DESIGN, DEVELOPMENT AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF MICONAZOLE NITRATE

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ABSTRACT

The primary goal of developing stable mucoadhesive formulations of miconazole nitrate using natural and synthetic mucoadhesive and rate retarding polymers is to treat fungal infections, particularly oral candidiasis and to study the effect of different polymers on drug release profiles for prolonged release. The powder bed's rheological properties such as bulk density, compressibility index and angle of repose were evaluated. Mucoadhesive buccal tablets were compressed on a Chamunda, Pilot Press II D-B using 8 mm flat faced punches and each batch was evaluated for weight variation, hardness, thickness, percent swelling index, mucoadhesive strength, and in vitro drug release using a USP TDT-081 dissolution testing apparatus, method II using a paddle at 50 rpm with the aid of a kinetic study. The prepared mucoadhesive formulations were additionally assessed for various quality control tests, as well as for antifungal activity and stability studies, which were carried out at 40°C/75°RH in a stability chamber for a period of six months.

KEYWORD: Buccal tablet, Miconazole Nitrate, Chitosan, Xanthan gum, Mucoadhesive properties.

INTRODUCTION

Drug delivery methods that use the bioadhesion of specific water soluble polymers that become adhesive upon hydration are known as mucoadhesive drug delivery systems. These methods can be used to target a drug to a specific area of the body for an extended period of time. Due to the presystemic metabolism of some therapeutic agents or their instability in the acidic environment associated with oral administration, transmucosal therapeutic agent delivery has attracted considerable attention since the early 1980s.(Salamat et al., 2005)

Candidiasis, also known as yeast infection or thrush, is a common condition that affects the mouth's mucous membranes. Baby mouth candidiasis is referred to as oral thrush, whereas adult mouth or throat candidiasis is a fungal infection (mycosis) of any of the Candida species, with Candida albicans being the most common. Thus, the term "candidiasis" refers to a variety of infections, from minor ones like vaginitis and oral thrush to more serious ones like systemic and potentially fatal illnesses. The second category of Candida infections, also known as candidemia, typically affects people with severely weakened immune systems, such as cancer, transplant, and AIDS patients, whereas superficial Candida infections of the skin and mucous membranes, which result in localised inflammation and discomfort, are widespread in many human populations.(Sangeorzan et al., 1994) Unless associated risk factors are treated or eliminated, untreated candidiasis typically lasts for months or years in most patients. Oropharyngeal candidiasis usually spontaneously resolves in newborns who are not immunosuppressed after 3 to 8 weeks(Dangi et al., 2010).

Miconazole nitrate is drug used for the management of topical and systemic fungal infections such as oral candidiasis(Jug and Bećirević-Laćan., 2004). Miconazole nitrate has a long plasma half-life of about 24 hrs and a low oral bioavailability. Therefore, the oral method is not much more efficient. As a result, the formulation is created as a bioadhesive tablet that reversibly adheres to the oral mucosa and releases miconazole nitrate while adhesion is taking place. The development of direct compression tablets has allowed for the creation of buccal mucoadhesive delivery systems.(Munasur et .al. 2006)

MATERIALS AND METHODS

Material

Miconazole Nitrate was provided as gift sample from Leben Laboratories Pvt. Ltd., Akola, Maharashtra, Chitosan, Mannitol, Xanthan gum and Gaur Gum were obtained from Mylochem

Ltd., Mumbai, while HPMCK15M was obtained from Trio Pharma Chem Paldi, Ahmedabad, Talc and Magnesium stearate were obtained from SD Finechem Limited, Mumbai.

Methods

A) Micromeretics Studies (Martin, 1993; Martin, 2001; Sinko, 2011; Maheshwari et al., 2018)

Angle of Repose: It was determined by fixed funnel method. Accurately weighed quantity (5gm) of drug was taken in a funnel; the height of the funnel is adjusted such that the tip of the funnel just touches the apex of heap of the blend. Then the drug is allowed to flow the funnel freely on to the surface. The diameter is then measured and angle of repose was calculated by following equation.

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ - angle of repose, h - height of the cone and r - radius of the cone base.

Table 1: Angle of Repose Parameter

Sr. No.	Angle of repose (θ)	Nature of Flow
1	< 20	Excellent
2	20 - 30	Good
3	30 - 40	Passable
4	> 40	Very poor

Bulk Density: It was determined by pouring a weighed quantity (5gm) of drug/excipients powder blend in to a graduated cylinder. The cylinder was dropped at 2 sec interval on hard wood surface three times from the height of 1 inch. It was then calculated by the equation given below.

Bulk Density = Weight of the Powder / Bulk Volume

Tapped Density: It was determined by pouring a drug/excipients powder blend (5gm) in a measuring cylinder. The cylinder was dropped at 2 sec interval on hard surface 100 times from the height of 1 inch. Then the final volume occupied by the drug was measured.

Tapped Density = Weight of the Powder / Final Volume

Compressibility Index: The compressibility index (Carr's index) is a measure of a powder to be compressed.

Carr's Index = [(Tapped Density- Bulk Density / Tapped Density)] × 100

Table 2: Carr's Index Parameter

Sr. No.	Carr's Compressibility Index (%)	Relative Flowability
1	5 - 11	Excellent
2	12 -16	Good
3	18 - 21	Fair
4	23 - 28	Slightly Poor
5	28 - 35	Poor
6	35 - 38	Very Poor
7	> 40	Extremely Poor

Hausner Ratio: The Hausner Ratio of powder was calculated according to equation given below,

$$\mathbf{Hausner\ Ratio = D_t / D_f}$$

Where, D_t = Tapped Density

D_f = Bulk Density

Table 3: Hausner Ratio Parameter

Sr. No.	Hausner Ratio	Type of Flow
1	1.0 - 1.12	Excellent
2	1.12 - 1.18	Good
3	1.19 - 1.25	Fair

