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Formulation and characterization of mouth dissolving films loaded with solid dispersion of griseofulvin

[1] Ankush Tiwari, [2]Sandeep Jain

[1] [2]IPS College of Pharmacy, Gwalior, Madhya Pradesh, India
*Corresponding Author Email Id – ipsgwa@gmail.com

Abstract: The main objective of the present work was to formulate mouth dissolving films containing griesofulvin solid dispersion to attain its maximum drug release with a very short time and also to have an easy and compliant administration of the drug through oral route. β-cyclodextrin was used to prepare solid dispersion in the ratio 1:1 for drug and polymer by solvent evaporation method. The solid dispersion was obtained in yield of approximately 96% suggesting completion recovery of the dissolved material. Pure griseofulvin was found to exhibit a solubility of 62.0 µg/mL after 24 hours whereas the solid dispersion exhibited a significant increase in solubility showing a solubility of 570 µg/mL. All the formulated batches exhibited quick drug release, rapid disintegration and optimal mechanical strength. The formulations neither exhibited much loss nor much uptake of moisture as observed from the results of the study. The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation.
Keywords; Mouth dissolving film , solid dispersion, griseofulvin, xanthan gum, β-cyclodextrin

1. Introduction

One of the major problems coupled with the use of conventional oral dosage forms is the time required for the onset of action, which is usually at least half an hour in case of the conventional dosage forms and higher in the controlled and sustained release dosage forms.[1] Difficulty in swallowing (dysphagia) of medicine is a universal problem with all age groups, especially the elderly and children, owing to the physiological changes associated with these groups. Other categories of people that experience problems in using conventional oral dosage forms include the mentally ill, and patients suffering from nausea, vomiting, motion sickness and sudden episodes of allergic attack or coughing. It is estimated that about 35-50% of the population is affected by the problem of swallowing the medication.[2-4] These problems led to the development of a novel type of solid oral dosage form called as mouth dissolving films (MDFs). These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in the swallowing of the medication. Upon ingestion, the saliva provides the necessary conditions to rapidly disperse/ dissolve the MDF. The saliva containing the dissolved medicament is absorbed from the mouth, pharynx and esophagus. The bioavailability of drugs is significantly increased in this case as compared to those observed from conventional dosage forms such as tablets and capsules.

Griseofulvin is a widely used antifungal with a half-life of 9 to 12 h and the peak plasma concentration occurs at 6-12 h.[5] The drug is poorly water soluble, hence it cannot be readily formulated as mouth dissolving preparations. Solid dispersions are known to improve aqueous solubility of drugs and several reports of solid dispersion of griseofulvin have been found in literature. Hence in the present investigation it was attempted to formulate solid dispersion of griseofulvin and formulate it as mouth dissolving films (MDFs) of with the intention of providing quicker onset of action of the medication, better therapeutic efficacy, patient compliance and convenience.[5-8]

2. Material and Methods

Preparation of solid dispersion of griseofulvin

The solid dispersion of griseofulvin was prepared using previously reported procedure to improve the solubility of the drug.[9] Briefly, 100 mg of griseofulvin was precisely weighed and placed in tared beaker. To this was added 100 mg of β-cyclodextrin and the solids were mixed thoroughly. Ethanol (20 mL) was added to this

mixture with stirring to dissolve the components and the components were stirred further for 10 min. The contents were poured in a petridish and the solvent was allowed to evaporate under mild heat (40°C). The residue left behind in the petridish was collected, dried properly, pulverized and sifted through sieve no. 80.

Solubility analysis of griseofulvin solid dispersion

25 mg of powdered dispersion was weighed and added into 25 mL of volumetric flask and the volume was made up to the mark with distilled water. The solution mixture was then filtered and the absorbance was taken.[10] The solubility was then calculated using the calibration curve.

Preparation of griseofulvin solid dispersion loaded MDFs[11,12]

The preparation of griseofulvin films was done using 3^2 factorial approach using xanthan gum as the variable X1 and PEG as variable X2. Both the variables were used at three different levels (+1, 0, -1) to obtain 9 different formulations. The design table for formulations has been presented as table 1.

