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Formulation, Evaluation and Characterization of Itraconazole Lozenges

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Abstract: *Candidiasis, caused by Candida albicans, is an extremely common, local fungal infection but can become systemic and life-threatening in immune-compromised patients. Itraconazole has been used for prophylaxis and treatment of invasive fungal diseases, such as candidiasis and aspergillosis for the last two decades. The present work is aimed to formulate different types of lozenges for topical delivery of Itraconazole for the treatment of oropharyngeal candidiasis. Compressed tablet lozenges were prepared by wet granulation technique using three different binders, at different concentrations. Soft lozenges (hand-rolled and PEG-base) lozenges were formulated using different excipients. They were evaluated for post-compression parameters by pharmaceutical standard methods. Stability studies were carried out according to ICH guidelines. The optimized formulations were subjected to microbial studies to see their antimycotic activity. The formulated lozenges were evaluated for physical parameters and the results complied with the pharmacopeial limits. In vitro dissolution studies showed 90% drug release by the end of 6o min. FTIR studies showed that there were no drug-excipient interactions. Stability studies indicated that the formulations were stable for 3 months and no significant drug degradation was observed. Itraconazole lozenges were successfully formulated and evaluated. The formulations were successful in delivering the drug for topical application.*

Key terms: *Compressed tablet lozenges, hand rolled lozenges, oropharyngeal candidiasis, PEG base lozenges, soft lozenges.*

I. Introduction

Candidiasis, especially that caused by *Candida albicans*, is extremely common; however, it is not clear why these usually harmless commensal organisms become pathogenic. Candidiasis can occur in most parts of the body. Infection is particularly common in young children and elderly people following antibiotic treatment. People with diabetes and suppressed immune systems are also vulnerable to candidiasis. Most infections are local, but for immune-suppressed patients they can become systemic and life-threatening, especially if they are infected with a drug-resistant strain. [1, 2, 3] The choice of antifungal agent used in the treatment of candidiasis is dependent upon the severity and nature of the infection. [4] In case of local infections, only topical therapy is preferred and in case of systemic infections, a combination of topical and systemic therapies is used as treatment regimen. [5]

Itraconazole (ITZ), a broad-spectrum antimycotic triazole has been used for both prophylaxis and treatment of invasive fungal diseases, such as candidiasis and aspergillosis for the last two decades. ITZ is classified as a class II drug according to the Biopharmaceutical Classification System. It has an extremely low aqueous solubility (S<1 µg/ml) and poor dissolution rate in the gastrointestinal tract and hence low and variable bioavailability.

The present study involves formulation of Itraconazole lozenges for topical therapy of oropharyngeal candidiasis. Lozenges are the flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. Lozenges are intended to relieve oropharyngeal symptoms, which are commonly caused by local infections. Topical application of drug prevents several drug interactions. Lozenges are considered to be better delivery system as the effective concentrations of the drug can be maintained in the oral cavity for a prolonged period as the lozenge is sucked slowly in the mouth. [6, 7, 8, 9, 10]

II. Materials And Methods

2.1. Materials

Itraconazole was kindly supplied as a gift sample from Cornelius Pharmaceuticals (p) Ltd. Hyderabad, India; Sucrose, Gelatin, PEG 1500, Sodium lauryl sulphate by s d fine-chem Limited; Acacia, tragacanth, PEG 400, Sodium hydroxide, Potassium phosphate, monobasic by Finar chemicals Limited; PEG 4000 by Loba Chemie Pvt. Ltd. Sucralose by Natura. All other chemicals were of analytical grade.

2.2. Methods

2.2.1 Analytical method development

2.2.1.1 Determination of λmax of Itraconazole in methanol

A 10 µg/ml standard solution of Itraconazole in methanol was scanned on a double beam UV spectrophotometer. From the UV spectrum of Itraconazole, λ_{max} was obtained.

