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FORMULATION AND EVALUATION OF BIOADHESIVE MATRIX TABLET OF AN ANTIFUNGAL DRUG

Ismail Khalid*, Gowtham M. and Vimal V.V.

Department of Pharmaceutics, Rajiv Gandhi Institute of Pharmacy, Trikaripur, Kerala-671310.

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***Corresponding Author**
Ismail Khalid
Department of Pharmaceutics, Rajiv Gandhi Institute of Pharmacy, Trikaripur, Kerala-671310.

ABSTRACT

The aim of this work was to develop a bioadhesive matrix tablet of poorly water soluble drug Miconazole Nitrate which is a broad spectrum imidazole antifungal agent used for treating candidiasis. An attempt was made to increase the solubility of the drug by forming a complex with water soluble polymer such as PEG 6000 using solid dispersion technique. Drug-excipients compatibility studies were performed by using FT-IR. The bioadhesive matrix tablets were prepared by direct compression method using different ratios of polymers like HPMC and Chitosan. The prepared tablets were evaluated for thickness, hardness, friability, weight variation, drug content, surface pH, bioadhesion strength, swelling index, *ex-vivo* residence time and *in-vitro* drug release. Among all the formulation, F2 was found to be the optimized formula as it possessed better post-compression parameters and *in-vitro* drug release profile. The optimized formula was subjected to stability studies to determine the physical stability of the formulation. Stability studies were carried out at 40^0C/75% RH for 1 month and no significant changes were identified during the study. *In-vitro* release kinetic studies showed that it fits well with zero order followed by Korsmeyer-peppas, Higuchi and release was found to follow non-fickian diffusion mechanism.

KEYWORDS: Bioadhesive Matrix Tablet; Miconazole Nitrate; HPMC; Chitosan; Solid Dispersion; Direct Compression.

BIOADHESIVE MATRIX TABLET[1-5]

Bioadhesive can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surface of the biological substrate for an extended period of time with the help of

natural or synthetic polymers. If adhesives are attached to the mucus or a mucus membrane then it is referred as mucoadhesion.

Mucoadhesion is defined as the interaction between mucus membrane and polymers or interaction of attractive forces (van der waals, hydrogen bonding) and repulsive forces (electrostatic, steric forces), ie, attractive force will be a more than repulsive force.

Mucoadhesive system can be used for targeting the drug to a particular site for a prolonged period of time due to the adhesion of bioadhesive polymer on hydration. Thus this system can be utilized for both local as well as systemic drug delivery. Local delivery was used for certain conditions such as gingivitis, oral candidiasis, oral lesions, dental caries, and xerostoma while systemic delivery was used for asthma, angina etc.

Mucoadhesive system can be used by various routes; they are

1. Oral drug delivery system
2. Vaginal drug delivery system
3. Rectal drug delivery system
4. Nasal drug delivery system
5. Ocular drug delivery system

Among these transmucosal routes, oral drug delivery systems are mostly preferred for controlled release dosage form because of their accessibility, high smooth muscles, and immobile mucosa.

Bioadhesive drug delivery through oral cavity was classified into three types; they are

1. Sublingual delivery: In which the drug administration take place through the membrane of the ventral surface of the tongue and the floor of the mouth.
2. Buccal delivery: In which administration of drug takes place through mucosal membrane lining the cheeks.
3. Local delivery: In which the drug will deliver into the oral cavity.

1.5.1 Characteristics Of An Ideal Buccoadhesive Systems[6]

- It should adhere quickly to the mucosa.
- It should have good patient compliance.
- It should promote rate & extent of drug absorption.
- The drug should release in a controlled fashion.

- Drinking, eating & talking should not be affected.
- Should need required mechanical strength.
- It should show good resistance against flushing action of saliva.

1.5.2 ADVANTAGES[7-11]

- Improved patient compliance.
- No gastric irritations.
- The convenience of administration as compared with injections or oral medication.
- Prolonged residence time, hence increase absorption & bioavailability.
- Rapid onset of action compared to oral route.
- Sustained drug delivery.
- Easy to remove, if therapy needs to discontinue.
- Dose related side effects are reduced.
- Ability to withstand environmental changes.
- The potential for delivery of peptide molecules.
- Avoid first pass metabolism.
- The drug is protected from degradation in an acidic environment in GIT.

1.5.3 DISADVANTAGES

- Rapid elimination of drug may occur due to flushing action of saliva.
- Once placed, the tablet should not be distributed.
- The possibility of swallowing formulation, if adhesion was not proper.
- The buccal membrane has low permeability compared to the sublingual route.
- Eating & Drinking should be reduced.
- Bitter taste drugs which irritate mucosa cannot be administered by this route.
- The occurrence of local ulcerous effect due to the prolonged contact of the drug with the membrane.

1.22 CANDIDIASIS[8-12]

In humans, fungal infections are caused as a result of defects in the immune system. Candidiasis is a fungal infection caused by an overgrowth of species candida. Candidiasis that develop in the mouth and throat is also known as thrush or oropharyngeal candidiasis (opc) or moniliasis. Different microorganisms are present in oral cavity including viruses, bacterias, fungus, and some protozoans. The main causative agent responsible for oral candidiasis is candida albicans. These species are normally present in the skin or mucous

membrane. When environment inside the mouth or throat become imbalanced, then overgrowth of candida take place and symptoms of thrush develop. It may appear on the inner surface of mouth and throat, lips and tongue as white or pale yellow spot. Oral candidiasis may develop in patients with diabetes mellitus, genetic disorders such as Down syndrome, a course of oral antibiotics, leukemia or lymphoma, chemotherapy, immunodeficiency diseases such as HIV/AIDS, malnutrition, use of inhaled steroids for certain lungs conditions. In worldwide oral candidiasis is a common infection in HIV positive patients which will spread from mouth through pharynx to esophagus. The incidence of candida albicans isolated from oral cavity has been reported in neonates is 45%, in healthy children is 45-65%, in patients undergoing chemotherapy and acute leukemia is 90%, and in HIV patients is 95%.

