Vol. 16(6), pp. 90-102, June 2022
DOI: 10.5897/AJPP2022.5293
Article Number: 193E36869254
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Formulation and evaluation of gastro-retentive floating tablets of griseofulvin

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Received 18 January, 2022; Accepted 16 March, 2022

About 50% of an oral dose of griseofulvin passes through the gastro-intestinal tract unabsorbed and is excreted in faeces. Short residence time of the low soluble griseofulvin, in stomach and small intestine, limits its dissolution. Griseofulvin is highly soluble in acidic pH, and so a gastro-retentive floating matrix system was developed to control dissolution rate and thereby enhance solubility to develop an improved and convenient dosage form. Preformulation studies included selection of excipients and evaluation of compatibility with griseofulvin. Tablets were prepared by wet granulation technique with varying ratios of Methocel™, Accurel MP and Polyvinylpyrrolidone as determined by Design Expert software. Buoyancy capability and dissolution studies were carried out to assess the influence of the tablet components. Tablets that float immediately upon contact with dissolution medium and continue floating for over 12 h were achieved with at least 28% of Accurel MP. An increase in tablet hardness reduced the rate of griseofulvin release only up to 120 min. Methocel™ had the most significant influence on griseofulvin release, with an indirect proportion to the rate of griseofulvin release. Using Design Expert software, optimized formulation was achieved with 1% Polyvinylpyrrolidone, 30% Methocel™, 60% Accurel MP and hardness ranging between 8 and 9 N. Tablets produced floated immediately upon contact with the medium and remained floating for at least 12 h. Griseofulvin was released from the optimized tablets in a near zero order fashion, with a total of 80.8% griseofulvin released at the end of the 12-h dissolution test period.

Key words: Griseofulvin, gastro-retentive, floating tablets.

INTRODUCTION

Gastro-retentive dosage forms are systems that retain in the stomach for a sufficient time interval against all the physiological barriers and release active moiety in a controlled manner (Foda, 2011). Gastric retention

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provides advantages such as the delivery of drugs which are absorbed over a small region of the gastro-intestinal tract (Narang, 2011). As well, longer residence time in the stomach is favorable for local action in the upper part of the small intestine (Kumar et al., 2013). This study employs the formulation of floating tablets of griseofulvin.

Griseofulvin is an antibiotic fungistatic drug used in the treatment of dermatophyte and ringworm infections. Dermatophytes affect approximately 20 to 25% of the world's population and are responsible for 30% of all skin fungal infections (Venturini et al., 2012). Griseofulvin has antimitotic properties, owing to its interference with the normal polymerization of microtubule protein (Rebacz et al., 2007). Griseofulvin is a metabolic product of *Penicilium grisofulvum* (Jiang et al., 2012). It is a white to pale cream odourless or almost odourless tasteless powder (BP, 2019). Griseofulvin is very slightly soluble in water (0.2 g/L at 25°C), sparingly soluble in ethanol and methanol, soluble in acetone, chloroform and dimethylformamide (BP, 2019). Despite its use for dermatophytes infections, griseofulvin is administered only orally due to its poor penetration of the skin. Generally, due to low aqueous solubility, about 50% of a dose of griseofulvin passes through the gastro- intestinal tract unabsorbed and is excreted in faeces (Merck Manual, 2010). To enhance the solubility and absorption of griseofulvin in pharmaceutical preparations, it is normally mixed with a non-toxic, water soluble polymer such as polyvinylpyrrolidone or hydroxypropyl cellulose and spray-dried before treatment with a wetting agent such as sodium lauryl sulphate or benzalkonium chloride. The resulting material is characterized as 'microsized' crystals of griseofulvin (Desai and Soon-Shiong, 2003). This has influenced griseofulvin to be commercially available as tablets containing 250 mg or 500 mg microsize or 125 mg or 165 mg ultramicrosize crystals of griseofulvin. It is also available as capsules containing 250 mg microsize griseofulvin and as an oral suspension containing 125 mg/5 ml microsize griseofulvin. However, micronization is costly and involves many steps. Griseofulvin has been observed to be highly soluble in acidic pH, making it a suitable candidate for gastro-retentive formulation in a bid to control dissolution rate and thereby enhance solubility and absorption (Persson et al., 2005). This study formulates floating tablets of griseofulvin using polypropylene foam powder (Accurel®), a low density polymeric carrier. Addition of Accurel® results in a matrix with a density less than 1 g/cm^3, allowing tablets to float on gastric juice (Al-achi et al., 2013).

MATERIALS AND METHODS

Griseofulvin (Aspen Pharmacare, South Africa) was the active ingredient. Accurel MP (Membrana, Germany) was used as a low density polymer. Hydroxy Propyl Methyl Celulose (Methocel™ K100, Colorcon, England) was selected as the rate controlling polymer. Polyvinylpyrrolidone (PVP K-30, Fluka, United States) was used as a binder. Magnesium stearate (BDH Chemicals Ltd, England) was chosen as lubricant and ethanol (Sigma Aldrich, South Africa) was used as a granulating agent.

Compatibility studies

Compatibility studies were carried out to investigate the potential interactions between drug and excipients before formulation. A DSC-60 Shimadzu (Kyoto, Japan) instrument was used to record the DSC thermograms. Thermograms obtained in DSC were analysed based on the changes in appearance, disappearance or shift of endothermic or exothermic peaks of griseofulvin-excipient mixtures as compared to the pure griseofulvin and excipients (Heljo, 2007).

Preparation of floating tablets of griseofulvin

A total of 25 runs, Table 1, were generated using Design Expert Software 9.0, specifically varying polymer ratios, binder concentration and compression force, as shown in Table 2. Magnesium stearate was kept at 1% for all the formulations. Tablets containing 100 mg of griseofulvin were prepared by wet granulation technique. Griseofulvin and all the other excipients were weighed accurately for a batch size of 200 tablets. To avoid segregation of materials, Accurel MP and other excipients were separately passed through 850 µm sieve in order to obtain finer particles of similar size. Materials were transferred into a 1000 ml plastic beaker and mixed thoroughly with a bowl and stand mixer (Kenwood, United Kingdom) mixer for 10 min to form a homogeneous mixture. To the above powder blend, 60% ethanol (granulating agent) was added followed by mixing until the end point of granulation was observed. The wet granules were then passed through an 850 µm sieve, transferred onto a stainless steel plate covered with aluminium foil and placed in an oven. The granules were dried at 40°C (Labotec, South Aftrica) until the moisture content was less than 1.5%. The dried granules were transferred into a 1000 ml plastic beaker and blended with previously weighed and screened magnesium stearate for three minutes using a spatula. The final granules were compressed using a 12 mm diameter compression tooling on a Cadmach compression machine (India). Tablets were formulated as per quality standards stipulated by United States Pharmacopoeia.

