Original Article

Preparation and evaluation of mucoadhesive buccal tablet for oral infection disease

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ABSTRACT

In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs. A drug administered through the buccal mucosa enters directly to the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastrointestinal effect. The objective of the project was to develop a stable and robust formulation of buccal tablet of the selected antifungal drug miconazole nitrate for the treatment of oral candidiasis. Oral candidiasis is an opportunistic infection of the mouth, highly prevalent in a specific group of patients including AIDS patients. Without treatment, the lesion may spread to the esophagus, causing invasive esophageal candidiasis, which is categorized as an AIDS-defining illness. Miconazole nitrate has a broad-spectrum of activity against most pathogenic fungi and Gram-positive bacteria. The drug has poor aqueous solubility. It has the potential to be used in the treatment of all forms of both mucosal and systemic candidiasis. The result of the project would provide a process that would provide stable formulation of buccal tablet. In this project, buccal tablet was prepared by direct compression. Among different trials with direct compression, the trial batch showed satisfactory *in vitro* drug release profile as compared to that of innovator for sustained release formulation.

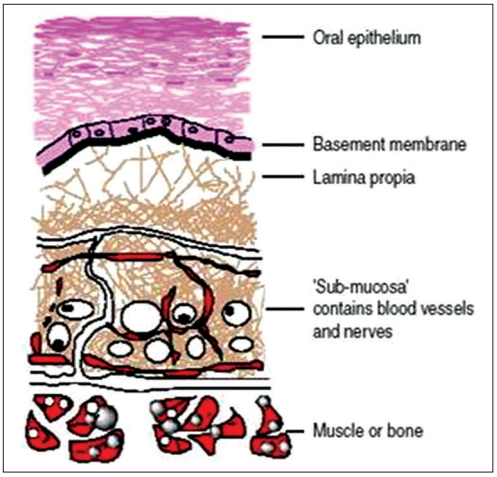
Keywords: Miconazole nitrate, mucoadhesion, mucosal drug delivery, oral candidiasis

Introduction

Buccal drug delivery system

Among the various routes of drug delivery, the peroral has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal tract. These disadvantages may limit or prevent the oral administration of certain classes of drugs, especially peptides and proteins. Transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first-pass effect and avoidance of presystemic elimination within the gastrointestinal tract (Bruschi *et al*., 2005). The mucosal layer lines a number of regions of the gastrointestinal tract, the airways, the ear, nose, and the eye, and hence, the mucoadhesive drug delivery system includes the following.

1. Buccal delivery system
2. Sublingual delivery system
3. Vaginal delivery system
4. Rectal delivery system
5. Nasal delivery system
6. Ocular delivery system.



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Drugs administered through the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and is finally taken up by the jugular vein. The gingiva and the hard palate are lined with a masticatory mucosa, where the epithelium has a cornified surface containing keratin. Keratin is found in the superficial cells of the epithelium which become flattened and virtually devoid of organelles. Keratinized tissue may be subdivided into ortho-keratinized and para-keratinized or non-keratinized. In orthokeratinized cells, a predominant granular layer is present, which is not present in para-keratinized tissue cells. The keratinized epithelia contain neutral lipids such as ceramides and acyl ceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia such as the floor of the mouth and the buccal epithelia do not contain acylceramides and possess only small amounts of ceramide. They contain few neutral but polar lipids, particularly cholesterol sulfate and glucosylceramides.[1-3]

Factors affecting mucoadhesion[4-6]

Polymer-related factors

Molecular weight

The bioadhesive strength of a polymer increases with molecular weights above 1,00,000. The fact that bioadhesiveness improves with increasing molecular weight for a linear polymer implies two things: (1) Interpenetration is more critical for low molecular weight polymer to be a good bioadhesive and (2) entanglement is important for high molecular weight polymers.

Concentration of active polymer

When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable.

Flexibility of polymer chains

Chain flexibility is critical for interpenetration and entanglement. As water soluble-polymers become cross-linked, mobility of an individual polymer chain decreases and thus the effective length of the chain that can penetrate into the mucus layer decreases which reduces bioadhesive strength.

Charge

Nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium.

Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network.

Swelling

Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network.

Environment-related factors

pH of polymer-substrate interface

pH can influence the formal charge on the surface of the mucus as well as certain ionizable bioadhesive polymers.

Physiological factors

Disease state

The physiochemical properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial, and fungal infections of female reproductive tract and inflammatory conditions of the eye.