Solvent casting method has been the most predominantly used method to prepare smooth films. The MDFs of griseofulvin solid dispersion were herein also prepared using the solvent casting method. An aqueous solution of the polymer was prepared by dissolving xanthan gum in 5 mL of distilled water and kept aside to remove any trapped air bubbles. Griseofulvin solid dispersion was dissolved in very small quantity of solvent and stirred to dissolve in the polymer solution. All the other excipients of MDF such as plasticizer, sweetener, saliva secreting agent etc were dissolved separately in distilled water. The excipient solution was mixed with continuous stirring to the polymer solution and continued stirring at 1000 rpm for further 15 minutes. The mixture thus obtained was casted on petriplates as a film and dried in hot air oven at 50°C for 24h. After 24 h the films were cautiously peeled off from the petriplates using forceps and observed for any imperfections. The films were wrapped in aluminum foils and stored in desiccator until further use.

Table 1: Composition of MDFs of Griseofulvin solid dispersion

S. No	Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Griseofulvin solid dispersion equivalent to griseofulvin (mg)	192.3	192.3	192.3	192.3	192.3	192.3	192.3	192.3	192.3
2	Xanthan gum (mg)	150	200	250	150	200	250	150	200	250
3	Poly ethylene glycol (mg)	40	40	40	50	50	50	60	60	60
4	Sodium starch glycolate (mg)	10	10	10	10	10	10	10	10	10
5	Citric acid (mg)	5	5	5	5	5	5	5	5	5
6	Sucrose (mg)	10	10	10	10	10	10	10	10	10
7	Water (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Dose calculation[13]

Area of petridish = 38.465 cm^2
No. of films of 2 cm^2 in whole plate = 19.23
Amount of drug in each film = 10 mg
Total amount of drug required = 192.3 mg
Label claim of films = 10 mg

Evaluation of MDFs[14,15]

Weight variation

The randomly selected films (10 nos.) from each formulation were weighted to calculate the average weight and then individually weighed using a high sensitivity electronic weighing balance. The percent variation in weight of the films from the average weight was recorded.

Thickness

The thickness of each film was measured at different positions by using Vernier caliper and the average thickness was calculated.

Folding endurance

Folding endurance was evaluated by folding repeatedly one film from the same place till it cracked or tore off. The number of times a film could be folded from the same place without breaking/ cracking provided the value of folding endurance.

Drug content test

The film was allowed to dissolve in 100mL of phosphate buffer pH 6.8 that has been enriched with 1% sodium lauryl sulfate. After the complete dissolution of the film, the amount of griseofulvin was estimated spectrophotometrically by measuring the absorbance at 295 nm.

Moisture Content

Films of 2 cm^2 areas were cut out, accurately weighed and stored in desiccator over fused anhydrous calcium chloride. After 24 h the films were removed and reweighed. The percent moisture content of the films was calculated by the following formula

% Moisture content = (Initial weight – Final weight)/Initial weight x 100

Moisture uptake

The pre-weighed films were exposed to relative humidity of 84% at 28°C for three days using a saturated solution of sodium chloride in a closed desiccator. After 3 days the films were removed from the desiccator and reweighed. The amount of moisture absorbed by the films was computed using the following formula

% Moisture uptake = (Final weight – Initial weight)/Initial weight x 100

In-Vitro Disintegration time

In order to determine the disintegration time, the films were placed on glass petriplates containing 10 mL of distilled water. The time required for breaking of the film was recorded as the *in vitro* disintegration time of the film.

In-Vitro Dissolution Study

A film of 2 cm^2 was placed in a glass petriplate and 25 mL of dissolution medium (phosphate buffer pH 6.8) was added to it. The solution was continuously stirred at 100 rpm for the entire period of the study. Aliquots of 2.5 mL were withdrawn at regular intervals of 1, 2, 3, 4, 5 and 10 minutes replenishing the medium with equal volume of fresh buffer. The collected samples were filtered and the concentration of griseofulvin in each sample was estimated by measuring its absorbance at 295 nm using UV spectrophotometer.

3. Results and Discussion

Preparation and solubility analysis of solid dispersion

The solid dispersion of griseofulvin was prepared using solvent evaporation method as it is a simple method that presents good yield and improves the solubility of the contained drug significantly.[16] The use of β-cyclodextrin has been widely made for formulation of inclusion complexes and solid dispersions to improve solubility of drugs. A drug to polymer ratio of 1:1 was used for preparation of solid dispersion, based on a previous study.[11]

The solid dispersion was obtained in yield of approximately 95% suggesting completion recovery of the dissolved material. The saturation solubility study was carried out on griseofulvin and the solid dispersion.