The management of uncomplicated oral candidiasis includes proper oral hygiene and topical antifungals. As first line treatment, topical antifungals are recommended. If systemic treatment is required then also topical treatment should continue to reduce the dose and duration of systemic treatment. The adverse effect and drug interaction take place with topical agents. Topical agents required sufficient contact time between drug and oral mucosa as well as adequate saliva to dissolve the drug. The oral suspensions, pastilles, creams, and tablets are available in the market.

MICONAZOLE NITRATE is an Antifungal drug (Azoles, Imidazole derivative) mainly Externally – Athlete's foot, Ring worm, Jock itch, Internally – Oral or Vaginal thrush (yeast infection) caused by candidiasis. Miconazole nitrate inhibits the ergosterol synthesis by interacting with 14-alpha demethylase, a cytochrome p-450 enzyme that is necessary for the conversion of lanosterol to ergosterol, which is an essential component of the membrane. Ergosterol synthesis inhibition results in increased cellular permeability, causing leakage of cellular contents.

MATERIALS AND METHODS

Miconazole Nitrate (Yarrow-chem. products, Dombivli), Chitosan (Yarrow-chem. products, Dombivli), HPMC K100M, PEG 6000, Avicel PH 102 Magnesium stearate, Talc (Global chem. Pvt. Ltd) were used. All other chemicals, either reagent or analytical grade, were used as received.

PREFORMULATION STUDIES

Characterisation of Miconazole Nitrate[13,14]

Visual Examination

A small quantity of miconazole nitrate powder was taken in butter paper and viewed in well-illuminated place.

Taste and odor

Very less quantity of miconazole nitrate was smelled to check the odor.

Solubility

The appropriate solubility of the drug was indicated in the following table no.5. Solvents such as water, methanol, ethanol, were used to check the solubility of the drug.

UV spectrum Analysis

100 mg of Miconazole nitrate was accurately weighed and transferred to 100ml volumetric flask. Then the drug was dissolved in methanol and made up to the mark by using pH 6.8 phosphate buffer solution and scanned in the range of 200-400 nm using methanol as blank.

CALIBRATION CURVE OF MICONAZOLE NITRATE

Preparation of Phosphate buffer solution (PBS) of pH 6.8[15]

Dissolve 250ml of 0.2M potassium dihydrogen phosphate and 112ml of 0.2M sodium hydroxide in sufficient quantity of distilled water was used to make up to 1000 ml.

Preparation of stock solution

100mg of miconazole nitrate was weighed accurately and transferred to the dried 100ml volumetric flask. The drug was dissolved in small amount of methanol and then 1% tween 80 was added. The volume was made up to 100 ml using phosphate buffer pH 6.8.

Scanning

From the stock solution, 10 ml was pipetted and transferred to another dried 100 ml volumetric flask and volume were made up to 100ml using phosphate buffer. From this solution, 2-12 µg/ml were prepared by pipetting 2,4,6,8,10,12 ml to the 100ml volumetric flask and the volume was made up to 100 ml using phosphate buffer pH 6.8. The UV scanning was done between 400 – 200 nm. The absorption maximum of miconazole nitrate was found at 272 nm and this wavelength was used for further studies.

COMPATIBILITY STUDIES

Compatibility studies are done in order to ascertain whether any interaction occurred between the polymer and drug substance. The drug and excipients should be compatible with one another to produce stable, efficacious, attractive and safe dosage form. It was done by using Fourier transform infrared spectroscopy (FT-IR).

FORMULATION OF BIOADHESIVE MATRIX MICONAZOLE NITRATE TABLET

Solubility Enhancement of Miconazole Nitrate by Solid Dispersion[16,17]

The solid dispersion can be prepared by different methods like fusion method, solvent evaporation method, melting method and by surface active carriers. Here melting method was used for solubility enhancement of Miconazole Nitrate.

In this method, the required amount of carrier such as PEG 6000 was melted in a china dish and then Miconazole Nitrate was added to the china dish with continuous stirring till a homogeneous mass was obtained. The obtained mass was allowed to solidify by placing at room temperature away from moisture. After solidification, the obtained mass was scratched, pulverized and sieved through mesh no. 100 and stored in a desiccator till used.

Pre-Compression Parameters[18]

Pre-compression parameters like Bulk Density (D_b), Tapped Density (D_t), Porosity, Compressibility/Carr's index, Hausner's ratio, Angle of repose, and Swelling index of excipients and formulations were carried out.

Formulae Design

Design of Experiment: 3^2 Factorial Designs

In statistics, a factorial experiment is an experiment whose design consists of two or more factors, each with discrete possible values or "levels". In this experiment, the design is 3^2 factorial design was used which of three levels ie, a higher level, an intermediate level and a lower level and two factors are selected as 2 polymer.

Table No. 1: Formulae for preparation of bioadhesive matrix miconazole nitrate tablet.

