World Journal of Pharmaceutical research

Volume 2, Issue 6, 3209-3219. Research Article ISSN 2277 – 7105

FORMULATION DEVELOPMENT OF MEDICATED LOZENGES

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Article Received on
19 August 2013,

Revised on 25 Sept. 2013,
Accepted on 31 October 2013

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ABSTRACT

Clotrimazole was formulated as a medicated 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 medicated lozenge of Clotrimazole. The benefits of these prepared medicated lozenges are increased bioavailability, reduction in gastric irritation by passing first pass metabolism. The medicated 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, moisture content, weight variation, thickness & diameter etc. The prepared formulations have a hardness of 10.5-11.5 Kg./cm^2, free from gritty particles, and good taste. Stability study of selected formulations were stored at 30±2°C/65±5%RH, elevated 40±2°C/75±5%RH 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 90.36% for C1, 88.25% for C2, 82.22% for C3, and 68.64% for C4, release of drug in 30 minutes, 98.21% in 15 minutes from C0 formulation. The prepared medicated lozenges were subjected for antimicrobial activity on causative organisms collected from a diseased patient under the supervision of ethical committee. Clotrimazole showed the zone of inhibition 24.00mm and pure Clotrimazole showed 22.33mm of zone inhibition. Thus the lozenges can provide an attractive alternative formulation in the treatment of oral thrush in pediatric patients.

Key words: Clotrimazole, Medicated lozenges, 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. Chronic thrush may develop, affecting the roof of the mouth in people who wear dentures. The Clotrimazole medicated lozenges are flavored medicated dosage forms intended to be sucked and hold in mouth / pharynx[1,2]. 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[3,4]. Administration of a drug via the buccal mucosa to the systemic circulation is defined as buccal delivery. Patient compliance is high with buccal delivery due to the accessibility of the check lining and lack of invasive measures. In the case of adverse reaction, administration of drug can be stopped at any time, the device can easily be removed apart from avoiding enzymatic degradation. Advantages of the Clotrimazole medicated 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, limitations on physical activity, insomnia nights and in some cases death[7,8]. The present work is aimed at preparing a formulation of Clotrimazole medicated lozenges, which provide prolonged retention time upto 30min. in oral cavity for relief of oral thrush as conventional form of medicated lozenges retention time being around 15 min.

EXPERIMENTAL SECTION

Clotrimazole was received a gift sample from Alkem Laboratories Pvt. Ltd., Mumbai, HPMC, HEC and MC were obtained from Himedia Laboratories Pvt. Ltd., Mumbai., Sodium CMC, 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 Medicated Lozenges with & without Added Hydrocolloids

Medicated lozenges were formulated in a Candy Industry (Hyderabad) on request following heating and congealing method[9]. The various steps involved in preparation of Medicated 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, color and flavorings 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 Clotrimazole Medicated lozenges were packed with the help of machine called Maksom Wrapper.

Physicochemical Characteristics of Formulated Clotrimazole Medicated Lozenges[10]

The prepared formulations were subjected to following parameters.

a) Hardness b) Weight Variation c) Thickness

d) Drug content uniformity e) Diameter Determination f) FT-IR spectral analysis etc.

***In Vitro* Drug Dissolution Studies**

The rate of the drug absorption was determined by the rate of drug dissolution from the Medicated lozenges. Thus, the rate of dissolution and bioavailability may be directly related to the efficacy of the medicated lozenge. The modified lozenges dissolution test apparatus (USP-II) was used and the dissolution medium phosphate buffer pH at 6.7, 100ml. was placed in the beaker containing the medicated 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 analyzed at 272nm using blank, by Shimadzu UV-Visible spectrophotometer. (Table-3) (Fig- 3).

Stability Studies

All the prepared formulations were subjected to stability studies at different temperature i.e., 30ºC / 65% RH and 40ºC /75% RH for a period of 6 months. There was no such considerable change in hardness of lozenge and no change in weight, thickness, drug content (no loss of drug more than 5%). Dissolution studies show no change in release.

Antimicrobial activity

The prepared formulations were studied for antimicrobial activity at 5-µg/ml concentration against the causative organisms collected from a diseased patient under the supervision of qualified pediatricians. The organisms inoculated in standard agar plates (brainheart infusion agar media) and grown as mother cultures. Subcultures were made separately to study the effect of medicated lozenges for zone inhibition studies.