Pure griseofulvin was found to exhibit a solubility of 62.0 µg/mL after 24 hours whereas the solid dispersion exhibited a significant increase in solubility showing a solubility of 570 µg/mL.

Evaluation of MDFs

Physical Parameters of films

The evaluation of the various physical properties of the formulated batches of films was performed as per the reported procedures and the results obtained are reported in table 2 and figure 1.

Table 2: Physiochemical Parameters of films

Formulation Batch	Weight Variation* (%)	Thickness (µm)#	Folding Endurance#	% Moisture loss#	% Moisture uptake#
F1	0.528 ± 0.003	50.33 ± 1.033	64.66 ± 0.577	5.5 ± 0.001	4.4 ± 0.001
F2	0.963 ± 0.059	50.33 ± 2.046	73.66 ± 1.527	5.8 ± 0.003	3.8 ± 0.002
F3	0.672 ± 0.004	54.67 ± 1.285	88.33 ± 4.463	6.3 ± 0.001	5.2 ± 0.001
F4	0.525 ± 0.006	52.67 ± 1.033	72.33 ± 0.577	5.9 ± 0.002	6.4 ± 0.001
F5	0.473 ± 0.004	54.33 ± 2.046	62.00 ± 1.732	6.3 ± 0.001	6.3 ± 0.003
F6	0.997 ± 0.001	59.00 ± 1.285	77.66 ± 0.577	6.4 ± 0.004	6.4 ± 0.003
F7	0.996 ± 0.004	57.33 ± 1.285	84.33 ± 1.154	6.3 ± 0.002	6.6 ± 0.001
F8	1.009 ± 0.003	58.67 ± 1.033	87.66 ± 1.154	6.4 ± 0.003	6.7 ± 0.002
F9	1.018 ± 0.003	69.67 ± 1.033	113.66 ± 3.055	6.6 ± 0.001	6.7 ± 0.001

*Mean ± SD of 10 replicates; #Values are mean ± SD of 3 replicates

The thickness of the films was measured at three different locations to ensure the uniformity of the results. The weight variation was calculated as deviation from the average weight and is reported as the percentage weight variation obtained from 10 films.

The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation.

Drug content estimation in films

The evaluation of drug content in the prepared film formulations was performed as per the reported methods and the amount of drug present in the formulations was calculated on the basis of absorbance of the sample at 295 nm in UV spectrophotometer. The results are reported in table 3.

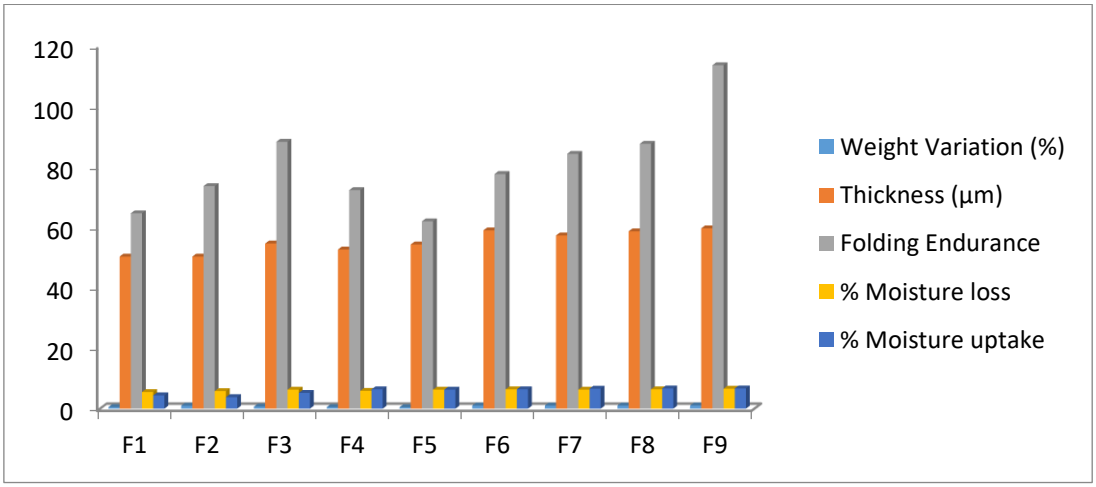

Fig 1: Physical characters of the prepared films

Table 3: Drug content in the MDFs

Formulation	Disintegration time (sec)	% Drug Content
F1	32	94.7 ± 2.18
F2	35	92.4 ± 1.31
F3	35	95.3 ± 4.89
F4	37	96.1 ± 3.42
F5	36	93.2 ± 6.26
F6	36	92.6 ± 6.26
F7	37	93.1 ± 5.33
F8	37	92.6 ± 6.66
F9	37	95.4 ± 4.33

