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Formulation Development and Evaluation of Mucoadhesive Buccal Tablets of Miconazole for Oral Candidiasis

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ABSTRACT:
The main objective of creating stable mucoadhesive formulations of miconazole with rate-retarding and mucoadhesive polymers, either synthetic or natural, is to treat fungal infections, especially oral candidiasis, and to investigate how various polymers affect drug release profiles for extended release. Rheological characteristics of the powder bed were assessed, including bulk density, compressibility index, and angle of repose. Mucoadhesive buccal tablets were compressed using 10 station rotary tablet compression machine. Each batch was assessed using a USP dissolution testing apparatus, method II, using a paddle at 50 rpm with the aid of a kinetic study. Each batch was also evaluated for weight variation, hardness, thickness, percent swelling index, and in vitro drug release and in-vitro antifungal activity.

KEYWORDS: Miconazole, Mucoadhesive, Buccal tablets, HPMC, Gelatin.

INTRODUCTION:

Oral candidiasis is an opportunistic infection of the oral cavity. It is prevalent in the elderly and sometimes goes undiagnosed, especially in those who wear dentures. Fortunately, it is frequently preventable with proper oral hygiene practices. It is also frequent in persons with impaired immune systems and may indicate systemic diseases like diabetes mellitus. Candida, a fungus that resembles yeast, overgrows or infects the oral cavity, leading to oral candidiasis. There are more than 20 species of Candida, however *Candida albicans* is the most prevalent and significant one that causes oral candidiasis [1]. About 50% of healthy adults usually have C. albicans, a dimorphic fungus organism, in their oral cavity in a non-pathogenic state. Under ideal circumstances, the organism which is often present as yeast can change into a pathogenic, or disease-causing, hyphae form. *C. tropicalis, C. glabrata, C. pseudotropicalis, C. guillierimondii, C. krusei, C. lusitaniae, C. parapsilosis, and C. stellatoideaare* a few other species [2]. The development of the infection can be facilitated by the use of broad-spectrum antibiotics, xerostomia, immune system failure, or detachable prosthetics or dentures. Fungal invasion and colonization are further facilitated by 6advancements in medical care such as central venous catheters, hemodialysis, organ transplantation, antineoplastic treatment, and parenteral feeding [3].

The oral route is the one that patients prefer among all the dosage forms. Oral delivery of drugs includes drawbacks, such as hepatic first pass metabolism and GI tract enzyme breakdown, which preclude the oral administration of some drugs types, including peptides and proteins. For systemic drug delivery, transmucosal drug delivery routes have clear advantages over oral drug administration. Mucoadhesion is

defined as a drug delivery method that makes use of the bioadhesion of specific water soluble polymers, which become sticky during hydration and may therefore be utilized to target a drug to a specific area of the body for an extended period of time [4].

Miconazole (MZ) is a potent azole antifungal medication that has been shown to have two distinct effects on candida albicans: it prevents the formation of ergosterol and inhibits peroxidases, which leads to cellular death. However, because of its cytotoxicity, resistance-building, and low water solubility and its limited dissolution property, a novel strategy is required to improve the physiochemical properties of miconazole with improved localization and to lessen its adverse effects, such as gastrointestinal disturbances and hepatotoxicity [5].

MATERIAL AND METHODS:

Materials:

Miconazole, Hydroxy Propyl Methyl Cellulose (HPMC) were obtained from research lab , Gelatine powder , D(-) Mannitol , Guar Gum were obtain from Loba Cheme pvt ltd, Carboxy Methyl Cellulose Sodium was obtained from Molychem and Magnesium sterate was obtained from Rankem.

Methods:

A) Micromeretics study:

The drug and excipient powder mix was subjected to following micromeretics study parameters.

1. Angle of repose
2. Bulk density
3. Tapped density
4. Compressibility index.

1. Angle of Repose:

The angle of repose is the maximum angle that forms between the surface of the powder pile and the horizontal surface. The angle of repose values for the majority of pharmaceutical powders fall between 25 and 45°; lower values denote better flow characteristics [6]. The fix funnel method was utilised for determining angle of repose. In the fixed funnel method, graph paper is laid on a level horizontal surface and a funnel is positioned with its tip at a predetermined height, H. Till the top of the conical pile just reaches the funnel's tip, powder or granulation is gently poured through the funnel. Next, the angle of repose is calculated using the diameter of the conical pile's base [7].