Sl. No.	Indredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Miconazole Nitrate	20	20	20	20	20	20	20	20	20
2	PEG 6000	20	20	20	20	20	20	20	20	20
3	HPMC	25	25	25	50	50	50	75	75	75
4	Chitosan	25	50	75	50	25	75	75	25	50
5	MCC	155	130	105	105	130	80	55	105	80
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2	2
	Total Tablet weight	250	250	250	250	250	250	250	250	250

In this investigation bioadhesive matrix, miconazole nitrate tablet was prepared by using direct compression method.

Evaluation of tablets

Thickness

The thickness of tablets was checked by using vernier calipers. Six tablets from each batch were tested and average thickness was calculated.

Hardness

The hardness of tablets was checked by using Monsanto hardness tester. It consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading is made. The upper plunger forced against the spring by rotating the bolt until the tablet gets fractured, and the force was recorded. It was repeated for three times and average hardness was recorded.

Friability

This test was performed by using Roche friabilator. 10 tablets were weighed and placed in the friabilator and rotated for 4 min. at 25 rpm. Tablets were taken and reweighed and recorded. Friability was calculated by using the following equation.

$$\text{Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Where

$W_{initial}$ = Initial weight of the tablet.

W_{final} = Final weight of the tablet.

Friability of tablets less than 1% was considered as accepted.

Weight Variation

20 tablets were individually weighed as per USP weight variation test. The average weight was calculated and compared with the individual weight. The tablet passes the USP test, if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than the percentage limit.

Percentage Drug Content[19,20]

5 tablets were taken and powdered using a glass mortar. The powder equivalent to 50mg of the drug was placed in a 100ml stoppered conical flask. Then the drug was extracted with methanol with vigorous shaking for 1 hour. It was then heated on a water bath for 30 minutes with occasional shaking and filtered into a volumetric flask of 50ml through cotton wool and the filtrate was made up to 50ml by using methanol through filter and absorbance was measured at 272 nm against a blank (methanol).

Swelling Studies[19]

Tablet swelling studies were performed using agar plate method (fig. 1). From each formulation, 3 tablets were weighed (W1) individually. Then the weighed tablets were placed in the petri dish and placed in an incubator at 37±0.1^{0}c for 6 hours. The tablets were removed at a regular interval of 1 hour until 6 hours. The swollen tablets were carefully taken and excess water on the tablets was removed by using filter paper and reweighed (W2). The swelling index was calculated using the formula:

$$S.I = \frac{W2 - W1}{W1} X\ 100$$

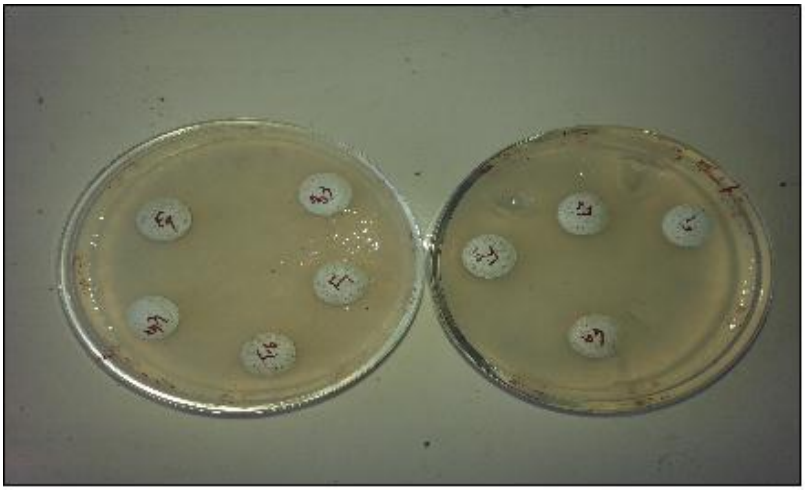

Figure 1: Swelling Index of tablets by agar plate method.

Surface pH of Tablets[21]

Tablets surface pH was studied in order check any possibility of mucosal irritation. The aim of this study was to keep surface pH of the tablets near to neutral pH because acidic or alkaline pH may produce irritation to the mucosal surface.

The tablets were placed in a petri dish containing phosphate buffer solution pH 6.8 for 2 hours. Surface pH of the tablets was checked by bringing pH meter electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min. After two hours the tablets pH were checked and done in triplicate and mean value was calculated.

Mucoadhesion Strength[19,20]

The apparatus used for checking the adhesion strength was assembled in the laboratory with help of physical balance using goat cheek as a mucosal membrane (fig.2). A double beam physical balance was taken and above both right and left pan a small beaker having same weight was placed in order to maintain the balance. Above the left side pan, a burrette was placed to withdraw the water as drop wise to the beaker. Below the left side pan a 500ml beaker was placed, and inside to that beaker 50ml beaker also placed.

METHOD

The balance was adjusted as mentioned above for this study. The goat cheek was collected, washed and placed over the 50ml beaker in which the mucosal side was facing upward. Then the phosphate buffer solution was poured into the beaker till the tissue gets moistened. Then tablets from each formula have taken and fixed on the lower side of the pan by using cyanoacrylate adhesive. The pan containing tablet and beaker were lowered till the tablet surface touches the mucosal surface. The balance was kept in this position for 3 minutes. After that, the pressure was removed and at the same time burette was allowed to withdraw the water in dropwise. As the weight of the water in pan increases the right side pan will start to separate. The total weight of water on the left-hand side will give the bioadhesive strength in grams. The mean value of three trails was taken for each formulation. After each measurement, tissues were washed with phosphate buffer and left for 5 minutes before the reading of new tablet of the same formulation. The time for the tablet to detach from goat buccal mucosa was recorded as mucoadhesion time.