The results show that all the formulations had drug content of more than 90% with the highest content in formulation F4 (96.1 ± 3.42%). The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X_1, the drug uptake by the polymeric matrix was slightly lower.

In vitro disintegration of MDFs

The *in vitro* disintegration of the films was performed using the petridish method in order to ascertain that the films will provide a rapid release of the griseofulvin. The results obtained for disintegration study of the films is shown in table 3.

The disintegration time of all the formulations was less than 40 seconds suggesting that all the batches of the films were quick dissolving and would be able to release the drug, rapidly. The amount of the disintegrating agent was therefore effective in maintaining the quick breakdown of the films.

***In vitro* release study**

The release of griseofulvin from the prepared films using different concentration of xanthan gum is presented in table 4. All the formulations were found to disintegrate in less than 40 seconds thereby paving the way for quick release of griseofulvin from the films (Figure 2). The ratio of polymer content and plasticizer was found to have no significant role in the disintegration time of the films.

Table 4: *In vitro* drug release of formulations

Time (minutes)	% Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21	23	19	20	17	16	20	15	20
2	29	30	27	26	29	25	30	27	26
3	36	41	30	34	37	34	42	40	37
4	48	52	44	45	48	47	50	51	49
5	64	66	60	57	62	60	64	60	62
10	88	87	84	90	83	87	89	88	85

The results reveal that all the film batches were able to release almost the whole quantity of drug within 10 minutes. The maximum amount of drug was released by F4 (90%) while F5 released the lowest amount of drug (83%) in the same period.

