t}$$

Q = Cumulative drug amount released in (t) time per unit area, Cs = drug solubility, D= Diffusion coefficient of drug in solvent, δ = Porosity of the dosage form. τ= Tortuosity of the dosage form (defined as the dimensions of the radius and pores and canals branching in the dosage form). Simplifying the equation above gives:

$$Q = K_H \times t^{1/2}$$

$$Mt/_{M\infty} = K_H t^{1/2}$$

Mt = Cumulative drug amount released at time (t), M∞ = Cumulative drug amount released at time (∞), $K_H$ = Higuchi constant. Plot of Cumulative % of drug release (Mt/M∞) versus $t^{1\backslash 2}$ produces a straight line with a slope of $K_H$. If correlation is high then a diffusion release mechanism has taken place.

Some assumptions made are that; Drug solubility is lower than initial drug concentration, perfect sink conditions are achieved and maintained, drug diffusivity is constant, swelling of polymer is negligible [10], diffusion occurs only in one dimension (edge effect negligible) [4, 9, 10].

**Hixon -Crowell model**

This cube root law explains the drug release from dosage forms where there is a reduction in surface diameter and area of particles or tablets (due to erosion). The defined area of the particles is proportional to its cube root of its volume [10]. One can apply this model to immediate release dosage form, conventional dosage form or dispersible dosage form. It is considered that the drug release rate is limited by drug particle dissolution rate and not by diffusion. The concept established was thus:

$$W_0^{1/3} - W_t^{1/3} = K_{HC}\,t$$

$W_0$ = Initial drug amount in the dosage form (Drug amount remaining at time 0), Wt. = Amount of drug released in time (t), $K_{HC}$ = Hixon- Crowell constant describing surface volume relationship. Release kinetics is drawn as cube root of the percentage of the drug remaining versus time.

**Korsmeyer – Peppas model (Power Law)**

The Higuchi plot ascertains if a diffusion release occurred while the power law describes drug release mechanism. Drug release could be described as Fickian or non- Fickian diffusion [8, 10]

$$Mt/_{M\infty} = K_{kp}t^n$$

Mt/M∞ = Fraction of drug released at time (t)

$$\boldsymbol{Log\ [Mt/M\infty] = Log\ K_{kp} + n \log t}$$

Mt = Cumulative drug amount released at (t) time, M∞ = Cumulative drug amount released at time (∞), KKP = Korsmeyer rate constant, n= diffusional release exponent. Release kinetics graph is plotted between log cumulative % drug release [log (Mt/M∞)] versus log time [log t]. The first 60% of drug release data is fitted to the Korsmeyer -Peppas model.

Some assumptions made are: the generic Power law equation is applicable to small values of time typically where Ct/C∞ < 0.6 and drug release is in a one-dimensional way [4].

**Weibull Model**

This has been used for different dosage formulations. It is an empirical model [11]. Its equation is:

$$log[-\ln(1-m)] = \beta \log(t - T_i) - \log \alpha$$

m= Accumulated portion of the drug, β = shape parameter, α = scale parameter, $T_i$ = Location parameter/ time lag usually zero, t= Time in hours. The α value in the Weibull model shows the time scale or apparent rate constant while the β value characterizes the shape of the curve. When β =1, the curve is said to be exponential and its kinetics corresponds to the first order kinetics. When β >1, the curve is sigmoidal and the rate of drug release increases as time increases, β<1 indicates a parabolic curve and the rate of drug release is said to reduce as time increases [12, 13]. Log of dissolved amount of drug vs log time give a linear graph. β is obtained from the slope of the graph while α is obtained from the y axis (1/a) at time t=1. Td can be used to replace the parameter α. Td is the time taken for 63.2% of the drug to be released and it can be defined by the equation below and can be obtained from the y axis of -ln(1-m) = 1.

$$\alpha = (T_d)^b$$

There is a relationship between the shape parameter (β) and the release exponent (n) of Weibull's and Korsmeyer's models respectively as shown in Table 1.