It is determined using the given formula,

$$\tan\emptyset = \frac{h}{r} \qquad (1)$$

where, h is height of pile, r is radius of pile [6].

Table 1: Angle of repose [8]

Sr.No.	Angle of Repose	Flowability
1	25-30	Excellent
2	31-35	Good
3	36-45	Fair possible
4	46-55	Poor
5	56-65	Very poor
6	>66	Very, very poor

2. Bulk Density:

The volume of a known mass of powder that went through the screen is used for determining the bulk density [6]. It is calculated by using the given formula,

$$Bulk\ density = \frac{M}{Vb} \qquad (2)$$

Where,

M= Mass of sample, Vb= Volume of sample [7].

3. Tapped density:

It is obtained by tapping the measuring cylinder containing known mass of powder and then measuring the volume of powder [9]. It was performed using the Electrolab's tapped density apparatus.

4. Compressibility index:

Carr's Compressibility index and Hausner ratio gives the indication about the ease with which a powder material can flow using following equations,

Carr's Compressibility index (CI):

$$\text{CI} = \frac{(\text{tapped density} - \text{bulk densiity})}{\text{tapped density}} \times 100 \qquad (3)$$

Hausner's ratio (HR):

$$\text{HR} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad (4)$$

Table 2: Scale of flowability for CI and HR [7]

Sr. No.	Carr's Index	Hausner's Ratio	Flowability
1	5-15	1.05-1.18	Excellent
2	12-16	1.14-1.20	Good
3	18-21	1.20-1.26	Fair passable
4	23-35	1.30-1.54	Poor
5	33-38	1.50-1.61	Very poor
6	>40	>1.67	Very very poor

B) Formulation of Mucoadhesive Buccal tablets:

50 mg of miconazole were contained in each mucoadhesive buccal tablet, which was made using the formula mentioned in the table. A precise weight of 50 mg of Miconazole was measured, along with other excipients such xanthan gum, guar gum, D Mannitol, HPMC K4M, Magnesium sterate and Talc were weighed and thoroughly mixed. Next, utilizing a 10 Station Rotary Tablet Compression Machine and an appropriate set of dies and punches, the powder mixture of Miconazole and excipients was compressed into tablets. Pre-compression factors including angle of repose, density, flowability, compressibility index, and hausner's ratio were among the parameters that were examined for the powder blend of miconazole and excipients [10].

Table 3: Formulation of Mucoadhesive Buccal tablets of Miconazole [10]

Ingredients (mg)	Formulation Batches				
	A	B	C	D	E
Miconazole	50	50	50	50	50
CMC sodium	30	60	30	60	30
HPMC	30	30	-	-	-

Gelatin	-	-	30	-	-
Guar gum	-	-	-	30	30
Mannitol	84	54	84	54	84
Mag. Sterate	2	2	2	2	2
Talc	4	4	4	4	4
Total tab.wt.	200	200	200	200	200

C) Evaluation of Tablets:

1. Appearance:

The most important factor in determining a tablet's acceptance is its appearance. Consumer approval is mostly dependent on general elegance and identity. Based on measurements of the following characteristics, such as size, color, form, odor presence or absence, taste, etc., batches of tablets have been accepted for their appearance [11].

2. Tablet thickness and diameter:

We took measurements with a digital vernier caliper on ten tablets that were chosen at random. Between ± 5% of the standard value should be adhered for both tablet thickness and tablet diameter [12].

3. Hardness:

Hardness is the measure of a tablet's resistance to mechanical shocks [11]. Monsanto hardness tester was used to perform this test. The Monsanto hardness tester is made up of two plungers holding a barrel with a compressible spring inside of it. Zero reading is obtained by contacting the tablet with the lower plunger. The tablet is then cracked by rotating a threaded bolt, which forces the upper plunger against a spring. A pointer travels along a gauge within the barrel to show the force as the spring compresses. The unit of measurement for fracture force is kilograms. Ten tablets are broken apart to determine there hardness [13].

4. Friability:

Sample of 10 entire tablets is taken if the average weight of the tablets is greater than 0.65 g, and a sample of whole tablets equating to approximately 6.5 g if the average weight of the tablets is less than 0.65 g. Gently dedust the tablets, then precisely weigh the necessary quantity of tablets. After placing the tablets, rotate the drum 100 times (25 rpm for 4 min). Take out the tablets, tidy them of any loose dust, and weigh them precisely.

Friability is calculated using following formula,

$$f = (1 - w/wo)100 \qquad (5)$$

Where,

wo is initial weight of tablets,

w is final weight of tablets [7,14].