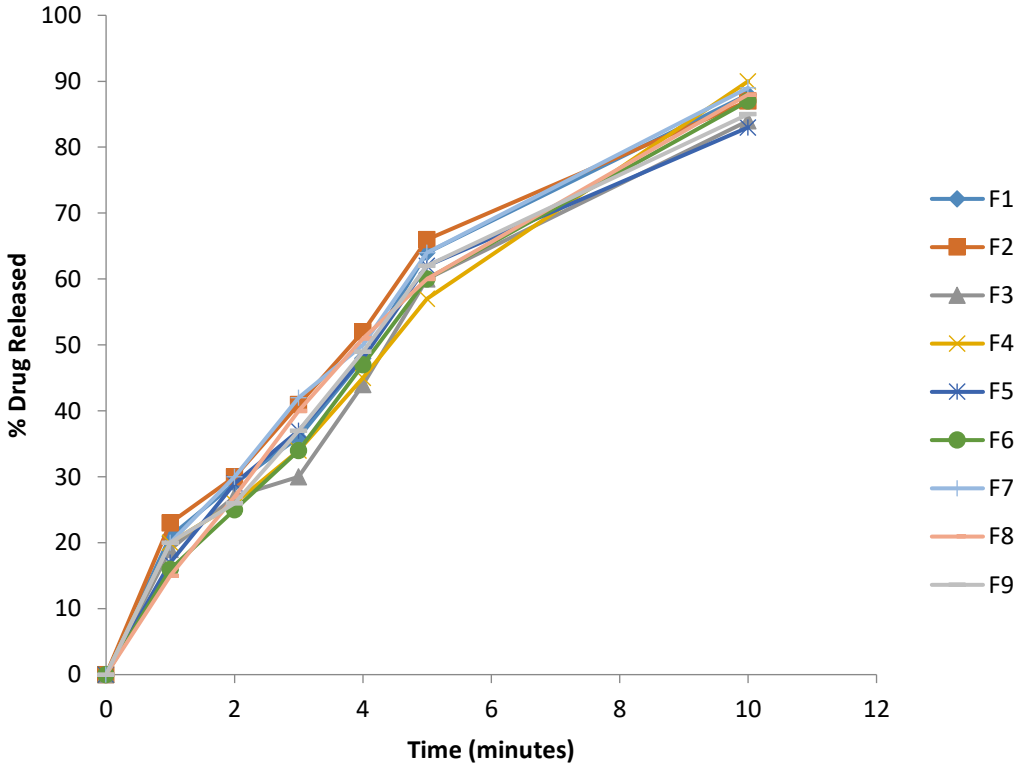

Fig 2: Release profile of mouth dissolving formulations

4. Conclusion

The objective of the present study was to formulate mouth dissolving films of griseofulvin solid dispersion for rapid release of the drug for quick relief along with improved patient compliance and ease of administration. The results of the study were able to rationalize the use of solid dispersion loaded films for rapid release of the drug using xantham gum as the polymeric matrix of the film and PEG-400 as the plasticizer. The drug release pattern from the films suggests that the mouth dissolving films can be an excellent approach for quickening the onset of action griseofulvin.

References

[1] Dahiya M, Saha S, Shahiwala A. A Review on Mouth Dissolving Films. Curr Drug Del. 2009; 6: 469-476.

[2] Patel AR, Prajapati DS, Raval JA. Fast dissolving films as a newer venture in fast dissolving formulations. Int J Drug Dev Res. 2010; 2(2): 232-246.

[3] Gavaskar B, Kumar SV, Sharan G, Madhusudan Y. Overview on fast dissolving films. Int J Pharmacy Pharm Sci. 2010; 2(3), 29-33.

[4] Squier C, Kremer M. Biology of oral mucosa and esophagus. J Natl Cancer Inst Monogr. 2001**;** 29, 7-15.

[5] https://go.drugbank.com/drugs/DB00400; assessed on 08/01/2023

[6] Badwar MR, Borse SL, Junagade MS, Jadhav AG. Formulation and evaluation of mouth dissolving tablet of amlodipine besylate. Int J Applied Pharmaceut. 2019; 11(4): 132-139

[7] Sharma PK, Sharma PK, Darwhekar GN, Shrivastava B. Development and evaluation of fast dissolving oral film of poorly water soluble drug Felodipine. Asian J Pharmaceut. 2018; 12(1): 256-267.

[8] Patel V, Patel R, Shah H, Purohit S, Pawar M, Pathan A. Solubility Enhancement of Azithromycin by Solid Dispersion Technique Using Mannitol and β-Cyclodextrin. Acta Scientific Pharmaceutical Sciences. 2021; 5(4): 48-54.

[9] Goswami RG, Mishra B, Mishra R. Dissolution enhancement of Cefprozil by solid dispersion technique. Journal of Pharmacology and Biomedicine. 2017; 1(4): 129-133

[10] Dash A, Mishra A. Method development, validation and stability study of griseofulvin in bulk and pharmaceutical dosage form by uv spectrometric method. In proceedings. 2012.

[11] Hanson KB, Hoff DJ, Lahren TJ, Mount DR, Squillace AJ, Burkhard LP. Estimating n-octanol-water partition coefficients for neutral highly hydrophobic chemicals using measured n-butanol-water partition coefficients. Chemosphere. 2019; 218: 616-623.

[12] Patel V, Patel R, Shah H, Purohit S, Pawar M, Pathan A. Solubility Enhancement of Azithromycin by Solid Dispersion Technique Using Mannitol and β-Cyclodextrin. Acta Scientific Pharmaceutical Sciences. 2021; 5(4): 48-54.

[13] Mashru R, Sutariya V, Sankalia M, and Parikh P. Development and Evaluation of Fast-Dissolving Film of Salbutamol Sulphate. Drug Dev Ind Pharm. 2005; 31, 25–34.

[14] Maheshwari KM, Devineni PK, Deekonda S, Shaik S, Uppala NP, Nalluri BN. Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy. J Pharmaceut. 2014; http://dx.doi.org/10.1155/2014/520949

[15] Bala R, Khanna S, Pawar P. Design Optimization and *In Vitro-In Vivo* Evaluation of Orally Dissolving Strips of Clobazam. J Drug Del. 2014; http://dx.doi.org/10.1155/2014/392783

[16] Adeli E. Preparation and evaluation of azithromycin binary solid dispersions using various polyethylene glycols for the improvement of the drug solubility and dissolution rate. Brazilian Journal of Pharmaceutical Sciences. 2016; 52(1): DOI: 10.1590/S1984-82502016000100002