4	1.26 - 1.34	Passable
5	1.35 - 1.45	Poor
6	1.46 - 1.59	Very Poor
7	> 1.60	Very Very Poor

B) Preparation of Mucoadhesive Buccal Tablets

(Jin et al., 2017; Dattatraya et al., 2016; Mohammed, F.A. and Khedr, H., 2003)

Mucoadhesive Buccal Tablets of Miconazole Nitrate each were containing 50 mg of drug prepared as per formula given in Table 5.6. Accurately weight quantity of Miconazole Nitrate equivalent to 50 mg drug was weighted and other excipients such as xanthan gum, chitosan, guar gum, carbopol 934P and HPMC K4M were weighed accurately and thoroughly mixed, following addition of magnesium stearate as lubricant and talc as glidant. The powder blend of Miconazole Nitrate and excipients was then subjected to compression into tablet with suitable set of dies and punches using 10 Station Rotary Tablet Compression Machine (Chamunda, Ahmadabad). The MCN and excipients powder blend was studied for the pre-compression parameters such as angle of repose, density, flowability, compressibility index and hausner's ratio etc.

Table 4: Formulation of Mucoadhesive Buccal Tablets of Miconazole Nitrate

Ingredients (mg)	Formulation								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Miconazole Nitrate	50	50	50	50	50	50	50	50	
Chitosan	30	60	30	30	60	30	30	60	30
HPMC K15M	30	30	60	-	-	-	-	-	-
Xanthan Gum	-	-	-	30	30	60	-	-	-
Guar Gum	-	-	-	-	-	-	30	30	60
Mannitol	84	54	54	84	54	54	84	54	54
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total Weight of Tablet	200	200	200	200	200	200	200	200	200

C) Physical Characterization of Tablets

Visual Inspection: Upper and lower punches were inspected by naked eye for presence of sticking or picking.

Diameter and Thickness: (Lachman et al., 2009; Saeedi et al., 2018)

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using the filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. 10 tablets were randomly picked from each batch and their thickness and diameter were measured at 3 different positions using a calibrated dial Vernier caliper. It is expressed in mm.

Tablet Hardness: (I.P., USP, Sweety et. al., 2016)

The resistance of tablet during shipping to breakage, under condition of storage, transportation and handling before use depends on its hardness. For each formulation, the hardness of 3 tablets was determined using the Pfizer hardness tester. The tablet was held along its oblong axis in between two jaws of taster. At this point, reading should be zero kg/cm2. Then constant force was applied until the tablet fractured. The value at this point was noted in kg/cm2.

Friability: (I.P., USP, Sweety et. al., 2016)

Friability is the measure of tablet strength. Roche friability Apparatus (Electrolab, India) was used for testing the friability. For each formulation, the friability of 20 tablets was determined. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing the plastic chamber which revolves at the speed of 25 rpm, dropping the tablet to a distance of 6 inches in each revolution. A sample of pre weight 20 tablets was placed in friabilator which was then operated for 100 revolutions i.e. 4 min. tablets were then dedusted and reweight. A

loss of less than 1% in weight is generally considered acceptable Friability (%) was calculated as follows,

% Friability = (Initial weight - Final weight) / Initial weight x100

Weight Variation Test: (I.P., USP, Sweety et. al., 2016)

The weight variation test was done by taking 20 tablets and weight accurately. The average weight of tablet was calculated.

Table 5: Weight Variation Test Parameter

Sr. No.	Average Weight of Tablet	Deviation (%)
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

Drug Content: (I.P., USP, Sweety et. al., 2016)

The drug content determination was done by taking 20 tablets & triturate. Take equivalent weight of powder (50 mg) was dissolved in 5 ml methanol and volume was made up to 50 ml with pH 6.8 phosphate buffer. The solution was filtered through Whatman filter paper no. 41. After appropriate dilutions with pH 6.8 phosphate buffer and analyzed spectrophotometrically at 272 nm (Shimadzu 1800, Japan). Drug content was calculated from the calibration curve of Carvedilol in pH 6.8 phosphate buffer.

Surface pH: (Mittal and Pawar, 2018; Patil et al., 2018)

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*, as an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. For the determination of the surface pH of the buccal tablets, a combined glass electrode is used. The bioadhesive buccal tablet was allowed to swell by keeping it in contact with 5 ml distilled water in a petri dish for 2 hr at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrating for 1 min.

Swelling Index: (Balaji et al 2014, Koradia, H. and Chaudhari, K., 2018)

Buccal tablets were weighed individually; initial weight was considered as W_1 and placed separately in petri dishes containing 10 mL of phosphate buffer (pH 6.8) solution. At time intervals of 2h, 4h, 6h, 8h, 10h and 12h, the buccal tablets were removed from the petri dishes using coverslips and excess surface water was removed carefully using the Whatman filter Paper. The swollen tablets were then reweighed (W_2). This experiment was performed in triplicate. The degree of swelling (water uptake) was calculated according to the following formula.

$$\textbf{Degree of swelling} = [(W_2 - W_1)/W_1] \times 100$$

Swelling index increases with increasing polymer concentration and thereby retarding the release of drug from the mucoadhesive buccal tablet.

Matrix Erosion Test: Tablets initial weight was noted down (W1). Swollen tablets were dried at 60°C for 24 hrs in an oven and kept in desecator for 48 hrs and reweighed (W3). % matrix erosion were calculated using following formula,

$$\textbf{\% Matrix erosion} = [(W1-W3) \div W3] \times 100$$

Tablet Wetting Time and Water Absorption Ratio: (Panchal et al., 2012)

A piece of double folded tissue paper was placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation:

$$R = 100 (W_a - W_b) / W_b$$

Where, W_b - Weight of tablet before water absorption

W_a - Weight of tablet after water absorption

Measurement of Bioadhesive Strength:

(Pritchard et al., 1996; Gupta et al., 1992; Garg et al., 2002; Patel et al., 2007)

An in-vitro assembly has been developed to measure and compare the bioadhesive strengths of Mucoadhesive Tablets proposed by Sanjay Garg et.al. The strength of the bond between the formulation and the membrane excised from goat buccal mucosa was determined using tensile experiment on a specially fabricated assembly.