2.2.1.2 Determination of λ_{max} of Itraconazole in pH 6.8 phosphate buffer with various concentrations of SLS

Itraconazole is soluble at acidic pH and has minimal solubility at neutral pH. While performing invitro drug release studies the amount of drug present in the sample could not be detected because of the solubility problem. Hence sodium lauryl sulphate (SLS) was added to increase the solubility of Itraconazole in pH 6.8 buffer. Various concentrations like 0.1%, 0.5%, 1%, 1.5% and 2% were tried to optimize the concentration of SLS to be added.

2.2.2 Formulation of different types of Itraconazole lozenges

2.2.2.1 Formulation of compressed tablet lozenges

Compressed tablet lozenges were prepared by wet granulation method. Accurately weighed amount of Itraconazole was added in small parts to sucrose and mixed thoroughly. This was granulated using binder solution (different concentrations of gelatin, acacia and tragacanth). The granules obtained were passed through sieve #16 and then dried. The dried granules retained on the sieve #18, along with 15% fines were mixed with weighed amounts of lubricant and glidant and were compressed in machine with maximum force to obtain a compact flat faced tablet lozenges. Color and flavor were added to the binder solution. (TABLES 1-3) (Fig. 1)

TABLE 1: FORMULATIONS WITH GELATIN AS BINDER

Ingredient	F1	F2	F3	F4	F5	F6
Sucrose	890 mg	890 mg	890 mg	890mg	890 mg	890 mg
Drug	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Gelatin solution (concentration, w/v)	2.5%	5%	7.5%	10%	12.5%	15%
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Color	q.s	q.s	q.s	q.s	q.s	q.s
Flavor	q.s	q.s	q.s	q.s	q.s	q.s

TABLE 2: FORMULATIONS WITH ACACIA AS BINDER

Ingredient	F7	F8	F9	F10
Sucrose	890 mg	890 mg	890 mg	890 mg
Drug	100 mg	100 mg	100 mg	100 mg
Conc. of Acacia solution	10 %	15%	20%	25%
Talc	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	5 mg	5 mg	5 mg	5 mg
Color	q.s	q.s	q.s	q.s
Flavor	q.s	q.s	q.s	q.s

TABLE 3: FORMULATIONS WITH TRAGACANTH AS BINDER

Ingredient	F11	F12	F13	F14
Sucrose	890 mg	890 mg	890 mg	890 mg
Drug	100 mg	100 mg	100 mg	100 mg
Conc. of tragacanth solution	10%	15%	20%	25%
Talc	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	5 mg	5 mg	5 mg	5 mg
Color	q.s	q.s	q.s	q.s
Flavor	q.s	q.s	q.s	q.s

Fig 1: Itraconazole Compressed tablet lozenge formulations

2.2.2.2 Formulation of soft lozenges

- Hand-rolled lozenges

The binders used in these lozenges were acacia, gelatin and tragacanth at different concentrations. The powdered sugar and drug were sifted together and sufficient binder solution was gradually added to make a mass of the proper consistency. The mass was rolled into the shape of a cylinder and cut into 10 even sections (approximately twice the length of the diameter). Allowed to air dry (TABLES 4-6).

TABLE 4: FORMULATIONS OF HAND-ROLLED LOZENGES USING ACACIA AS BINDER

Ingredient	F15	F16	F17	F18
Sucrose	5 gm	5 gm	5 gm	5 gm
Drug	500 mg	500 mg	500 mg	500 mg
Acacia mucilage	10%	15%	20%	25%
Water	q.s	q.s	q.s	q.s
Color	2-3 drops	2-3 drops	2-3 drops	2-3 drops
Flavor	q.s	q.s	q.s	q.s