**Table 1: Weibull's and Korsmeyer's Models' Relationships [14]**

| Release Exponent (n) | Weibull's Parameter (β) | Drug Transport Mechanism | Rate as a Function of Time |
|---|---|---|---|
| n<0.45 | | Quasi-Fickian diffusion | $t^{-0.5}$ |
| 0.45 | β ≤ 0.75 | Fickian diffusion | $t^{-0.5}$ |
| 0.45<n<1.0 | 0.75 < β < 1 | Anomalous (non-Fickian) transport | $t^{n-1}$ |
| 1.0 | | Case II transport | Zero order release |
| Higher than 1.0 | β > 1 | Super Case-II transport | $t^{n-1}$ |

Several works have been done on improving the aqueous solubility of griseofulvin tablets but there is need to compare the effect of different surfactants in improving the aqueous solubility of griseofulvin. There is also limited literature on the use of DD solver to fit dissolution profiles to kinetic models and comparison of results obtained from DD solver and results obtained from kinetic plots. This study was carried out to compare the ability of the PEG 4000 to improve the dissolution of griseofulvin in tablets and also to compare the use of the Excel Add in app DD solver and kinetic graphs in evaluating the kinetic release of griseofulvin tablets.

In this research, griseofulvin tablets were formulated with the surfactant Polyethylene glycol (PEG) 4000 in different concentrations to improve the dissolution characteristics of the drug. The batch of drugs produced with the surfactants that gave the best release profiles were further analysed with the mathematical models.

## EXPERIMENTAL

### Materials

Mycoxyl – 500® tablets (Bangkok lab and cosmetics Co Ltd, Bangkok, Thailand) – commercial brand., maize starch, dimethylformamide (Qualikems), n-hexane (JHD chemicals Ltd. Guangdong, China), powdered potassium dichromate (JHD chemicals Ltd. Guangdong, China, talc (BDH chemicals Ltd. Poole, England), hydrochloric acid (JHD chemicals Ltd. Guangdong, China), lactose, magnesium stearate (BDH chemicals Ltd. Poole, England), methanol (JHD chemicals Ltd. Guangdong, China), Micronized Griseofulvin (Chifeng Pharmaceuticals Co. Ltd, China), PEG 4000.

### Sample Authentication

Using the Electrothermal® melting point device, the melting point of the sample was measured (England). In addition, 5 mg of the sample was dissolved in 1 ml of sulphuric acid reagent, then 5 mg of powdered potassium dichromate reagent was added. The formation of a dark crimson solution reveals the presence of griseofulvin [15].

Dimethylformamide reagent was also used to dissolve 0.75 g of the sample which was then diluted to 10 ml using the same solvent. The creation of a colourless solution confirms the presence of griseofulvin [15].

### Formulation of Griseofulvin Tablets

Wet granulation was used to make the tablets, which were then compressed using an Erweka® D-63150 (GmbH Heusentamm, Germany) single punch tableting press. Table 2 shows the batch composition as well as the batch codes.

**Table 2**: Formula used for griseofulvin granules and tablets preparations

| Ingredient | Amount (%) | | | |
|---|---|---|---|---|
| | Control | P1 | P2 | P3 |
| Griseofulvin (mg) | 250 | 250 | 250 | 250 |
| Maize starch (disintegrant) | 10 | 10 | 10 | 10 |
| PEG 4000 | - | 6.25 | 12.5 | 15 |
| Maize starch (binder) | 5 | 5 | 5 | 5 |
| Magnesium stearate | 1 | 1 | 1 | 1 |
| Talc | 0.5 | 0.5 | 0.5 | 0.5 |
| Lactose q.s. (mg) | 365 | 365 | 365 | 365 |

### Granules' Evaluation

### Granules' particle size analysis

The method of sieve analysis was used for each batch [16]. Granules of 20 g were placed on the stack of sieves of sizes, 1000 µm (no 18), 500 µm (no 35), 250 µm (no 60), 125 µm (no120), 63 µm (230) and 45 µm (325), arranged in a descending order of aperture size and the sieve shaker was operated for ten minutes. The equation below was used in calculating average diameter.

$$\frac{[\sum(\%\ retained)\ \times (mean\ aperture)]}{100}$$

### Particle/ true density

This was determined by the liquid displacement method [17]. A 28 ml- empty pycnometer was weighed (w). It was filled with n-hexane, stoppered, thoroughly cleaned of excess liquid and weighed (W1). A 1 g quantity of granule (Ws) was transferred to the hexane-filled pycnometer. The pycnometer was stoppered, excess fluid was cleaned off the pycnometer and weighed (W2). Dw is the density of n-hexane. This was carried out thrice for each granule batch. Particle density was obtained from the equation below:

$$True\ density = \frac{Dw * (Ws)}{Ws - (W2 - W1)}$$

### Granules' bulk and tapped densities

These were determined for each batch [7]. A 20 g quantity of granules from each batch was transferred to a 100 ml measuring cylinder, the volume occupied was recorded as the bulk volume. The 100 ml measure was tapped on a hard-wooden surface several times until a constant volume was obtained. The volume observed was recorded as the tapped volume. Five replicate determinations were made for each batch and calculated thus:

$$Bulk\ density = \frac{Mass\ (g)}{Bulk\ Volume\ (ml)}$$

$$Tapped\ density = \frac{Mass\ (g)}{Tapped\ Volume\ (ml)}$$

### Hausner's quotient and Carr's index

These were calculated thus [18, 19]

$$Hausner's\ quotient = \frac{Tapped\ density}{Bulk\ density}$$

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100\%$$

**Packing fraction, powder porosity, bulkiness, and void ratio**

The equations below were used to calculate these [20, 21]:

$$Packing\ fraction = \frac{Bulk\ Density}{True\ Density}$$

$$Bed\ porosity = (1 - Packing\ fraction) * 100$$

$$Bulkiness = \frac{1}{Bulk\ Density}$$

$$Void\ ratio = \frac{1 - packing\ fraction}{Packing\ fraction}$$

**Flow rate and Angle of repose:**

The flow under gravity [22] and the fixed funnel [21] methods were used for determining flow rate and angle of repose respectively. Five replicate determinations were made for each batch and using each method. The equations below were used to calculate flow rate and angle of repose.

$$Flow\ rate = \frac{Mass\ of\ granule\ (g)}{Time\ (\text{secs})}$$

$$Angle\ of\ repose\ (\theta) = Tan^{-1}(\frac{2(height\ of\ heap)}{Diameter\ of\ heap})$$

**Evaluation of Tablets**

**Organoleptic properties**

The appearance of the compressed tablets was noted and recorded. This includes the shape, colour, presence or absence of odour, and taste of the tablets.

**Uniformity of weight, tablet thickness and diameter**

Twenty tablets from each batch including the commercial brand (Mycoxyl -500®) were tested for weight variation using the AdventurerTM Ohaus analytical weighing balance applying the official method [23]. Thickness and diameter of the tablets were determined using a micrometre screw gauge and a Vernier calliper respectively. Results were expressed as mean ± standard deviation (SD).

**Crushing strength test**

A Monsanto hardness tester was used in determining the crushing strength of 10 tablets from each batch including the commercial brand. Results were expressed as mean ± standard deviation (SD).

**Friability test**

Friability of ten random tablets from each batch and the commercial brand was tested using the Friabilator (Erweka® GmbH, Heusentamm, Germany) at 25 rpm for 4 min. Friability was obtained using the equation below:

$$F = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times\ 100$$

**In-vitro disintegration test**

Six tablets from each batch and the commercial brand were selected randomly. A tablet was placed in each of the 6 glass tubes of the disintegration apparatus. The basket rack was positioned in 700 mL of 0.1N HCl at 37 ± 2 °C. The time it took for each of the tablets to disintegrate or become a soft mass without a firm core was noted and recorded as the disintegration time.

**Drug content uniformity test**

Twenty tablets from each batch including the commercial brand were weighed and crushed to powder. Weight of the powder equivalent to 250mg of griseofulvin was weighed out and dissolved in 250ml of absolute methanol producing a 1mg/ml concentration. The mixture was agitated for one hour, centrifuged for 30 minutes, supernatant was collected and diluted. The diluted samples were analysed at wavelengths of 292 nm. The content of active ingredients of each batch was calculated with reference to calibration curve previously plotted for griseofulvin/absolute methanol and which had $R^2$ value of 0.99.

**In-vitro dissolution test**

Dissolution test was carried out using previously established protocols with slight modifications [24]. Dissolution medium was 1000 mL of 80% methanol in a covered dissolution apparatus. The test was carried out for 2 hours. This was carried out in triplicates.

**Kinetics of drug release**

The dissolution profiles of the formulated batches with untransformed data were fitted to different kinetic models: zero order, first order, Higuchi model, Hixon-Crowell model, Korsmeyer -Peppas model and the Weibull kinetic model using the Excel Add-in DD solver version 1 [11, 25]. Lowest Akaike information criterion (AIC), highest model selection criterion (MSC) and highest adjusted coefficient of determination ($R^2$ adj) values were used in selecting the model with the best fit [26, 27].

