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Formulation, *in-vitro* Evaluation and Dissolution Enhancement of Griseofulvin by Solid Dispersion Method

Gopal Pokhrel[1], Bikash Dani[1], Srijana Shrestha[1], Rakshya Chaudhary[1], Ramesh Dhami[1], Barnabas Sunuwar[1], Sharad Pudasaini[2], Vijay Yadav[2], Lalit Mohan Pant[2] and Rajan Ghimire[3]

1. Department of Pharmacy, Karnali College of Health Sciences, Kathmandu, Nepal

2. Department of Pharmacy, HOPE International College, Lalitpur, Nepal

3. Deurali-Janta Pharmaceuticals Pvt. Ltd., Kathmandu, Nepal

Abstract: Introduction: Griseofulvin is an antifungal drug belonging to Biopharmaceutical Classification System (BCS class II) having low solubility. **Objectives**: To formulate, evaluate and enhance the dissolution of poorly water soluble drug Griseofulvin by using solid dispersion method. **Methods**: Six formulations were prepared by solid dispersion method using Polyethylene Glycol (PEG 6000) 125 mg, 0 mg, 62.5 mg, 100 mg, 25 mg, 150 mg and superdisintegrants Crospovidone 0 mg, 125 mg, 62.5 mg, 100 mg, 25 mg, 150 mg in all batches respectively. **Findings**: Satisfactory results were obtained from evaluation of physical characteristics of Griseofulvin tablets including: carr's compressibility index (17.5 ± 0.19% to 11.76 ± 0.67%), Hausner ratio (1.21 ± 0.01 to 1.13 ± 0.02) and post compression parameters including: thickness (5.16 ± 0.02 mm to 4.57 ± 0.19 mm), friability (0.024% to 0.322%), hardness (4 ± 0.28 kg/cm ^{2} to 5 ± 0.57 kg/cm ^{2}), disintegration time (14-870 seconds). **Conclusions**: F3 was best formulation among all formulated batches with *in-vitro* drug release 30.05% in 10 minutes, 69.21% in 30 minutes and 97.11% in 45 minutes. This indicated that formulation F3 batch with PEG 6000 of 62.5 mg and crospovidone 62.5 mg showed increased dissolution.

Key words: Griseofulvin, formulation, solid dispersion, solubility, evaluation.

1. Introduction

Griseofulvin is an oral antifungal with poor solubility and low bioavailability, widely used for the treatment of dermatophytes infection [1]. It is on the World Health Organization (WHO) list of essential medicines, the safest and most effective medicines needed in health system [2].

Solid dispersion is one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties [3]. Two components, a poorly water-soluble drug and a water-soluble polymer are involved in this method. Examples are polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) [4].

Poor bioavailability of drugs has been the major challenge with oral dosage forms. The poor oral bioavailability usually results from poor solubility and low permeability of drugs [5]. Biopharmaceuticals Classification System (BCS) is a scientific classification of a drug and drug substance based on its aqueous solubility and intestinal permeability [6]. Solubility of such drugs can be improved by incorporating the drug in a hydrophilic carrier's materials obtaining a product called solid dispersion. Solid dispersion is another efficient method for increasing the drug dissolution rate and is carried out by melting method or solvent evaporation method [7].

Corresponding author: Gopal Pokhrel, Lecturer, research field: pharmacology. Email: gopalpokhrel70@gmail.com

Griseofulvin, an example of BCS Class II shows low solubility and high permeability. Most of the tablets of BCS Class II are reported to suffer low solubility, poor absorption, increased half-life and slow elimination [5]. BCS class II drugs shows poor solubility that results in poor absorption of drug which will ultimately decrease the bioavailability of drug [8]. Thus, this study is an investigation to formulate Griseofulvin by solid dispersions method to improve the dissolution rate and its bioavailability.

2. Methodology

2.1 Pre-formulation Studies [9, 10]

2.1.1 Determination of solubility

The solubility of Griseofulvin as active pharmaceutical ingredient (API) was performed in solvents such as water, dichloroform, methanol, ethanol, acetone, chloroform, benzene, acetic acid, ethyl acetate.

