Research Article

Available online through
www.ijrap.net

IJRAP
ISSN 2229-3566

STUDIES ON CANDY BASED KETOCONAZOLE PEDIATRIC TABLET LOZENGES

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Received on: 03/01/2011 Revised on: 30/01/2011 Accepted on: 11/02/2011

ABSTRACT
Ketoconazole was formulated as a tablet lozenge to provide slow release medicament for the treatment of oral thrush in pediatric patients. There are dosage forms like syrups, tablets in the market but still there is a need for new dosage forms which acts effectively and locally. So the present investigation aims to design, prepare and evaluate tablet lozenge of Ketoconazole. The benefits of these prepared lozenges are increased bioavailability, reduction in gastric irritation by passing first pass metabolism. The lozenges were prepared by heating and congealing method in a candy based industry on request using sucrose as base. All the formulations prepared were subjected to various physico-chemical parameters like hardness, content uniformity, friability, weight variation etc. The prepared formulations have a hardness of 12-13 Kg./cm², free from gritty particles, and good taste. Stability studies of selected formulations were also carried out at 35ºC for a period of six months. Selected formulations were tested for drug excipient interactions subjecting to IR Spectral analysis. In-vitro drug dissolution studies showed 81.12% for F1 and 72.43% for F2 release of drug in 30 minutes, 95.01% in 7 minutes from F0 formulation. The tablet lozenges can provide an attractive alternative formulation in the treatment of oral thrush in pediatric patients.
KEY WORDS: Ketoconazole , lozenges, oral thrush.

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INTRODUCTION

Oral thrush is a disorder caused by infection of the mouth due to fungus (yeast) Candida albicans. In babies it may be a severe infection some time causing epidemics in schools by cross infection. The Ketoconazole lozenges are flavoured medicated dosage forms intended to be sucked and hold in mouth / Pharynx[1,2] . The present investigation is designed to improve patient compliance. These preparation are commonly used for the purpose of local or system effects through the buccal mucosa[3,4]. Advantages of the ketoconazole tablets, lozenges as dosage forms include increase in bioavailability, reduction in dose size and in gastric irritation, bypass first pass metabolism[5,6]. When it is not effectively treated, oral thrush often leads to hospitalization, limitation on physical activity, insomnia nights and in some cases death[7,8]. The present work is aimed at preparing a formulation of Ketoconazole tablet lozenges, which provide prolonged retention time up to 30 min. in oral cavity for relief of oral thrush as conventional form of lozenges retention time being around 7 min.

MATERIALS AND METHODS

Ketoconazole was received a gift sample from Glenmark Pvt. Ltd., Daman, Hydroxy Propyl Methyl cellulose (HPMC) and Hydroxy Ethyl cellulose (HEC) were obtained from Loba Chemicals Pvt. Ltd., Mumbai. Sucrose and citric acid were obtained from SD fine Chemicals Pvt. Ltd., Mumbai. All other chemicals and solvents were of analytical reagent grade.

Preparation of Tablet Lozenges With & Without Added Hydrocolloids

Lozenges were formulated in a Candy Industry (Hyderabad) on request following heating and congealing method[9]. The various steps involved in preparation of tablet lozenges are Preparation of syrup and maintenance of temp. at 150ºc till it becomes thick.

The syrup is then placed in vacuum chamber for about 30 minutes to remove the traces of water molecules and to give plasticity to the base prepared. The drug, mucoadhesive polymers, citric acid, colour and flavouring agents were added manually and mixed thoroughly. Then this solidified mass was placed between the rollers of the batch former to form a rope size and shape. Hot air was blown over the product (Lozenges) in the rotating drying chamber (velocity of 1500-3000 ft/mins as the lozenges passed from the cooling belts). The prepared Ketoconazole Lozenges were packed with the help of machine called Maksom Wrapper.

Physicochemical Characteristics of Formulated Ketoconazole Tablet Lozenges

The prepared formulations were subjected to following parameters[10].

Hardness, Weight Variation, Thickness, Drug content uniformity and Diameter Determination

***In Vitro* Drug Dissolution Studies**

The rate of the drug absorption was determined by the rate of drug dissolution from the tablet lozenges. Thus, the rate of dissolution and bioavailability may be directly related to the efficacy of the tablet lozenge. The modified tablet dissolution test apparatus (USP-II) was used and the dissolution medium phosphate buffer pH at 6.5, 100ml. was placed in the beaker containing the tablet lozenge and stirred at 100 rpm. 5ml aliquot samples were withdrawn at 5 min. interval and replaced immediately with an equal volume of fresh fluid i.e., simulated salivary fluid. Each aliquot was diluted and they were analysed at 262nm using blank, by Shimadzu UV-Visible spectrophotometer. (**Table-3**) (**Fig-2 and 3**)

Stability Studies

All the prepared formulations (F0, F1, F2) were subjected to stability studies at different temperature i.e., 30ºC / 65% RH and 40ºC /75% RH for a period of 3 months. There was no such considerable change in hardness of tablet and no change in weight, thickness, drug content (no loss of drug more than 5%). Dissolution studies show no change in release.

