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Review article

Formulation, evaluation and optimization of clotrimazole solid dispersion incorporated gels

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ABSTRACT

The goal of the present investigation was to design and evaluate gels for topical delivery of water insoluble antifungal agent; Clotrimazole is a broad spectrum imidazole derivative useful in the treatment of superficial fungal infections. Purpose was to improve the solubility, *in-vitro* characteristics and dissolution properties of Clotrimazole by the preparation of its solid dispersion with beta cyclodextrin using kneading method by using different drug carrier ratios. Prepared solid dispersion was evaluated for percent practical yield, drug content uniformity, *in vitro* dissolution rate, DSC and IR studies. Solid dispersions was optimized based on the release characteristics, and were incorporated into gels. Faster dissolution was exhibited by solid dispersion containing l: l ratio of drug: β-cyclodextrin by kneading method. The gels were formulated by using Carbopol 940, HPMC, and Methyl cellulose and evaluated for pH, drug content, spread ability, extra ability, viscosity determination and diffusion study. *In-vitro* drug release of Clotrimazole solid dispersion with Carbopol gels showed higher drug release when compared to HPMC, methyl cellulose gels. In conclusion, the optimized gel showed good physicochemical properties, better drug release, and reasonable stability.

Keywords: *Solid dispersion, clotrimazole, β Cyclodextrin, Kneading method, Carbopol.*

INTRODUCTION

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system. It affords to maintain applied preparation intact for a prolonged time and this has resulted in its increasing use as a route of administration whether for local, regional or systemic effects. Topical antifungals are the agents, meant for topical use for fungal infection. Topical application of drug at the affected site offers potential advantage of delivering drug directly to the site of action. Local infection can be treated by application of products which forms transparent water vapors and air permeable film over the skin surfaces, from which drug releases continuously to the skin site and skin structure infection and the disease of the patient would be treated. At present, there are number of antifungal agents used in topical applications like clotrimazole, griseofulvin, itraconazole, fluconazole etc. Clotrimazole was used as a model drug. Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity. It acts by inhibiting biosynthesis of ergosterol, an important component of fungal cell membranes. It is widely used for the treatment of local candidiasis, vaginal yeast infections; topical applications include fungal infections such as ring worm, athlete's foot and jock itch. Its action leads to increased membrane permeability and apparent disruption of enzyme systems bound to the membrane. The major drawback of this drug is its insolubility in water.

The techniques generally employed to enhance the solubility of poorly water- soluble drugs are, use of surface-active agent, hydrates and solvates, polymorphism, complexation, solid dispersion. Among this Solid dispersion is a unique technique used to increase solubility, dissolution and bioavailability of poorly water-soluble drugs. Conventional method for preparing solid dispersion includes solvent wetting method, physical mixture, complex formations, and solvent evaporation techniques.Creams, gels, ointments and pastes are some of the topical semisolids in use for many decades**.** The extensive studies on release properties have revealed that the active ingredients in gel based formulations are better percutaneously absorbed than cream or ointment bases [1].

MATERIAL AND METHOD

Chemicals

Clotrimazole I.P. (Gift sample from Chethana P'aceuticals, perinthalmanna, Kerala), β cyclodextrin , Carbopol 940, hydroxyl propyl methyl cellulose,methyl cellulose, Methyl paraben (Hi media Laboratories pvt.Ltd , Mumbai), propylene glycol (Lobha chemie pvt.ltd, Mumbai),triethanolamine, ethanol (Sd fine chem. Ltd,Mumbai.

Methods of Preparation of Clotrimazole solid dispersion

Solid dispersions of clotrimazole in β cyclodextrin containing three ratios (1:1, 1:2, 1:3 w/w) were prepared by kneading method. Here betacyclodextrin was taken in mortar and little amount of ethanol was added and triturated to obtained a homogenous slurry like consistency. Slowly the drug was incorporated into the slurry, and trituration was continued for 1 hour and then dried at 25^0 C for 24 hours, pulverized, sieved through mesh no.100.The resultant formulations were stored in desiccators until further investigation.

Characterization of Clotrimazole solid dispersion Percent Practical Yield Percentage practical yield were calculated to know about percent yield, thus it helps in selection of appropriate ratios of solid dispersion. Solid dispersions were collected and weighed to determine practical yield from the following equation Percentage Yield = Practical Mass * 100 Theoretical Mass (Drug +carrier) [2].

Drug Content

Preparation equivalent to 50 mg of model drug was weighed accurately and dissolved separately in 50 ml methanol. The solutions were further diluted and absorbance of solutions was determined at 262 nm by UV spectrophotometer.

FT-IR spectroscopy

FT-IR spectra of clotrimazole beta- cyclodextrin solid dispersions were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm^{-1}.