Pre-compression studies

Pre-compression studies were done to assess the flow properties of granules before compression. Bulk density, tapped density, angle of repose, loss on drying and compressibility of the granules were analysed before compression of the tablets, as per methods described by Wells and Aulton (2007).

Post-compression studies

Tablets were evaluated for the post-compression parameters which include physico-chemical parameters like weight variation, thickness, diameter, hardness, friability, in-vitro drug release (dissolution) and assay.

Buoyancy studies

Buoyancy test was performed as per the method of Taghizadeh et al. (2013). To determine the floating lag time, 6 tablets were put in

Table 1. Composition of Griseofulvin floating tablet formulations generated by Design Expert Software Version 9.0.

Run	Methocel (mg)	Accurel mp (mg)	PVP k – 30 (%)	Hardness (N)
1	65.500	100.000	2.080	10.000
2	25.000	91.375	1.000	9.000
3	72.625	25.000	2.17483	9.000
4	25.000	80.500	2.460	12.000
5	25.000	100.000	3.000	8.000
6	56.741	62.500	2.000	8.000
7	65.500.000	100.000	2.080	10.000
8	100.000	25.000	3.000	8.000
9	64.000	65.125	3.000	10.000
10	73.000	92.500	1.000	12.000
11	56.741	62.500	2.000	8.000
12	85.000	25.000	1.000	8.000
13	25.750	26.875	1.000	11.000
14	25.000	25.000	2.750	9.000
15	100.000	51.340	1.700	11.000
16	100.000	100.000	3.000	12.000
17	100.000	98.125	3.000	8.000
18	100.000	95.875	1.693	11.000
19	72.250	25.000	2.750	12.000
20	100.000	51.340	1.700	11.000
21	25.000	100.000	1.220	12.000
22	64.000	65.125	3.000	10.000
23	64.000	65.125	3.000	10.000
24	100.000	100.000	1.000	8.000
25	54.513	52.375	1.724	12.000

Table 2. Factors and levels for factorial design.

Factor	Level	
	Lower	Upper
X_1 Methocel (mg)	0	100
X_2 Accurel Mp (mg)	0	100
X_3 PVP k- 30 (%)	1	3
X_4 Tablet hardness (N)	8	12
Dependent variable 1	Lag time	
Dependent variable 2	Floating time	
Dependent variable 3	Drug release	

100 mL of 0.1 N HCL in a beaker, and the timerequired for each tablet to rise to the surface was measured. Then, the duration of each tablet that remained on the surface was determined as total floating time. Mean and standard deviation were calculated for the measurements obtained from 6 tablets.

Assay of tablets

Assay of the manufactured tablets was performed to assess the amount of griseofulvin contained, following BP method (BP, 2019). Twenty tablets per formulation run were weighed and powdered. To a quantity of powder containing 35 mg of griseofulvin, 60 ml of ethyl acetate was added. The solution was mixed and heated to 60°C with shaking for 20 min. The solution was allowed to cool and was diluted to 100 ml with ethyl acetate. Afterwards, the solution was centrifuged and two 5 ml aliquots of the clear supernatant liquid were transferred into separate 100 ml graduated flasks. To the first flask, 5 ml of 2 M methanolic methanesulfonic acid was added and the solution was allowed to stand at 20°C for 30 min. The solution

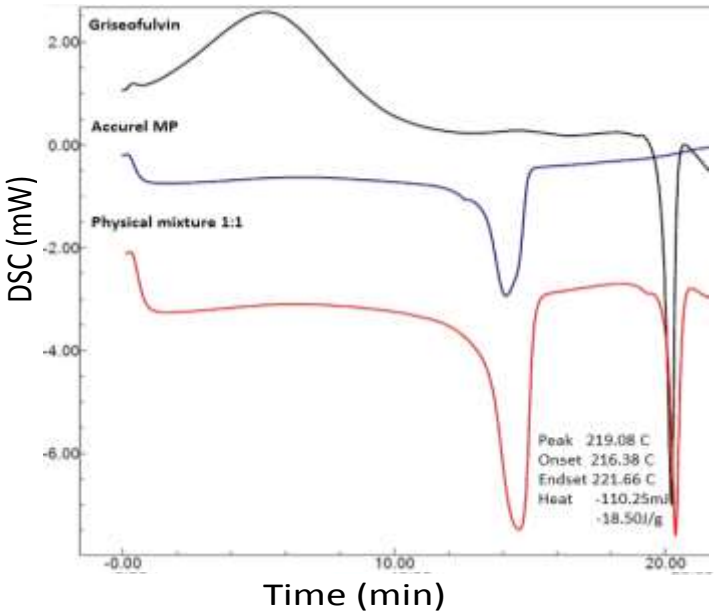

Figure 1. Thermograms of griseofulvin, Accurel MP and 1:1 (w/w) griseofulvin / Accurel MP mixture.

was diluted to 100 ml with methanol and labelled solution A. The contents of the second flask were diluted to 100 ml with methanol and labelled solution B. To a third flask, 5 ml of 2 M methanolic methanesulfonic acid was added and diluted to 100 ml with methanol. This solution was labelled solution C. The absorbance of each solution was measured at 266 nm. The content of griseofulvin was calculated from the difference between the absorbance obtained with solution A and the sum of the absorbances obtained with solutions B and C and from the difference obtained by repeating the operation using 35 mg of griseofulvin BPCRS (British Pharmacopoeia Catalogue Reference Standard, 2014) in place of the powdered tablets and from the declared content of griseofulvin in griseofulvin BPCRS. Acceptance criteria used: 95.0 - 105.0%.

In-vitro analysis of griseofulvin release from the floating tablets

A dissolution apparatus 2 (paddle apparatus) was used in 900 ml of dissolution medium containing 0.1 N hydrochloric acid and 4% sodium lauryl sulphate at 37 ± 0.5°C and a pH of 1.2. Rotation speed of paddle used was 100 rpm (USP, 2016). Samples (5 ml) were taken from the dissolution apparatus at set time intervals: 30, 60, 90, 120, 180, 240, 360, 480 and 720 min. The amount of griseofulvin dissolved was determined by employing a UV spectrophotometer at 296 nm. A standard calibration curve of griseofulvin in 0.1 N hydrochloric acid with 4% sodium laurylsulphate was plotted and regression coefficient calculated to validate method.

RESULTS AND DISCUSSION

Compatibility studies

A comparison of the thermogram of griseofulvin to that of 1:1 (w/w) griseofulvin/Accurel MP mixture showed no significant change in enthalpy peak shape or onset, indicating the compatibility of griseofulvin with Accurel MP, as shown in Figure 1. No significant change was observed in the thermoanalytical profiles of griseofulvin and Methoce™l, as shown in Figure 2. As well, no significant changes were observed in the endothermic peaks of griseofulvin and magnesium stearate (Figure 3). Magnesium stearate is the most common lubricant used in tableting. It is a white powder, which is insoluble in nature. Magnesium stearate reduces both wall friction and internal friction of powder and granules. This makes materials (powder/granules) glide better and be non-adherent, thereby enhancing flowability (Li and Wu, 2014).