Mucin turnover

The mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. Second, mucin turnover results in substantial amounts of soluble mucin molecules.

Materials and Methods

Materials

The following drug, polymers, and chemicals were used for the formulation and evaluation of tablets.

List of solvents and chemical:

- Distilled water
- Methanol
- Acetone
- Concentrated hydrochloric acid
- Ammonium acetate
- Acetonitrile.

(All the chemicals used were of analytical reagent grade) (Tables 1 and 2).

Results and Discussion

Preformulation study[7,8]

Identification of drug

Identification of drug was carried out by melting point determination, infrared spectroscopy, and differential scanning calorimetry (DSC).

Melting point method

Melting point method is prime confirmation of drug. In this method, temperature was noted at which point sample start melt to finish. The melting point of MCN was measured and

Table 1: List of materials and chemicals used with their source

Materials	Manufacturer (supplier)
MCN U.S.P.	Merck Pharma, Goa, India
HPMC K4M	Doshion Pharma-Polymer Division, Ahmedabad, India
NaCMC	Doshion Pharma-Polymer Division, Ahmedabad, India
Sod. alginate	Doshion Pharma-Polymer Division, Ahmedabad, India
Carbomer	Corel Pharmaceuticals, Ahmedabad, India
Agar	Marine Chemical, Kerala, India

found to be in the range of 186-188°C. It was confirmed with the reported melting point of MCN, i.e., 182-186°C (Clark's analysis, Vol. 2, 1282).

Fourier transform infrared (FTIR) spectroscopy

IR spectrum of the drug was measured in the solid state as potassium bromide dispersion. The bands (cm^{-1}) have been assigned. An FTIR spectrum of miconazole nitrate was obtained using an FTIR spectrometer-430 (8400S, Shimadzu, Japan).

Melting point determination by DSC

The melting point of drug was determined using DSC. Thermograms for MCN were obtained using DSC (Cyrus-DSC Wipro GE DX-300, Perkin Elmer, USA).

Drug-excipient interaction study[9]

The drug-excipients interaction study was carried out by using FTIR and DSC.

FTIR spectroscopy

Infrared spectroscopy is used to predict possible drug-excipients interaction study. IR spectrum of drug was measured in the solid state as potassium bromide dispersion. The drug, polymers, and physical mixture were filled in pre-washed and dried ampoules and sealed with aluminum paper. The sealed ampoules were kept at 37 ± 0.5°C for 28 days in stability chamber (TH 90 G, Thermolab, Thane, India) (Table 3).

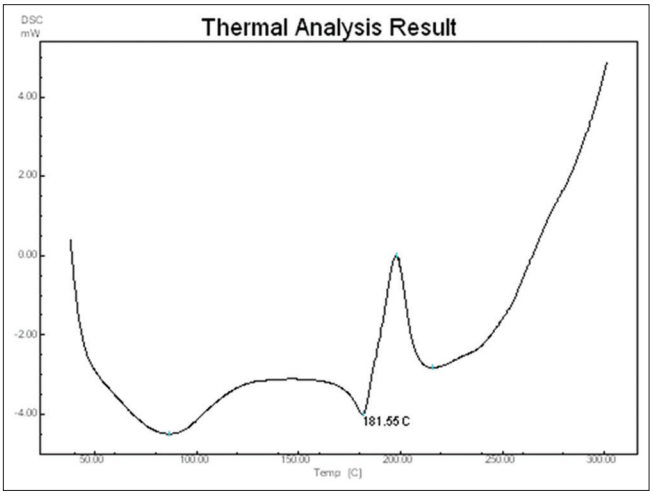
Table 2: List of equipments used with their make

Equipment	Manufacturers
Weighing balance	PG 403-S Mettler Toledo, Columbus, OH
pH meter	Cyberscan pH 1500, Thermo Electron Corporation, Waltham, MA, USA
Tap density tester (USP-II)	ETD -1020, Electrolab, Mumbai, India
27 station tablet machine	CMB3-D27 Cadmach, Ahmedabad, India
Hardness tester	Dr. Schleunizer Pharmaton (5 y), Manchester, USA
Friability tester	EF-1W Electrolab, Mumbai, India
Vernier caliper scale	Mitutoyo, Aurora, USA
Malvern particle size analyzer	Morphology G3, Malvern, Worcestershire, UK
Stability chamber	TH 90 G, Thermolab, Thane, India
Mechanical shaker	RO-123R, Remi International, Mumbai, India
Dissolution test apparatus	TDT 08L Plus, Electrolab TDT 08L Plus
HPLC	LC 2010, SHIMADZU, Japan
DSC	Cyrus-DSC Wipro GE DX-300, Perkin Elmer, Massachusetts, USA
FTIR	8400S, SHIMADZU, Japan
Ultraviolet spectrophotometer	1800, SHIMADZU, Japan