Ex vivo Mucoadhesion Time (Shankar et al., 2009; Singh and Ahuja, 2002; Kadam., 2004)

The ex vivo mucoadhesion time was determined using a locally modified USP disintegration apparatus. The medium was composed of 200 ml of phosphate buffer (pH 6.8) maintained at 37±1°C. The goat buccal mucosa was tied to the surface of a glass slab, vertically attached to the disintegration apparatus. The buccal tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by applying a light force with fingertip for 30 seconds. The glass slide allowed moving up and down and hence that, the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. After 2 min, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 h. The time for detach from the goat buccal mucosa was recorded as the mucoadhesion time. The experiments were performed in triplicate (n=3) and mean values were used to calculate the ex vivo mucoadhesion time.

Detachment Force Measurement (Madhusudan et al., 1998; Sudarshan et al., 2015)

This is the method used to measure in vitro mucoadhesive capacity of different polymers. It is a modified method developed by Martti Marvola to assess the tendency of Mucoadhesive materials to adhere to the esophagus. The assembly consists of single organ bath, a stand, for keeping beaker and a reservoir for addition of water into beaker, Aerator.

The force in Newton in calculated by the equation,

$$F = 0.00981\ W/2$$

Where;

W- The amount of water.

The following characteristics were studied:-

1. The effect of the contact time for
2. Which the product remains in the intestine and the force needed to detach it.
3. The strength of different mucoadhesive polymers and the effect of amount of polymer in the formulation on the force needed to detach it.

D) In-Vitro Dissolution Study

The release rate of Miconazole Nitrate from Bioadhesive tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml buffer pH 6.8, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The solution was appropriately diluted and the absorbance of these solutions was measured at 272 nm.

E) Kinetic Study

(Suvakanta et al., 2010; Lokhandwala et al., 2013; Paarakh et al, 2018)

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

Zero Order Kinetics: Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation:

$$Q_t = Q_o + K_o t$$

First Order Kinetics: To study the first order release kinetics the release rate data were fitted to the following equation.

$$\text{Log } C_t = \log C_o + K_t / 2.303$$

Higuchi Model: Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$Q_t = K_H \times t^{1/2}$$

Korsmeyer - Peppas Model: To study this model, the release rate data is fitted to the following equation.

$$Mt / M = K. t^n$$

F) Accelerated Stability Studies of Optimized Formulation

(Grimm, 1998; Bagul, et al 2009; Chime et al., 2013)

Short-term accelerated stability testing was carried out according to ICH guidelines considering 40 ± 2°C/75 ± 5% relative humidity (RH) in a stability chamber for a period of 6 month. The mucoadhesive buccal tablets of miconazole nitrate of optimized formulation B3 was subjected to stability chamber at a minimum of three-time points, including the initial, intermediate and final time points (e. g., 0, 3, and 6 month). At the end of 3rd and 6th month of the tablets exposed to stability chamber, the mucoadhesive buccal tablets were again analyzed for their physical appearance, assay (%) and *in vitro* drug release profile.

G) In - Vitro Antifungal Studies of Optimized Formulation

(Swamy et al., 1974; Sawyer, et al 1975; Scorzoni et al., 2007)

The activity of selected formulations containing miconazole nitrate was determined. For this, formulation B3 was selected amongst the various formulation as optimized one. An agar diffusion technique was applied using C. albecans ATTC 10231 organism. The tablet was placed on the agar surface. The zone of inhibition diameter was measured after 24 h incubation at 35ºC. Also, the placebo tablets were subjected to the same conditions to detect any activity of the used polymers.

RESULT AND DISCUSSION

Micromeretics Studies: The results of micromeretic properties all formulations B1 to B9 of mucoadhesive buccal tablets of Miconazole Nitrate are shown in Table 6.2 , which were evaluated for various parameters such as Bulk Density, Tapped Density, % Compressibility Index, Hausner's Ratio and Angle of Repose. The % Compressibility Index was in the range of 10.91-18.21 for all the formulations B1 to B9 indicating good flow property. The values of angle of repose for formulations ranged from 23.40-29.47, indicating the good flow properties of all the formulation's powder blend.

The flow property of study such as the Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio and Angle of Repose for all the formulations were found to be good and all parameter obtained within range as per official standard.

Table 6: Micromeretic Studies on Powder Blend

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose	Carr's Index	Hausner's Ratio
B1	0.39±0.032	0.68±0.029	26.09±0.83	14.23±0.65	1.13±0.021
B2	0.41±0.054	0.61±0.036	28.65±0.48	16.23±0.51	1.16±0.036
B3	0.35±0.025	0.78±0.028	23.40±0.62	10.91±1.09	1.17±0.077
B4	0.34±0.033	0.57±0.030	27.63±0.52	15.62±0.62	1.18±0.062
B5	0.39±0.041	0.63±0.034	29.47±0.76	17.37±1.23	1.21±0.024
B6	0.38±0.028	0.71±0.040	25.01±0.39	18.21±0.87	1.17±0.043
B7	0.42±0.052	0.67±0.031	26.81±0.46	13.39±0.27	1.19±0.052
B8	0.40±0.035	0.69±0.027	28.97±0.80	12.98±0.57	1.15±0.029
B9	0.36±0.029	0.72±0.038	27.36±0.44	13.75±0.46	1.14±0.037

(Standard Deviation, n=3)

Physical Characterization of Tablets

Visual Inspection: There is no sticking or picking on the compressed tablets. The punches were crisp, and the tablet logos were visible.

Evaluation of Mucoadhesive Buccal Tablets of Miconazole Nitrate: The mucoadhesive buccal tablets of Miconazole Nitrate were formulated using direct compression method. All the formulations evaluated for the important parameters such as Diameter, Thickness, Hardness, Friability, Weight Variation, Drug Content, Surface pH etc. as indicated in Table 7 and 8 respectively.

