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FORMULATION DEVELOPMENT AND PHARMACOTECHNICAL EVALUATION OF MUCOADHESIVE DRUG DELIVERY SYSTEM FOR ORAL CANDIDIASIS

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ABSTRACT: Itraconazole is an anti-fungal drug. It prevents growth of several types of fungi by preventing the fungi from producing the membranes that surround the fungal cells. It is active against fungal infections such as aspergillosis, blastomycosis, histoplasmosis, and candidiasis, as well as fungal infection localized to the toenails and fingernails (onychomycosis). The oral liquid is typically used in patients with oral thrush, especially AIDS, and in the prophylaxis of fungal infections in leukemia or after bone marrow transplantation. The present study is aimed to develop mucoadhesive buccal tablet containing itraconazole. Various approaches to combine hydrophilic (HPMC, chitosan) polymers have been made to prepare total six formulations. Further, these formulations were subjected to different evaluation studies like content uniformity, surface pH, friability, bio adhesiveness and dissolution tests. Results for in vitro drug release and bio adhesiveness studies suggest that the formulation (F5) containing chitosan (20%w/w) and HPMC (80%w/w) has shown better mucoadhesive property. Thus, the present investigation suggests the combination of HPMC and chitosan, as hydrophilic polymers for preparation of Itraconazole mucoadhesive tablets.

INTRODUCTION: Oral diseases are a health problem in immuno-suppressed patients around the world since the oral cavity provides a diverse environment for colonization by a wide variety of microorganisms. Most of mouth infections are mainly due to candidiasis and bacterial infections. It has been reported that more than 300 bacterial species have been identified in the periodontal pockets. Oropharyngeal candidiasis (OPC) is among the most common opportunistic infections observed in persons infected with human immunodeficiency virus.

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The oral liquid is typically used in patients with oral thrush, especially AIDS, and in the prophylaxis of fungal infections in leukemia or after bone marrow transplantation [1].

Oral liquids does not remain in contact with oral sub-mucosa layer for prolonged time. In the last two decades, mucoadhesion has shown renewed interest for prolonging the residence time of the dosage forms in oral cavity. Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow [2-4]. Itraconazole is an anti-fungal drug in the same class of drugs as fluconazole (Diflucan), ketoconazole (Nizoral), and miconazole (Micatin, Monistat). It is used for the treatment of fungal infections in both HIV- and non-HIV-infected individuals. It is active against fungal infections such as aspergillosis, blastomycosis, histoplasmosis, and candidiasis, as

well as fungal infection localized to the toenails and fingernails (onychomycosis) [5].

The present work is aimed at developing Itraconazole containing mucoadhesive tablet which would allow treatment of recently-acquired oropharyngeal candidiasis. To prepare mucoadhesive tablet hydrophilic polymers in combination were used, i.e, Chitosan and Hydroxy Propyl methyl cellulose.

MATERIALS AND METHODS:

Itraconazole drug was procured from Pell Tech Healthcare Pvt. Ltd., Mumbai, India, HPMC K100M was procured from Colorcon, Goa, India and chitosan from Mehtani Chitosan, Gujarat, India. All other chemicals purchased were of analytical grade as received.

Formulations Development of Mucoadhesive Tablet:

Swelling and Gelling property for the Screening of polymers:

A simple test was carried out for obtaining arbitrary information on swelling and stiffness of gel to screen polymers for further studies. Several polymers like, methyl cellulose, alginate, carbopol, HPMC, Xanthan gum, Guar Gum and chitosan were studied for their swelling and gelling properties. Swelling index was measured as per the method described in the literature.[6] Gelling property was done by immersing the glass rod in the swollen mass in above test.

TABLE 1: COMPOSITION OF BUCCAL TABLETS OF ITRACONAZOLE

Ingredients mg/tablet	Formulation code					
	C-100	C-80/HP20	C-60/HP-40	C-40/HP-60	C-20/HP-80	HP-100
	F1	F2	F3	F4	F5	F6
Itraconazole	100	100	100	100	100	100
HPMC K100M	-	20	40	60	80	100
Chitosan	100	80	60	40	20	-
Magnesium Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total Weight	204	204	204	204	204	204

Method of Preparation of mucoadhesive tablets:

Wet granulation method was employed to prepare Itraconazole buccal tablets using, Chitosan and HPMC K100M as a polymers. Mucoadhesive matrix tablet each containing 100mg of Itraconazole were prepared by non-aqueous granulation method (using isopropyl alcohol). All the ingredients except drug and lubricants were weighed and blended for 10 min in an inflated polyethylene pouch.

Itraconazole was then added in this mixture and mixed for 2 min for uniform mixing. Granulation was done with PVP solution (3%w/v). Resultant wet granules were air dried at room temperature and passed through 30-40# Sieve. The dried granules were lubricated using magnesium stearate (1% w/w) and talc (1% w/w) and compressed using 8-station rotary compression machine with 8 mm flat punch. The total weight of the resultant tablets was 204mg and had 5-8 kg/cm^2 hardness. Formulations composition of the prepared mucoadhesive buccal tablets of Itraconazole is given in **Table 1**.