TABLE 5: FORMULATIONS OF HAND-ROLLED LOZENGES USING TRAGACANTH AS BINDER

Ingredient	F19	F20	F21	F22
Sucrose	5 gm	5 gm	5 gm	5 gm
Drug	500 mg	500 mg	500 mg	500 mg
Tragacanth mucilage	10%	15%	20%	25%
Water	q.s	q.s	q.s	q.s
Color	2-3 drops	2-3 drops	2-3 drops	2-3 drops
Flavor	q.s	q.s	q.s	q.s

TABLE 6: FORMULATIONS OF HAND-ROLLED LOZENGES USING GELATIN AS BINDER

Ingredient	F23	F24	F25	F26
Sucrose	5 gm	5 gm	5 gm	5 gm
Drug	500 mg	500 mg	500 mg	500 mg
Gelatin solution	2.5%	5%	7.5%	10%
Water	q.s	q.s	q.s	q.s
Color	2-3 drops	2-3 drops	2-3drops	2-3 drops
Flavor	q.s	q.s	q.s	q.s

- PEG-base lozenges

Blend the powders together until uniformly mixed. Melt PEG and add the powder mix to the molten base and blend thoroughly. Cool to less than 55ºC, add the flavor and mix well. Pour into troche molds and cool. They have to be stored under refrigeration. (TABLES 7-9) (Fig. 2)

TABLE 7: FORMULATIONS OF PEG-BASE LOZENGES WITH VARIABLE CONCENTRATIONS OF PEG 4000 AND PEG 400

Ingredient	F27	F28	F29	F30	F31	F32	F33	F34	F35
PEG 4000: PEG 400	10 : 0	9:1	8:2	7:3	6:4	5:5	4:6	3:7	2:8
Drug	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Silica gel	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sweetener	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Color	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

TABLE 8: FORMULATIONS OF PEG-BASE LOZENGES WITH VARIABLE CONCENTRATIONS OF ACACIA

Ingredients	F36	F37	F38	F39	F40	F41	F42
PEG 1500	3 gm	3 gm	3 gm	3 gm	3 gm	3 gm	3 gm
Acacia	-	50 mg	100 mg	150 mg	200 mg	250 mg	300 mg
Drug	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Silica gel	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sweetener	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops

Color	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s

TABLE 9: FORMULATIONS OF PEG-BASE LOZENGES WITH VARIABLE CONCENTRATIONS XANTHAN GUM

Ingredients	F43	F44	F45	F46	F47	F48
PEG 1500	3 gm	3 gm	3 gm	3 gm	3 gm	3 gm
Xanthan gum	50 mg	100 mg	150 mg	200 mg	250 mg	300 mg
Drug	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Silica gel	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sweetener	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops	1-2 drops
Color	q.s	q.s	q.s	q.s	q.s	q.s
Flavor	q.s	q.s	q.s	q.s	q.s	q.s

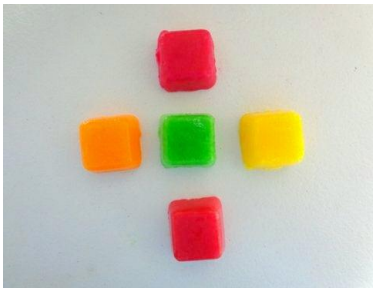

Fig 2: Itraconazole PEG-base soft lozenge formulations

2.2.3 Evaluation and characterization

The prepared lozenges were evaluated for parameters like flow properties of granules, weight variation, hardness, friability, thickness and diameter, disintegration time, drug content uniformity and drug-excipient compatibility studies (FTIR).

2.2.3.1 Weight variation

The weight variation was conducted by weighing 20 lozenges individually and calculating the average weight and comparing the individual lozenges weight to the average value.

2.2.3.2 Hardness

The hardness (Kg/ cm^2) of the prepared lozenges was determined using Monsanto hardness tester.

2.2.3.3 Thickness and diameter

Control of physical dimensions of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using screw gauge. It is measured in mm.