Plots were also made to evaluate the kinetics and mechanism of drug release of the tablet batches using transformed data in some cases. The correlation coefficient of highest degree establishes the kinetic model that best fits the drug's release [10]. The release exponent (n) of the Korsmeyer -Peppas model and shape parameter (β) of the Weibull model were obtained from the slope of their respective plots [10, 28].

**Statistical Analysis**

The mean and standard deviations of all results were calculated with GraphPad prism version 6.0 and Microsoft Excel 365(2018). T-test and one- way ANOVA were used to analyse mean differences using GraphPad prism version 6.0 at $p \leq 0.05$. Excel Add-in DD solver version 1 was used in fitting the release profiles to kinetic models.

## RESULTS AND DISCUSSION

**Sample Authentication**

All the tests confirmed that the sample was griseofulvin

**Granule Properties**

Carr's index, Hausner's quotient, and angle of repose ranged from 11.31 ±1.68 -13.37 ± 3.09 %, 1.13 ± 0.02 – 1.16 ± 0.04, 16.90 ± 1.73 – 20.74 ± 0.51° respectively, as shown in Table 3. This demonstrates that all the granules had good flow. Poor granule flow is indicated by angles of repose more than 30°, Carr's index greater than 20%, and Hausner's quotient greater than 1.5 [29]. In most cases, there is no significant difference between the tapped and bulk density of a free-flowing powder [30]. A t-test at $p \leq 0.05$ revealed no significant difference between the tapped and bulk densities of any of the tested granule batches.

The packing properties of the formed grains are shown in Table 4. Bulkiness is the inverse of bulk density. The larger a

powder's bulkiness, the weaker its flow [29]. The packing fraction describes the proportion of the powder bed that is packed with powder particles. Packing fractions for dense randomly packed spheres and dense randomly packed discs are 0.65 and 0.83, respectively [20, 29]. Table 4 shows packing fractions below 0.65 indicating that the particles of the sampled granules were not densely packed. The larger the granule packing percentage, the greater the cohesive forces present and the poorer the flowability [31]. Loosely packed particles with larger porosity can be readily vibrated from the powder bed, resulting in greater flowability [29]. Closest or rhombohedral packing has a porosity of 26%, whereas most open, loosest, or cubic packing has a theoretical porosity of 40%. Real powders typically have a bed porosity of 30 % to 50 %. Table 4 demonstrates that the granules from the various batches had porosities ranging from 50 to 65 % and low packing fractions ranging from 0.36 to 0.51, indicating satisfactory flow characteristics.

Figure 1 demonstrates that the granule particle size spans from 481.62 µm to 553.28 µm, indicating that the particles are of the granular solid type [23]. The optimal particle size for excellent flow is 400 µm – 800 µm, while particles smaller than 10 m oppose gravity flow owing to high cohesive forces [29]. The granule sizes were within the recommended range for optimal flow.

The granules made with PEG 4000 had the best flow characteristics. This is in line with the fact that PEG 4000 may be utilised as a powder flow enhancer [32].

**Table 3:** Flow properties of the batches of formulated griseofulvin granules

| Batch | Bulk density ($g/cm^3$) | Tap density ($g/cm^3$) | Particle density ($g/cm^3$) | Carr's index (%) | Hausner's ratio | Flow rate (g/s) | Angle of repose (°) |
|---|---|---|---|---|---|---|---|
| Control (Ctrl) | 0.48 (0.02) | 0.56 (0.00) | 1.28 (0.00) | 13.37 (3.09) | 1.16 (0.04) | 14.47 (1.06) | 20.74 (0.51) |
| P1 | 0.61 (0.00) | 0.70 (0.01) | 1.44 (0.20) | 12.46 (1.62) | 1,14 (0.02) | 16.36 (1.00) | 17.67 (0.89) |
| P2 | 0.63 (0.01) | 0.71 (0.01) | 1.25 (0.12) | 11.31 (1.63) | 1.13 (0.02) | 17.01 (0.84) | 16.90 (1.73) |
| P3 | 0.60 (0.01) | 0.69 (0.01) | 1.26 (0.13) | 12.57 (0.61) | 1.14 (0.01) | 15.39 (0.68) | 20.70 (0.57) |

Key: Data is shown as mean (standard deviation (SD)) after 5 determinations. Standard deviations are in brackets

