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A REVIEW ON – GRISEOFULVIN MOUTH DISSOLVING TABLET

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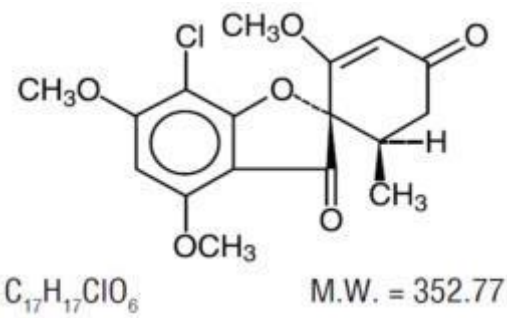
ABSTRACT
The main objective of the present work is to formulate mouth dissolving films containing griseofulvin solid dispersion to attain its maximum drug release with a very short time and also to have an easy and compliant administration of the drug through oral route. β-cyclodextrin was used to prepare solid dispersion in the ratio 1:1 for drug and polymer by solvent evaporation method. All the formulated batches exhibited quick drug release, rapid disintegration and optimal mechanical strength. 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.

INTRODUCTION
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. 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.[1] 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.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.[2-4] Difficulty in swallowing (Dysphagia) of medicine is auniversal problem with all age groups, especially the elderly and children, owing to thephysiological changesassociated with these groups. Other categories of people that experience problems inusing 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.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 inthis case as compared to those observed from conventional dosage forms such as tablets and capsules.[5-8]

Drug label information
Description
Ultramicrosizegriseofulvin tablets, USP contain ultramicrosize crystals of griseofulvin, an antibiotic derived from a species of *Penicillium*. Griseofulvin crystals are partly dissolved in polyethylene glycol 8000 and partly dispersed throughout the tablet matrix.

The chemical name of griseofulvin, USP is 7-Chloro-2',4,6-trimethoxy-6'β-methylspiro [benzofuran-2(*3H*),1'- [2] cyclohexene]-3,4'-dione. Its structural formula is:



$C_{17}H_{17}ClO_6$ M.W. = 352.77

Griseofulvin, USP occurs as a white to creamy white, odorless powder which is very slightly soluble in water, soluble in acetone, dimethylformamide, and chloroform and sparingly soluble in alcohol. Each ultramicrosizegriseofulvin tablet contains 125 mg or 250 mg griseofulvinultramicrosize. The inactive ingredients for ultramicrosizegriseofulvin tablets, 125 mg or 250 mg, include: corn starch, lactose anhydrous, magnesium stearate, polyethylene glycol 8000, and sodium lauryl sulphate.

Adverse reaction

There have been post-marketing reports of severe skin and hepatic adverse events associated with griseofulvin use. When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria, erythema multiforme-like drug reactions, and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesia of the hands and feet have been reported after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities. Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs. When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

Dosage and Administration

Accurate diagnosis of infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium. Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tineacapitis, 4 to 6 weeks; tineacorporis, 2 to 4 weeks; tineapedis, 4 to 8 weeks; tineaunguium–depending on rate of growth–fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tineapedis. In some forms of athlete's foot, yeasts and bacteria may be involved as well as fungi. Griseofulvin will not eradicate the bacterial or monilial infection. Ultramicrosizegriseofulvin tablets may be swallowed whole or crushed and sprinkled onto 1 tablespoonful of applesauce and swallowed immediately without chewing.

Adults: Daily administration of 375 mg (as a single dose or in divided doses) will give a satisfactory response in most patients with tineacorporis, tineacruris, and tineacapitis. For those fungus infections more difficult to eradicate, such as tineapedis and tineaunguium, a divided dose of 750 mg is recommended.

Pediatric use: Approximately 7.3 mg per kg of body weight per day of ultramicrosizegriseofulvin is an effective dose for most pediatric patients. On this basis, the following dosage schedule is suggested:
16-27 kg: 125 mg to 187.5 mg daily.
Over 27 kg: 187.5 mg to 375 mg daily

Children and infants 2 years of age and younger–dosage has not been established. Clinical experience with griseofulvin in children with tineacapitis indicates that a single daily dose is effective. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

Indications and Usage

Ultramicrosizegriseofulvin tablets are indicated for the treatment of the following ringworm infections; tineacorporis (ringworm of the body), tineapedis (athlete's foot), tineacruris (ringworm of the groin and thigh), tineabarbae (barber's itch), tineacapitis (ringworm of the scalp), and tineaunguium (onychomycosis, ringworm of the nails), when caused by one or more of the Following genera of fungi: *Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleini.* **Note**: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical agents alone. Griseofulvin is *not* effective in the following: bacterial infections, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), tineaversicolor and nocardiosis.

Contraindication

Two cases of conjoined twins have been reported since 1977 in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients. If the patient becomes pregnant while taking this drug, the patient should be

apprised of the potential hazard to the fetus.This drug is contraindicated in patients with porphyria or hepatocellular failure and in individuals with a history of hypersensitivity to griseofulvin.

Precautions

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic, and hematopoietic, should be done. Since griseofulvin is derived from species of *Penicillium*, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty. Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Lupus erythematosus or lupus-like syndromes, have been reported in patients receiving griseofulvin.

Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Barbiturates usually depress griseofulvin activity, and concomitant administration may require a dosage adjustment of the antifungal agent. There have been reports in the literature of possible interactions between griseofulvin and oral contraceptives. The effect of alcohol may be potentiated by griseofulvin, producing such effects as tachycardia and flush.

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP.

Hepatotoxicity

Elevations in AST, ALT, bilirubin, and jaundice have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. Patients should be monitored for hepatic adverse events and discontinuation of griseofulvin considered if warranted.

Animal toxicology

Chronic feeding of griseofulvin, at levels ranging from 0.5%-2.5% of the diet resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Thyroid tumors, mostly adenomas but some carcinomas, have been reported in male rats receiving griseofulvin at levels of 2.0%, 1.0% and 0.2% of the diet, and in female rats receiving the two higher dose levels. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusion in this regard. In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Animal reproduction Studies

It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Suppression of spermatogenesis has been reported to occur in rats, but investigation in man failed to confirm this.[9-11]

Preparation of solid dispersion of griseofulvin

The solid dispersion of griseofulvin was prepared using previously reported procedure toimprove the solubility of the drug. 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 dispersion25 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.[12-13]

Evaluation of MDF

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 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 vitrodisintegration 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.[14-15]

RESULTS AND DISCUSSION

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. 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. The evaluation of drug content in the prepared film formulations was performed as per the reportedmethods 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.[16]

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 ableto 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.

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