HPLC: High-performance liquid chromatography, DSC: Differential scanning calorimetry, FTIR: Fourier transform infrared

DSC[10,11]

Drug, polymers, and physical mixtures were filled in the pre-washed and dried ampoules and sealed. The sealed ampoules were kept at 37 ± 0.5°C for 28 days in stability chamber (Thermolab, Thane, India). At the end of 28 days, ampoules were removed from stability chamber and proceed for interaction study.



Analysis of drug[12,13]

Solubility study of MCN in different solvents

Drug solubility was determined by preparing saturated drug solutions in distilled water and buffer medium, maintained at 37 ± 0.5°C in a water bath, and continually shaken using mechanical shaker (RO-123R, Remi Instruments, Mumbai, India) up to 24 h (Table 4).

Standard calibration curve of drug

Standard stock solution

Accurately weighed 10 mg of MCN USP was taken and transferred in 100 ml volumetric flask. Diluent (0.2 M ammonium acetate buffer:acetonitrile:methanol 20:30:50) was added to dilute the solution up to 100 ml.

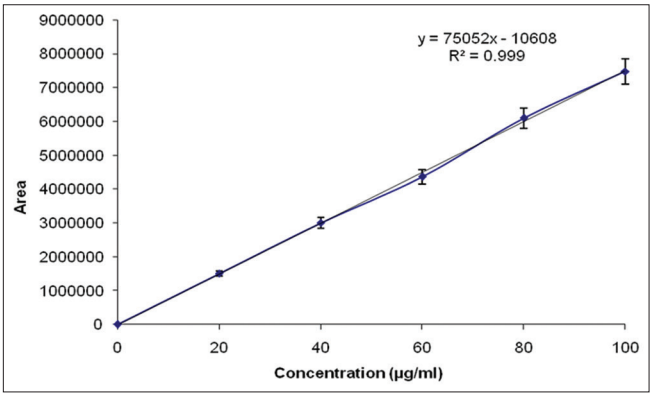


Table 3: FTIR spectra

Polymer	Drug peak	Polymer peak	Drug+polymer peak	Interaction
HPMC	812.92, 827.49, 1038.67, 1319.50	852.56, 944.19	812.92, 827.49, 858.35, 949.01, 1038.67, 1319.50	No
NaCMC	812.92, 827.49, 1038.67, 1319.50	1327.07, 1585.18	812.92, 827.49, 1038.67, 1319.50, 1330.93, 1588.85	No
Sod. Alginate	812.92, 827.49, 1038.67, 1319.50	637.96, 855.46, 1036.92, 1470.27	637.49, 812.92, 827.49, 859.32, 1039.67, 1319.50, 1472.70	No
Carbomer	812.92, 827.49, 1038.67, 1319.50	1168.90, 1216.09	812.92, 827.49, 1038.67, 1168.90, 1216.16, 1319.50	No

Formulation of buccal tablet[14,15]

Mucoadhesive buccal tablets were prepared by a direct compression procedure (Table 5).

Evaluation of pre-compression parameters[16,17]

Drug and polymers were characterized for their physical properties such as particle size distribution, angle of repose, density, compressibility, and Hausner's ratio. Results are shown in Table 6.

Particle size determination[18,19]

For many active substances, particle size has an impact on powder flow; content uniformity, and drug dissolution. To assure consistent product quality, the particle size of the API has been characterized (By Malvern mastersizer, Dry method). From the results obtained, the limits will be derived which will be routinely applied by the API manufacturer during analysis of drug (Table 7).

Angle of repose, density, compressibility index, Hausner's ratio

Pre-compression parameters of tablets powder blends[20,21]

The tablet of optimized formula powder blend shows good flow property (angle of repose more than 30 and <35). Results are shown in Table 8.

Post compression parameters

Prepared tablets were evaluated for post compression parameters (Tables 9 and 10).