**Table 4:** Packing properties of the batches of formulated griseofulvin granules

| Batches | Bulkiness ($cm^3/g$) | Packing Fraction | Bed Porosity (%) | Void Ratio |
|---|---|---|---|---|
| Ctrl | 2.10 (0.09) | 0.37 (0.01) | 62.67 (1.45) | 1.68 (0.11) |
| P1 | 1.65 (0.00) | 0.43 (0.05) | 57.40 (5.38) | 1.38 (0.32) |
| P2 | 1.58 (0.03) | 0.51 (0.05) | 49.31 (4.90) | 0.99 (0.18) |
| P3 | 1.68 (0.03) | 0.48 (0.05) | 52.31 (4.86) | 1.11 (0.20) |

Key: Data is shown as mean (standard deviation (SD)) after 5 determinations. Standard deviations are in brackets

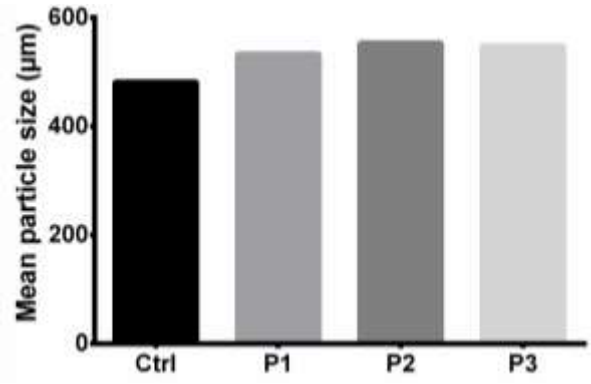


Figure 1: Particle size analysis of the batches.

**Tablet Properties**

The formulated tablets were white, odourless, slightly bitter, discoid in shape and thick with smooth surfaces. Table 5 gives the other properties of the tablets. The BP requirement for uniform thickness and diameter was met as maximum deviations from mean tablet thickness and diameter were 0.02 and 0.06 respectively which were not up to the 5%. limit at $p \leq 0.05$, there was no significant difference in the dimensions (thickness and diameter) amongst formulated tablets within a batch and across batches. Formulated tablets passed the weight variation tests. For tablet weights of 250mg and more, no two tablets should deviate by 5% and no one should deviate by 10% [24]. Tablet weight for formulated tablets ranged from 357.9 ± 4.10 mg – 367.8 ± 3.78 mg. The dimensions and weight of the commercial brand were different from the lab formulated griseofulvin tablets. This is because Mycoxyl-500 was formulated in a different location and with different specifications. All batches passed the friability test (below 1%) and the hardness tests (4 – 8 KgF is acceptable). All the batches except the ctrl batch passed the disintegration test which should not be above 15 minutes [23]. Disintegration time may be increased at low packing fraction [33, 34], since there is adequate room for the disintegrant (maize starch) to expand without disturbing particles immediately. This might explain why the tablets took longer to disintegrate, despite the fact that only the control batch failed the disintegration test. The drug assay for all the granules including the commercial brand ranged from 90.81% to 103.56% conforming with the BP requirements of 90% - 115%.

**Table 4: Tablet properties**

| Batches | Tablet Weight (mg) | Tablet Thickness (cm) | Tablet Diameter (cm) | Hardness (KgF) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|---|
| Ctrl | 367.8 (3.78) | 0.46 (0.00) | 0.86 (0.05) | 6.10 (0.10) | 0.19 | 18.44 (4.24) |
| P1 | 357.9 (4.10) | 0.50 (0.02) | 0.86 (0.05) | 5.90 (1.05) | 0.10 | 7.42 (1.22) |
| P2 | 361.1 (1.57) | 0.50 (0.01) | 0.84 (0.05) | 6.95 (0.96) | 0.16 | 10.08 (2.56) |
| P3 | 362.4 (2.36) | 0.49 (0.01) | 0.79 (0.02) | 6.35 (1.03) | 0.13 | 8.48 (1.46) |
| Brand | 603.4 (1.64) | 0.53 (0.01) | 1.27 (0.02) | 7.50 (1.58) | 0.13 | 10.20 (2.15) |

Key: Data is shown as mean ± standard deviation (SD). Standard deviations are in brackets.