Figure 2: Experimental design for Bioadhesion strength measurement of tablets.

Ex-Vivo Residence Time[22]

Locally modified Disintegration test apparatus was used for the study of the ex-vivo residence time of tablets (fig. 3). The goat mucosa was collected and cut into 2X2 size pieces. These pieces were fixed on the disintegration test apparatus glass tubes by using a cyanoacrylate adhesive. The tablet was placed in phosphate buffer to get it hydrated and attached to the mucosal surface. The medium used was 800ml phosphate buffer pH 6.8. Then the apparatus was allowed to start the process. The time required to detach the tablet from the mucosa was noted as the ex-vivo residence time.

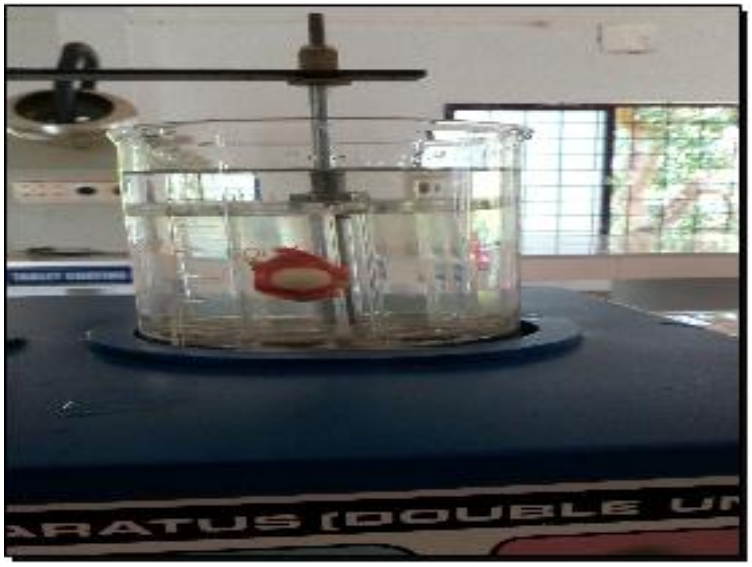

Figure 3: Experimental design for ex-vivo residence time of tablets.

In-vitro Dissolution Studies[19,20,23]

In-vitro dissolution studies of bioadhesive, buccal tablets were done by using tablet dissolution test apparatus-II, containing a paddle stirrer. The dissolution medium used was 900ml of pH 6.8 phosphate buffer solution maintained at 37 ± 0.5^{0}c. One tablet was used in each test. One side of the tablet was fixed on the 2X2 cm glass slide using a cyanoacrylate adhesive. Then it was placed on the medium and rotated at 50 rpm.

At predetermined time interval(ie, 0.5,1,2,3 to 9 hrs.) 10 ml samples were withdrawn with a pipette and filtered using filter paper, the volume withdrawn at each interval was replaced with the same volume of fresh buffer solutions. Then the drug release was measured by taking absorbance at 272 nm using a UV-Visible spectrophotometer.

Stability Studies[22]

Stability of a drug is defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The aim of this study is to prove the quality of a drug substance or drug product which varies with time effect of a variety of environmental factors such as temperature, humidity, and light.

The International Conference on Harmonisation (ICH) Guidelines titled, "stability testing of new drug substance and product" describes the stability test requirements for drug

registration application in the European Union, Japan, and United States of America. ICH specifies the length of study and storage conditions.

Long-term testing:- 25^0c ± 2^0 C/ 60% RH ± 5% for 12 months.

Accelerated testing:- 40^0 c ± 2^0 C/ 75% RH ± 5% for 6 months.

Accelerated stability studies were carried out at 40^0C / 75% RH for the best formulation for 1 month.

Kinetics of drug release[24,25]

The in-vitro release data of the drug from the investigated bioadhesive matrix tablet formulation was analyzed by curve fitting method to different kinetic model of Zero order, First order, Higuchi model, and Korsmeyer-Peppas models.

- ***Zero order*** kinetics where the drug release rate is independent of its concentration. For study of release kinetics, the graph plotted between Percentage cumulative drug release (CDR) Vs Time

$$C = C_0 - K_o t$$

Where,

C- Amount of drug released

C_0- Initial concentration of drug

K_0- Zero order rate constant

t- Time

- ***Higuchi model*** which describes drug release from insoluble matrix system. The data obtained were plotted as cumulative percentage drug release (%CDR) Vs square root of time (t^2)

$$Q = K_H t^{1/2}$$

Where,

Q- Amount of drug released

K_H- Higuchi release constant

t- Time

- ***Korsmeyer-Peppas model*** was used to find out the mechanism of drug release from the vesicular formulations. The plot made by log cumulative percentage drug release (log %CDR) Vs log time (log t).

$$M_t/M_\infty = Kt^n$$

Where,

M_t/M_∞- Drug released at a time t

K- Release rate constant

n- Release exponent

In this model, the value of 'n' characterizes the release mechanism of the drug.

If $n \leq 0.45$, the release of drug follow Fickian mechanism.

If $0.5 \leq n \leq 0.8$, the release of drug follow non-Fickian mechanism.

If $0.8 \leq n \leq 1$, the release of drug follow zero order mechanism.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

UV Spectrum Analysis

In UV spectrum analysis, the maximum wavelength of Miconazole Nitrate was found at 272 nm in pH 6.8 buffer solution, when scanned in a range of UV spectrum from 400 – 200 nm.