Table 7: Evaluation of Mucoadhesive Buccal Tablets of Miconazole Nitrate

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)
B1	7.9±0.05	4.1±0.03	4.3±0.05
B2	8.1±0.04	4.0±0.04	4.1±0.04
B3	8.0±0.03	4.0±0.02	4.5±0.01
B4	8.3±0.05	3.6±0.01	4.0±0.02
B5	8.1±0.03	3.4±0.03	3.8±0.02
B6	8.2±0.04	3.4±0.02	4.2±0.05
B7	8.1±0.03	3.3±0.02	3.6±0.03
B8	8.1±0.03	3.1±0.01	3.7±0.04
B9	8.1±0.03	3.2±0.02	4.3±0.06

Table 8: Evaluation of Mucoadhesive Buccal Tablets of Miconazole Nitrate

Formulation	Friability (%)	Weight Variation (mg)	Drug Content (%)	Surface pH
B1	0.53±0.005	203±1.00	96.37±0.02	6.95±0.006
B2	0.69±0.006	199±0.33	101.24±0.06	7.14±0.03
B3	0.59±0.004	201±0.57	100±0.04	7.20±0.05
B4	0.63±0.003	200±0.25	98.67±0.03	6.48±0.008
B5	0.72±0.003	206±1.15	99.45±0.01	6.83±0.02
B6	0.49±0.004	204±0.93	102.31±0.07	6.25±0.01
B7	0.75±0.005	198±0.22	99.21±0.04	6.85±0.05
B8	0.66±0.006	200±0.31	97.98±0.04	7.10±0.08
B9	0.52±0.004	197±0.19	98.51±0.02	6.68±0.009

(Standard Deviation, n=3)

Swelling Index and Matrix Erosion Study of Mucoadhesive Buccal Tablets:

All the tablet formulations containing varying concentration of mucoadhesive and rate retardant polymers were stable throughout the period of swelling, without any disintegration being observed. The swelling index of all formulations was found to be more or less superimposable, due to the low invariance amongst their chosen polymer compositions. The swelling index profile of all formulation prepared as per the experimental design, is shown in Table 9 and Figure 1.

Table 9: Swelling and Matrix Erosion Study of Mucoadhesive Buccal Tablets of Miconazole Nitrate							
Formulation	**% Swelling Index After Time (hr)**						**Matrix Erosion (%)**
	2 hr	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**	
B1	17	26	38	52	57	69	26±0.02
B2	18	27	40	56	62	71	28±0.01
B3	19	39	51	68	83	100	30±0.05
B4	20	45	64	75	89	101	29±0.03
B5	11	16	22	31	37	50	31±0.06
B6	17	40	59	77	90	104	26±0.04
B7	18	36	53	72	91	103	29±0.02
B8	20	35	56	78	95	107	28±0.05
B9	21	43	64	82	101	110	32±0.07

(Standard Deviation, n=3)

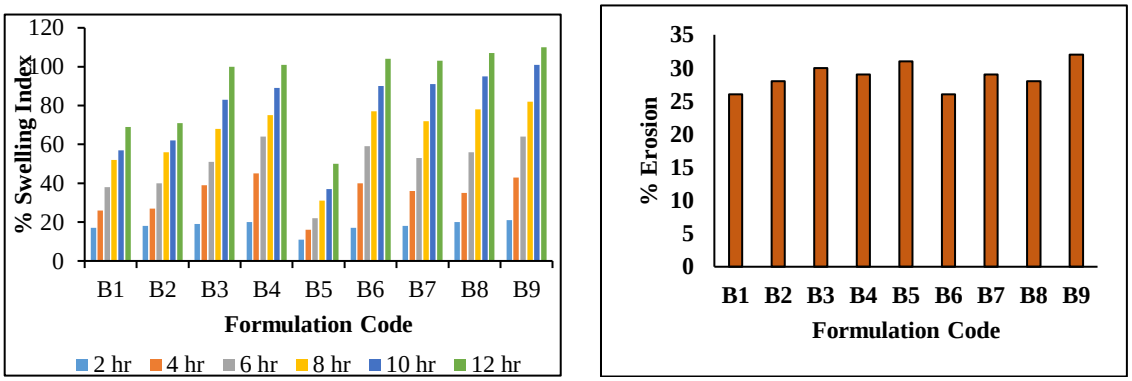

Figure 1: % Swelling Index and Matrix Erosion of Mucoadhesive Buccal Tablets

Study of Bioadhesive Strength, Ex vivo Mucoadhesion Time and Detachment Force Measurement of Mucoadhesive Buccal Tablets of Miconazole Nitrate:

The result bioadhesive properties of tablet were shown in Table 10. As the concentration of polymer in the formulation increase, the mucoadhesive strength of tablets was increases. The strength of tablet was dependent on the property of mucoadhesive polymers, which adheres to the mucosal surface and also on the concentration of polymer used. The polymers in the maximum concentration were necessary to achieve maximum duration of bioadhesion. The decrease in the polymer concentration resulted in decrease in bioadhesive time. Chitosan is the most widely used mucoadhesive polymer in the pharmaceutical industry, in various dosage forms such as transdermal bioadhesive patches, tablets, capsules, fast disintegrating films, and mucoadhesive films. Thus, chitosan was used chosen in this study for imparting mucoadhesive property to the tablets. The data obtained indicated that mucoadhesion time was significantly increased by increases in the concentration of chitosan.