Oral Mucosal Compatibility studies

The promising results of oral mucosal compatibility studies of prepared formulations on

human volunteers under the supervision of Staff, Dept. of Pediatrics, M.R. Medical & General Hospital, Gulbarga. For this test the formulations of mucoadhesive polymers without drug were prepared and used.

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 Clotrimazole sweetened medicated lozenges were designed for the effective treatment of oral thrush in pediatric patient. This chronic disorder frequently needs frequent drug dose administration. Results of prepared formulation and physicochemical characteristics revealed that the prepared Clotrimazole medicated lozenges were spherical in shape 3 grams in weight, with 13mm in thickness, with 17mm in diameter with a hardness of 11-12 Kg/cm^2. The drug content estimation showed uniform drug content in all the formulations. and found to be within the pharmacopoeial limits. In both the drugs I.R. studies revealed that there was no drug excipients interactions showing undisturbed drug peaks in formulations. The results of In vitro dissolution studies revealed that the drug release in 30 minutes under simulated salivary conditions was 90.36% from methyl cellulose, 88.25% from sodium CMC, 82.22% from HPMC based formulation and 68.64% from HEC based formulation in 30 minutes. However, 98.21% drug release in 15 min. from formulation containing without hydrocolloid. The formulations prepared were found to be stable during the study period of six months. The prepared formulations were subjected for antimicrobial activity. The zone inhibition of various prepared formulations were found to be equal on comparison with the activity of pure drug. The results of in-vivo studies in healthy human volunteers revealed that the prepared formulations were compatible in oral mucosa and oral cavity.

Table-1 : Formula for the preparation of medicated lozenges

S. No.	Ingredient	Formulations				
		Without hydrocolloids C_0	With MC C_1	With NaCMC C_2	With HPMC C_3	With HEC C_4
1	Clotrimazole	10 gms	10 gms	10 gms	10 gms	10 gms
2	Sugar	680 gms	680 gms	680 gms	680 gms	680 gms

3	Liquid Glucose	290 gms	280 gms	280 gms	280 gms	280 gms
4	Methyl Cellulose	-	10gms	-	-	-
5	Sodium CMC	-	-	10gms	-	-
6	Hydroxy propyl Methyl Cellulose	-	-	-	10gms	-
7	Hydroxy ethyl Cellulose	-	-	-	-	10gms
8	Citric Acid	12 gms	12 gms	12 gms	12 gms	12 gms
9	Flavoring Agent	7.0 gms	7.0 gms	7.0 gms	7.0 gms	7.0 gms
10	Colouring Agent	1.0 gms	1.0 gms	1.0 gms	1.0 gms	1.0 gms
Total Weight		**1 000 gms**	**1 000 gms**	**1 000 gms**	**1 000 gms**	**1 000 gms**

Each medicated lozenges contains 30mg of drug.

Each medicated lozenges contains weight of 3gms

Table-2 Physicochemical Parameters of the Clotrimazole medicated lozenges

S. No.	Parameters	Standard Limits	Formulations prepared				
			Without hydrocolloids C_0	With MC C_1	With NaCMC C_2	With HPMC C_3	With HEC C_4
1	Hardness (kg/cm²)		10.8	11.2	11.3	11.4	11.5
2	Weight variation (mg)	>250mg - 5%	3.0 gms	3.03 gms	3.05 gms	3.05 gms	3.02 gms
3	Thickness (mm)		13.05	13.03	13.05	13.04	13.01
4	Drug content (%)	95 – 105%	98.2 ± 0.21	99.2 ± 0.03	99.4 ± 0.21	99.61 ± 0.12	99.12 ± 0.26
5	Diameter (mm)		17.05	17.13	17.15	17.17	17.11

- Each reading is a mean of three replicates.
- Each medicated lozenge contains 30 mg of Clotrimazole.
- Each medicated lozenge contains weight of 3 gms.

Table-3 Comparative *In-vitro* drug release studies of all prepared Clotrimazole medicated lozenges

Time (mins)	Formulations prepared				
	Without hydrocolloids (C_0)	With MC (C_1)	With Na CMC (C_2)	With HPMC (C_3)	With HEC (C_4)
5	28.01	20.96	18.86	13.69	10.84
10	59.16	53.47	51.36	37.86	28.86
15	98.21	64.32	62.21	49.44	35.23
20	--	74.83	72.92	57.76	44.21
25	--	79.97	77.86	66.17	55.87
30	--	90.36	88.25	82.22	68.64

Each reading is a mean of three replicates.

Each medicated lozenge contains 30 mg of Clotrimazole.