2.1.2 Scanning for the determination of wavelength (λmax) for Griseofulvin

Weighing 100mg of Griseofulvin in 100ml volumetric flask maintained up to mark with methanol. From this pipetting out 5 ml solution and diluted with methanol up to mark in 100 ml volumetric flask. The spectrum of this solution was run from 200-400 nm range in UV-Visible spectrophotometer.

2.1.3 Preparation of standard calibration curve

Accurately weighed 100mg of drug was dissolved in methanol and volume was made up to 100 ml by methanol which is stock solution containing 1000 µg/ml concentration. From this stock solution, 10 ml was pipette and added to 100 ml volumetric flask and volume was made 100 ml with methanol. Similarly, from the stock solution different aliquot of 5, 10, 15, 20, and 25 µg/ml were prepared respectively. Then, the absorbance was measured at 291 nm using UV Spectrophotometer. The standard curve was obtained by plotting absorbance versus concentration in µg/ml.

2.1.4 Formulation of oral tablets of Griseofulvin

The followings are the two methods by which oral tablets of Griseofulvin were prepared:

- Preparation of solid dispersion by using solvent evaporation method

Griseofulvin and water-soluble carriers PEG 6000 and Crospovidone are added into ethanol in mortar with constant stirring. Subsequently, ethanol was evaporated using oven at 60 ℃ and resulting solid dispersion was stored for 24 hours in a desiccator to remove traces of organic solvent. The dried powder was passed through 80 mesh sieve size [9].

- Direct compression method

In this method, direct compressible and soluble ingredients, lubricants and superdisintegrants were used. Then the powder mix was compressed using tablet pressing machine of 10.5 mm flat punch by 8-station rotary tablet punching machine. Six batches of Griseofulvin tablets were prepared by varying the concentrations of crospovidone and polyethylene glycol 6000 with different others excipients.

2.2 Formulation Chart of Griseofulvin Oral Tablet

Six batch of Griseofulvin were prepared using the formulation shown in Table 1.

Table 1 Composition of Griseofulvin oral tablet.

Formulation	Ingredients (mg)		
	Griseofulvin	PEG 6000	Crospovidone
F1	125	125	0
F2	125	0	125
F3	125	62.5	62.5
F4	125	100	25
F5	125	25	100
F6	125	150	25

2.3 Post-compression Study

The tablets were evaluated by the following post-compression parameters [11, 12];

Weight Variation: Twenty tablets of each formulation was randomly selected and weighed individually by using electronic balance. The average weight was calculated and individual weight of tablet was compared with average weight. Weight variation of tablet was calculated by using the formula below:

$$\text{Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \text{ X } 100$$

Tablet thickness: The thickness of tablet was calculated by using digital Vernier caliber. Ten tablets from prepared formulation randomly taken and thickness were measured.

Tablet Hardness: Tablet hardness testing was done to determine the breaking point of tablets. The hardness tester used for the study was Monsanto hardness tester, which performed by pressing specifically dimensioned and loaded object into surface of tablet.

Friability test: Friability testing was done to test the durability of tablets during transit. Friability testing was done by using Roche friabilator. Individual weight of ten tablets of each formulation were weighed (Wo) and then were carefully de dusted at 100 revolutions and accurately weighed (W) again. Percentage friability was calculated by using given equation below:

$$\text{Friability} = \frac{\text{Initial weight(Wo)} - \text{Final weight(W)}}{\text{Initial weight}} \text{ x } 100\%$$

Disintegration time: Disintegration test was carried out using tablet disintegration apparatus. Six tablets of each formulation were placed in each of the six tubes of basket assembly. The assembly was suspended in 1000 ml beaker containing water maintained at 37 ± 2 ℃. The time required for complete disintegration was recorded.

2.4 For Assay

Standard solution preparation: Weigh approximately 100 mg of Griseofulvin references standard solution in 100 ml volumetric flask with methanol.

