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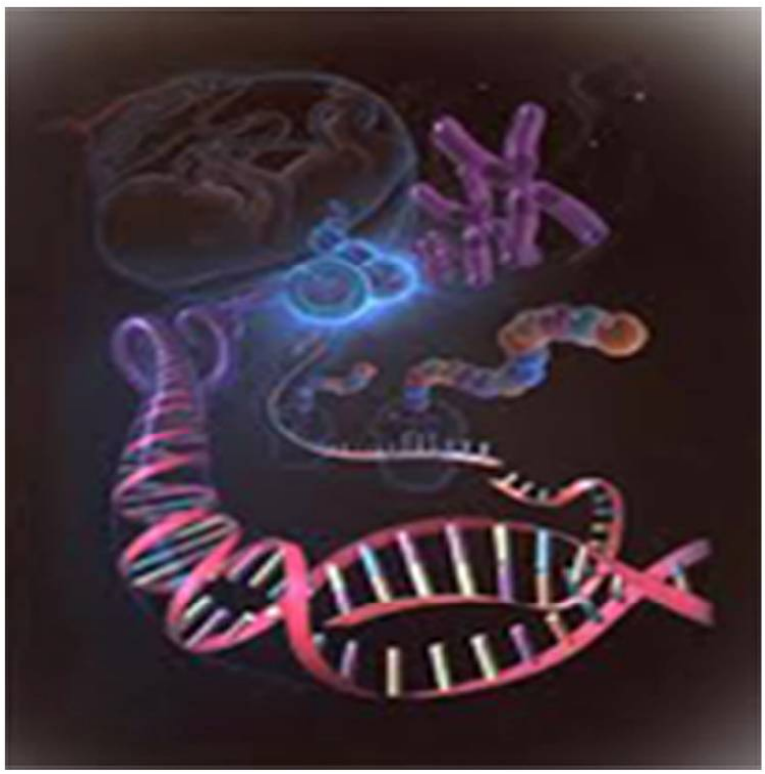

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Research Paper

MEDICATED LOLLIPOPS FOR THE TREATMENT OF ORAL THRUSH IN CHILDREN

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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 sometimes causing epidemics in schools by cross infection. The "lozenges are flavored medicated dosage forms intended to be sucked and hold in the mouth/pharynx. These preparations are commonly used for the purpose of local effect or systemic effect". Advantages of the lozenges as dosage forms include increase in bioavailability, reduction in gastric irritation, bypass of first pass metabolism and increase in onset of action. New drug design to this area always benefit for the patient, physician and drug industry. In the present investigation an attempt has been made to prepare and evaluate medicated lollipops of Ketoconazole. The lollipops were prepared by heating and congealing method in a candy based industry with sucrose 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 10-12 Kg./cm², with good taste. Stability studies of selected formulations were carried out at 37ºC 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 95.35% for K1 and 73.24% for K2 release of drug in 30 minutes, 99.43% in 7 minutes from K0 formulation. The prepares lozenges were subjected for anti microbial studies by agar cup plate method using the organisms collected from a diseased pediatric patient under the supervision of dental physicians and with the permission of ethical committee. The prepared lollipops were also subjected for preclinical studies to find out oral compatibility in healthy human volunteers. The tablet lozenges can provide an attractive alternative formulation in the treatment of oral thrush in pediatric patients.

Keywords: Ketoconazole, Lollipops, Oral thrush.

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 sometimes causing epidemics in schools by cross-infection. *Candida albicans* is a normal