The thermogram of griseofulvin/PVP k-30 mixture showed a slight broadening of the endothermic peak of griseofulvin, indicating a low degree of incompatibility between griseofulvin and PVP k-30 (Figure 4).

Polyvinylpyrrolidone, also known as povidone is a binder used in both wet and dry granulation. Polyvinylpyrrolidone facilitates agglomeration of powder material to form granules of desired hardness and size (Cantor et al., 2008).

Pre-compression studies

Table 3 shows results of pre-compression studies. All formulations had values of Carr's Index and Hausner ratios of less than 20.0 and 1.25, respectively. Run 2 had

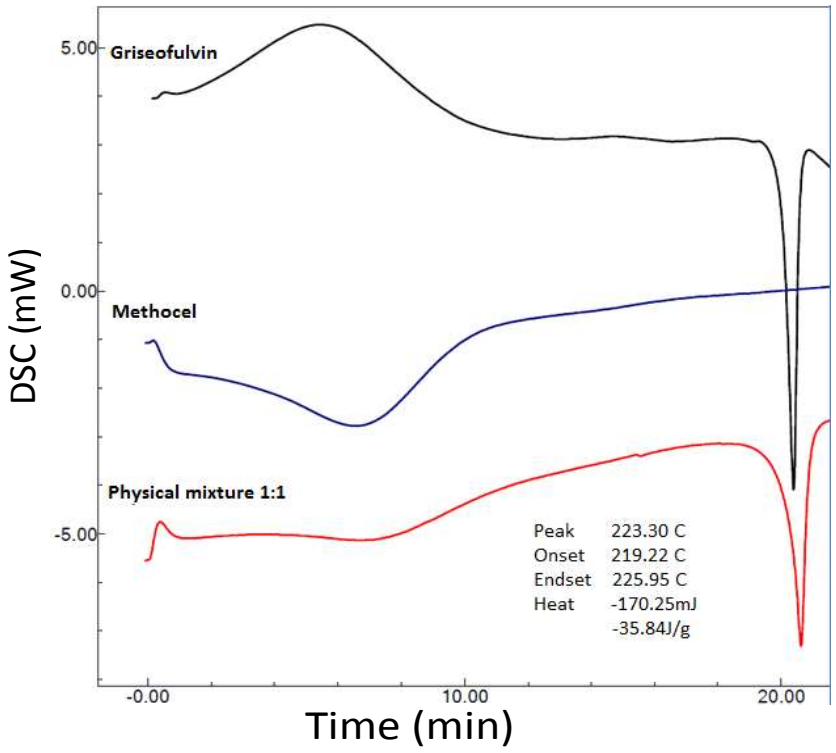

Figure 2. Thermograms of griseofulvin, Methocel™ and 1:1 (w/w) griseofulvin / Methocel™ mixture.

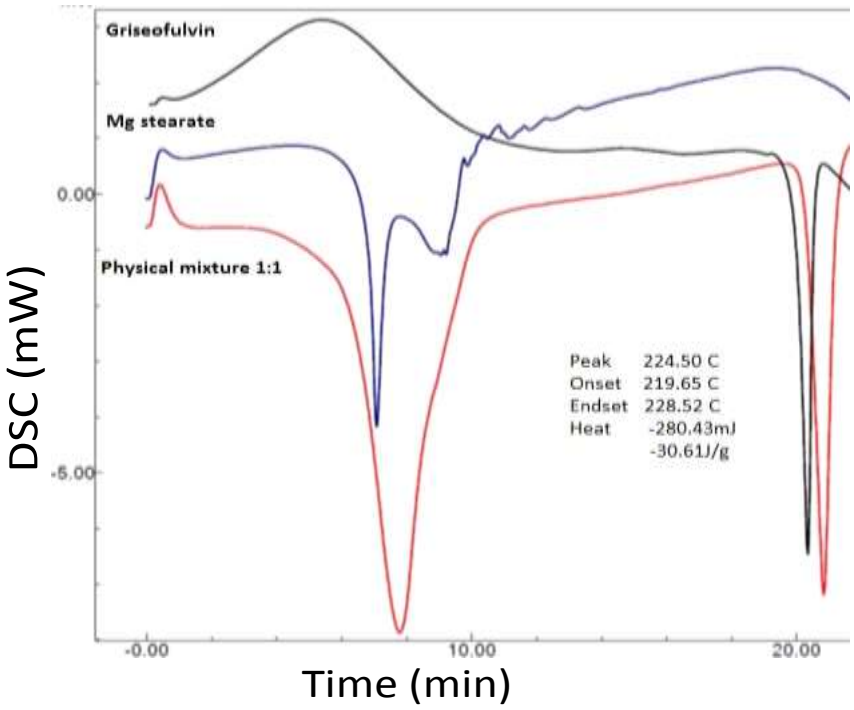

Figure 3. Thermograms of griseofulvin, magnesium stearate and 1:1 (w/w) Griseofulvin / magnesium stearate.

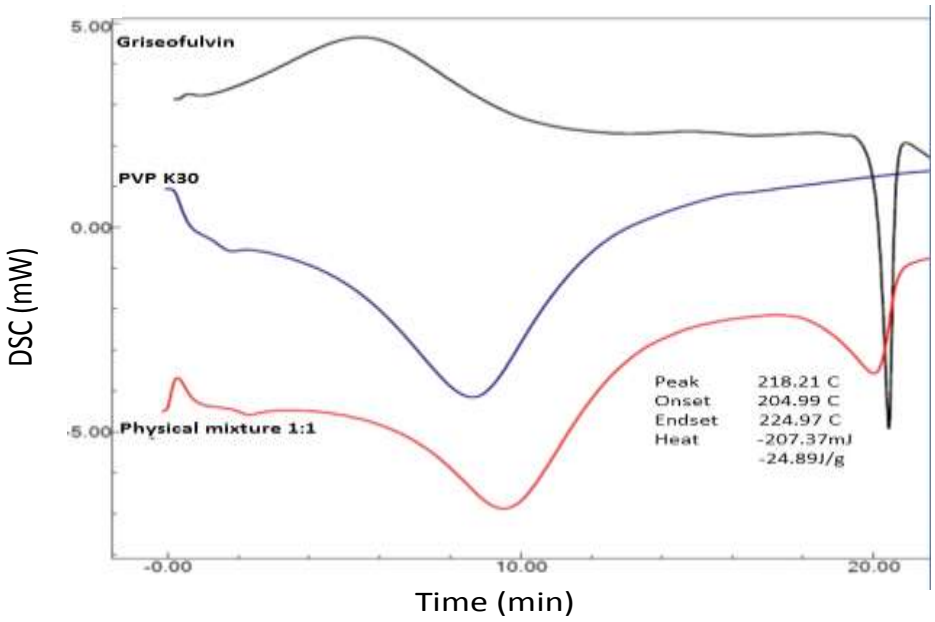

Figure 4. Thermograms of griseofulvin, PVP-k30 and 1:1 (w/w) griseofulvin/PVP- k30 mixture.