Sample solution preparation: Powder 20 tablets of each batch and the powder sample (equivalent to 100 mg) Griseofulvin was accurately weight in 100 ml of volumetric flask and maintained volume up to make with methanol. Then filter the solution through filter paper No.1.

In vitro dissolution study: The in-vitro drug release studies for all formulations were studied using USP type - II (Paddle) dissolution test apparatus. 900 ml of 4% Sodium lauryl sulphate (SLS) solution was used as dissolution medium. The speed of the paddle was set at 50 r.p.m. and the temperature of the medium was maintained at 37 ± 0.5 ℃ and 10 ml sample was withdrawn at predetermined intervals up to 50 min. and replacements were done with fresh dissolution medium. The samples were suitably diluted and analyzed for drug content by UV spectroscopy at 291 nm [13].

3. Results and Observations

Determination of solubility (Table 2).

Table 2 Composition of Griseofulvin oral tablet

Solvent	Solubility
Water	Insoluble
Dichloromethane	Freely soluble
Methanol	Soluble
Ethanol	Soluble
Acetone	Soluble
Chloroform	Soluble
Acetic acid	Insoluble
Benzene	Sparingly soluble
Ethyl acetate	Insoluble

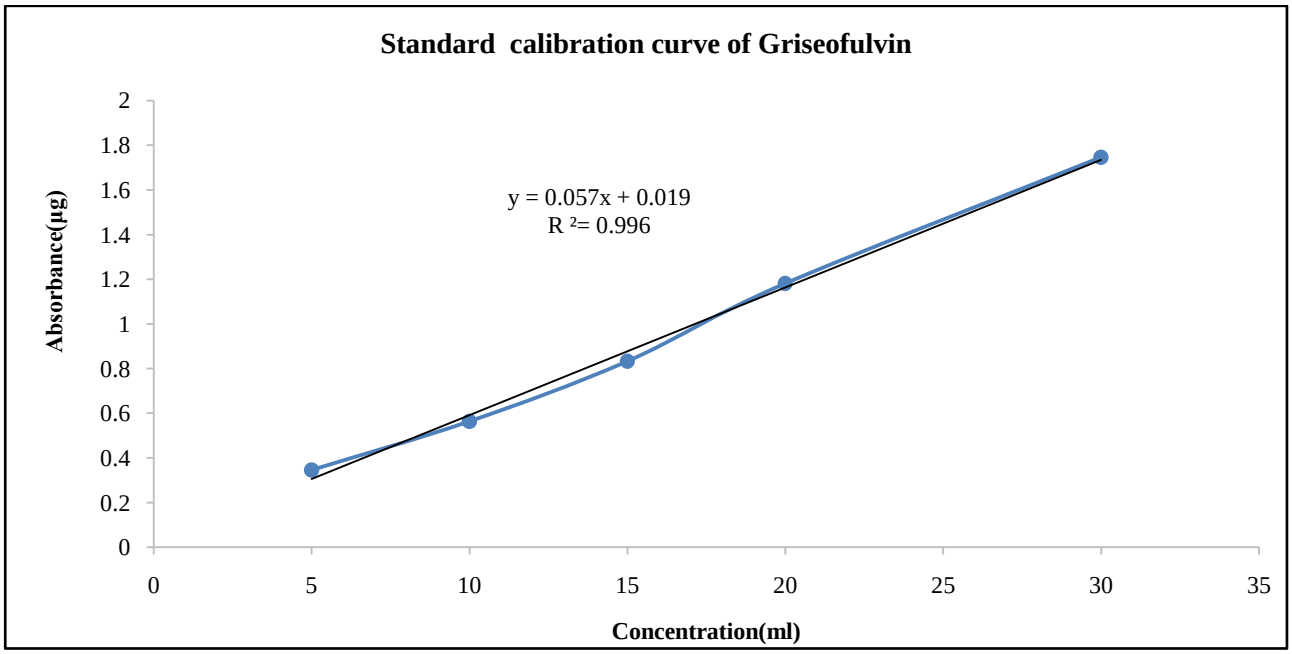

Fig. 1 Standard calibration curve of Griseofulvin.