Calibration Curve of Miconazole Nitrate

Standard Calibration Curve of Miconazole Nitrate at 272nm.

The absorbance of the standard solution of Miconazole Nitrate at 0-12 µg/ml were plotted by taking absorbance versus concentration which gave a straight line passing through the origin with correlation coefficient 0.999. Thus it followed Beer – Lambert's law at the concentration range of 0-12 µg/ml.

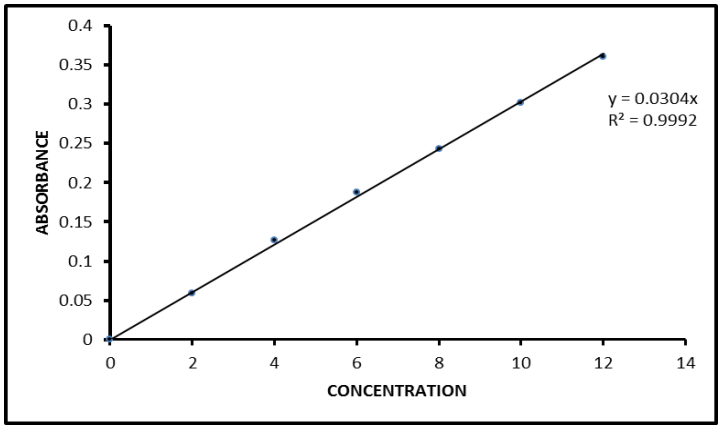

Figure 4: Standard calibration Curve of Miconazole Nitrate at 272nm.

The Miconazole Nitrate present in the formulation were confirmed by FT-IR spectra. The characteristic peaks was shown in fig. 5&6.

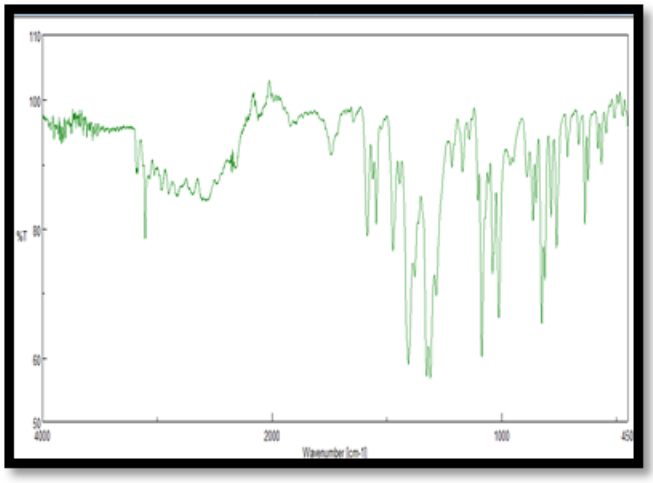

Figure 5: FT-IR Spectrum of Miconazole Nitrate(MN)[sample A].

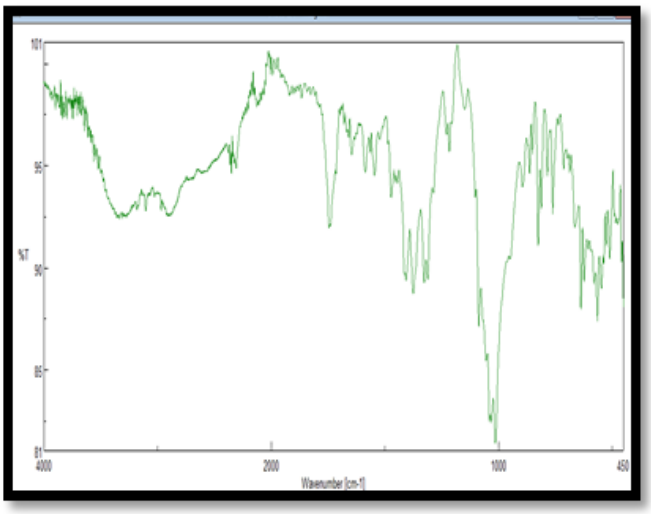

Figure 6: FT-IR Spectrum of Final formulation.

PRE-COMPRESSION PARAMETERS

Evaluation of Pre-Compression Parameters of Excipients

The pre-compression parameters like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratios and swelling index for excipients were performed. The data obtained are shown in table no. 2.

Table No. 2: Evaluation of pre-compression parameters of excipients.

Ingredients	Evaluation of Pre-compression parameters						
	Angle of Repose (ɵ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Porosity (%)	Carr's Index (%)	Hausner's Ratio	Swelling Index(%)
HPMC K100 M	39.64	0.349	0.485	0.28	27.9	1.38	37.35
Chitosan	36.50	0.778	1.06	0.26	26.67	1.36	20.69
Microcrystalline Cellulose	28.14	0.357	0.405	0.12	11.85	1.13	9.12

The angle of repose, Carr's index and Hausner's ratio of HPMC K 100 M and chitosan showed poor flow when compared to MCC which indicates that glidants are to be added to improve the flow. The swelling index of HPMC was high compared to chitosan and MCC which will helps to control the release of drug from the tablets.

Evaluation of Pre-Compression Parameters of Formulations

The pre-compression parameters like angle of repose, bulk density, tapped density, porosity, Carr's index, and Hausner's ratios for formulations were performed. The data obtained are shown in table no.3.

Table No. 3: Evaluation of pre-compression parameters of formulations.