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inhabitant of the oral cavity found in 30% to 40% of the population. Typically, oral candidiasis takes the form of an adherent white, curd like, circumscribed plaque anywhere within the oral cavity. There are many drugs dosage forms like lozenges, tablets, inhalers, and syrups, are in markets for the treatment of the same.The "lozenges are flavoured medicated dosage forms intended to be sucked and hold in the mouth/ pharynx. These preparations are commonly used for the purpose of local effect or systemic effect". Advantages of the lozenges as dosage forms include increase in bioavailability, reduction in gastric irritation, bypass of first pass metabolism and increase in onset of action. New drug design to this area always benefit for the patient, physician and drug industry.There are several dosage forms like in the market, there is a need for more dosage forms which acts effectively and locally as well as systematically. 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 sometimes causing epidemics in schools by cross-infection. The Ketoconazole tablet lozenges are flavoured medicated dosage forms intended to be sucked and hold in mouth / pharynx(Devi V K, 2006; and Firriolo John F, 1994). The present investigation is designed to improve patient compliance. These preparations are commonly used for the purpose of local or systemic effects through the buccal mucosa (Gibbs K P and Portlock J C, 1999; and Herbert A Lieberman, Leon Lachman, 1991). Advantages of the lozenges as dosage forms include increase in bioavailability, reduction in dose size, and in gastric irritation, bypass first pass metabolism (Harsh Mohan, 2000; and Jain N K, 2005). When it is not effectively treated, oral thrush often leads to hospitalization, limitations on physical activity, insomnia nights and in some cases death (Jelvehgari Mitra, 2006; and Shojaei H A, 1998). The present work is aimed at preparing a formulation of Ketoconazole lollipops to provide prolonged retention time upto 30 min. in oral cavity for relief of oral thrush as conventional form of logenzes retention time being around 7 min.

MATERIALS AND METHODS

Ketoconazole was received a gift sample from Leads Pharmaceuticals Ltd Hyderabad, A.P., Hydroxy Propyl Methyl Cellulose (K4 M), Hydroxy Propyl Methyl Cellulose (K100), 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.

Phase-I Studies: Preparation of Medicated Lollipops : Medicated lollipops of 3 gms. in weight spherical in shape, 3.1 cm diameter and 0.6mm thickness were prepared in a local candy industry on request. The Method followed for the preparation was heating and congealing technique (Rawlins E A, 1995). Syrupy base was prepared in a copper vessel dissolving the required amounts of sugar in water on heating and stirring at 110°C for about 90 min (Table 1). Corn syrup was added and stirring continued for 2 hrs. by raising the temperature to 160°C. The material was transferred to a cooling slab and temperature was brought down 90°C till a plastic mass was obtained. Drug, polymer, colour, flavour were added and mixed the material for 30 min. The material was size roped on moving rollers which were then sized into 3 gms lollipops and air dried for about 2 hrs in a rolling drying chamber. The prepared lollipops were seal wrapped in polythene wrappings. An altogether three batches of formulations were prepared i.e., without added

Table 1: Working Formulae to Prepare Ketoconazole Tablet Lozenges

S. No.	Ingredient	Formulations		
		Without hydrocolloids k_0	HPMC(K4M) k_1	HPMC(K100) k_2
1.	Sugar	680 gms	680 gms	680 gms
2.	Liquid Glucose	286 gms	286 gms	286 gms
3.	Drug	10 gms	10 gms	10 gms
4.	Hydroxy Propyl Methyl Methyl cellulose.(K4M).	–	10 gms	—
5.	Hydroxy Propyl Methyl Cellulose.(K100).	—	—	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)

Note: * Each lollipop contains 15 mg of Drug; * Each lollipop weights of 3 gms.

hydrocolloid, Hydroxy Propyl Methyl Cellulose (HPMC), K4 M and K 100. added medicated lollipops.

Phase-II Studies: Characterisation of Prepared Lillipops: Ross and Wilson (2001) the prepared formulations were subjected to drug content uniformity, uniform hardness, diameter, weight variation by following pharmaceutical standard methods (Table 2) .

Phase-III Studies: Drug-Excipient Compatibility Studies: The studies were carried out using IR method with the help of perkin-elmer 1615 spectrophotometer (Figures 1 to 3).

Phase-IV: Stability Studies: The stability studies were performed at two temperatures i.e., 37°C and 45°C over a period of six months for the tablet lozenges containing formulation (K1 and K2). Sufficient number of lollipops (10) were packed in amber coloured screw capped bottles and kept in incubator maintained at 37°C. Samples were taken at intervals of 15 days for the drug content estimation.

Phase-V: Drug release studies under simulated salivary conditions.