Table 10: Study of Bioadhesive Properties of Mucoadhesive Buccal Tablets of Miconazole Nitrate				
Formulation	**Bioadhesive Strength (gms)**	**Ex vivo Mucoadhesion Time (hr)**	**Water Required (ml)**	**Force of Adhesion (N)**
B1	10.52±0.312	12.2±0.03	189.5	0.929
B2	9.45±0.092	12.3±0.01	203	0.995
B3	13.20±0.168	12.5±0.2	230	1.128
B4	12.43±0.543	11.3±0.02	212.5	1.042
B5	9.50±0.741	11.6±0.01	171	0.838

B6	9.82±0.221	12.2±0.01	183.5	0.900
B7	11.19±0.323	11.7±0.1	200	0.981
B8	10.65±0.441	12.2±0.01	209	1.025
B9	10.28±0.234	11.1±0.23	197	0.899

(Standard Deviation, n=3)

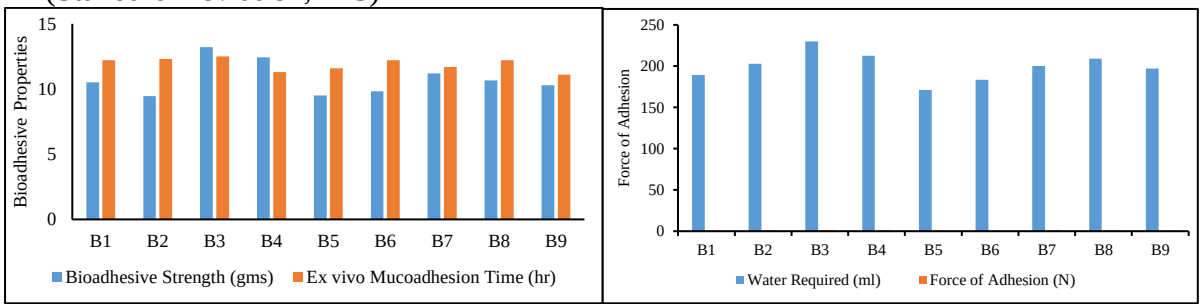

Figure 2: Detachment Force Measurement of Mucoadhesive Buccal Tablets of Miconazole Nitrate

In Vitro Dissolution Study of Mucoadhesive Buccal Tablets of Miconazole Nitrate: The tablets belonging to the all nine formulations (B1 – B9) were examined, showed a sustain release pattern of drug release up to 12 hrs as given in Table 11. The results showed that as the concentration of polymer present within the formulation increased, the amount of drug released was retarded, showed that formulation B1, B5, B6 and B7 showed the drug release upto 90 % in 12 hrs. Which contains rate retardant polymer HPMC, guar gum and Xanthan gum. (Figure 3). The overall rate of drug release upto 12 hrs. using mucoadhesive HPMC and rate retardant polymer. The formulation B2, B3, B8 and B9 showed maximum drug released 93, 96, 91 and 91% drug release respectively up to 12 hrs. The comparison of the mechanism of drug release from swellable matrices could be determined by several physicochemical phenomenon. In the case of HPMC K15M, guar gum and xanthan gum which is also a hydrophilic swellable polymer, a retarded drug release pattern was observed. As a result, drug release was found to be decreased as the concentration of hydrophilic polymer was increased. Chitosan and HPMC had a combined effect on MCZ drug release from the mucoadhesive tablets. The release data revealed a significant and inverse relationship between chitosan and HPMC concentrations, and drug release from the tablets. Thus proved the sustained-release property of both chitosan and HPMC.

Table 11: In vitro Drug Release Study of Mucoadhesive Buccal Tablets of Miconazole Nitrate

Time (Hrs)	**Formulation Code**								
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
1	8	9	7	12	5	8	7	8	12
2	17	18	17	18	12	15	14	16	24
3	29	30	29	25	24	21	25	26	35
4	44	42	40	35	36	28	37	40	50
5	56	55	53	42	50	34	52	52	61
6	65	64	62	50	61	46	61	63	70
7	74	72	71	59	71	56	70	70	75
8	80	76	78	65	75	64	74	75	80
9	85	82	83	72	81	70	80	80	86
10	89	88	88	79	86	76	85	85	90
11	90	92	91	83	88	84	87	86	91
12	90	93	96	86	90	90	89	91	91

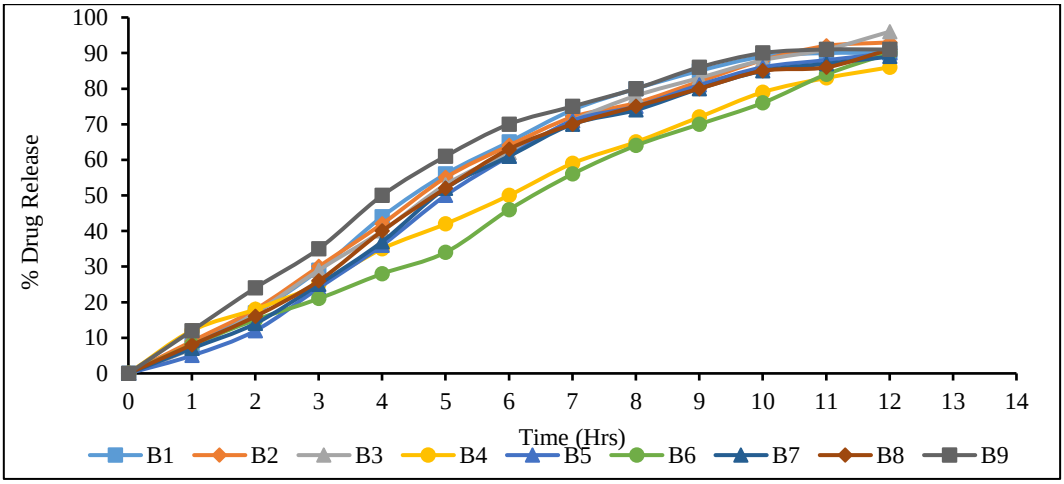

Figure 3: Drug Release Study of Mucoadhesive Buccal Tablets of Miconazole Nitrate

Drug Release Kinetics of Optimized Formulation: In case of most of the formulations the R^2 values were higher for Zero order model than for First order model indicating that the drug release from the formulation followed Zero order kinetics. Higuchi model, indicating that the drug release mechanism from the tablets was diffusion controlled. Obtained values of n lies between 0.5 - 1.0 indicating Non-Fickian release kinetics, which is indicative of drug release mechanisms involving, diffusion mechanisms. Therefore, the release of drug from the prepared tablets is controlled by swelling of the polymers, followed by drug diffusion through the swelled polymer.