Formulation code	Evaluation of Pre-compression parameters					
	Angle of Repose (ɵ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Porosity (%)	Carr's Index (%)	Hausner's Ratio
F1	25.78	0.45	0.489	0.08	7.99	1.08
F2	25.50	0.462	0.480	0.03	3.91	1.04
F3	29.46	0.472	0.50	0.05	5.6	1.05
F4	30.59	0.475	0.494	0.03	3.8	1.04
F5	30.61	0.468	0.483	0.03	3.27	1.03
F6	31.08	0.478	0.523	0.08	8.6	1.09
F7	33.38	0.489	0.535	0.08	8.59	1.09
F8	32.41	0.459	0.495	0.07	7.27	1.07
F9	31.96	0.457	0.517	0.11	11.6	1.13

From the angle of repose data, F1-F3 showed good flow and F4-F9 showed poor flow. The Carr's index and Hausner's ratio of all formulation showed good flow properties. The porosity of all formulations was within the limits.

Evaluation of Post-Compression Parameters

Thickness of Tablets

The thickness of tablets was checked by using vernier caliper. The average thickness with standard deviation is shown in table no.4.

The thickness of all formulations ranged from 2.53 mm to 2.62 mm.

Hardness of Tablets

The hardness of tablets was checked by using Monsanto hardness tester. The average values with standard deviations are shown in table no. 4.

The hardness of all formulations was within the acceptable range ie, 4 – 8 kg/cm^2, expect F6(3.93), F7(3.63) and F9(3.8).

Friability of Tablets

Friability test of tablets was performed by using Roche friabilator. The average values with standard deviations are shown in table no.4.

The friability range of all formulations was showed between 0.446 – 0.736%, which was within the acceptable range ie, less than 1%. In this investigation, F1 and F5 showed less percent friability than other formulations.

Weight variation of Tablets

Weight variation of tablets was performed as per USP weight variation test. The average weight variation with standard deviation is shown in table no.4.

The weight variation test showed that all formulation passed the test because all formulations were in the range of 0.221 to 0.567%, which was within the limits of USP (ie, not more than 7.5%).

Percent Drug content

Percent drug content of the tablet was performed by using methanol. The average percent drug with standard deviation are showed in table no.4.

All the formulations showed percent drug content in between 97.5 – 102.5%, which was in the acceptable range of I.P.

Swelling Index of Tablets

Swelling index of tablets was performed using agar plate method. The swelling index data after 6 hours with standard deviation are shown in table no.5.

Swelling index plays an important role in the release of drug from the matrix system. Swelling index study of all formulations ranged between 15.89 – 22.64%. Formulation F2 and F1 showed less swelling index ie, (15.89 and 15.95) than other formulations. As the content of HPMC increases swelling index also increases.

Surface pH of Tablets

Surface pH of tablets as performed by using pH 6.8 phosphate buffer. The average surface pH with standard deviation is shown in table no.5.

The surface pH of all formulations lied between 6.38 – 6.82, which was near to the neutral pH. Thus this formulation does not produce any irritations in the mucosal cavity.

Bioadhesion Strength Measurement

Bioadhesion strength measurement of the tablet was performed by using modified physical balance (Fig:30). The average bioadhesion strength with standard deviation is shown in table no.5.

Bioadhesion strength is the force required to detach the tablets from the mucus membrane. In this study F2, F3 and F6 showed more bioadhesive strength compared to other formulation ie, (0.1777, 0.1832, 0.1717). The bioadhesion strength was decreased in the following order ie, F3>F2>F6>F5>F7>F1>F4>F9>F8. Thus it can be concluded that, as the concentration of chitosan increasesd, the bioadhesive strength was also found to be increased.

Ex-Vivo Residence Time

Ex-vivo residence time was measured by using locally modified disintegration test apparatus. The residence time of all formulation showed more than 8 hours.(table no. 5).

Table No. 4: Evaluation of post-compression parameters.

Formulation code	Thickness (mm) (n=6)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=3)	Weight variation (mg) (n=3)	Percent drug content per tablet (%) (n=3)
F1	2.53 ± 0.018	5 ± 0.5	0.446 ± 0.03	0.567 ± 0.09	101.66 ±1.41
F2	2.55 ± 0.023	4.55 ± 0.22	0.546 ± 0.02	0.427 ± 0.06	99.16 ± 1.01
F3	2.60 ± 0.020	4.1 ± 0.1	0.59 ± 0.036	0.388 ± 0.06	102.5 ± 1.58
F4	2.57 ± 0.021	4.3 ± 0.1	0.586 ±0.025	0.457 ± 0.19	98.33 ± 1.09
F5	2.55 ± 0.022	4.4 ± 0.36	0.483 ± 0.015	0.315 ± 0.18	100 ± 1.08
F6	2.61 ± 0.024	3.93 ± 0.25	0.736 ± 0.047	0.378 ± 0.23	100.83 ±1.26
F7	2.55 ± 0.028	3.63 ± 0.23	0.663 ± 0.06	0.368 ± 0.13	99.16 ± 1.41
F8	2.59 ± 0.020	4.06 ±0.11	0.556 ± 0.03	0.221 ± 0.05	97.5 ± 1.48
F9	2.62 ± 0.023	3.8 ± 0.1	0.623 ± 0.05	0.335 ± 0.07	98.33 ± 1.20