**In vitro Dissolution**

Figure 2 shows the drug release profiles. When analysed using GraphPad prism 6.0, the tablets produced with the surfactant - PEG 4000 had better drug release than the control (ctrl) batch, which did not contain a surfactant ($p < 0.0001$). The tablet batches formed with PEG 4000 (P1, P2 and P3) and the commercial brand had 100% drug release after 2 hours, indicating that they had better release profiles than the control batch. A one-way ANOVA revealed no significant differences in the drug release profiles of the commercial brand and batches P1, P2 and P3 ($p = 0.06$, DF = 3, F=3.758). The shows that PEG 4000 improved the drug release of griseofulvin tablets. The drug solubilization location is the polyethylene tail of PEG, and the hydrophobic drug – griseofulvin was contained there and solubilized there [35].

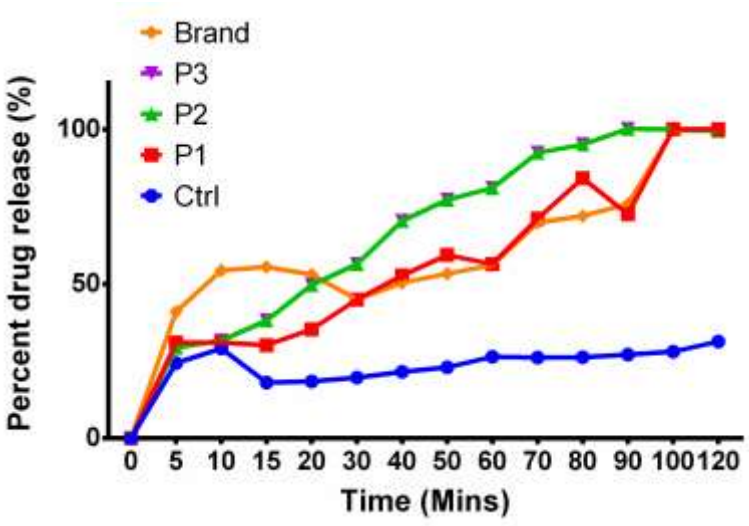


**Figure 2:** Drug release profiles of the batches of tablets

**Kinetics of drug release**

The release profiles of the commercial brand, P1, P2 and P3 were subjected to further analysis using the mathematical models – Zero order, first-order, Higuchi, Hixon – Crowell, Korsmeyer-Peppas and Weibull. To determine the best kinetic model, two methods were used: linear regression with plots of the models and the Excel Add-in DD solver application using the parameters $R^2$ adj, MSC, and AIC. Table 5 shows that the zero order does not have a high $R^2$adj value except for batch P1 showing that it did not fit well with any of the batches. With $R^2$ adjusted of 0.96 and 0.95, the first order fits Batches P2 and P3, respectively. Only P2 and P3 were compatible with the Hixson-Crowell model, while Batches P1–P3 were compatible with the Higuchi model. Though the Weibull and Korsmeyer's model are empiric and semi-empiric models [11, 36], their parameters could be applied to characterize the release mechanism of pharmaceuticals [37] and they fit throughout the batches P1-P3. Comparing the models for each batch, disregarding the empiric models, Table 5 shows that the Higuchi model had the best fit across the batches P1 – P3 signifying that drug release was mostly by diffusion; though batches P2 and P3 exhibited a little drug release by erosion-controlled drug release as signified by the high $R^2$ adjusted of the Hixon -Crowell plot.

Figure 2 show the plots of the kinetic models for the commercial brand and P1. P2 and P3 which resulted in the regression coefficient summary shown in Table 6. Table 6 shows that the first order model fit the batches P2 and P3, Higuchi model again best fits P1 -P3 while the Hixon-Crowell model fits batch P3 only. Observe that even though the results displayed in Tables 5 and 6 cannot be used to definitely categorize the release mechanism of the commercial brand, it can be seen to have the best fit with the Higuchi kinetic model.

These plots correspond to the result obtained from the DD solver application as Table 5 and Table 6 show that Higuchi model was the best fit for drug release of the griseofulvin tablets for batches P1 -P3. It can be inferred from this that griseofulvin was released from P1, P2 and P3 tablet formulations mostly through diffusion-controlled mechanism. Using the parameters of n and β of the Korsmeyer-Peppas and Weibull models respectively, the diffusion process of griseofulvin drug release can be further described.