Table 12: Drug Release Kinetics of Optimized Formulation B3

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer - Peppas
B3	R^2	R^2	R^2	R^2
	0.9702	0.9489	0.945	0.8513

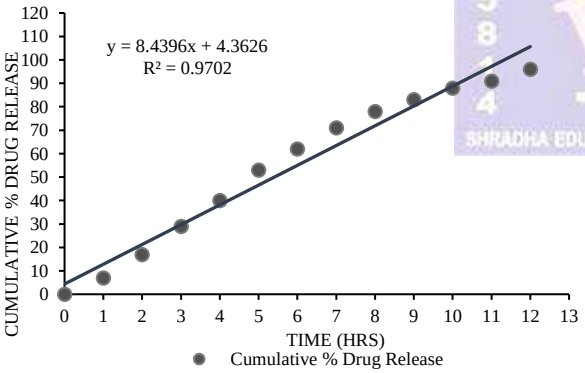

Figure 5: First Order Kinetic Plot for Formulation B3

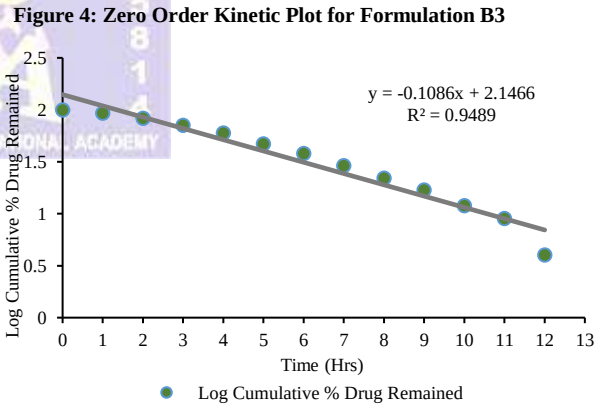

Figure 4: Zero Order Kinetic Plot for Formulation B3

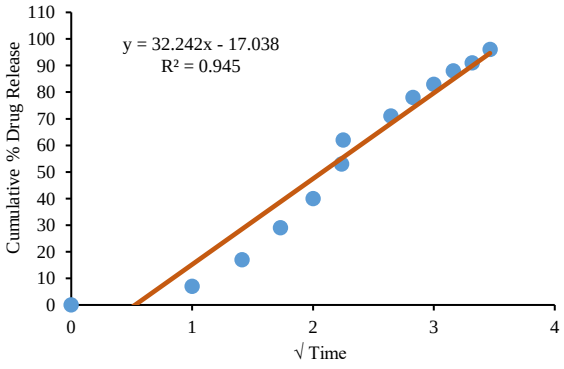

Figure 6: Higuchi Kinetic Plot for Formulation B3

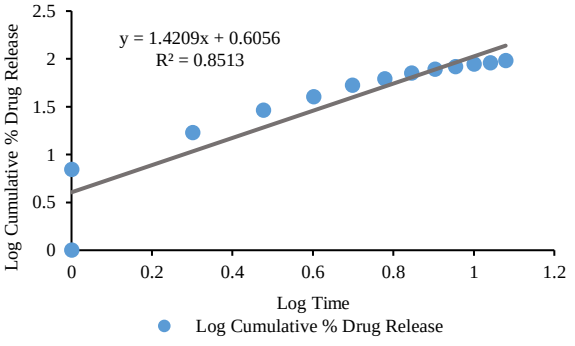

Figure 7: Korsmeyer - Peppas Kinetic Plot for Formulation B3

Stability Study of Optimized Formulation: All the Mucoadhesive Buccal Tablets of Miconazole Nitrate were screened for accelerated stability studies and showed slight physical changes during the study period. The drug content was observed (n=3) for all the Mucoadhesive Buccal Tablets (Table 13) which was quite stable at accelerated storage conditions. The stability of Mucoadhesive Buccal Tablets were proved by determining the percentage content under the above said accelerated storage condition. Values of all parameter slightly changes indicated that all the Mucoadhesive Buccal Tablets were stable without any alteration on the physical characters.

Table 13: Accelerated Stability Study of Optimized Formulation B3

Evaluation Parameter	Before Stability Storage	After 3 Months Storage	After 6 Months Storage
Hardness (Kg/cm^2)	4.5±0.1	4.4±0.1	4.4±0.2
Friability (%)	0.59±0.004	0.61±0.013	0.65±0.018
Weight Variation	201±0.057	200±0.063	200±0.084
Drug Content (%)	100±0.04	99±0.07	98±0.06
Surface pH	7.20±0.05	7.20±0.07	7.15±0.03
Swelling Index (%)	100	98	97
Matrix Erosion (%)	30±0.05	29±0.06	29±0.09
Bioadhesive Strength (gms)	13.20±0.168	12.92±0.172	12.70±0.213
Ex vivo Mucoadhesion Time (hr)	12.5±0.2	12±0.4	11.3±0.3
Water Required	230	220	215
Force of Adhesion	1.1258	1.120	1.095
In vitro Drug Release (%)	96	95.50	94.28

Antifungal Study of Optimized Formulation: The antifungal activity of the optimized formulation B3 of mucoadhesive buccal tablet of miconazole nitrate was determined using agar-cup diffusion method. Table 14 and Figure 8 show the zone of inhibition diameter obtained. The optimized formulation B3 tested, showed activity against *C. albicans*. Also, the placebo tablet was subjected to the same conditions to detect any activity of the used polymers. The control placebo tablet showed no zone of inhibition.