2.2.3.4 Friability

Friability was determined using Roche friabilator. Speed of friabilator was set at 25 rpm. Pre-weighed tablets (6 tablets) were placed in the friabilator and it was subjected to 100 revolutions. The tablets were re-weighed and the percentage friability was calculated.

2.2.3.5 Drug content

Ten lozenges from each batch were selected and weighed individually and crushed in a mortar. Drug was extracted with 50 ml of methanol. The drug content was determined spectrophotometrically at 262 nm with blank lozenge extract as the reference.

2.2.3.6 Disintegration test

The disintegration time of lozenges were determined by USP Disintegration apparatus and disintegration time was noted in pH 6.8 phosphate buffer containing 2% SLS at 37ºC.

2.2.3.7 In vitro dissolution studies

In-vitro dissolution studies were carried out using USP dissolution test apparatus type II (paddle type) at 100 rpm and 37 ±0.5ºC. pH 6.8 buffer containing 2% SLS was used as dissolution medium for in vitro dissolution studies. A lozenge was placed in each flask of the dissolution apparatus and samples of 5ml were withdrawn at predetermined time intervals for 60 min. In order to maintain sink conditions, an equal volume of medium was replaced. The samples were analyzed by using UV-Visible spectrophotometer at 262 nm and

percentage drug released was calculated. This experiment was done in triplicate and the average percentage release was calculated.

2.2.3.8 Drug-excipient compatibility studies (FTIR)

Fourier transform infrared analysis was conducted to study the drug-excipient interactions Samples were scanned in the range from 400-4000 cm^{-1}.The detector was purged carefully by clean dry helium gas to increase the signal level and reduce moisture.

2.2.3.9 Antimicrobial activity

This was determined in the agar diffusion medium employing Cup plate technique. Pure drug solution was used as standard. Drug extracted from formulations using methanol was used as test solution. The standard solution and the developed formulations (test solution) were taken into separate cups bored into sterile nutrient agar previously seeded with organism (*Candida albicans*). After allowing diffusion of solutions for two hours, the plates were incubated for 48 hrs at 25 ºC. The zone of inhibition (ZOI) was compared with that of the standard. The optimized formulation was tested in triplicate.

2.2.3.10 Stability studies

The stability studies of optimized formulations F2 and F48 were performed at 40°C±2°C/75±5% RH and 25ºC±2ºC/60±5%RH respectively for 3months. The formulations were examined visually for physical changes. The drug content was also determined at the end of every month for 3 months.

III. Results And Discussion

3.1 Analytical method development

3.1.1 Determination of λ_{max} of Itraconazole in methanol

The λ_{max} of Itraconazole in methanol was scanned. An absorption maximum of 262 nm was obtained.

3.1.2 Determination of λ_{max} of Itraconazole in pH 6.8 phosphate buffer with various concentrations of SLS

All the scans with different concentrations of SLS showed absorption maximum around 262 nm which coincides with the absorption maxima value found in the literature. This shows that the solubility of Itraconazole in pH 6.8 buffer was enhanced by the addition of SLS.

3.2 Evaluation of lozenges

3.2.1 Compressed tablet lozenges

The prepared Itraconazole lozenges were evaluated for their weight variation, hardness, friability, drug content uniformity and disintegration time. The percentage weight variation was within the specified IP limits and varied between 0.98% and 1.21%. Hardness of the tablet was in the range of 5.5 kg/cm^2 to 13.5 kg/cm^2. Friability was less than 1% in all the batches, which indicates the tablet's ability to withstand shock during handling. Drug content was found to be in the range of 91.07% and 97.01%. Disintegration time was found to be in the range of 35 min and 46 min. It is clear from the above results that the evaluated parameters were within the limits. (TABLE 10)