IN-VITRO DRUG DISSOLUTION STUDIES

The rate of the drug absorption was determined by the rate of drug dissolution from the prepared formulations. Thus, the rate of dissolution and bioavailability may be directly related to the efficacy of the formulation.The modified tablet dissolution test apparatus (USP-II) was used and the dissolution medium phosphate buffer pH at 6.7, 100 ml was placed in the beaker containing the lollipop and stirred at 100 rpm 5 ml 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 271.8 nm using blank, by Shimadzu UV-Visible spectrophotometer (Table-3).

Anti-Microbial Studies : Microbiological studies were carried out to ascertain the antifungal activity of the prepared formulations as against the pure

Table 2: Physicochemical Parameters of the Ketoconazole Lollipops

S. No.	Parameters	Standard Limits	Formulations prepared		
			Without hydrocolloids k_0 12.2	With HPMC(K4M) k_1 12.4	With HPMC(K 100) k_2 12.5
1.	Weight variation (mg)	>220 mg. – 5%	3.04 ± 0.12 gms	3.69 ± 0.14 gms	3.023.08 ± 0.14gms
2.	Thickness (mm)	–	12.01	12.32	12.62
3.	Drug content (mg)	95 – 105%	99.5 ± 0.22	99.02 ± 0.14	99.02 ± 0.14
4.	Diameter (mm)	–	17.51	17.03	12.46

Note: * Each reading is a mean of three replicates; * Each lollipop contains 15 mg. of Ketoconazole; * Each lollipop contains weight of 3 gms.

Table 3: Comparative *In-vitro* Drug Release Studies of All Prepared Lollipops

Time (in mins.)	Formulations prepared		
	Without hydrocolloids k_0	With HPMC(K4M) k_1	With HPMC(K 100) k_2
5	28.96	24.85	22.74
10	60.71	57.36	55.25
15	99.43	67.98	64.10
20	–	78.82	76.81
25	–	83.86	81.75
30	–	95.35	73.24

Note: * Each reading is a mean of three replicates; * Each lollipop contains 15 mg. of Ketoconazole; * Each lollipop contains weight of 3 gms.

Figure 1: IR Data of Ketoconazole Pure Drug

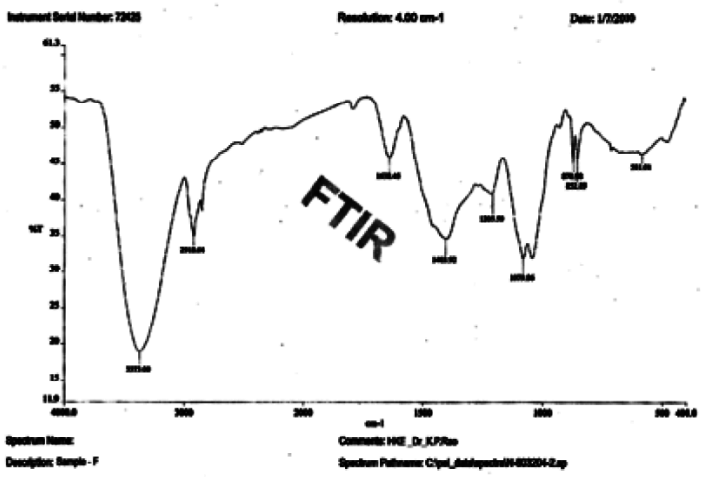


Figure 2: IR Data of Ketoconazole Lollipops Containing with Formula 'A' (K1)