RESULTS

Pediatric formulations are helpful to treat the patients more effectively. Patient compliance is one of the important aspect for administration of drugs especially those which are bitter in taste. For patient compliance, attractive, taste masking formulations are the need of the hour. In the present study Ketoconazole sweetened tablet lozenges were designed for the effective treatment of oral thrush in children. This chronic disorder frequently needs frequent drug dose administration. Results of prepared formulation and physicochemical characteristics revealed that the prepared Ketoconazole tablet lozenges were spherical in shape having 12.6(kg.) hardness, 0.7 mm thickness of 99% drug content uniformity and 3cms. of diameter and found to be within the pharmacopoeial limits. For any formulation, drug excipient interactions plays an important role and hence the formulations were subjected to infrared spectral analysis , it was observed that undisturbed drug peaks revealing the compatibility drug. Stability studies at ambient temperatures show that the formulations were found to have uniform drug content upto 3 months. The results of phase-IV studies revealed that the drug release in 30 minutes under simulated salivary conditions was 81.12% from Hydroxy Propyl Methyl Cellulose (HPMC) based formulation and 72.43% from Hydroxy Ethyl Cellulose (HEC) based formulation in 30 minutes. However, 95.01% drug release in 7 min. from formulation containing without hydrocolloid.

DISCUSSION

From the present study, it is suggested that sucrose based medicated tablet lozenges will be ideal dosage forms for pediatric patients of oral thrush. Addition of natural hydrophyllic polymers Hydroxy Propyl Methyl Cellulose (HPMC) and Hydroxy Ethyl Cellulose (HEC) yielded good results to prolong oral retention time of tablet lozenge in simulated salivary pH conditions for a period of 30 minutes. The stability studies proved that the prepared tablet lozenges were found to be stable when stored at air tight container or strips. These finding could be of potential use in designing such formulations for pediatric patients.

ACKNOWLEDGEMENTS

The authors are thankful to M/s.Candy Craft, Hyderabad for providing necessary industry facilities to carry out this work with great ease and precision, Cipra Labs, Hyderabad for providing facilities of IR spectral analysis and Al-Badar Rural Dental College and Hospital, Gulbarga for expert suggestions.

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Table 1: Working Formula to Prepare Tablet Lozenges

Sl. No.	Ingredient	Formulations		
		Without hydrocolloids F_0	**Hydroxy Propyl Methyl cellulose (HPMC) F_1**	**Hydroxy Ethyl cellulose (HEC) F_2**
1	Sugar	680gms	675 gms	675gms
2	Liquid Glucose	283 gms	278 gms	278 gms
3	Drug (Ketoconazole lozenges)	20 gms	20 gms	20 gms
4	HPMC (1%)	--	10 gms	---
5	HEC (1%)	--	---	10 gms
6	Citric Acid	10 gms	10 gms	10 gms
7	Flavoring Agent	6.7 gms	6.7 gms	6.7 gms
8	Colouring Agent	0.3 gms	0.3 gms	0.3 gms
	Total Weight	1 Kg (1000 gms)	1 Kg (1000 gms)	1 Kg (1000 gms)

* Each tablet lozenges contains 20 mg of drug.
* Each tablet lozenges contains weight of 3 gms.

Table 2: Physico-Chemical Parameters of Prepared Ketoconazole Tablet Lozenges

Sl. No.	Parameters	Standard Limits	Formulations prepared		
			Without hydrocolloids F_0	**Hydroxy Propyl Methyl cellulose (HPMC) F_1**	**Hydroxy Ethyl cellulose (HEC) F_2**
1	Hardness (kg/cm²)	--	12.3	12.5	12.7
2	Weight variation (gms)	250 mg -5gms	3.22 ± 0.16	3.37 ± 0.12	3.33 ± 0.12
3	Thickness (mm)	--	0.7	0.7	0.7
4	Drug content (mg)	95 – 105%	99.10	99.23	99.56
5	Diameter (cms)	--	3.2	3.2	3.2

* Each reading is a mean of three replicates.
* Each lozenge contains 20mg of Ketoconazole.

Table 3: *In-vitro* Drug Dissolution Studies of Ketoconazole Tablet Lozenges Containing Hydroxy Propyl Methyl Cellulose (HPMC) & Hydroxy Ethyl Cellulose (HEC) (pH 6.5)

Sl. No.	Time (min)	Hydroxy Propyl Methyl cellulose (HPMC) (F_1)			Hydroxy Ethyl cellulose (HEC) (F_2)		
		% cum Amt. of drug release ± S.D	% cum Amt. of drug remaining	Log % cum drug remaining	% cum Amt. of drug release ± S.D	% cum Amt of drug remaining	Log % cum drug remaining
1	5	31.63±0.91	68.37	1.8349	28.93±0.12	71.07	1.8517
2	10	39.24±0.72	60.76	1.7836	37.81±0.21	62.19	1.7937
3	15	48.91±0.23	51.09	1.7083	49.82±0.63	50.18	1.7005
4	20	59.43±0.31	40.57	1.6082	58.23±0.13	41.77	1.6209
5	25	72.31±0.14	27.69	1.4433	67.62±0.41	32.38	1.5103
6	30	81.12±0.21	18.88	1.2760	72.43±0.14	27.57	1.4404