Table 7 shows the β values and n values of the commercial brand and batches P1 -P3. The parameter values were derived

from excel add-in DD solver version 1 and the empirical plots. Release exponent (n) describe drug release as quasi-Fickian, Fickian, non-Fickian or anomalous. A quasi-Fickian drug release means a release that is predominantly diffusional with a little case of polymer swelling. Fickian drug release (case I) shows a diffusion-controlled drug release, a non-Fickian (case II) drug release shows polymer relaxation/ swelling controlled drug release while anomalous drug release follows both diffusion and erosion-controlled mechanism [9, 38]. The n value in Table 7 shows that batch P1 had a quasi-Fickian release (since n < 0.45) proportional to the square root of time according to the DD solver derived value (corresponding to the results shown in Tables 5 and 6 for P1) while also showing an anomalous drug release (0.45<n<1.0) from the plotted graph. P2 exhibited non-Fickian (anomalous) drug release while F3 also exhibited a non -Fickian (anomalous) drug release. The commercial brand exhibited a quasi-Fickian drug release. The batch Ctrl had a poor fit to the kinetic models as shown by the kinetic model plots and the DD solver generated values.

The shape (β) parameter describes the shape of the drug release curve [39]. The β values showed a parabolic curve (β ≤ 1) for the brand, P1 and P2 while showing an exponential curve for P3 (β = 1). A parabolic curve signifies an initial rise in the drug release rate followed by a decrease in drug release as time passes while an exponential curve as seen with P3 indicates a first order kinetics [14]. The first order kinetics here for P3 corresponds to the plot regression coefficient of 0.94 and the DD solver derived value of 0.95 for the first order kinetics for batch 9. One disparity that cannot be fully explained is that in the regression analysis, the $R^2$ values for the commercial brand and P1 -P3 for the zero-order model were high but not as high for the DD solver generated values. But a consistent observation is that the zero-order model fitted P1 more than the other batches. In all cases the control batch without surfactant had different values from the other formulations and it was discovered to have a quasi -Fickian release.

Drug release from a polymer formulated tablet is either through diffusion of the drug from the matrix and or erosion of the matrix and release of the drug through holes filled with water [38, 39]. For a hydrophilic polymer like PEG 4000, the dissolution medium first penetrates the matrix, causes swelling of the polymer, thereafter linkages in the polymer can be disintegrated leading to erosion. From results displayed, P1 followed the Higuchi model and showed an anomalous drug release meaning that the drug release from P1 was both diffusion-controlled (following the Fick's law of diffusion and proportional to the square root of time) and through a swollen matrix with water filled pores. P2 and P3 followed the Higuchi model, first order and Hixon-Crowell's and the Korsmeyer's model detected an anomalous drug release. This means that the release of the drug through the batches P2 and P3 was diffusion controlled, dependent on their drug concentration gradient and proportional to square root of time, and also through the swollen matrix with holes. These observations in the release mechanism of the PEG – 4000 formulated batches correspond with the characteristics of PEG- 4000 matrices. PEG 4000 is a hydrophilic polymer which allows ingress of water/dissolution medium into the tablet, creating pores and leading to erosion of the tablet [40]. The ability of PEG 4000 to swell makes it suitable for sustained release drug formulations at higher concentrations of PEG-4000 as it delays the diffusion of the drug.

**Table 5:** Statistical parameters to evaluate goodness of fit obtained after application of various models to the dissolution profiles of brand, ctrl and batches P1 -P3 using the DD solver.

| Models | Ctrl | | | P1 | | | P2 | | | P3 | | | Brand | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ ADJ | AIC | MSC | $R^2$ ADJ | AIC | MSC | $R^2$ ADJ | AIC | MSC | $R^2$ ADJ | AIC | MSC | $R^2$ ADJ | AIC | MSC |
| **Zero Order** | -1.40 | 107.50 | -2.15 | 0.73 | 102.48 | 1.15 | 0.36 | 114.19 | 0.29 | 0.66 | 107.27 | 0.92 | -3.62 | 124.41 | -1.69 |
| **First Order** | -6.83 | 98.36 | -2.21 | 0.87 | 93.29 | 1.85 | 0.96 | 78.46 | 3.04 | 0.95 | 83.42 | 2.76 | -1.98 | 118.69 | -1.25 |
| **Hixon Crowell** | -7.16 | 98.90 | -2.25 | 0.86 | 93.55 | 1.83 | 0.94 | 82.95 | 2.69 | 0.95 | 82.77 | 2.81 | -2.37 | 120.29 | -1.37 |
| **Higuchi** | -2.62 | 88.35 | -1.44 | 0.92 | 87.34 | 2.31 | 0.96 | 78.27 | 3.05 | 0.96 | 79.38 | 3.07 | -1.10 | 114.17 | -0.90 |
| **Korsmeyer -Peppas** | 0.15 | 70.38 | -0.06 | 0.92 | 87.72 | 2.28 | 0.97 | 76.16 | 3.21 | 0.96 | 80.65 | 2.97 | 0.08 | 104.29 | -0.14 |
| **Weibull** | 0.14 | 70.45 | -0.07 | 0.93 | 85.75 | 2.43 | 0.99 | 59.75 | 4.47 | 0.98 | 68.87 | 3.88 | 0.21 | 103.03 | -0.04 |