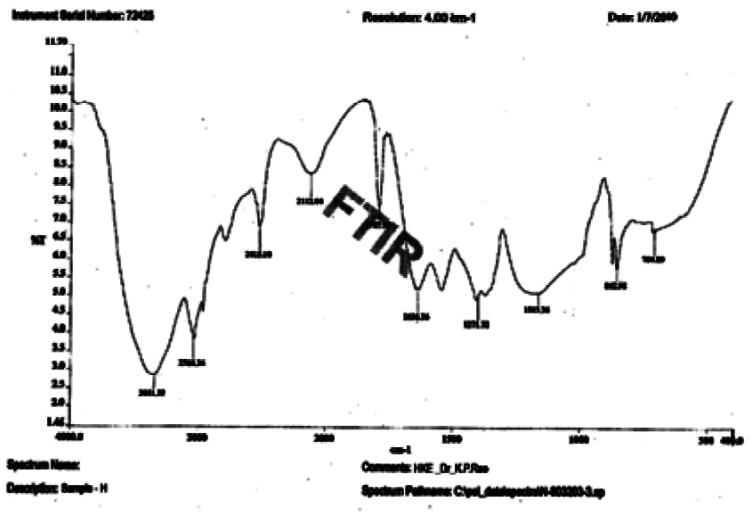
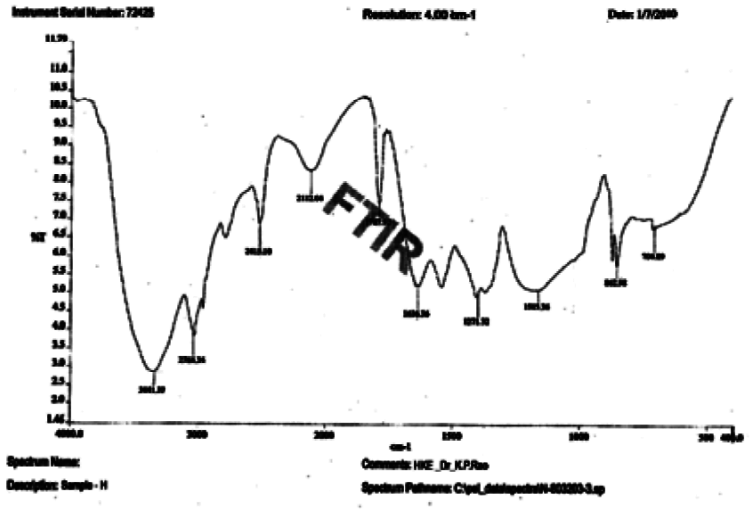


Figure 3: IR Data of Ketoconazole Lollipops 'B' (K2)



drug. Ketoconazole is known to possess superior antibacterial and antifungal activity against a wide range of infections. In the present work antibacterial and antifungal activity of Ketoconazole was tested by using the yeast *Candida albicans*, which is the most frequently encountered human fungal pathogen being responsible for a wide range of superficial infections. The prepared formulations were evaluated for *in vitro* antibacterial and antifungal activity using standard Agar cup-plate method. The test organism *Candida albicans* was a clinical isolate obtained from a diseased patient suffering from oral candidiasis from Al-Badar Dental College and General Hospital, Gulbarga. The microorganism was collected by sweeping cotton-swab on the tongue of patient and dipping this swab in peptone water under the supervision of dental physicians

Phase-IV Studies*:* Skin Irritation test of oral mucosa in human volunteers.

METHODOLOGY

Oral mucosal skin irritation studies of prepared formulations without drug were carried out in human volunteers under the supervision of staff, Al-Badar-Deantal College and General Hospital. Gulbarga.

Test Procedure

No. of Human volunteers	- 16 in number
Age group of Human volunteers	- 8 to 15 years
Weight of Human volunteers	- Between 20 to 70 Kgs.
Hygiene Regime	- Brushed and Gargled twice a day
Total number of administration	- 3 lozenges / volunteer
Duration of administration	- 24 hrs of time internal/ administration
Conditions implied on volunteers	- Fasted for atleast 3hrs before each administration of lozenge. Abstained from taking any medicines, chocolates, chewing gum etc. for over 30 hrs at start of test and during entire 72 hrs study.

Oral Mucosal Irritancy Assessment

It will be performed primarily by examining each volunteer oral cavity barely with naked eyes using focus and lens to notice any changes in tissues aftertheusage of formulations. Then photographic imaging of oral cavity of humanvolunteers will be taken after subsequent application for 72hrs i.e., at completionof study period and these images will be compared to determine the differencewith the images taken at 0 hour of study i.e., prior to first usage of formulation. Moreover, mucosal irritation will be evaluated by questioning the human volunteers at regular interval of time about the feeling of irritancy,which appears to be highly subjective for the study. Finally, the oral mucosal skin irritancy will be evaluated for any changes like oral erythema, inflammation,redness, haemorrhagic lesions or acute painful ulcers (canker sores).