Evaluation of Granules for buccal tablets of Itraconazole:

The formed granules were evaluated for bulk and tapped density, angle of repose, Hausner's ratio and Carr's index [7].

Evaluation of buccal tablets of Itraconazole:

Itraconazole mucoadhesive tablets were evaluated for their thickness, weight variation, hardness and friability as per the method explained in Indian Pharmacopoiea [8]. Results are in **Table 2**.

The friability of tablets was determined by using Veego Friabilator (Model: VFT-2D, India). It was expressed in percentage (%).The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

TABLE 2: POST-COMPRESSION EVALUATION OF ITRACONAZOLE BUCCAL TABLETS.

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)
F1	7.33±1.67	3.53±0.202	0.50	196.5± 0.55
F2	6.33±1.00	3.42±0.32	0.52	194.8±0.09
F3	6.67±1.33	3.5 ±0.25	0.60	195.7±0.06
F4	7.67±0.67	3.49± 0.30	0.63	196.2±0.02
F5	5.67±0.67	3.51 ±0.23	0.30	197.1±0.05
F6	6.67±1.00	3.46 ±0.32	0.47	193.2±0.01

Drug content uniformity:

Ten tablets were weighed and powdered. An amount of the powder equivalent to 100mg of Itraconazole was dissolved in 100ml of pH 6.8 buffer, filtered, diluted suitably and analyzed for drug content at 262 nm using UV-Visible spectrophotometer.

Tablet Surface pH:

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo* [9]. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 1ml of buffer solution pH 6.8 for 2 hr. and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 min. This test was done in triplicates and mean was calculated. Results are depicted in **Table 3**.

TABLE 3: FORMULATIONS CHARACTERISTICS OF ITRACONAZOLE BUCCAL TABLETS.

Formulation Code	Drug Content (%)	*In-Vitro* Residence Time	Mucoadhesive Strength	Surface pH
F1	99.50±0.87	>12 hrs	13.67±1.67	6.73±0.21
F2	99.63f±0.43	>12 hrs	15.33±1.33	6.55±0.04
F3	99.63±0.63	>12 hrs	23.00±2.00	6.84±0.09
F4	99.75±1.12	>12 hrs	25.33±3.33	6.32±0.09
F5	99.88±0.24	>12 hrs	31.00±1.00	6.04±0.26
F6	99.88±0.98	>12 hrs	34.00±2.00	5.91±0.04

Swelling index: [10]

The swelling index of the buccal tablet was evaluated by using pH 6.8 phosphate buffer. The initial weight of the tablet was determined (w1). The tablets was placed in pH 6.8 phosphate buffer (25 ml) in a Petri-dish placed in an incubator at 37 ± 1˚C and tablet was removed at different time intervals (1.0, 2.0, 3.0, 4.0, 5.0, 6.0 hr) excess water was removed using filter paper without pressing and reweighed (w2). The swelling index was calculated using following formula:

Swelling index = 100 (w2-w1) / w1

Mucoadhesion strength:

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by Gupta et al using sheep buccal mucosa as model mucosal membrane [11]. The balance adjusted as described in the literature was used for the study. The sheep buccal mucosa, excised and washed was tied stuck with mucosal side upward using cyanoacrylate adhesive over the base of inverted 100 ml glass beaker. This beaker suitably weighted was lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37˚C such that the buffer reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass vial using cyanoacrylate adhesive.

The 5gm weight on right hand side was applied; this causes application of 5 gm of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 minutes and then slowly weights were increased on the right pan, till tablet separates from mucosal membrane. The total weight on right pan gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and

thoroughly washed with isotonic phosphate buffer and left for 5 minutes before reading a new tablet of same formulation to get reproducible multiple results for the formulation.

Determination of the *Ex Vivo* Residence Time:
The *ex vivo* residence time was found using a locally modified USP disintegration apparatus.

The disintegration medium was composed of 500 ml pH 6.8 phosphate buffer maintained at 37±0.5°C. The sheep buccal tissue was glued to the surface of a glass slab using cyanoacrylate adhesive, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 ml of phosphate buffer pH 6.8 and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted.[11]

***In vitro* drug release study:**
This was carried out in USP XXIII tablet dissolution test apparatus (ElectroLab EDT-06P), employing paddle stirrer at 50 rpm and 500 ml of pH 6.8 phosphate buffers as dissolution medium. The release study was performed at 37±0.5 ˚C. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Wattman filter paper and analyzed for Itraconazole after appropriate dilution by measuring the absorbance at 262 nm.[8, 12]

Stability studies:
Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. In the present work stability studies were carried out at accelerated temperature (45°C, RH 75%) for 1 month.[13]

RESULTS AND DISCUSSION: Mucoadhesive buccal tablet of Itraconazole was prepared using hydrophilic polymer in combination. A total six batches were prepared at different levels of chitosan and HPMC. In order to study the effect of combination of hydrophilic polymers on mucoadhesion and drug release, two batches containing only individual polymers, i.e, chitosan and HPMC were also studied.