Table 3. Pre-compression parameters of Griseofulvin tablets formulation runs.

Batch	BD (g/ml)	TD (g/ml)	CI (%)	H	C	AR (ɵ) ± S.D	FP	LOD (%)
Run 1	0.18	0.27	17.73	1.18	Fair	37.4 ± 1.3	Fair	0.43
Run 2	0.20	0.21	7.59	1.08	Excellent	32.2 ± 1.4	Good	0.21
Run 3	0.22	0.26	18.00	1.18	Fair	34.5 ± 1.5	Good	0.32
Run 4	0.18	0.21	14.89	1.18	Fair	32.2 ± 0.9	Good	1.65
Run 5	0.17	0.19	10.76	1.12	Good	30.5 ± 0.7	Good	2.71
Run 6	0.19	0.22	13.69	1.16	Good	32.8 ± 1.4	Good	0.54
Run 7	0.18	0.22	19.56	1.24	Fair	33.6 ± 1.3	Good	3.43
Run 8	0.23	0.27	16.67	1.20	Fair	33.3 ± 0.8	Good	2.21
Run 9	0.18	0.21	12.35	1.14	Good	33.9 ± 2.1	Good	0.25
Run 10	0.18	0.21	12.50	1.14	Good	32.4 ± 0.6	Good	1.58
Run 11	0.19	0.22	13.57	1.16	Good	34.4 ± 0.7	Good	2.73
Run 12	0.26	0.30	12.69	1.15	Good	34.9 ± 1.4	Good	4.65
Run 13	0.21	0.25	13.72	1.16	Good	34.4 ± 0.7	Good	2.54
Run 14	0.22	0.27	19.35	1.24	Fair	33.8 ± 1.9	Good	3.44
Run 15	0.19	0.22	14.2	1.17	Good	35.1 ± 0.7	Good	0.87
Run 16	0.19	0.21	11.98	1.14	Good	34.9 ± 1.2	Good	1.74
Run 17	0.18	0.21	13.78	1.16	Good	35.7 ± 1.7	Good	1.32
Run 18	0.18	0.20	12.80	1.14	Good	32.4 ± 1.6	Good	0.13
Run 19	0.20	0.23	14.46	1.17	Good	35.6 ± 1.4	Good	3.72
Run 20	0.19	0.22	12.09	1.14	Good	33.2 ± 2.0	Good	1.93
Run 21	0.16	0.19	14.16	1.16	Good	32.4 ± 1.3	Good	1.21
Run 22	0.19	0.23	14.52	1.17	Good	32.8 ± 1.5	Good	0.34
Run 23	0.19	0.21	12.78	1.15	Good	33.1 ± 1.3	Good	2.38
Run 24	0.19	0.21	13.00	1.15	Good	33.4 ± 1.4	Good	0.67
Run 25	0.19	0.22	13.59	1.16	Good	35.2 ± 1.2	Good	2.43

*BD = Bulk Density, TD = Tapped Density, CI = Compressibility Index, H = Hausner ratio, AR = Angle of Repose, LOD = Loss On Drying, C = Compressibility, FP = Flow properties; S.D: Standard deviation.

Table 4. Post-compression parameters of griseofulvin floating tablets formulation runs.

Batch	WV (g) ± S.D	H (N) ± S.D	D (mm) ± S.D	T (mm) ± S.D	F (%)
Run 1	0.2909 ± 0.009	10.1 ± 1.2	12.00 ± 0.1	3.40 ± 0.1	0.14
Run 2	0.2282 ± 0.006	8.8 ± 0.6	12.00 ± 0.1	2.70 ± 0.1	0.06
Run 3	0.2357 ± 0.018	10.8 ± 1.6	12.01 ± 0.1	2.22 ± 0.1	0.08
Run 4	0.2274 ± 0.012	8.6 ± 1.0	12.03 ± 0.1	2.52 ± 0.1	0.10
Run 5	0.2392 ± 0.010	11.3 ± 1.1	12.02 ± 0.1	2.48 ± 0.1	0.05
Run 6	0.2474 ± 0.007	9.0 ± 1.0	12.00 ± 0.1	2.68 ± 0.1	0.21
Run 7	0.2834 ± 0.014	11.4 ± 1.8	12.00 ± 0.1	3.08 ± 0.1	0.12
Run 8	0.2652 ± 0.009	8.6 ± 0.7	12.00 ± 0.1	2.58 ± 0.1	0.06
Run 9	0.2491 ± 0.009	11.7 ± 0.9	12.01 ± 0.1	2.52 ± 0.1	0.08
Run10	0.2981 ± 0.009	12.1 ± 1.3	12.00 ± 0.1	3.20 ± 0.1	0.14
Run11	0.2278 ± 0.017	9.1 ± 0.5	12.00 ± 0.1	2.00 ± 0.1	0.06
Run 12	0.1963 ± 0.014	7.2 ± 1.5	12.00 ± 0.1	1.90 ± 0.1	0.04
Run 13	0.1292 ± 0.005	6.6 ± 1.4	12.00 ± 0.1	1.18 ± 0.1	0.12
Run 14	0.1546 ± 0.008	9.7 ± 0.4	12.00 ± 0.1	1.24 ± 0.1	0.06
Run 15	0.2512 ± 0.010	11.0 ± 1.3	12.04 ± 0.1	2.50 ± 0.1	0.02
Run 16	0.2922 ± 0.013	10.4 ± 0.6	12.00 ± 0.2	3.26 ± 0.1	0.07
Run 17	0.3062 ± 0.013	10.0 ± 0.8	12.00 ± 0.1	3.38 ± 0.1	0.08
Run 18	0.3069 ± 0.014	8.4 ± 0.9	12.02 ± 0.1	3.46 ± 0.1	0.04
Run 19	0.1871 ± 0.009	8.2 ± 0.3	12.00 ± 0.1	1.64 ± 0.1	0.14
Run 20	0.2497 ± 0.016	11.4 ± 1.6	12.00 ± 0.1	2.30 ± 0.1	0.01
Run 21	0.2258 ± 0.009	11.3 ± 1.0	12.00 ± 0.1	2.30 ± 0.1	0.04
Run 22	0.2442 ± 0.010	10.5 ± 1.0	12.03 ± 0.2	2.54 ± 0.1	0.08
Run 23	0.2447 ± 0.006	11.0 ± 0.5	12.00 ± 0.1	2.51 ± 0.1	0.11
Run 24	0.3267 ±0.014	10.0 ± 1.0	12.00 ± 0.1	3.84 ± 0.1	0.05
Run 25	0.2113 ± 0.007	11.6 ± 0.7	12.01 ± 0.1	2.06 ± 0.1	0.08

*WV = Weight Variation, H = Hardness, D = Diameter, T = Thickness, T = Thickness, F = Friability & S.D: standard deviation.

excellent compressibility, 18 runs had good compressibility and 6 runs had fair compressibility. Carr's Index and Hausner ratios which reflect the impact of tapping on particle packing and are influenced by particle size, shape and cohesivity predicted that all the formulations were compressible. Twenty four of the runs had granules with good flowability. The only exception, Run 1, had granules with fair flowability. However, all formulations had an angle of repose less than 40°, an angle acute enough to predict weak intermolecular forces of attraction between granules. It was thus satisfactory to proceed to compression without any further recommendations to aid flowability of the granules. All formulation runs had water content (loss on drying) of less than 5.0%.

