

Formulation and evaluation of buccoadhesive tablets of clotrimazole

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The buccoadhesive tablet is one of delivery systems that can be used for different drugs in order to improve the efficacy of drugs in patients. Hydrophilic polymers are using to prepare these types of tablets with appropriate adhesion and stability in order to deliver the drug for a period of time and also in a specific place in month. The purpose of the study was to formulate and evaluate mucoadhesive buccal tablets of clotrimazole. The tablets were evaluated for weight variation, hardness, friability, disintegration, content uniformity, surface pH, mucoadhesive strength, swelling index and *in vitro* drug release. Increasing hydroxypropylmethylcellulose (HPMC) concentration resulted in decreasing the swelling index and increasing surface pH. The surface pH of all tablets was found to be satisfactory, close to neutral pH; hence, no irritation would observe with these tablets. The maximum bioadhesive strength was observed in tablets formulated with high content of HPMC. Lower release rates were observed by increasing the content of HPMC in the formulation. The *in vitro* release results demonstrated that drug is released by non-Fickian diffusion mechanism with zero-order kinetics.

Key words: Buccal tablets, buccoadhesives, clotrimazole

INTRODUCTION

Candidiasis in the oral cavity is an opportunistic infectious condition caused by a ubiquitous, saprophytic fungus of the genus *Candida*, the most common of which is *Candida albicans*. *C. albicans* is a resident commensal fungus of the normal oral flora. It can infect when predisposing factors such as antibiotic therapy, corticosteroid therapy, xerostomia (dry mouth), diabetes mellitus, chemo/radiation therapy and immunosuppression are present. Recently the advent of the human immunodeficiency virus infection has resulted in a resurgence of oral *Candida* infections. General debilitation, poor oral or dental hygiene and ill-fitted dentures are some of the other predisposing factors responsible for the cause of oral candidiasis. Fungal opportunistic infections, including oral candidiasis, are a major cause of morbidity and mortality in cancer patients. Oral *Candida* infections are observed in more than 90% of HIV-positive patients at some time during their disease, particularly in advanced immunosuppression.^[1-5]

Buccal mucosa is a potential site for the delivery of

drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly in the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastrointestinal effect. Buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent accidental swallowing. Therefore, adhesive mucosal dosage forms were suggested for oral delivery. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site. Buccal compacts or buccal bioadhesive drug devices designed to remain in contact with buccal mucosa and release the drug over a long period of time in a controlled fashion. In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period. Hence buccoadhesive drug delivery systems have been

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developed basically to increase the retention of drug in the oral cavity. The route provides intimate contact between a dosage forms and absorbing tissue thereby resulting in high drug concentration in a local area and hence continuous release of drug from the medication toward medium from where it is constantly removed. Such dosage forms are very much useful for the treatment of buccal diseases among which oral candidiasis in one.^[6]

In recent years, hydrophilic matrices have attracted considerable attention as sustained drug release devices. Various types of polymers can be used in the hydrophilic matrix and the hydration of these polymers results in the formation of an outergel layer that controls drugs release. Hydroxypropylmethylcellulose (HPMC), the nonionic cellulose ether, is commonly used in the formulation of hydrophilic matrix systems.^[7]

A wide range of polymers of synthetic, semisynthetic and natural origin like carbopol, polycarbophil, sodium carboxymethylcellulose (SCMC), HPMC, chitosan and xanthan gum have been described for the formulation of bioadhesive systems but none of these polymer possess all the characteristics of an ideal polymer (nontoxic, nonirritant, strong noncovalent adhesion, sustained release, stable and cheap) for a bioadhesive drug delivery system.^[8]

Clotrimazole (CTZ) is the first line broad-spectrum antifungal agent that has been extensively used for the prophylaxis and treatment of oral and vaginal candidiasis. It is known to be very effective locally and only a small percentage of the drug applied to the oral mucosa can be detected in the serum or urine. Presently, for the topical treatment for oral candidiasis, CTZ is available only in the form of troche (a common brand is Mycelex[®] troche, Miles Pharma, USA) which is required to be taken three to five times a day for 14 days. Therefore, there is a need for the development of CTZ buccal bioadhesive-controlled release formulation. A mucoadhesive buccal tablet could be stuck on to the inner surface of the cheek and which would maintain the salivary concentration of the drug. Recent years have seen an increasing interest in the development of novel buccal bioadhesive dosage forms. These are useful for both for systemic delivery of drugs, as well as for local targeting of drugs to a particular region in the body.^[9-12]

In this study different formulations of buccoadhesive tablets were prepared and their physicochemical properties were evaluated.