Differential Scanning Calorimetry Differential scanning calorimetry was performed by

Differential scanning calorimeter Shimadzu to obtain suitable thermograms. The

accurately weighed sample was placed in an aluminium Screening Models for the Assessment of Antiulcer Activity

Gastric lesions induced by HCl/ethanol. The anti-ulcerogenic activity of ethanolic extract, ethyl acetate and isolate fractions, derived from and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow; at a scanning rate 10 ^{0}c /min. in range of 40 - 200 ^{0}C.

In-vitro Dissolution Studies

The USP dissolution apparatus (Type-II) was used for evaluation of in vitro release profile of solid dispersions. The dissolution medium was 900ml phosphate buffer of pH 7.4 kept at 37 ± 0.1°C. Solid dispersion was taken in muslin cloth and then kept in the basket of dissolution apparatus, which was then rotated at 100 rpm. Samples of 5ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 262 nm. Withdrawn samples were replaced by fresh buffer solution. Each preparation was tested in triplicate and then mean values were calculated.

Evaluation of optimized Clotrimazole solid dispersion incorporated gels

In-vitro antifungal studies

The anti-fungal activity of the optimized Clotrimazole solid dispersion incorporated gel was compared with marketed clotrimazole gel, was determined using Candida albicans. The suspension of Candida albicans was poured evenly on plates of Sabourauds dextrose agar. Agar wells were cut from the seeded agar medium using a sterile cork borer. These wells were filled with 10 mg of formulated gel prepared with 1% drug and also without drug. Moreover, 10 mg of marketed clotrimazole gel (1%) was used for comparison. Plates were then incubated at 37˚C for about 3 days and compared the zone of inhibitions. The bases without clotrimazole (blank gel), and pure clotrimazole solution were used as controls [3].

Skin irritation test

The skin irritation test was performed on healthy white rabbit of average weight 1.75 to 2.25 kg. About 9 cm^2 area on the dorsal surface of the rabbits in each group was shaved and cleaned with spirit. Rabbits were divided into three groups (n = 3) as follows:

Group - I (control): - There was no application on the surface of the rabbit skin.

Group –II (marketed gel)):- 1 gm of the gel containing 10 mg of clotrimazole was applied to 9cm^2 area on the dorsal surface of the rabbit. The visual inspection was observed for 3 days to check evidence of skin irritation (sign of edema and erythema).

Group - III (Formulated gel, F2):- 1 g of gel containing 10 mg of clotrimazole was applied to 9cm^2 area on the dorsal surface of the rabbit

(10-11). The visual inspection was observed for 3 days to check any evidence of skin irritationSkin irritation test was conducted to evaluate the irritancy of the optimized clotrimazole gel on the intact skin of rabbits [4].

RESULTS

All the Solid dispersions prepared were found to be fine and white colored free flowing powders.

Percent practical yield

The results of percent practical yield studies are shown in The % practical yield of the prepared solid dispersions was found to be in the range of 88.2 - 92 %. The maximum yield was found 92 % in S1 formulation.

Drug content

The actual drug content of all the 3 formulations is shown in Table 1. The drug content of the prepared Solid dispersions were in the range of 83.4- 95 %. The maximum percentage of drug content was found 95.0% in S1 formulation [].

***In-vitro* dissolution study**

The *in vitro* release studies of different batches of solid dispersions are shown in figure 1. Among the solid dispersions prepared 1:1 ratio showed greater solubility than the others. Because of enhanced/ greater release solid dispersion prepared with 1:1 (S1) drug carrier ratio.

IR spectroscopy

IR studies indicated that no chemical interaction between drug and carrier took place during preparation of solid dispersion of Clotrimazole

Differential Scanning calorimetry

In Clotrimazole β cyclodextrin inclusion complex DSC plot, two melting ranges were obtained. In one peak, melting process started at 80.37 ^{0}C and completed at 111 ^{0}C. In another peak, process was started at l41.96 ^{0}C and completed at

148.42 ^{0}C was suggested that clotrimazole and β cyclodextrin used for the formulation was nothing but a mixture of both.

Clotrimazole solid dispersion incorporated gels

Physical characteristics of Clotrimazole solid dispersion incorporated gels were measured according to the methods describe above.

***In-vitro* diffusion studies**

The *in vitro* diffusion studies were performed by over a period of 8 hours and results are shown in figure 4. F2 showed better release (73.88 ± 0.42 %)

Optimized Clotrimazole solid dispersion incorporated gels *In-vitro* antifungal study

In-vitro antifungal activity of optimized gel F2, marketed clotrimazole gel M, blank gel B , control C were determined by cup plate method using *Candida* .

Skin irritation test

The optimized formulation F2 was subjected for skin irritation test. The Skin irritation tests were performed on healthy white rabbits and were observed for a period of 72 hr. From the results of the study it was clear that there was no erythema and edema found after 72 hr, and hence it was concluded that the gel was free from skin irritation [6, 7].

CONCLUSION

In conclusion, the anti-ulcer activity demonstrated in the present study provides additional support for the traditional use of this plant in the treatment of gastric and intestinal ulcers in future research.

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