Determination of λmax: λmax of Griseofulvin was found to be 291 nm. A standard calibration curve of Griseofulvin was obtained by measuring absorbance at 291 nm and by plotting graph of absorbance versus concentration (Figure 1).

Assay of Formulated batch (Table 3).

Table 3 Assay of Formulated batch.

S.N.	Formulation	Assay (%)
1	F1	99.68
2	F2	98.86
3	F3	98.79
4	F4	100.05
5	F5	99.1
6	F6	95.38

Pre-compression parameter test (Table 4).

Table 4 Flow properties of solid dispersion of Griseofulvin formulation additives.

Formulation	Bulk density (gm/cm ³) (Mean ±S.D)	Tapped density (gm/cm ³) (Mean ±S.D)	Angle of repose (Θ)	Compressibility index (%) (Mean ±S.D)	Hausner's ratio (Mean ±S.D)
F1	0.57 ±0.017	0.68 ±0.025	38.14	16.17 ±1.11	1.19 ±0.03
F2	0.58 ±0.017	0.68 ±0.20	33.3	14.7 ±0.53	1.17 ±0.06
F3	0.64 ±0.025	0.74 ±0.06	36.4	17.5 ±0.18	1.15 ±0.04
F4	0.66 ±0.03	0.8 ±0.11	35.6	17.5 ±0.19	1.21 ±0.01
F5	0.55 ±0.01	0.64 ±0.06	31.2	14.06 ±0.53	1.16 ±0.01
F6	0.6 ±0.02	0.68 ±0.01	42.6	11.76 ±0.67	1.13 ±0.02

Post-compression parameters: General appearance: All tablets were white in color and round shaped (Table 5).

Table 5 Post compression parameters.

Formulation	Thickness (mm) (Mean ± S.D)	Hardness (kg/cm^2) (Mean ± S.D)	Weight variation (mg) (Mean ± S.D)	Friability (% *W/W*)	Disintegration time (minutes)
F1	4.57 ± 0.19	5 ± 1.89	0.404 ± 0.0017	0.22	14
F2	5.16 ± 0.02	4 ± 0.28	0.399 ± 0.0023	0.293	8
F3	4.8 ± 0.015	5 ± 0.00	0.399 ± 0.0022	0.322	5
F4	4.65 ± 0.01	5 ± 0.14	0.399 ± 0.0024	0.74	11
F5	4.97 ± 0.04	4 ± 0.57	0.400 ± 0.0051	0.346	10
F6	4.6 ± 0.09	5 ± 0.29	0.401 ± 0.0026	0.024	13

In-vitro Drugs Release (Table 6)

Table 6 Cumulative Drug Release.

Formulation	Time (minutes)		
	10 min	30 min	45 min
F1	22.72%	54.76%	84.14%
F2	25.38%	60.25%	87.31%
F3	30.05%	69.21%	97.11%
F4	22.92%	53.63%	75.77%
F5	22.22%	46.54%	70.37%
F6	23.44%	57.57%	89.17%
Marketed Drug	31.88%	70.02%	99.22%

F3 was best formulation due to the increase dissolution and similar drug release pattern when compared with marketed drug (Figure 2).