Table 14: Antifungal Study of Optimized Formulation B3

Sr. No.	Zone of Inhibition (mm)	Mean
1	27	28
2	29	
3	28	

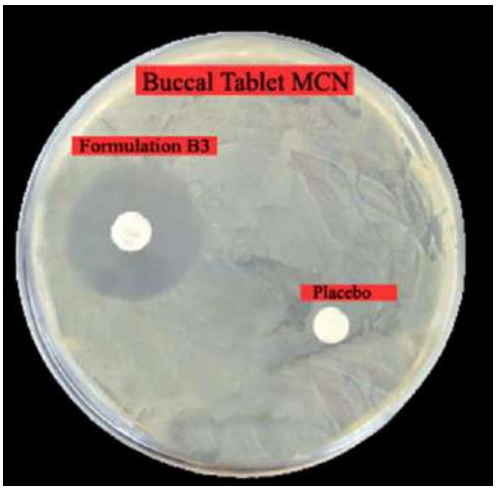

Figure 8: Inhibition Zone of Mucoadhesive Buccal Tablet of MCN

REFERENCES

Ahmed, T.A., Mahmoud, M.F., Samy, A.M., Badawi, A.A. and Gabr, K.E., 2011. Formulation, evaluation and optimization of miconazole nitrate tablet prepared by foam granulation technique. *International Journal of Drug Delivery*, *3*(4), p.712.

Bagul, U., Gujar, K., Dhat, S., Aphale, S. and Bhavsar, M., 2009. In vitro study of mucoadhesive strength of polymers for mucoadhesive drug delivery systems. *Int J Curr Pharm Res*, *1*(1), pp.42-46.

Balaji A, Radhika V and Goud V., 2014. Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. *Int J Pharm Sci & Res, 5(11)* pp. 4699-08.

Bouckaert, S. and REMON, J.P., 1993. In-vitro Bioadhesion of a Buccal, Miconazole Slow-release Tablet. *Journal of pharmacy and pharmacology*, *45*(6), pp.504-507.

Bouckaert, S. and REMON, J.P., 1993. In-vitro Bioadhesion of a Buccal, Miconazole Slow-release Tablet. *Journal of pharmacy and pharmacology*, *45*(6), pp.504-507.

Chime, S.A., Onunkwo, G.C. and Onyishi, I.I., 2013. Kinetics and mechanisms of drug release from swellable and non swellable matrices: A review. *Res J Pharm Biol Chem Sci*, *4*(2), pp.97-103.

Dangi, Y.S., Soni, M.L. and Namdeo, K.P., 2010. Oral candidiasis: A review. *Int J Pharm Pharm Sci*, *2*(4), pp.36-41.

Dattatraya M. S., Aarif S. K., and Ravindra B. S., 2016. Formulation and evaluation of mucoadhesive buccal tablet of miconazole nitrate. *European Journal of Biomedical and Pharmaceutical sciences*, (3)10, pp.205-212.

Giannola, L.I., De Caro, V., Giandalia, G., Siragusa, M.G., Tripodo, C., Florena, A.M. and Campisi, G., 2007. Release of naltrexone on buccal mucosa: permeation studies, histological aspects and matrix system design. *European Journal of Pharmaceutics and Biopharmaceutics*, *67*(2), pp.425-433.

Grimm, W., 1998. Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to countries of climatic zones III and IV. *Drug development and industrial pharmacy*, *24*(4), pp.313-325.

Gupta, A., Garg, S. and Roop, K., 1992. Khar., Measurement of Bioadhesive strength of Mucoadhesive Buccal Tablets: Design of an In-vitro Assembly., Ind. *Drugs Sep*, *30*(4).

Gupta, K.R., Pounikar, A.R. and Umekar, M.J., 2019. Drug excipient compatibility testing protocols and charaterization: a review. *Asian J Chem Sci*, *6*(3), p.1e22.

Indian, P., 2010. Government of India, Ministry of Health and Family Welfare, Vol-I, Appendix 4.1, pp 560, 562

Jain, N.K. ed., 1997. *Controlled and novel drug delivery*. CBS publishers & distributors.

Jin, Q., Chen, W. and Wu, W., 2017. Development and evaluation of miconazole mucoadhesive tablets for oropharyngeal candidiasis. *Tropical Journal of Pharmaceutical Research*, *16*(10), pp.2325-2330.

Kadam, S.S., Yeole, D., Unjavani, H.K., Ganure, A.G. and Kabra, R.P., 2014. Formulation and Evaluation of Mucoadhesive Buccal Tablets Containing Carvedilol. *Int J Curr Pharm Res*, *1*, pp.67-80.

Kuncahyo, I.L.H.A.M. and Choiri, S., 2014. The influence of magnesium stearate, purified talc and combination of both on ternary/quaternary interactive mixture of freely and poorly water-soluble drug. *Int J Pharm Pharm Sci*, *7*(1), pp.397-402.

Lachman, L., Lieberman, H.A. and Kanig, J.L., 2009. The theory and practice of industrial pharmacy. Varghese Publishing house.

Lokhandwala, H., Deshpande, A. and Deshpande, S.H.I.R.I.S.H., 2013. Kinetic modeling and dissolution profiles comparison: an overview. *Int. J. Pharm. Bio. Sci*, *4*(1), pp.728-73.

Maheshwari, R., Todke, P., Kuche, K., Raval, N. and Tekade, R.K., 2018. Micromeritics in pharmaceutical product development. In *Dosage form design considerations* (pp. 599-635). Academic Press.

Martin, A., 1993. Micromeritics. *Physical pharmacy*, pp.423-452.

Martin, A., 2001. Micromeritics In: Physical Pharmacy, pp: 423-454. *Edn.,(editors: Baltimore MD) Lippincott Williams and Wilkins*.

Mittal, S. and Pawar, S., 2018. Design and evaluation of buccal mucoadhesive tablets of pantoprazole sodium. *Eur J Pharmaceut Med Res*, *5*, pp.514-22.