Post-compression studies

The results of quality control tests done on formulated tablets are presented in Table 4. Consistency of tablet weight within each run was assessed by the weight variation test. From a sample of twenty tablets from each run, not more than two tablets were outside a weight range of 7.5% from their mean. This confirmed consistency of weight uniformity and all formulation runs passed weight variation test.

Tablets with high content of Methocel™ were compressed to the required hardness, whereas tablets with high content of Accurel MP compared to Methocel™ were difficult to compress to the required hardness due to its less compressibility associated with reduced friction between particles.

The values of diameter, thickness and hardness for all formulation runs were taken and the deviation of each calculated. None of the deviations of diameter, thickness or hardness exceeded ± 5%. All formulation runs passed the diameter, thickness and hardness test. All formulation runs had friability of less than 1%. Therefore, all formulation runs passed friability test and confirmed that the tablets produced were capable enough to resist breakage under stress conditions during handling. The tablets produced were of acceptable quality according to USP standards.

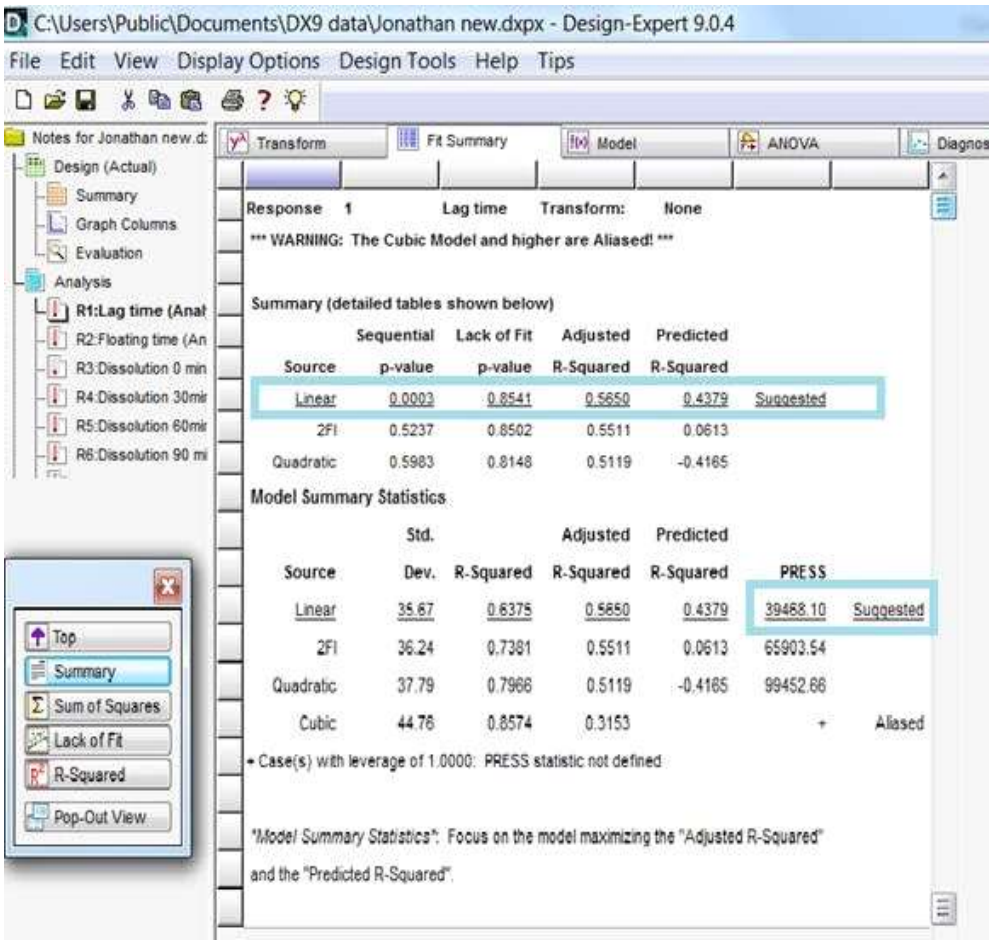

Figure 5. Statistical analysis of model of fit for lag time using design expert.

Buoyancy studies

All formulation runs that produced tablets that floated had densities less than 0.00091 g/cm^3. Using Design Expert 9.0, a linear model was the best fit model for both lag time and floating time with sequential p-values of 0.0003 and 0.0021, and lack of fit values of 0.8541 and 0.9118, respectively (Figures 5 and 6).

It was determined that only Accurel MP had a significant influence on lag time and floating time, with a “Probability > F” value of less than 0.0001. An increase in Accurel MP decreased lag time, as shown in Figure 7. Accurel MP, polypropylene foam powder, is a low density polymer used in floating drug delivery systems. When included in a matrix, Accurel MP adsorbs the drug, excipients and entraps air. The entrapped air reduces the density of the formulation and allows the unit to float when exposed in an aqueous environment (Al-Achi et al., 2013). Accurel Mp was directly proportional to floating time. Approximately 28% w/w of Accurel MP was sufficient to achieve immediate floatation of tablets and floatation of at least 24 h.

Assay of griseofulvin tablets

The quantity of griseofulvin in the compressed tablets was calculated and results obtained are shown in Table 5.

The British Pharmacopoeia (BP) specifies that griseofulvin tablets should contain not less than 95.0% and not more than 105.0% of the labelled amount. As shown in Table 5, all formulation runs had percentage griseofulvin content within the acceptable range and hence the formulated tablets complied with the USP specification. The formulated tablets contained the claimed amount of griseofulvin, 100 mg.