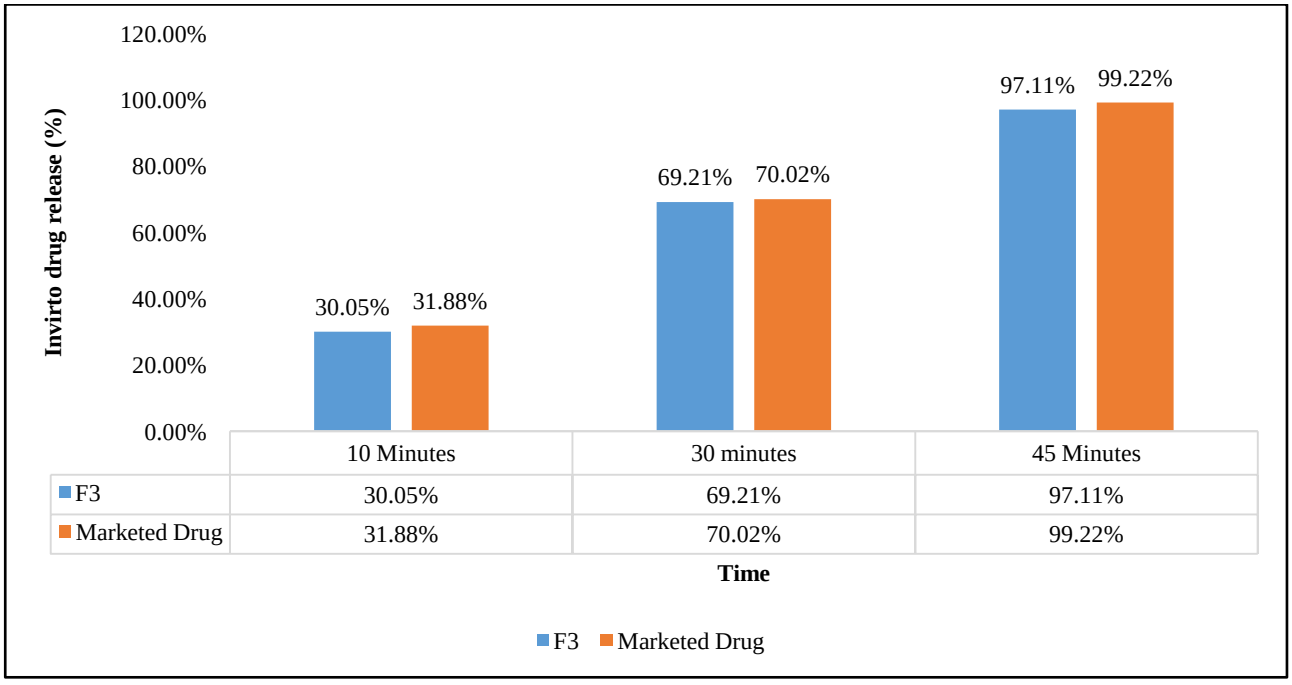

Fig. 2 Comparison of dissolution profile of formulated F3 drug and marketed drug.

Comparison of formulated tablet F3 with marked tablet suggested that in-vitro drug release was 97.11% in 45 minutes for F3 and 99.22% drug release for marketed drug in 45 minutes.

4. Discussion

Dissolution enhancement of poorly water soluble drug using solvent evaporation method of solid dispersion techniques was a promising approach to achieve increased dissolution, absorption, and bioavailability of drug like Griseofulvin that suffer low solubility and limited by dissolution rate.

For preparation of Griseofulvin tablets (F1-F6) was done using direct compression method using superdisintegrant like crospovidone, microcrystalline cellulose as diluents, polyethylene glycol 6000 as carriers and other excipients such as lubricant, binder etc. The prepared tablets were found to have good physicochemical properties and were evaluated for *in-vitro* disintegration time, friability testing, hardness, *in-vitro* dissolution time, weight variation. From this study it was found that weight variation for formulated tablets ranges from 0.399 ± 0.0022 to 0.404 ± 0.0017 and passed the weight variation limit according USP of 5%.

All the formulations found the evaluation results within the limit. During the study, suitable analytical method based on double beam UV-Visible spectrophotometer was developed for Griseofulvin at λmax 291 nm in methanol. This study suggested that standard calibration curve of Griseofulvin having regression analysis for linearity showed very good correlation (R^2= 0.9974).

5. Conclusions

Among all the formulated batches, F3 (PEG 6000 62.5 mg and crospovidone 62.5 mg) was best formulation produced showing solubility enhancement. The *in-vitro* drug release of F3 was 30.05%, 69.21%, 97.11% in 10 minutes, 30 minutes and 45 minutes respectively. This study showed that combination of carriers and superdisintegrants to solid dispersion of drug is promising approach to enhance dissolution of Griseofulvin.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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