Key: $R^2$ adj - Adjusted coefficient of determination, AIC – Akaike information criterion, MSC – Model selection criterion.

A best fit is one with highest $R^2$ adj, lowest AIC and highest MSC values

**Table 6:** Regression coefficients of batch 7, batch 8, batch 9 and the brand

| Models | Regression coefficients of batches P1, P2, P3, the ctrl and the commercial brand | | | | |
|---|---|---|---|---|---|
| | Ctrl | P1 | P2 | P3 | Brand |
| **Zero order** | 0.403 | 0.9229 | 0.8677 | 0.9131 | 0.7491 |
| **First order** | 0.4366 | 0.7350 | 0.9409 | 0.9439 | 0.6462 |
| **Higuchi** | 0.5292 | 0.9419 | 0.9778 | 0.9727 | 0.7967 |
| **Hixon Crowell** | 0.1077 | 0.7879 | 0.9206 | 0.9538 | 0.7081 |
| **Korsmeyer – Peppas** | 0.2062 | 0.8217 | 0.9590 | 0.8876 | 0.6202 |
| **Weibull** | 0.1886 | 0.8855 | 0.9726 | 0.9434 | 0.6146 |

Key: A best fit is one with the highest regression coefficient

**Table 7: β and n values of the brand, ctrl and batches P1 to P3 derived from DD solver and the slope of the model plots respectively**

| Batches | $\beta^a \pm SD$ | $n^a \pm SD$ | Diffusional mechanism | $\beta^b$ | $n^b$ |
|---|---|---|---|---|---|
| **Ctrl** | 0.1±0.00 | 0.09 ±0.00 | Quasi - Fickian | 0.08 | 0.08 |
| **Batch 7** | 0.90 ±0.00 (parabolic) | 0.57 ±0.00 | Anomalous | 0.84 | 0.31 |
| **Batch 8** | 0.91 ±0.00 (parabolic) | 0.46 ±0.00 | Anomalous | 0.91 | 0.46 |
| **Batch 9** | 1.00±0.00 (Exponential) | 0.53 ±0.00 | Anomalous | 1.01 | 0.47 |
| **Brand** | 0.15 ±0.00 (parabolic) | 0.11 ±0.00 | Quasi -Fickian | 0.22 | 0.23 |

Key: **a** = values generated from the application DD solver version 1, **b** = values obtained from slopes of the plots Weibull and Korsmeyer respectively, **β** = shape parameter of the Weibull model, **n**= release exponent from Korsmeyer – Peppas model.

## CONCLUSION

This study was carried out to evaluate the surfactant –PEG 4000 in varying concentrations in the formulation of griseofulvin tablets and to evaluate the drug release mechanism using DD solver version 1 and the kinetic plots. The formulations were further analysed using the mathematical models – Zero order, first-order, Higuchi, Hixon -Crowell, Korsmeyer -Peppas and Weibull, in order to describe the mechanism of their drug release. Plots of the kinetic models were made and high linearity ($R^2$) signified best fit with those kinetic models. An application – Excel Add-in DD solver was also used to test for model with best fit using parameters $R^2$ adjusted, AIC and MSC. The PEG – 4000 formulated batches P1 -P3 had the best dissolution profile compared with the control. P1 -P3 had comparable and identical qualities to that of the commercial brand – Mycoxyl – 500. P1 -P3 showed drug release that was Fickian diffusion controlled (where by solute diffusion time is shorter than the polymer relaxation time) and also diffusion through a swollen matrix took place (where polymer relaxation time =solute diffusion time) therefore having anomalous drug release pattern.

The results on the kinetic release mechanism of the drugs obtained from the Excel Add-in DD solver version 1 and kinetic model plots generally gave the same observations. This means that both methods can be used to fit dissolution profiles to kinetic models, though it is easier to analyse drug release using the DD solver than using kinetic graphical plots.

## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest

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