In-vitro drug release studies

Highest percentage drug release was achieved by formulation runs that had the least amount of Methocel™

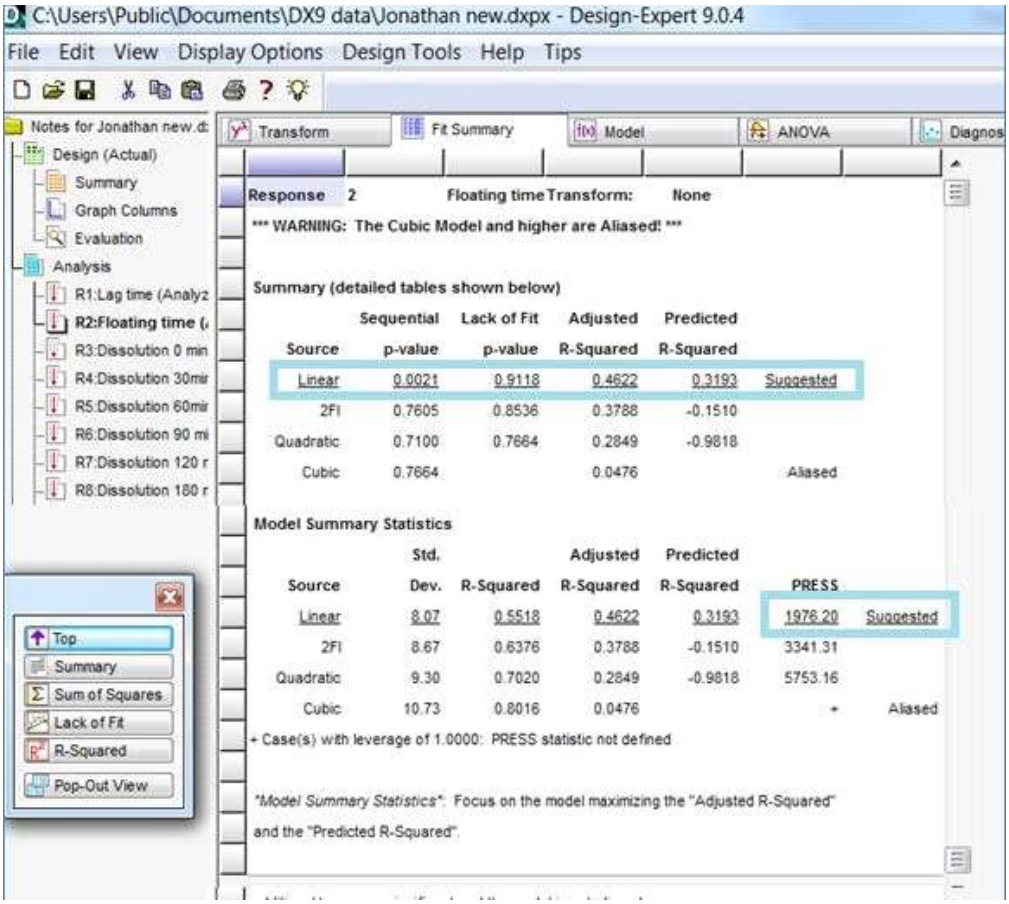

Figure 6. Statistical analysis of model of fit for floating time using design expert.

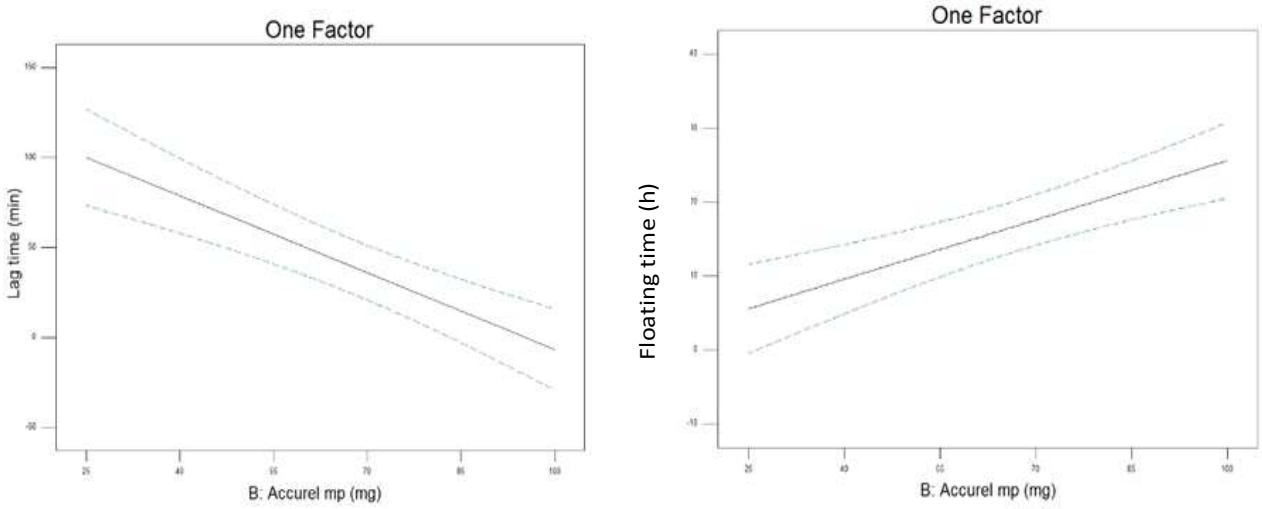

Figure 7. Influence of Accurel MP on lag time and total floating time.

of 25 mg, whilst formulation runs that had the highest amount of Methocel™, 100 mg showed the least drug release rate and the least total drug release, as shown in Figure 8.

Table 5. Assay of griseofulvin tablets.

Batch	Quantity ± SD (mg)	Percentage assay	Batch	Quantity ± SD (mg)	Percentage assay
Run 1	98.7 ± 2.4	98.7	Run 14	104.6 ± 0.4	104.6
Run 2	95.7 ± 1.6	95.7	Run 15	101.6 ± 2.7	101.6
Run 3	102.9 ± 2.6	102.9	Run 16	96.4 ± 2.1	96.4
Run 4	99.4 ± 2.1	99.4	Run 17	97.8 ± 2.4	97.8
Run 5	95.7 ± 0.9	95.7	Run 18	95.3 ± 1.5	95.3
Run 6	96.6 ± 2.1	96.6	Run 19	96.3 ± 2.1	96.3
Run 7	97.9 ± 1.5	97.9	Run 20	98.1 ± 2.4	98.1
Run 8	97.0 ± 1.8	97.0	Run 21	95.3 ± 1.3	95.3
Run 9	96.2 ± 1.1	96.2	Run 22	95.5 ± 1.2	95.5
Run 10	104.6 ± 0.4	104.6	Run 23	97.6 ± 1.3	97.6
Run 11	101.6 ± 1.9	101.6	Run 24	96.2 ± 1.8	96.2
Run 12	96.4 ± 2.2	96.4	Run 25	97.8 ± 2.1	97.8
Run 13	97.8 ± 3.1	97.8	-	-	-