Table no. 5: Evaluation of post-compression parameters

Formulation code	SI ± SD (after 6 hrs) (n=3)	Surface pH (n=3)	Bioadhesion Strength (Newton) (n=3)	Residence Time (time of detachment hrs)
F1	15.95 ± 0.31	6.48 ± 0.06	0.1263 ± 0.003	>8
F2	15.89 ± 0.55	6.82 ± 0.07	0.1777 ± 0.005	>8
F3	16.38 ± 0.62	6.58 ± 0.08	0.1832 ± 0.007	>8
F4	18.72 ± 0.29	6.70 ± 0.12	0.1232 ± 0.002	>8
F5	19.10 ± 0.86	6.8 ± 0.05	0.1463± 0.002	>8
F6	21.03 ± 0.57	6.69 ± 0.04	0.1717± 0.003	>8
F7	22.64 ± 0.17	6.77 ± 0.06	0.1315 ± 0.003	>8
F8	21.77 ± 0.34	6.38 ± 0.15	0.1025 ± 0.003	>8
F9	21.76 ± 0.90	6.73 ± 0.10	0.1220 ± 0.004	>8

In-vitro Dissolution Study

In dissolution study was performed by using tablet dissolution test apparatus II, containing paddle stirrer. The average percentage cumulative drug release with standard deviation are shown in table no.6.

Table no. 6: *In-vitro* dissolution study of tablets.

TIME (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	7.15 ± 0.23	14.51 ± 0.69	7.46 ± 0.53	8.38 ± 0.38	13.08 ± 0.53	8.38 ± 0.61	5.62 ± 0.63	5.67 ± 0.61	5.11 ± 0.69
1	17.36 ± 0.40	31.35 ± 0.78	17.57 ± 0.61	18.64 ± 0.61	29.11 ± 0.66	14.95 ± 0.69	12.49 ± 0.95	15.63 ± 0.96	12.34 ± 0.54
2	25.50 ± 0.34	43.83 ± 0.94	33.90 ± 0.92	42.55 ± 0.76	36.89 ± 0.76	22.94 ± 0.63	27.81 ± 0.76	31.50 ± 0.53	25.08 ± 0.30
3	39.15 ± 0.23	49.29 ± 0.76	41.28 ± 0.52	50.79 ± 0.83	43.26 ± 0.76	39.17 ± 0.44	35.70 ± 0.91	41.06 ± 0.57	35.95 ± 0.72
4	52.90 ± 0.48	57.69 ± 0.48	46.28 ± 0.52	56.86 ± 0.92	50.29 ± 0.18	45.59 ± 0.95	38.38 ± 0.83	49.10 ± 0.45	43.83 ± 0.99
5	59.58 ± 0.74	63.60 ± 0.23	51.79 ± 0.99	65.15 ± 0.92	57.47 ± 0.84	51.10 ± 0.84	44.24 ± 0.74	54.45 ± 0.71	47.83 ± 0.95
6	67.56 ± 0.80	70.88 ± 0.49	59.83 ± 0.94	68.49 ± 0.99	66.77 ± 0.30	56.61 ± 0.86	47.12 ± 0.90	61.43 ± 0.31	52.02 ± 0.47
7	72.92 ± 0.61	77.15 ± 0.48	66.20 ± 0.69	70.91 ± 0.91	75.82 ± 0.54	62.57 ± 0.54	50.11 ± 0.60	64.36 ± 0.99	57.84 ± 0.95
8	80.46 ± 0.84	86.50 ± 0.78	72.93 ± 0.83	75.16 ± 0.75	81.84 ± 0.68	67.12 ± 0.40	52.84 ± 0.25	67.70 ± 0.80	62.64 ± 0.32
9	84.40 ± 0.54	94.94 ± 0.80	79.40 ± 0.85	78.65 ± 0.69	88.26 ± 0.40	72.73 ± 0.54	56.93 ± 0.15	69.52 ± 0.39	65.57 ± 0.95

*All values are expressed as average ± SD; (n=3)

From the above data, it was clear that formulation F2 showed more drug release than other formulations ie, 94.94%. F5 and F1 showed drug release of 88.26 and 84.40%, rest of formulations showed the release rate less than 80%. From this, it is evident that an intermediate amount of bioadhesive polymer is required to obtain a sustained release of drug from the tablets.

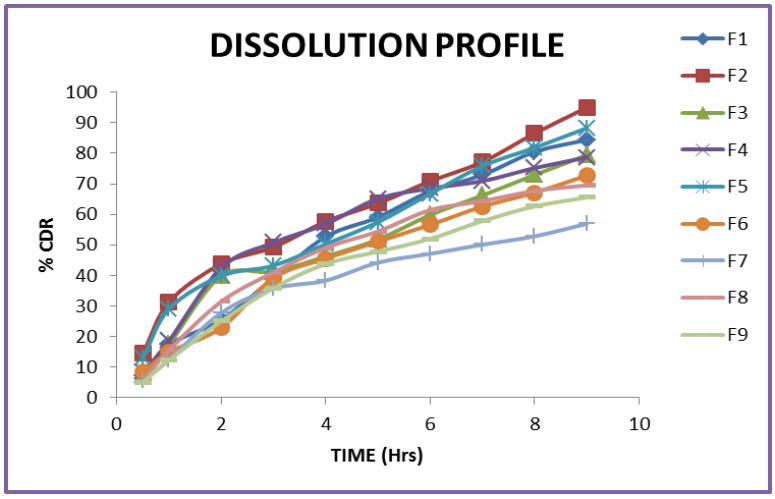

Figure 7: Graph showing dissolution profile of formulations (F1-F9).