F0(without hydrocolloid) F1(with HPMC) F2(with HEC)

Figure 1: Models of Prepared Ketoconazole Tablet Lozenges

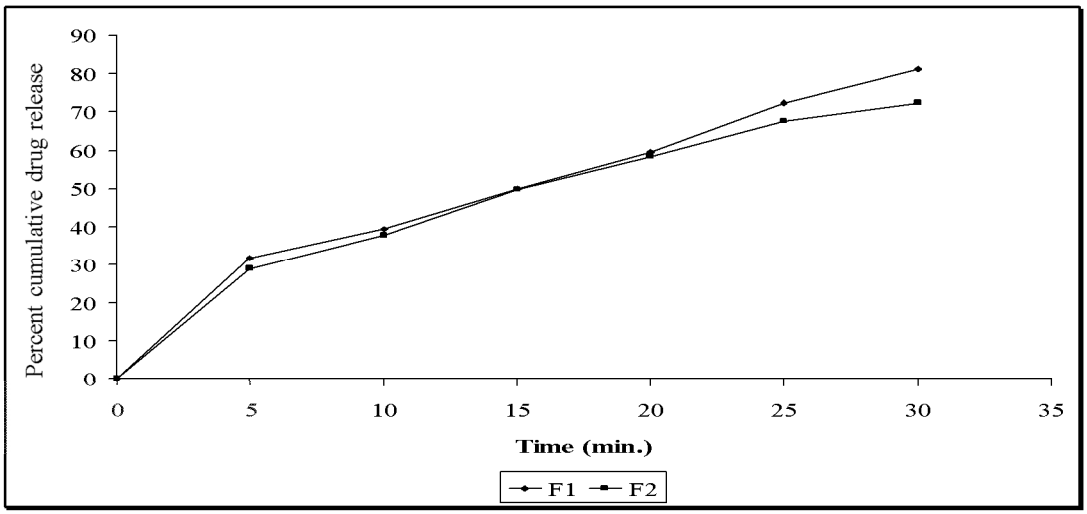

Figure 2: Percent Cumulative Amount of Drug Released Versus Time Plots of Ketoconazole Tablet Lozenges Containing Hydroxy Propyl Methyl Cellulose (HPMC) and Hydroxy Ethyl Cellulose (HEC) (F1 and F2)

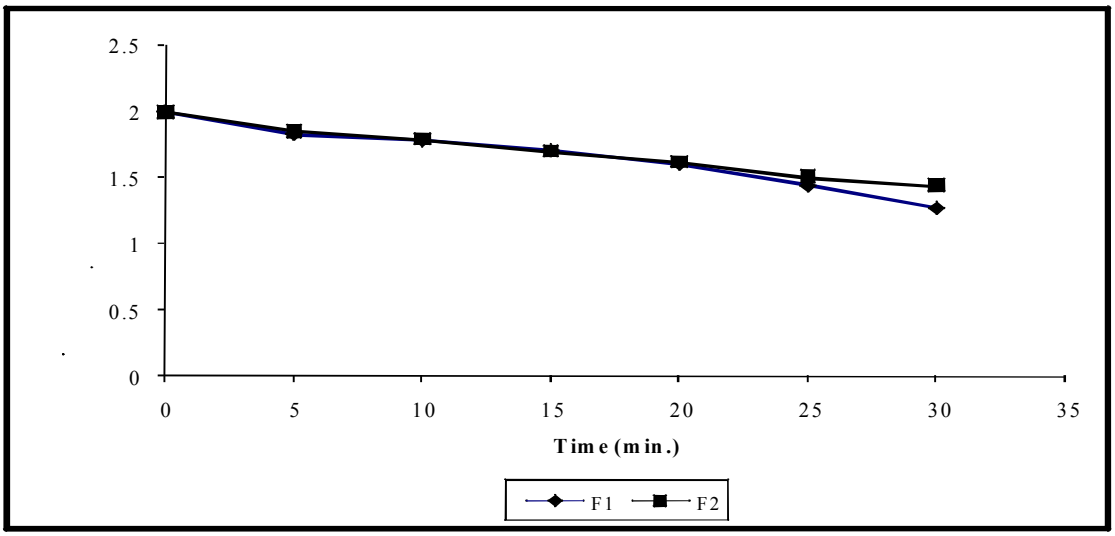

Figure 3: Log Percent Cumulative Amount of Drug Remaining Versus Time Plots of Ketoconazole Tablet Lozenges Containing Hydroxy Propyl Methyl Cellulose (HPMC) and Hydroxy Ethyl Cellulose (HEC) (F1 and F2)

Source of support: Nil, Conflict of interest: None Declared