5. Weight variation test:

The USP weight variation test is carried out by weighing each of the twenty tablets separately, calculating out their average weights, and then comparing each tablet's weight to the average. The weight variation test's value is given as a percentage.

It is calculated by using the following formula,

Weight variation = (Iw – Aw)/ Aw × 100. (6)

Where, Iw is individual weight of tablet,

Aw = Average weight of tablet [15].

Table 4: Limits for weight variation test as per IP, BP, and USP [16,17,18].

Average mass (mg)		Percent Deviation (%)
IP/BP	USP	
80 mg or less	130 mg or less	10%
More than 80 mg but less than 250 mg	130 mg to 324 mg	7.5%
250 mg or more	More than 324 mg	5%

6. Swelling index:

Each buccal tablet was weighed independently; the first weight was designated as W1, and each tablet was then put in a separate petri dish with 10 mL of phosphate buffer (pH 6.8) solution. The buccal tablets were taken out of the petri dishes using coverslips at intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr. Any extra surface water was carefully wiped away with the Whatman filter paper. Next, the enlarged tablets were weighed again (W2). It was carried in triplicate.

Degree of swelling = [(W2 – W1) / W1] x 100 (7) [10].

7. In- Vitro Dissolution Study:

Using the USP dissolving testing device II (Paddle type), the release rate of Miconazole from Bioadhesive tablets was ascertained. The dissolution test was conducted at 37 ± 0.5°C and 50 rpm with 900 ml of pH 6.8 buffer. Every hour for 12 hours, a sample of the solution (5 ml) was taken out of the dissolving equipment and replaced with new dissolving medium. The absorbance of these solutions was measured at 272 nm after the solution had been suitably diluted [10].

8. In –Vitro Anti-Fungal Activity:

Activity of selected batch were determined, for these purpose batch E was selected. The organism *C. albecans* ATTC 10231 was used in an agar diffusion procedure. On top of the agar surface, the tablet was placed. After incubating at 35ºC for 24 hours, the diameter of the zone of inhibition was measured [10,19].

RESULT AND DISCUSSIONS:

Micromeretics study:

The result of micromeretics properties of all the batches from A to E of mucoadhesive buccal tablets of miconazole are shown in table 5. These batches were evaluated for parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The value for angle of repose were in the range of 35 to 41 showing fair passable flow property the value for carr's index was is in the range of 28 to 34 and for hausner's ratio between 1.42 to 1.53. All the values were in the acceptable range.

Table 5: Result of Micrometics study on powder blend

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of repose	Carr's Index	Hausner's Ratio
A	0.4390	0.6732	39.9	34.78	1.53
B	0.4426	0.6640	41.1	33.34	1.50
C	0.4480.	0.6250	37.08	28.32	1.42
D	0.4527	0.6606	35.79	31.81	1.46
E	0.4504	0.6640	39.23	31.80	1.466

Evaluation of Tablets:

Appearance:

The tablets were round in shape and have off white colour without any uneven colour distribution. The tablets were free of any objectionable odour.

Evaluation for thickness, diameter, hardness and friability:

All the formulations were evaluated for parameters such as thickness, diameter, hardness and friability. There values are given in table no.6, all the values were in the acceptable limit as per the standards.

Table 6: Result for tablet thickness, diameter, hardness and friability

Batch	Thickness (mm)	Diameter (mm)	Hardness (kg/m)	Friability (%)
A	3	8	3 – 3.3	0.68
B	3	8	3.5 – 3.7	0.72
C	3	8	3.6 - 3.8	0.80
D	3	8	3.9 – 4	0.60
E	3	8	3.5 – 4.2	0.79

Weight variation test:

Tablets were evaluated for weight variation test, all the batches were within the acceptable limits as per the IP, BP and USP. The result for the test is given in table 8.

Table 7: Average tablet weight of each batch.