MATERIALS AND METHODS

Materials

HPMC 4-M, SCMC, Mg Stearate, lactose was obtained from Merck Co., Germany and CTZ was obtained from Amoli Organic, India.

Methods

Formulation of CTZ buccoadhesive tablets:

In this research, direct compression method has been employed to prepare buccal tablet with HPMC and SCMC as polymers, lactose and Mg Stearate [Table 1].

Ten milligrams of CTZ was used in preparation of each tablet formulation. The powder blends of various proportions were compressed into tablets with 11 mm by single punch machine using stainless steel flat surface dies and punches. Tablets weight maintained constant at 300 mg. The compression force was maintained in such a way that the hardness of resulting tablets ranged between 74.7 and 82.4 N. According of three phase diagram more than 30 formulations were prepared but the following formulations which have optimum properties selected for other evaluations.

Evaluation of buccal tablets of CTZ

Physical evaluation

According to the methods mentioned in monograph of CTZ in pharmacopiea, the hardnesses, weight variations and friability of formulations F₁, F₂, F₃, F₄ using analytical balance, Erweka hardness and Erweka friability tester, were studied.

Content uniformity

Ten tablets were selected from each formulation randomly. They were grinded in a glass mortar and the powder equivalent to 0.1 mg of drug was placed in a testing tube then 10 ml of phosphate buffer pH 6.8 was added. Samples were mixed for 10 minutes in an ultrasonic water bath constantly and their absorbance measured at 227 nm.

Standard calibration curve of CTZ in phosphate buffer (pH 6.8) with dilution ranged from 0.625 to 10 µg/ml were prepared and the concentration of the above samples were calculated [Figure 1].

Water uptake study (swelling index)

The swelling index (SI) of the three tablets of each formulation was determined in room temperature. The water uptakes of tablets were studied by means of USP dissolution test apparatus II. The medium used was distilled water. The medium was maintained at 37±0.5 °C throughout the study. After selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed.^[13]

$$SI = \frac{W_t - W_0}{W_0}$$

W_t → weight of swollen tablet

W₀ → initial weight of tablet

Table 1: Formulations of buccoadhesive tablets of CTZ

Ingredients	F ₁	F ₂	F ₃	F ₄
Clotrimazole	10	10	10	10
SCMC	114.8	86.1	57.4	28.7
HPMC	143.5	172.2	200.9	229.6
Lactose	28.7	28.7	28.7	28.7
Mg stearate	3	3	3	3

In vitro dissolution studies

In vitro dissolution studies of buccal tablets of CTZ were carried out in USP tablet dissolution test apparatus-II, employing a paddle stirrer at 50 rpm using 900 ml of phosphate buffer (pH 6.8) at 37±0.5°C as dissolution medium. One tablet was placed in each vessel. At predetermined time intervals 5 ml of the samples were withdrawn by means of a syringe and the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The samples were analyzed for drug release by measuring the absorbance at 227 nm using UV spectrophotometer.

Tablet surface pH evaluation

The surface pH of the three tablets of each formulation was determined in order to investigate the possibility of in vivo side effects. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was our attempt to keep the surface pH as close to neutral as possible. The tablets were first allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.5±0.05) for 2 hours in glass tubes. The surface pH was then noted by bringing glass micro electrode near the surface of tablet and allowing it to equilibrate for 1 min.^[14]

RESULTS AND DISCUSSION

Physicochemical properties

It could be observed that all the prepared tablets fulfill the IP requirements for physicochemical properties. The hardness of prepared buccal tablets was found to be in the range of 74.7-82.4 N.

The friability of all tablets was less than 1% i.e., in the range of 0.34-0.67%. The percentage deviation from mean weights of all the formulations of tablets was found to be within the prescribed limits in USP. The low values in standard deviation indicates uniform drug content in all the formulations prepared as observed from data table given in table 2.