Mohammed, F.A. and Khedr, H., 2003. Preparation and in vitro/in vivo evaluation of the buccal bioadhesive properties of slow-release tablets containing miconazole nitrate. *Drug development and industrial pharmacy*, *29*(3), pp.321-337.

Munasur, A.P., Pillay, V., Chetty, D.J. and Govender, T., 2006. Statistical optimisation of the mucoadhesivity and characterisation of multipolymeric propranolol matrices for buccal therapy. *International journal of pharmaceutics*, *323*(1-2), pp.43-51.

Paarakh, M.P., Jose, P.A., Setty, C.M. and Christoper, G.P., 2018. Release kinetics–concepts and applications. *Int. J. Pharm. Res. Technol*, *8*(1), pp.12-20.

Panchal, A.V., Mehta, M., Shah, V.H. and Upadhyay, U., 2012. Formulation and in-vitro evaluation of mucoadhesive bilayered buccal tablets of rosuvastatin calcium. *International Journal of Pharmaceutical Sciences and Research*, *3*(8), p.2733.

Patel, V.M., Prajapati, B.G. and Patel, M.M., 2007. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. *Aaps Pharmscitech*, *8*(1), pp.E147-E154.

Patil, C.C., Pawar, V.V., Karajgi, S.R. and Kalyane, N.V., 2018. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Ondansetron Hydrochloride. *Res J. Pharm. Tech*, *11*(2), pp.581-586.

Pritchard, K., Lansley, A.B., Martin, G.P., Helliwell, M., Marriott, C. and Benedetti, L.M., 1996. Evaluation of the bioadhesive properties of hyaluronan derivatives: detachment weight and mucociliary transport rate studies. *International journal of pharmaceutics*, *129*(1-2), pp.137-145.

Qushawy, M., Nasr, A., Abd-Alhaseeb, M. and Swidan, S., 2018. Design, optimization and characterization of a transfersomal gel using miconazole nitrate for the treatment of candida skin infections. *Pharmaceutics*, *10*(1), p.26.

Rockville, M.D., 2018. United States Pharmacopeia and National Formulary USP 41-NF 36 ed. In *United States United States Pharmacopeial Convention*, p.p. 2738.

Roy, A.K., Basha, S.J., Haque, R. and Karki, R., 2013. Formulation and evaluation of Mucoadhesive buccal tablets of Valsartan. *International Journal of Drug Development and Research*, *5*(4).

Saeedi, M., Akbari, J., Morteza-semnani, K., Rostamkalaei, S., Fathalinejad, F. and Khoshvishkaie, E., 2018. Evaluation of Carbomer, CMC and HPMC on Dissolution and Bioadhesion of buccoadhesive Cinnamaldehyde Tablets. *Journal of Mazandaran University of Medical Sciences*, *27*(157), pp.70-82.

Sagar Kishor Savale, UV spectrophotometric method development and validation for quantitative estimation of miconazole nitrate (MIC), *Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry*, 5(4), 2017, 156-159.

Salamat-Miller, N., Chittchang, M. and Johnston, T.P., 2005. The use of mucoadhesive polymers in buccal drug delivery. *Advanced drug delivery reviews*, *57*(11), pp.1666-1691.

Sangeorzan, J.A., Bradley, S.F., He, X., Zarins, L.T., Ridenour, G.L., Tiballi, R.N. and Kauffman, C.A., 1994. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. *The American journal of medicine*, *97*(4), pp.339-346.

Sawyer, P.R., Brogden, R.N., Pinder, R.M., Speight, T.M. and Avery, G.S., 1975. Miconazole: a review of its antifungal activity and therapeutic efficacy. *Drugs*, *9*(6), pp.406-423.

Scorzoni, L., Benaducci, T., Almeida, A.M.F., Silva, D.H.S., Bolzani, V.D.S. and Gianinni, M.J.S.M., 2007. The use of standard methodology for determination of antifungal activity of natural products against medical yeasts Candida sp and Cryptococcus sp. *Brazilian Journal of Microbiology*, *38*, pp.391-397.

Shanker, G., Kumar, C.K., Gonugunta, C.S.R., Kumar, B.V. and Veerareddy, P.R., 2009. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. *AAPS pharmscitech*, *10*(2), pp.530-539.

Singh, B. and Ahuja, N., 2002. Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters. *Drug development and industrial pharmacy*, *28*(4), pp.431-442.

Sinko, P.J., 2011. Micromeritics. In *Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences: Sixth Edition* (pp. 442-468). Wolters Kluwer Health Adis (ESP).

Sudarshan, S. and Sunil B, B., 2015. In vivo mucoadhesive strength appraisal of gum Manilkara zapota. *Brazilian Journal of Pharmaceutical Sciences*, *51*, pp.689-698.

Swamy, K.S., Sirsi, M. and Rao, G.R., 1974. Studies on the mechanism of action of miconazole: effect of miconazole on respiration and cell permeability of Candida albicans. *Antimicrobial Agents and Chemotherapy*, *5*(4), pp.420-425.

Sweety, P., Patel, A. and Narkhede, S., 2016. Formulation Evaluation and Optimization of Buccal Tablet of Ivabradine Hydrochloride. *J Pharm Sci Bio scientific Res*, *6*(3), pp.329-337.

USP, The United States Pharmacopoeia, 2011, 34th Ed., Rockville,MD: Pharmacopoeial Convention, Inc.

Vermani, K., Garg, S. and Zaneveld, L.J., 2002. Assemblies for in vitro measurement of bioadhesive strength and retention characteristics in simulated vaginal environment. *Drug development and industrial pharmacy*, *28*(9), pp.1133-1146.

Zhou, Y., Yao, Y.W., Qi, Q., Fang, Y., Li, J.Y. and Yao, C., 2013. A click-activated fluorescent probe for selective detection of hydrazoic acid and its application in biological imaging. *Chemical Communications*, *49*(53), pp.5924-5926.