TABLE 10: EVALUATION PARAMETERS OF ITRACONAZOLE COMPRESSED TABLET LOZENGES

Formulations	Weight variation (n=20)	Hardness Kg/cm^2 (n=3)	Thickness mm (n=3)	Friability (%) (n=6)	Drug content (%)	Disintegration time (min)
F1	1.17	9.2	3.07	0.89	96.2	45
F2	1.13	10.3	3.01	0.97	94.5	51
F3	1.03	11.6	2.98	0.84	95.8	53
F4	1.05	12	3.17	0.16	96.7	56
F5	1.15	13	3.08	0.05	97.1	40
F6	0.98	13.5	3.05	0.12	95.8	41
F7	0.99	5.5	3.11	0.23	91.7	44
F8	1.11	6.2	3.10	0.18	93.3	46
F9	1.21	7.5	3.12	0.27	92.4	35
F10	1.18	8.3	2.98	0.65	94.5	42
F11	1.19	5.3	3.06	0.73	91.6	43
F12	1.16	6.3	2.99	0.54	93.5	43
F13	1.12	7.1	3.09	0.87	96.6	45
F14	1.09	7.5	3.14	0.82	92.9	44

3.2.2 Soft lozenges

The prepared Itraconazole soft lozenges were evaluated for their weight variation, hardness, thickness, drug content uniformity and disintegration time. From the results obtained, it is clear that the physical parameters evaluated for different batches were within the specified IP limits. (TABLES 11-12)

TABLE 11: EVALUATION PARAMETERS OF HAND-ROLLED LOZENGES

Formulations	Weight variation (n=20)	Hardness (kg/cm^2)	Drug content (%)	Disintegration time (min)
F15	1.15	2.3	96.6	30
F16	1.12	2.5	93.8	31
F17	1.04	2.75	94.7	31
F18	1.06	2.8	96.7	32
F19	1.14	2.4	97.1	29
F20	0.98	2.56	96.8	30
F21	0.99	2.7	92.7	31
F22	1.12	2.8	92.3	31
F23	1.21	2.3	95.4	40
F24	1.19	2.5	94.5	45
F25	1.18	3.2	92.6	46
F26	1.17	3.9	97.5	47

TABLE 12: EVALUATION PARAMETERS OF PEG-BASE LOZENGES

Formulations	Weight variation (n=20)	Hardness (kg/cm^2)	Thickness mm (n=3)	Drug content (%)	Disintegration time (min)
F27	1.28	3.9	5.17	96.1	20
F28	1.35	3.6	5.26	94.5	18
F29	2.8	3.1	5.01	95.8	15
F30	3.5	2.8	5.21	96.4	13
F31	4.1	2.3	4..99	97.12	12
F32	3.6	1.9	5.23	95.69	9
F33	1.12	1.2	4.98	91.54	7
F34	-	-	-	-	-
F35	-	-	-	-	-
F36	1.12	2.1	5.15	94.5	12
F37	1.04	2.9	5.13	91.06	15
F38	1.06	3.1	5.16	93.06	18
F39	1.14	3.41	5.11	96.65	20
F40	0.98	3.63	5.17	95.4	22
F41	0.99	3.74	5.23	92.1	25
F42	1.12	3.8	5.19	94.3	26
F43	1.21	2.9	5.24	95.6	20
F44	1.19	3.3	5.22	92.3	26
F45	1.18	3.6	5.19	93.7	30
F46	1.17	3.75	5.20	95.6	33
F47	0.96	4.2	5.16	96.1	37
F48	1.12	4.5	5.14	95.65	45

3.2.3 In vitro dissolution studies

Based on the in vitro drug release studies, two formulations, F2 and F48 were optimized. They showed a cumulative percentage drug release of 89.60% and 90.45% respectively by the end of 60 min. (TABLE 13) (Fig. 3-4)

TABLE 13: DRUG RELEASE PROFILE OF OPTIMIZED FORMULATIONS

Time (min)	Cumulative percentage drug released	
	F2	**F48**
10	11.21	28.7
20	17.85	43.6
30	25.76	50.1
40	41.54	74.34
50	50.69	85.67
60	89.60	90.45