Each medicated lozenge contains weight of 3 gms.

Table-4 Oral Mucosal Compatibility studies (Test Procedure)

No. of Groups	**05 Groups**
No. of Human volunteers participated	15 in number
Age group of Human volunteers and groups size	8 to 15 years: One groups contains 3 (three) human volunteers
Weight of Human volunteers	Between 20 to 45 Kg.
Hygiene Regime	Brushed and Gargled twice a day
Total number of administration	1 lozenge / volunteer per day for 3 days / early morning.
Duration of administration	24 hrs. of time internal / administration

Conditions implied on volunteers	Fasted for at least 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 72hrs study.

Figure-1: Models of Prepared Clotrimazole Medicated Lozenges

(C_1)

(C_2)

(C_0)

(C_3)

(C_4)

Figure-2: Antimicrobial studies showing the comparative zone of inhibition of drug as pure and in formulation (c_0-c_4)

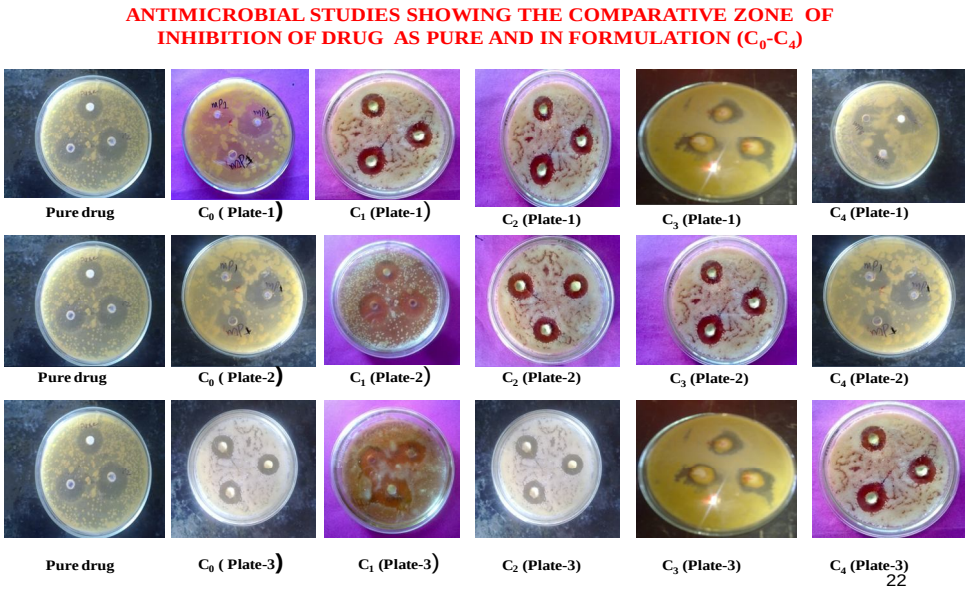

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Figure 3 : Comparative studies of Clotrimazole medicated lozenges with and without hydrocolloids (C_0, C_1, C_2, C_3 and C_4)