Sr no.	Batch	Average weight (mg)
1	A	206
2	B	207.6
3	C	207.2
4	D	205.8
5	E	206.6

Table 8: Weight variation test results

Tablet No.	Batch No (% weight variation)				
	A	B	C	D	E
1	3.5	0.28	0.86	1.06	1.16
2	2.4	0.67	1.06	0.87	0.77
3	0.48	5.4	1.35	1.85	1.25
4	0.48	0.67	2.31	2.33	0.77
5	1.4	0.28	1.83	2.52	1.25
6	0.98	1.25	1.54	2.33	0.77
7	0.48	3.17	1.35	0.38	1.25
8	7.2	0.13	0.57	2.04	3.67
9	2.4	1.63	0.86	3.50	2.12
10	4.3	0.19	1.83	3.79	3.09
11	1.9	4.62	3.95	1.36	4.64
12	2.4	1.25	1.35	2.04	0.19
13	2.4	0.19	0.09	1.06	1.25

14	0.48	1.25	4.72	1.06	1.64
15	0.48	2.21	2.50	2.81	3.19
16	6.3	1.15	1.83	2.81	2.12
17	0.48	0.28	2.02	1.55	1.16
18	0.98	2.60	4.92	2.32	3.09
19	4.3	1.15	0.38	2.04	1.16
20	1.4	1.63	1.54	0.38	0.29

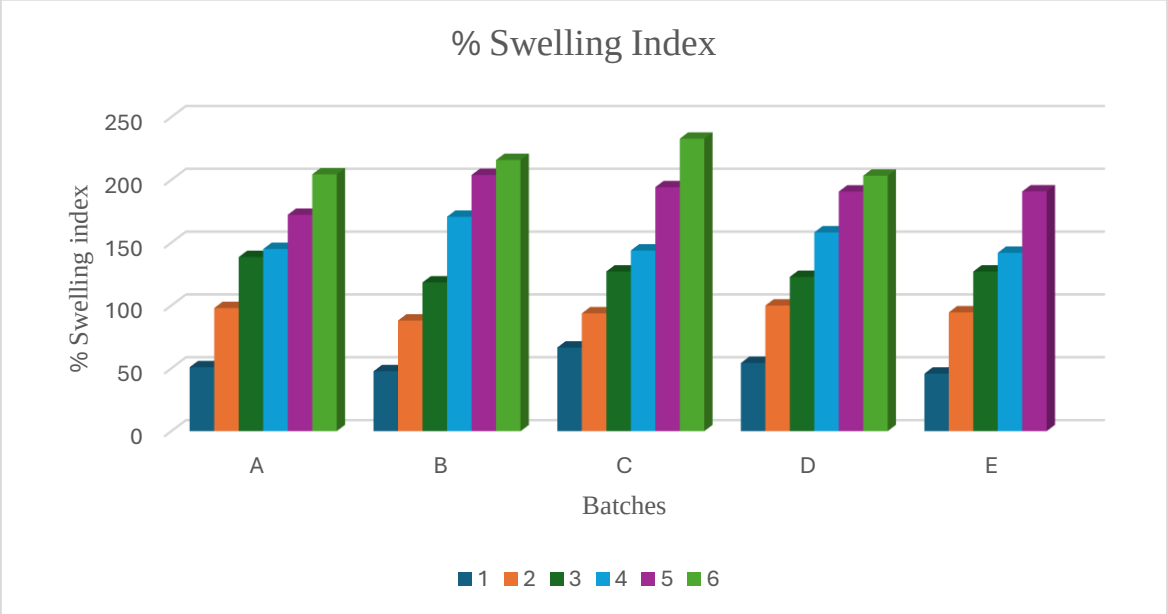
Swelling Index:

Throughout the swelling period, no disintegration was seen in any of the tablet formulations with different concentrations of mucoadhesive and rate-retardant polymers. Because the chosen polymer compositions of each formulation had low invariance, it was discovered that all of the formulations' swelling indices were found to be little to more superimposable. The swelling index profile of all the batches is given in table 9 and figure 1.

Table 9: Swelling index profile

Batch	% Swelling index after time t in hrs.					
	1	2	3	4	5	6
A	50.92	98	138.6	145	172.2	204.4
B	47.7	88.05	118.4	170.64	203.9	215.9
C	66.6	93.8	127.1	143.8	194.2	232.8
D	54.3	100	122.8	158.2	190.7	203.3
E	45.8	94.6	127.05	142	190.8	207.7

Figure 1: % Swelling index profile



In-vitro Dissolution Test:

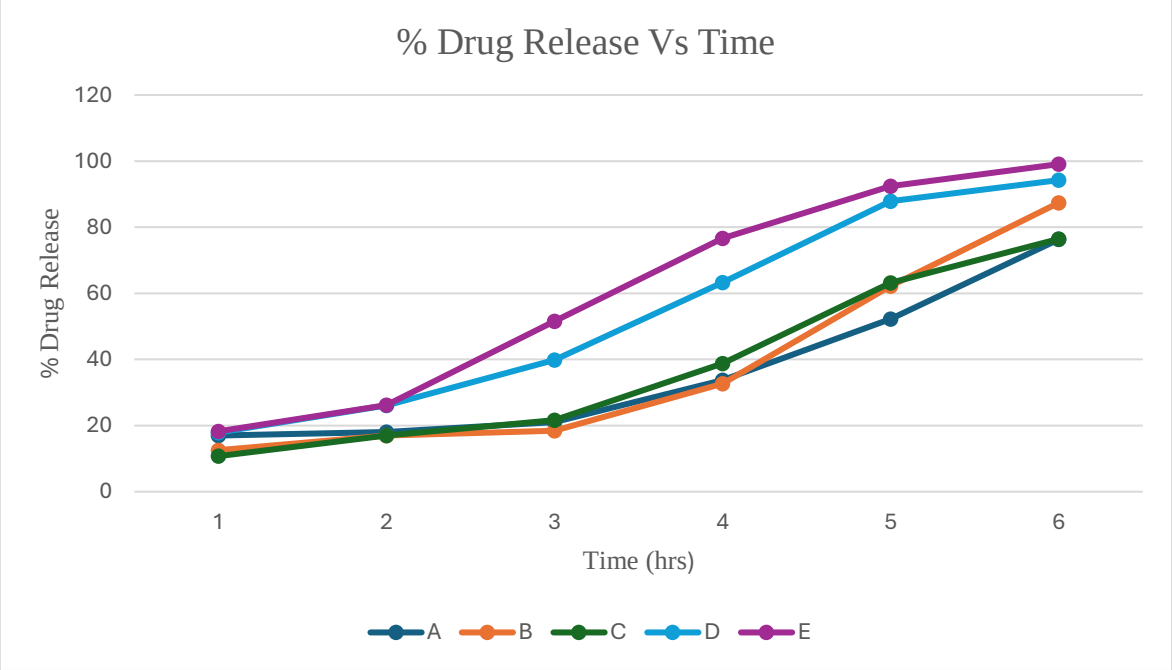
The tablets belonging to all the 5 formulation (A to E) were evaluated, all showed sustained release pattern for drug release for upto 6 hrs as given in table. The test result showed that as the concentration of polymer

was increased the amount of drug release was retarded. The formulation batches D and E showed the drug release about 90%. These batches contain CMC sodium and Guar Gum as rate retardant polymers.

Table 10: % Drug Release profile

Time (hrs)	Formulation Batch (% Drug Release)				
	A	B	C	D	E
1	16.99	12.56	10.76	17.89	18.26
2	18.03	16.99	16.99	26.06	26.21
3	21.04	18.44	21.68	39.85	51.55
4	33.76	32.70	38.79	63.24	76.65
5	52.24	62.20	63.18	87.89	92.45
6	76.32	87.40	76.47	94.25	99.08

Fig 2. Drug release study of mucoadhesives buccal tablets of Miconazole



In-vitro Antifungal activity:

The antifungal activity of the optimized formulation batch E of miconazole tablet was determine using the agar cup diffusion method. The figure 3 and table 11 shows the zone of inhibition diameter obtained. These formulation showed the antifungal activity against *C. albicans.*

Table 11: Zone of Inhibition of batch E

Sr. No	Zone of inhibition (mm)	Mean
1	5	5.5
2	6	
3	5.5	

Figure 3: Zone of Inhibition

CONCLUSION:

Miconazole is an azole antifungal with a broad spectrum of activity that also exhibits some efficacy against Gram-positive bacteria. Although intravenous miconazole is no longer accessible, a wide range of suppositories, creams, gels, and tablet-based medications are available for the treatment of mucosal yeast infections, including both oral and vaginal infections. Miconazole has very long half life of 24 hours but it is poorly absorbed from the topical cream formulations in the systemic circulation and requires frequent daily dosing also has poor stability in gastrointestinal tract. We formulated the Mucoadhesive Buccal tablet of Miconazole to improve its absorption in systemic circulation via increase in contact time with oral mucosa and bypassing first pass effect. We used various rate retardant polymers such as HPMC k4m, guar gum, CMC sodium and studied there effect on drug release pattern for 6 hours. We found upto 99% drug release from formulation E in 6 hours using guar gum as rate retardant. The dose of drug with buccal formulations was reduced to 50 mg from 500 mg of Miconazole topical formulation.

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