Table 4: Solubility in different solvents

Solvent/media	Solubility %
Water	0.03±0.01
0.1N HCL	97.33±0.58
0.2 M ammonium acetate buffer	34.5±0.46

Table 5: Formulation composition of prepared batches

Composition (mg)	Batch code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
MCN	10	10	10	10	10	10	10	10	10	10
HPMC	35	30	30	20	-	10	15	25	10	60
NaCMC	50	-	20	35	40	45	50	55	25	15
Sod. alginate	-	50	35	25	45	30	20	5	50	10
Carbomer	5	10	5	10	5	5	5	5	5	5
Total	100	100	100	100	100	100	100	100	100	100

Swelling index

Table 11 shows swelling index of miconazole nitrate buccal tablet.

Ex vivo bioadhesion study

Table 12 shows *ex vivo* bioadhesion study of prepared miconazole nitrate buccal tablet.

In vitro drug release profile

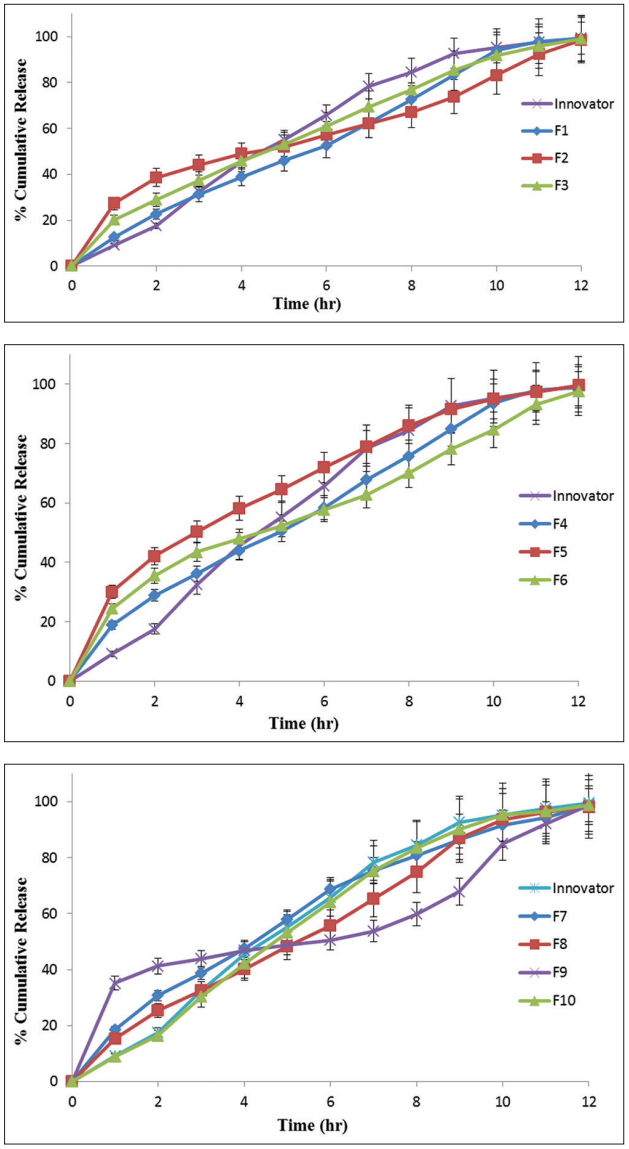


Table 6: Physical parameters of drug and polymers

Ingredients	Parameter				
	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Compressibility index (%)	Hausner's ratio (HR)
Miconazole nitrate	33.05±0.15	0.21±0.06	0.53±0.10	36.04±0.41	1.34±0.1
HPMC	32.91±0.79	0.360±0.05	0.42±0.03	23.35±0.61	1.2±0.03
NaCMC	34.22±1.5	0.30±0.15	0.43±0.015	30.23±1.45	1.43±0.34
Sod. alginate	26.24±0.15	0.36±0.3	0.46±0.04	21.67±0.67	1.29±0.03
Carbomer	33.32±1.7	0.25±0.01	0.28±0.028	10.75±0.14	1.12±0.34

All values are mean±SD, n=3. SD: Standard deviation

Table 7: Particle size distribution of miconazole nitrate

Particle size distribution	µm
D (v, 0.1)	1.92
D (v, 0.5)	6.46
D (v, 0.9)	28.81

Conclusion

1. In the pre-formulation study (compatibility study), compatibility of the excipients used in the formulation with drug was done by FTIR and DSC. Results of the compatibility study reveal

Table 8: Pre-compression parameters of tablets powder blend

Ingredients	Parameter				
	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio (HR)
Optimized formula powder blend	31.66±0.12	0.36±0.014	0.75±0.041	25.47±0.69	1.17±0.065