RESULTS AND DISCUSSION

Patient compliance is one of the important aspect for administration of drugs. Attractive, taste masking formulations are the need of the hour. In the present study Ketoconazole sweetened lollipops were designed for the effective treatment of oral thrush in children. This chronic disorder frequently needs frequent drug dose administration. Results of Phase-I and Phase-II studies revealed that the prepared Ketoconazole lollipops were spherical in shape having 12.1 (kg.) hardness, 0.6 mm. thickness of 99% drug content uniformity and 3.1cms. 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 in phase-III studies, 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

Table 4 : Anti Microbial Studies of Prepared Lollipops

Formulation code	Statistical zone of inhibition (mm) after 36 hrs			Mean ± S.D
	Zone 1	Zone 2	Zone 3	
Pure Drug	22	23	24	22.66 ± 0.57
K0	23	20	21	21.33 ± 1.53
K1	20	21	22	20.33 ± 1.53
K2	21	22	20	21.00 ± 1.00

Table 5: Oral Mucosal Skin irritation test data of prepared lollipops without Drug in Healthy Human Volunteers

Formulation Code	Human Volunteers	Before Application of Application			After 24 hrs. of Application			After 48 hrs. of Application			After 72 hrs. of Application		
K_0		I	R	E	I	R	E	I	R	E	I	R	E
	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
K_1	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x
K_2	Male-I	x	x	x	x	x	x	x	x	x	x	x	x
	Male-II	x	x	x	x	x	x	x	x	x	x	x	x
	Female	x	x	x	x	x	x	x	x	x	x	x	x

95.35 % from Hydroxy Propyl Methyl Cellulose (HPMC) (K4M), and 73.24 % from Hydroxy Propyl Methyl Cellulose(HPMC) (K100) based Lollipops. The prepared formulations were found to be compatable when subjected for clinical studies in healthy human volunteers (Table 5).

CONCLUSION

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 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 findings could be of potential use in designing such formulations for pediatric patients.

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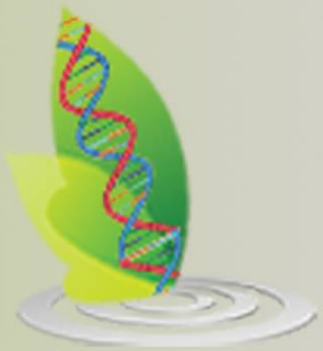
REFERENCES

1. Devi V K (2006), "Orodispersible Fluconazole Tablets – Preparation and Evaluation", *Indian Drugs*, July, Vol. 23 No. 7, pp. 548-552.
2. Firriolo John F (1994), "Oral Candidiasis, History, Classification and Clinical Presentation, Oral Surg. Med. Oral Pathol", *Louisville*, Vol. 78, No. 2, pp. 189-193.
3. Gibbs K P and Portlock J C (1999), *Clinical Pharmacy and Therapeutics*, 2nd Edition, Published Walker Edwards, Scotland, pp. 347-367.
4. Herbert A Lieberman, Leon Lachman (1991), "Pharmaceutical Dosage Forms – Tablet Series, "Medicated Lozenges" Marcel Dekker Inc. New York and Basel, 2nd Edition, Vol. 1, pp. 339-467.
5. Harsh Mohan (2000), *Text Book of Pathology – The Oral Cavity and Salivary Glands*, 4th Edition, pp. 494-496, Jaypee Brothers, Medical Publishers (P) Ltd., New Delhi.
6. Jain N K (2005), Controlled and Novel Drug Delivery, Chapter 16-Mucoadhesive Drug Delivery, CBS Publishers and Distributors, New Delhi, pp. 353-376.
7. Jelvehgari Mitra (2006), "Mucoadhesive and Drug Release properties of Benzocaine Gel", *Iranian Journal of Pharmaceutical Science*, Autumn, Vol. 2, No. 4, pp. 184-194.
8. Shojaei H A (1998), "Buccal Mucosa as a Route for Systemic Drug Delivery: A Review", *Journal of Pharmaceutical Sciences*, Vol. 1, No. 1, pp. 15-30.
9. Rawlins E A (1995), "Bentley's Text Book of Pharmaceutics", Chapter-9 *Rheology*, Bailliere Tindall, London, 8th Edition, pp. 123-39.
10. Ross and Wilson (2001), *Anatomy and Physiology in Health and Illness – Diseases of the Mouth* 9th Edition, p. 319 Churchill Livingstone.



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