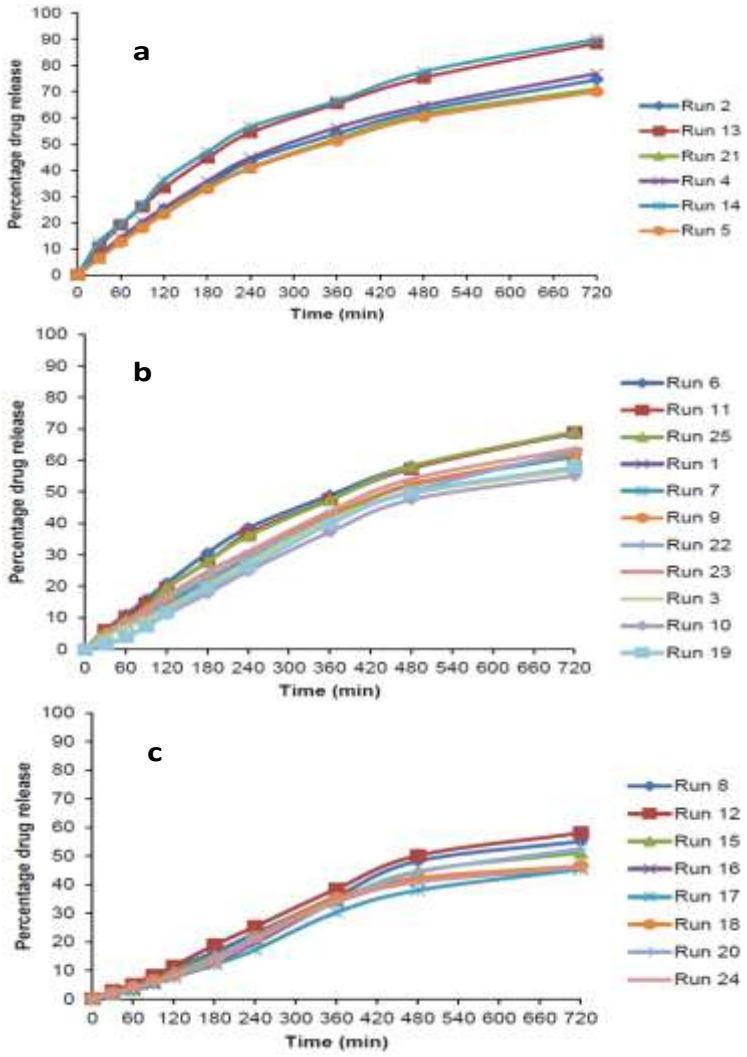

Figure 8. *In-vitro* drug release profile of the formulation runs with (a) 25% Methocel^{TM}, (b) 50 to 75% Methocel^{TM} and (c) 100% Methocel^{TM}.

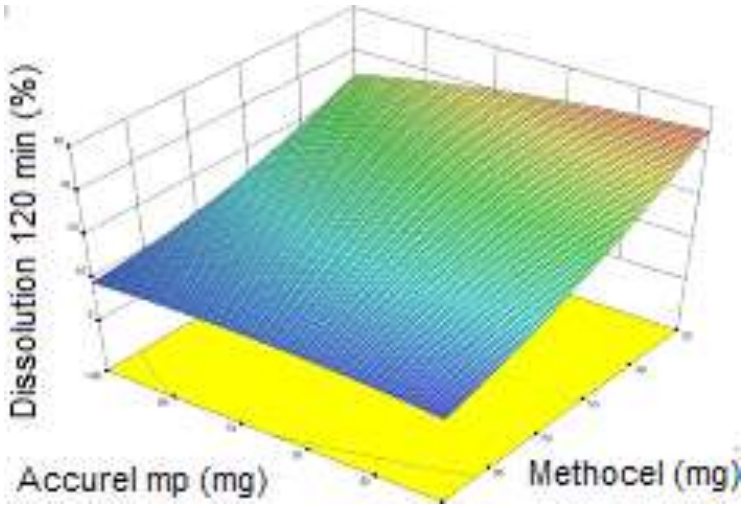

Figure 9. Combined effect of Methocel™ and Accurel MP on initial release of griseofulvin.

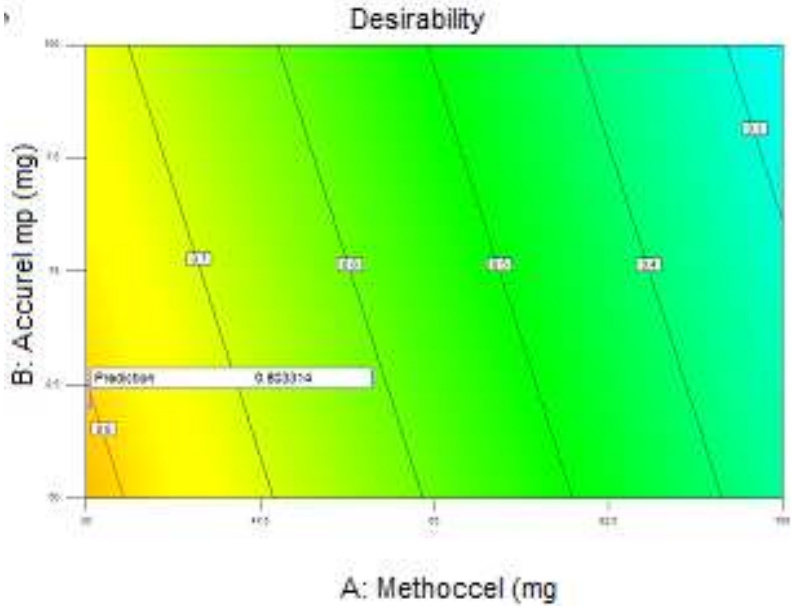

Figure 10. Optimized formula.

Initial drug release followed a quadratic model, with a sequential p-value of 0.0290 and a lack of fit p-value of 0.0208. Methocel™ had the most pronounced effect on initial drug release whilst Accurel MP had less effect on drug release and an increase in tablet hardness slightly decreased release of griseofulvin (Figure 9). Methocel™, also known as hydroxypropyl methylcellulose (HPMC), is a water-soluble, non-ionic cellulose ether. It retains chemical stability over a pH range of 3.0-11.0 and resists enzymatic degradation (Dow, 2000). HPMC has a cellulose backbone with ether linked methoxyl and hydroxypropyl side group substituents attached through ether linkages to the cellulose chain hydroxyl groups. A combination of 30 mg Methocel™ and 60 mg Accurel MP provided the most optimum formulation (Figure 10).

The formulation produced tablets that floated immediately with floating time above 12 h with 80.8% release of griseofulvin (Figures 11 and 12). Evaluation of drug release kinetics revealed a zero order model to best fit griseofulvin release data from the tablets, with a

Figure 11. Tablets assessed for buoyancy capabilities.