Bioadhesive strength measurement

The values of bioadhesive strength Figure 1 were decreased in the following order: F₄>F₃>F₂>F₁. Therefore, increasing HPMC concentration increases the bioadhesion [Figure 2]. This increase in the bioadhesion could be due to the formation of secondary mucoadhesive bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, while other polymers undergo only superficial bioadhesion. The peak detachment force was considered to be dependent on the formation of hydrogen

bonds between the functional groups of the bioadhesive and the mucus. HPMC alone had poor adhesive properties, but when used in combination with carbopol, its overall adhesion was increased. Very strong bioadhesion could damage the epithelial lining of buccal mucosa.

In vitro water uptake studies

In vitro water uptake studies are of great significance as variation in water content causes a significant variation in mechanical properties of formulations. The capacity of the formulation to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of the drug on the mucosal surface. Corresponding Figure 3, water-absorbing capacity of system (SI after 6 hours) decreased in this order: F₁> F₂> F₃> F₄.

The surface pH

The Surface pH of all formulations was found to be within ± 1

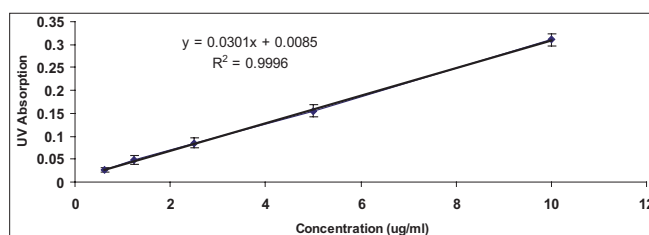


Figure 1: Standard calibration curve of CTZ in phosphate buffer (pH 6.8)

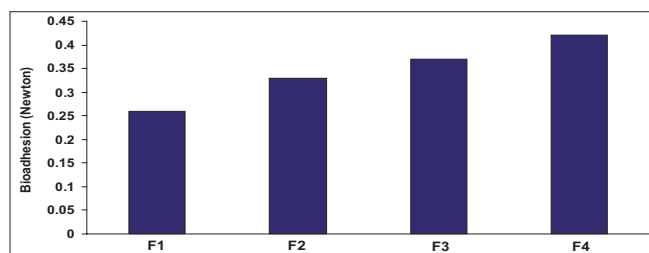


Figure 2: Bioadhesive strength measurement of formulations

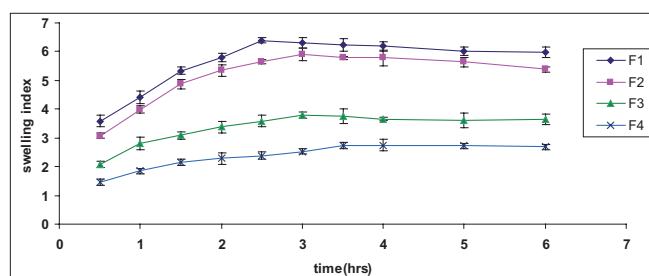


Figure 3: Swelling index vs time for buccoadhesive tablets of CTZ

Table 2: Evaluation of formulations of buccoadhesive tablets of CTZ

Formulation code	Mean hardness Newton	Friability % w/w	Average weight (mg)±SD	Mean drug content% ± SD	SI (after 6 hrs) ± SD	Tablet surface pH
F ₁	74.7	0.67	299.8±3.39	98.97±1.41	5.97±0.04	6.98
F ₂	75.1	0.66	303.3±5.58	100.55±1.39	5.38±0.14	7.11
F ₃	78.8	0.34	293.2±5.88	103.93±0.95	3.65±0.05	7.23
F ₄	82.4	0.65	299.5±4.88	98.87±0.87	2.69±0.047	7.36

Table 3: Kinetic Data of Formulations of buccoadhesive tablets of CTZ

Formulations	R ² Zero Order	R ² First Order	R ² Higuchi Equation	R ² Peppas Equation
F ₁	0.9899	0.9168	0.9829	0.985
F ₂	0.9896	0.8966	0.987	0.9848
F ₃	0.9924	0.8652	0.9842	0.9913
F ₄	0.9907	0.8546	0.9817	0.9908

units of neutral pH hence these formulations should not cause any irritation in buccal cavity [Figure 4].