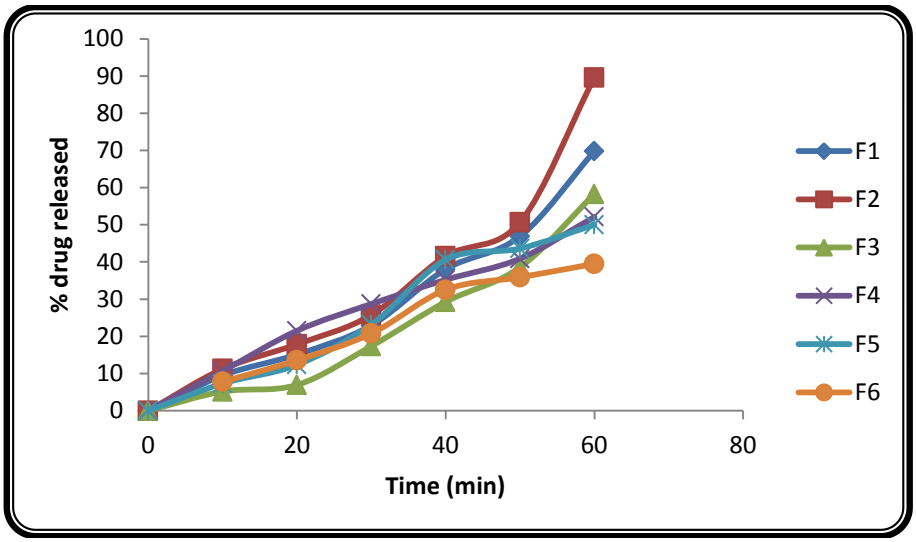

Fig 3 : Drug release profile of formulation F2

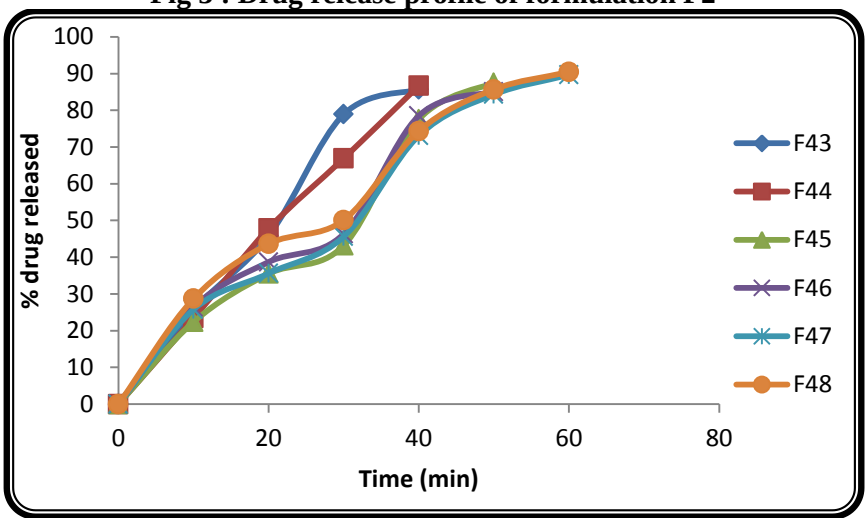

Fig 4: Drug release profile of formulation F48

3.2.4 Drug-excipient compatibility studies

The IR spectrum of the formulation F2 and formulation F48 recorded by FTIR spectrometer which are compared with standard functional group frequencies of Itraconazole. The characteristic peaks of the optimized formulations followed the same trajectory as that of the drug alone with minor differences. Thus there may be no drug-excipient interactions.

3.2.5 Antimicrobial activity

The optimized formulations showed antifungal activity when tested microbiologically by the Cup-Plate technique using drug solution as standard. The results obtained are as shown in Fig. 5 and 6.