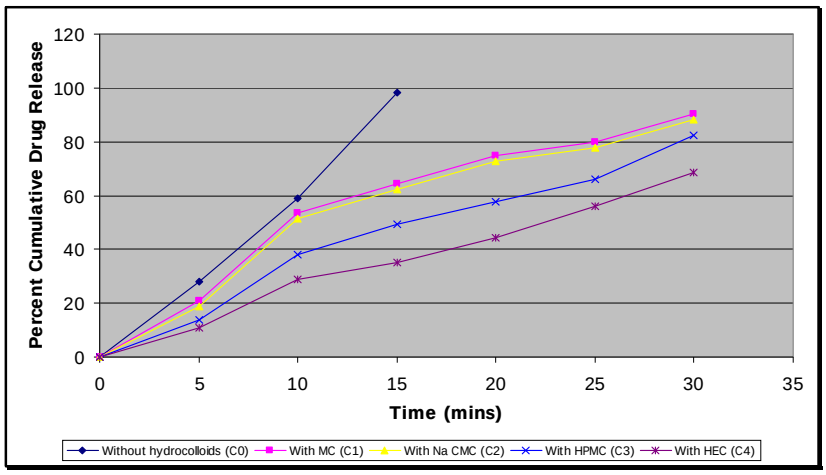
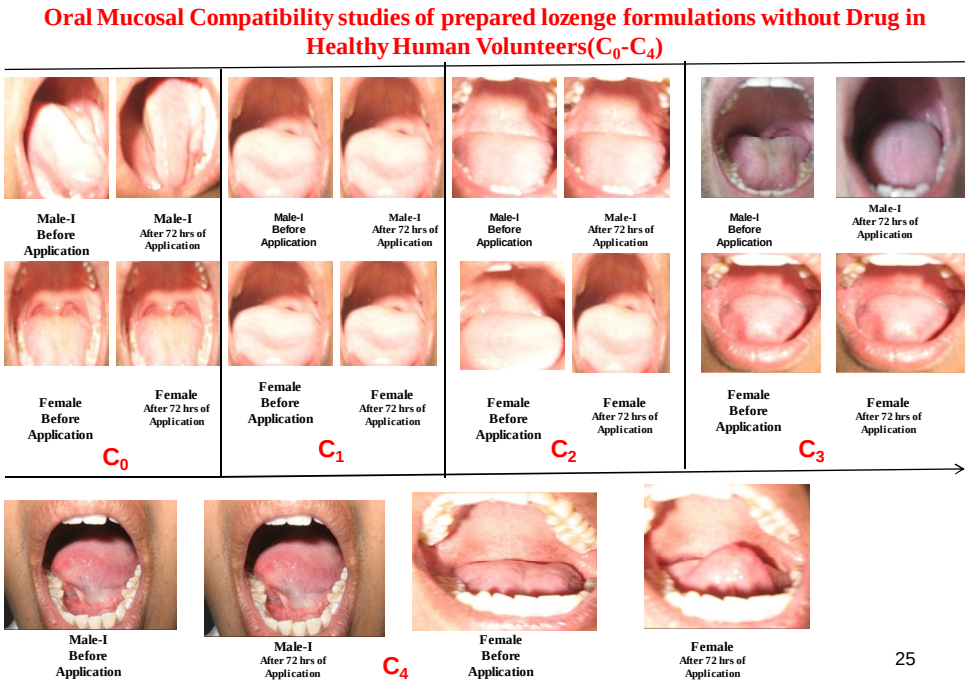


Figure 4: Oral Mucosal Compatibility studies of prepared lozenge formulations without Drug in Healthy Human Volunteers(C_0-C_4)



DISCUSSION

From the present study, it is suggested that sucrose based medicated lozenges will be ideal dosage forms for pediatric patients of oral thrush. Addition of hydrophilic polymers like HPMC, HEC, MC & Sodium CMC yielded good results to prolong oral retention time of medicated lozenge in simulated salivary pH conditions for a period of 30 minutes. The stability studies proved that the prepared medicated lozenges were found to be stable when stored at air tight container or strips. The Results of antimicrobial activity reveled that prepared formulations produces promising antimicrobial activity equivalent to pure drug. These finding could be of potential use in designing such formulations for pediatric patients.

CONCLUSIONS

Following conclusions can be drawn from the results obtained in the present investigation:

It is found that sucrose based Medicated Lozenges will be ideal dosage forms for pediatric patients. These will have additional advantages of patient compliance, convenience and comfortness for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economic. The Physico-chemical characterization revealed that all the formulations were found to be shown acceptable thickness, diameter, weight variation and hardness. The drug content estimation showed uniform drug content in all the formulations.

IR spectroscopic studies indicated that there were no drug-excipients interactions. Addition of hydrophilic Mucoadhesive polymers like methyl cellulose, hydroxy propyl methyl cellulose, hydroxy ethyl cellulose, carboxy methyl cellulose sodium yield good results to prolong dissolution time and the drug release in salivary pH conditions for a period of 30 minutes. Among various polymers used methyl cellulose was found to be suitable in prolongation of dissolution of medicated lozenges for a period of 30 minutes. The stability studies proved that the prepared Medicated lozenges were found to be stable when stored at air tight containers or twist strips. Hence the present piece of investigation will be used for industry, research and development division. The anti-microbial study reveals that zone inhibition of various prepared formulations was found to be equal on comparison with the activity of pure drug. This indicates that there is no change in the molecular activity of the drug present in the formulations. Results of *In-vivo* studies in healthy human volunteers under the supervision of qualified team of pediatricians revealed that no redness or ulcer formation or any irritation on oral mucosa was observed. Hence, the formulations prepared were compatible to use as drug delivery. The present work Medicated Lozenges are industry oriented as these offers patient convenience, compliance and comfortness in application and transportation with effective treatment.

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 M.R. Medical College and Hospital, Gulbarga for expert suggestions.

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