In vitro drug release study

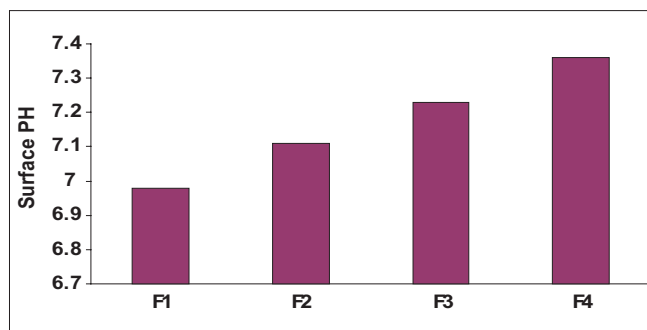
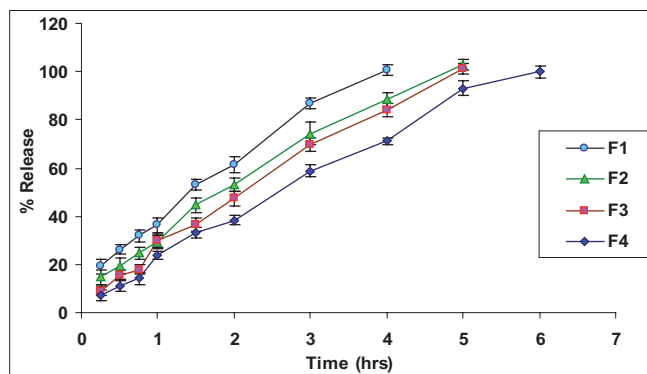
The Figure 5 shows the % drug release from formulations after 4 hours. Tablets from F₁ to F₄ show the slower % drug release; these results were due to slower hydration and low viscosity of HPMC and higher hydration and dissolution of NaCMC which forms colloidal dispersion.

Drug release kinetics

To study the release kinetics of CTZ from the tablets, the goodness-of-fit method was applied and different kinetic equations were applied to interpret the release rate from the matrices. In the present study, the linear nature of the curves obtained for zero-order, first order, Higuchi model and Korsmeyer-Peppas model as demonstrated by very close and higher R² values [Table 3] suggests that the release from the formulations may follow any one of these models. When the higher correlation coefficient values are considered, the release data seem to fit better with the zero-order kinetics [Table 3].

Therefore, the release rate $dQ/dt=k_0$ is independent of its concentration or amount of drug incorporated in the formulation which could be considered as an advantage for fabricated systems. There is almost a good coincidence with the results obtained from the equation of Korsmeyer-Peppas in which n value is nearly 1 and the best fitted equation for drug release, according to the zero-order and/or first-order release kinetics. According to Higuchi model, the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion. Lower linearity observed in this model is coincident with n values close to unity in Korsmeyer-Peppas and indicates that Fickian diffusion mechanism could be ruled out.

In vitro drug release data of all the buccal tablet formulations was subjected to goodness of fit from the data, it can be seen that except formulation F₄, other formulations containing have displayed zero order release kinetics (R^2 values in the range of 0.9924-0.9896). Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths. When the thickness of the gelled layer and thus the diffusional path lengths remain constant, zero-order release can be expected, as seen for formulations.

**Figure 4:** Surface pH of buccoadhesive tablets of CTZ**Figure 5:** Cumulative percent drug released vs time (zero order) of buccoadhesive tablets of CTZ

But F₄ has followed the Korsmeyer-Peppas equation then it is evident that the drug is released by non-Fickian diffusion mechanism. This is because as the proportion of polymers in the matrix increased there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer.

CONCLUSIONS

In conclusion, a new bioadhesive system for the controlled release of CTZ was developed by using NaCMC and HPMC in appropriate ratios. Increasing HPMC concentrations resulted in decreasing the swelling index and increasing surface pH. The surface pH, was found to be close to neutral pH. The bioadhesive strength was observed to increase with increasing HPMC content of tablets. Lower release rates were observed by increasing the content of HPMC and decreasing of NaCMC. The buccoadhesive CTZ tablets containing 66.97% HPMC and 19.1% NaCMC, showed suitable physicochemical properties and release kinetics (R^2 zero order = 0.9924).

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