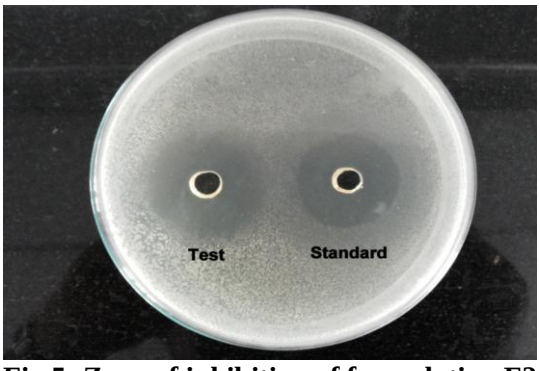

Fig 5: Zone of inhibition of formulation F2

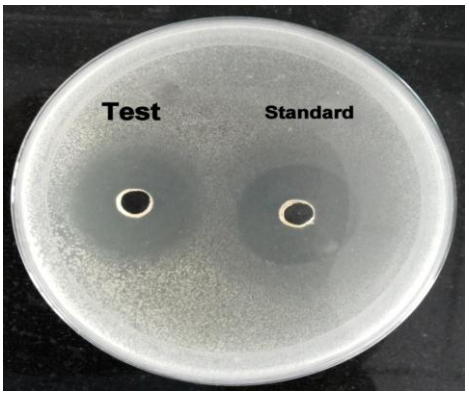

Figure 6: Zone of inhibition of formulation F48

3.2.6 Stability studies

It was observed that there was no change in the physical appearance of the formulation. The drug content was analyzed and the results were found to be in the range within the limits as per IP and ICH guidelines. The stability data of formulation F2 and F48 are illustrated in the tables. As observed from the data shown in the tables, the formulations showed no significant changes in the drug content, hardness, friability and in vitro drug release profiles. Hence, it is confirmed that the formulations were stable at elevated temperatures. (TABLES 14-16)

TABLE 14-16: STABILITY DATA OF OPTIMIZED FORMULATIONS

TABLE 14

Time interval	Hardness		Friability		Drug content	
	F2	F48	F2	F48	F2	F48
After 1 month	10.1	4.31	0.97	-	96.51	96.98
After 2 months	9.9	4.22	1.12	-	96.42	96.65
After 3 months	9.8	4.16	1.13	-	96.21	95.87

TABLE 15

Time (min)	Cumulative percentage drug released		
	1 month	2 months	3 months
10	10.21	9.92	9.04
20	16.85	15.43	14.97
30	24.76	23.76	22.45
40	41.45	40.76	40.21
50	50.41	50.01	49.97
60	88.60	88.45	88.23

TABLE 16

Time (min)	Cumulative percentage drug released		
	1 month	2 months	3 months
10	28.21	27.92	27.04
20	42.85	42.43	41.97
30	49.76	48.76	48.45
40	73.45	72.76	72.21
50	85.41	85.01	84.97
60	89.60	89.45	89.23

IV. Conclusion

Rationale of the study was to develop Itraconazole lozenges for topical therapy of oropharyngeal candidiasis. Topical application of drug prevents several drug interactions and lozenge is a better delivery system as the effective concentration of drug can be maintained in the oral cavity for a more prolonged period of

time. Different types of Itraconazole lozenges were formulated and the formulations were evaluated for weight variation, hardness, drug content uniformity and disintegration time. In vitro drug release studies were carried out using USP dissolution apparatus type II. Two formulations, F2 and F48 were optimized based on in vitro drug release studies. The optimized formulations were also subjected to drug-excipient interaction studies, microbial studies and stability studies.

The lozenges were optimized by all the above parameters and the following conclusions were made from the studies.

- No drug-excipient interactions were seen.
- The formulations were stable for 3 months and no significant drug degradation was observed.
- The formulations had sufficient antimycotic activity.

It can be stated that the objective of the study was met. Itraconazole lozenges were successful in delivering the drug for topical application.

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