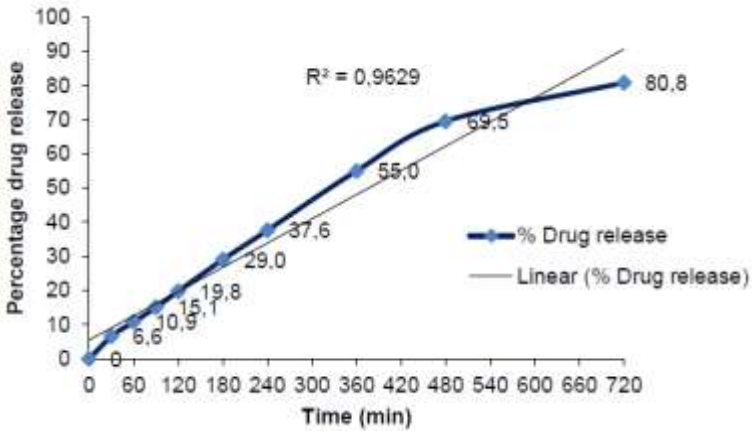

Figure 12. *In-vitro* drug release profile of the optimized batch.

correlation coefficient of 0.9983 (Figure 13).

Conclusion

Design Expert generated 25 formulation runs which were compressed to assess the influence of Methocel™, Accurel MP, tablet hardness and polyvinylpyrrolidone on buoyancy and drug release. Accurel MP concentration was directly proportional to lag time and total floating time of tablets. Methocel™ concentration was indirectly proportional to release rate of griseofulvin from tablets. The optimized formulation, of ratio Methocel™:Accurel MP:hardness 30:60:8-9, respectively was chosen and floating tablets were compressed. Compressed tablets float immediately upon contact with dissolution medium

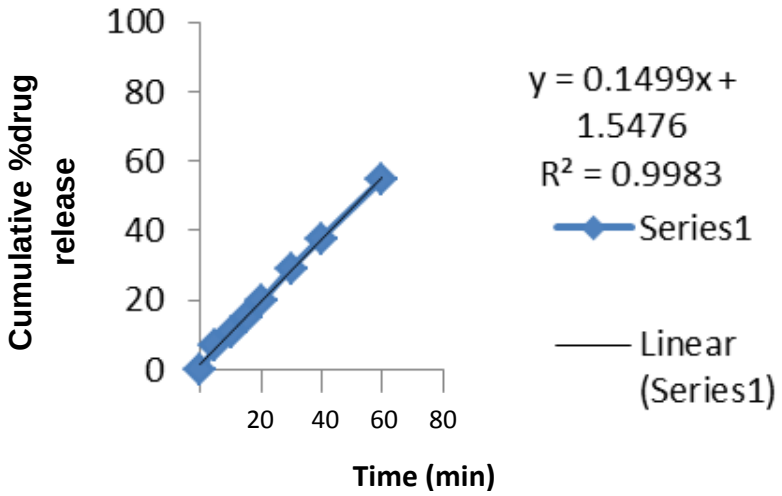

Figure 13. Drug release kinetics - Zero order release model.

and float for more than 12 h. Griseofulvin was released in a zero order fashion over 12 h, with 80.8% released within that period. Tablets were of acceptable quality according to USP standards.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

The authors appreciate the University of Limpopo for resources and facilities.

REFERENCES

Al-achi A, Gupta MR, Stagner WC (2013). Integrated Pharmaceutics: Applied Preformulation, Product Design, and Regulatory Science", John Wiley & Sons P 77.

Cantor S, Ausburger L, Hoag S, Gerhardt (2008). Pharmaceutical granulation processes, mechanism, and the use of binders in pharmaceutical dosage form: Tablets. Augsburger and SW Hoag, Informa Healthcare USA, Inc 1:261-301.

Desai NP, Soon-Shiong P (2003). Compositions and methods for administration of pharmacologically active compounds. US Patent pp. 1-21.

Dow T (2000). Using Methocel™ cellulose ethers for controlled release of drugs in hydrophilic matrix systems. Midland (MI): The Dow Chemical Company pp. 1-36.

Foda N (2011). Gastroretentive drug delivery systems as a potential tool for enhancing the efficacy of antibiotics: a review. International Journal of Pharmaceutics and Biological Sciences 2(4):94-105.

Heljo P (2007). Thermo mechanical compatibility study of drug containing siloxone matrices [Online]. Available at: http://www.pharmtech.helsinki.fi/seminaarit/vanhat/esitelma_phelijo.pdf [Accessed 9 July, 2017].

Jiang W, Gao S, Yang L, Zhang X, Sun H (2012). Distribution and elimination of griseofulvin residue in rabbit tissues. Proceedings 10th World Rabbit Congress, Sharm El-Sheikh, Egypt pp. 973-977.

Kumar MR, Satyanarayana B, Paladugu ND, Neerukondavamsi SM, Pasha SI, Vemireddy S,(2013). A comprehensive review on gastro retentive drug delivery system. Acta Chimica Pharmaceutics Indica 3(2):149-164.

Li J, Wu Y (2014). Lubricants in pharmaceutical solid dosage forms. Lubricants 2(1):21-43.

Merck Manual (2010). Antifungal agents. [Online] Available at: http://www.merckmanuals.com/vet/pharmacolgy/antifungal_agents/griseofulvin.ht ml [Accessed 2 September, 2017].

Narang N (2011). An updated review on: floating drug delivery system (FDDS). International Journal of Applied Pharmaceutics 3(1):1-7.

Persson EM, Gustafsson A, Carlsson AS, Nilsson RG, Knutson L, Forsell P (2005). The effects of food on the dissolution of poorly soluble drugs in human and in model small intestinal fluids. Pharmaceutical Research 22(12):2141-2151.

Rebacz B, Larsen TO, Clausen MH, Ronnest MH, Loffler H, HO AD, Kramer A (2007). Identification of griseofulvin as an inhibitor of centrosomal clustering in a phenotype-based screen. Cancer Research 67(13):6342-6350.

Taghizadeh DE, Noordin IM, Kadivar A, Kamalidehghan B, Farjam (2013). Preparation and characterization of a gastric floating dosage form of capecitabine. Biomed Research International pp. 1-8.

United States of Pharmacopoeia (USP) (2016). USP 31-NF 23. Rockville, MD: United States Pharmacopoeial Convention, Inc.

Venturini J, Alvares AM, DE Camargo MR, Marchetti CM, Campos Fraga-Silva DE, Thais Fernanda Luchini AC, De Arruda MSP (2012). Dermatophyte-host relationship of a murine model of experimental invasive dermatophytosis. Microbes and Infection 14(13):1144-1151.

Wells JI, Aulton ME (2007). Pharmaceutical preformulation. In: Aulton, ME (Ed). The design and manufacture of medicines. 3rd Edition. Elsevier: Hungary pp. 336-360.