All values are expressed as mean±SD, n=3. SD: Standard deviation

Table 9: Thickness, diameter, hardness, and weight variation of prepared buccal tablets

Formulation code	Parameter			
	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight variation (mg)
F1	2.60±0.19	6.54±0.02	4.7±0.04	105.7±0.4
F2	2.65±0.08	6.52±0.06	4.4±0.11	100.7±0.13
F3	2.60±0.14	6.64±0.04	4.4±0.04	104.0±0.36
F4	2.71±0.2	6.68±0.07	3.7±0.11	105±0.19
F5	2.81±0.05	6.54±0.03	4.0±0.05	106.4±0.64
F6	2.74±0.05	6.53±0.06	4.4±0.05	105.9±0.18
F7	2.81±0.18	6.54±0.07	5.4±0.15	100.7±0.52
F8	2.65±0.18	6.54±0.08	3.7±0.18	101.3±0.58
F9	2.62±0.19	6.50±0.07	4.5±0.09	100.7±0.67
F10	2.73±0.12	6.58±0.05	4.7±0.15	100.2±0.47

All values are expressed as mean±SD, n=3. SD: Standard deviation

Table 10: Friability, drug content, surface pH of prepared buccal tablet

Formulation code	Parameter		
	Friability (%)	Drug content (%)	Surface pH
F1	0.21±0.04	99.35±0.63	6.50±0.01
F2	0.47±0.01	97.10±0.16	5.98±0.02
F3	0.48±0.02	99.34±0.23	6.44±0.10
F4	0.44±0.05	98.85±0.62	6.42±0.03
F5	0.05±0.01	96.40±1.21	6.94±0.12
F6	0.06±0.02	99.03±0.49	6.40±0.09
F7	0.02±0.06	98.56±0.52	6.13±0.07
F8	0.04±0.03	98.05±0.36	6.13±0.04
F9	0.27±0.02	100.02±0.46	6.41±0.30
F10	0.24±0.02	100.02±0.45	6.45±0.02

Table 11: Swelling index of miconazole nitrate buccal tablet

Formulation	Swelling index (h)				
	1	2	4	8	12
F1	78.84±0.04	87.47±0.02	89.14±0.03	92.19±0.03	90.88±0.08
F2	60.89±0.04	69.36±0.03	73.47±0.13	77.74±0.07	76.50±0.08
F3	72.48±0.07	81.90±0.05	84.43±0.09	87.43±0.03	85.99±0.07
F4	50.57±0.10	62.39±0.07	68.00±0.05	75.08±0.07	73.21±0.05
F5	61.05±0.08	6913±0.12	74.12±0.05	79.83±0.04	78.20±0.04
F6	57.21±0.07	66.76±0.09	70.20±0.05	76.08±0.04	74.43±0.03
F7	47.50±0.08	58.13±0.14	65.08±0.13	71.70±0.04	70.00±0.08
F8	70.49±0.02	79.75±0.01	84.54±0.01	87.92±0.01	86.12±0.01
F9	44.31±0.08	55.21±0.07	64.65±0.05	69.30±0.09	67.85±0.05
F10	84.52±0.02	92.98±0.04	93.40±0.08	93.97±0.05	92.10±0.04

Table 12: *Ex vivo* bioadhesion study of prepared miconazole nitrate buccal tablet

Formulation code	Bioadhesive strength (g)	Bioadhesion force (N)
F1	13.4±0.20	1.315±0.02
F2	13.7±0.40	1.347±0.04
F3	13.9±0.32	1.360±0.03
F4	14.5±0.23	1.419±0.02
F5	14.4±0.31	1.416±0.03
F6	13.8±0.10	1.354±0.01
F7	13.5±0.62	1.324±0.06
F8	13.8±0.15	1.357±0.01
F9	13.8±0.44	1.354±0.04
F10	14.7±0.20	1.442±0.02

that the drug was compatible with all excipients used in the formulation.

2. Here, direct compression strategy found satisfactory for all formulation. Hence, direct compression strategy was adopted.
3. Various physicochemical parameters such as content uniformity, thickness, weight variation, bioadhesive strength, surface pH, swelling study, and matrix erosion were evaluated.
4. Among different trials with direct compression, trial F10 had satisfactory *in-vitro* dissolution profile in comparison to the innovator. Hence, these batches tablets were selected for the preparation of tablets.
5. Stability study was carried out for the optimized formulation at 40° C/75% RH for 3 months. The result shows no significant change in physical and chemical parameter of the tablet; hence, the formulation was found to be stable.

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