Several polymers were screened for their application as a mucoadhesive polymer using gelling and swelling property. Out of all screened hydrophilic polymers, HPMC and Chitosan were found to be suitable candidate for mucoadhesive buccal tablet formulation.

Buccal tablets containing Itraconazole were prepared using wet granulations method and subjected to pharmacotechnical evaluation. The granulation affects the flow characteristics, compression as well as release from delivery system. Individually drug powder, with a crystalline nature, has good flow property. Chitosan and HPMC in powder form show poor to passable flow properties. The granules of drug and polymers in presence of lubricant and glidant shows passable to good flow property. The difference in compressibility of the mixture may be due to the difference in particle nature of ingredients.

All the formulations showed satisfactory results in terms of weight variation, content uniformity, hardness and thickness. Hardness of tablets was in the range of 5-8 kg/cm^2. Percent weight loss in the friability test was found to be less than 0.65% in all the formulations. Content uniformity was found within 100 ± 2% for itraconazole. Results are given in Table 2 and 3.

Ex-vivo mucoadhesion measurement:
The results of the detachment force of itraconazole bioadhesive tablets are given in Table 3. Batch of 100% HPMC and 100% Chitosan were also prepared to study the effect of combinations of these two polymers. But it was observed that combination works better then the single polymer.
In all the polymer combination formulations, as the HPMC proportion increases, the detachment force increases. Increasing the concentration of polymer

may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhesive strength. The polymer in the tablet first gets activated by moistening and gets adhered to mucus membrane and after that formation of intimate contact between mucus and polymer chains takes place leading to formation of bonds and strengthening the adhesive joints. Very strong bioadhesion could damage the epithelial lining of the mucosa, so the concentration of polymer should be optimum because high concentration may cause inflexible confirmation of polymer coils that cannot participate actively in adhesion with mucus macromolecule.

In vitro Dissolution study:

In vitro dissolution study was carried out using USP dissolution apparatus. Chitosan and HPMC are hydrophilic polymers. When tablets containing these polymers come in contact with water, it allows gradual hydration of the tablet matrix, leading to swelling of the tablets. Water decreases the glass transition temperature of the polymers to the experimental temperature. At this temperature, glassy polymer is transformed into a rubbery state. Mobility of polymeric chains is enhanced in this state. This favors the transport of water into tablet and consequently transport of the dissolved drug from tablet core to the dissolution medium. Drug release from matrix tablet is determined by drug characteristics, delivery system and destination (site of drug release). Drug content of each tablet was 100 mg and 500 ml of dissolution medium was used for dissolution studies. From the in-vitro dissolution results it can be revealed that retardation of drug release from the formulations could be attributed to the properties of polymers used in the formulations as shown in **Figure 1**.

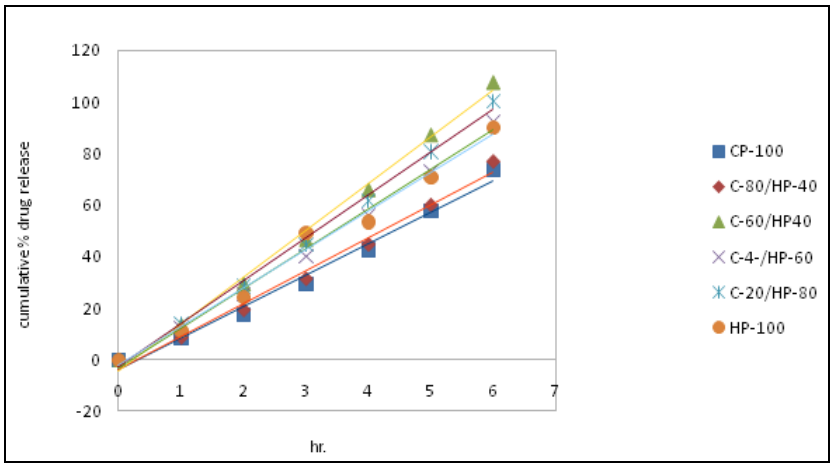

FIGURE 1: *IN-VITRO* DRUG RELEASE OF ITRACONAZOLE BUCCAL TABLET FORMULATIONS

Stability studies:

In the present work stability studies were carried out at accelerated temperature (45°C, RH 75%) for 1 month. The formulations were evaluated for mucoadhesive strength and drug content. The samples were found to be stable at the above storage conditions.

CONCLUSION: Chitosan and HPMC K100M can be promising polymers for mucoadhesive buccal tablet. High bioadhesive strength of the formulation is likely to increase its buccal residence time, and eventually improve the extent of bioavailability. Swelling studies indicated significant water uptake and contributed in drug release; swelling could also help in bioadhesiveness. The optimized formulation F5, sustained the release up to 6 h. Sustained drug release with high bioadhesive strength was observed in case of optimized formulation. The swollen tablet also maintained its physical integrity during the drug release studies. The optimized formulation was found to stable in short-term accelerated stability testing at 45°C at 75% RH for a period of 1 month.

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