Stability Studies of Optimized Formulation

Stability studies were performed on optimized formula F2 at 40 $\pm 2^0$ C/75% RH for 1 month. The parameters like hardness, percentage drug content, swelling index and in vitro dissolution studies were performed.

Physical Evaluation

Table no. 7: Physical evaluation of optimized formula after stability study

Test	Specification	Observation
	1st Day	30th Day
Color	Creamy white	No change
Odor	Odorless	No change

There were no significant changes in its physical appearance during storage at 40 ± 2^0C/75% RH for 1 month.

Hardness, Percent drug content and Swelling index

Table no. 8: Stability studies of optimized formulation F2.

Time (days)	Hardness	% Drug Content	Swelling Index
1st Day	4.55 ± 0.22	99.16 ± 1.01	15.89 ± 0.86
30th Day	4.55 ± 0.22	99.12 ± 0.87	15.73 ± 0.56

*All values are expressed as average ± SD; (n=3)

Above data of hardness, percentage drug content and swelling index indicate that there were no significant changes after one month of stability studies.

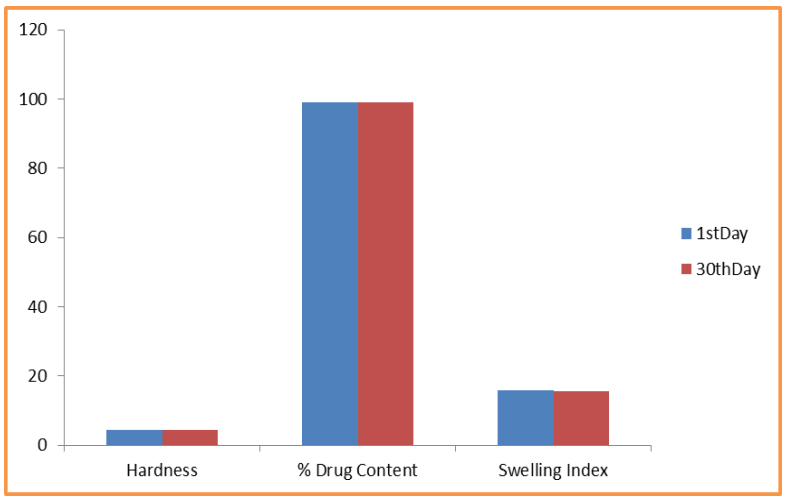

Figure 8: Graph showing hardness, percent drug content and swelling index of optimized formulation (F2).

***In-Vitro* Dissolution Study**

Table No. 9: Percentage cumulative drug release after stability study.

Time(Hrs)	Cumulative Percent of Drug Release ± SD at 40 ± 2^0C	
	1st Day	30th Day
0.5	14.51 ± 0.69	14.41 ± 0.70
1	31.35 ± 0.78	29.58 ± 0.66
2	43.83 ± 0.94	41.86 ± 0.46
3	49.29 ± 0.76	49.19 ± 0.53
4	57.69 ± 0.48	58.75 ± 0.72
5	63.60 ± 0.23	63.80 ± 0.93
6	70.88 ± 0.49	69.97 ± 0.84
7	77.15 ± 0.48	74.72 ± 0.45
8	86.50 ± 0.78	85.03 ± 0.83
9	94.94 ± 0.80	93.83 ± 0.98

*All values are expressed as average ± SD; (n=3)

The in-vitro release study also indicates that there was no significant reduction in the release from the optimized formula after one month.

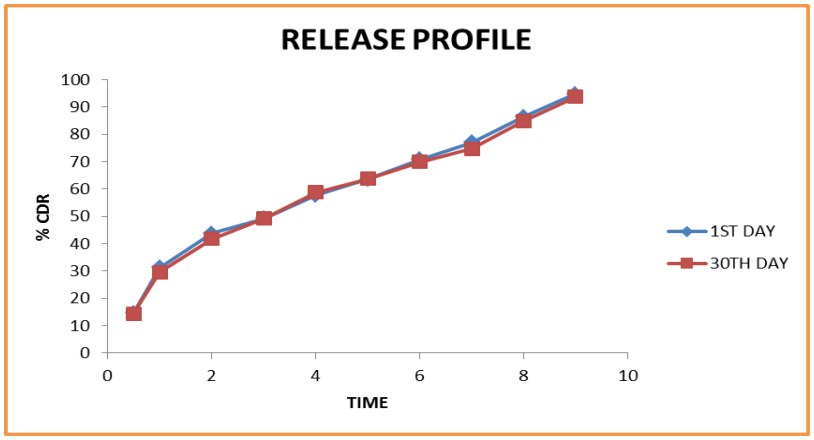

Figure 9: Graph showing percentage cumulative drug release after stability study.

Kinetics of Drug Release

The drug release mechanism of the optimized formulation was checked with zero order, Higuchi model and Korsmeyer-Peppas in Fig.36-38 The correlation values of above models are shown in table no.31.

Table No. 10: In-vitro drug release kinetic data of optimized formulation.

Time(hours)	$\sqrt{t}$	Log t	% CDR	Log % CDR
0	0	0	0	0
1	1	0	29.58	1.470998
2	1.414214	0.30103	41.865	1.621851
3	1.732051	0.477121	49.19555	1.691926

4	2	0.60206	58.75056	1.769012
5	2.236068	0.69897	63.80611	1.804862
6	2.44949	0.778151	69.97367	1.844935
7	2.645751	0.845098	74.72611	1.873472
8	2.828427	0.90309	85.03945	1.92962
9	3	0.954243	93.83611	1.97237

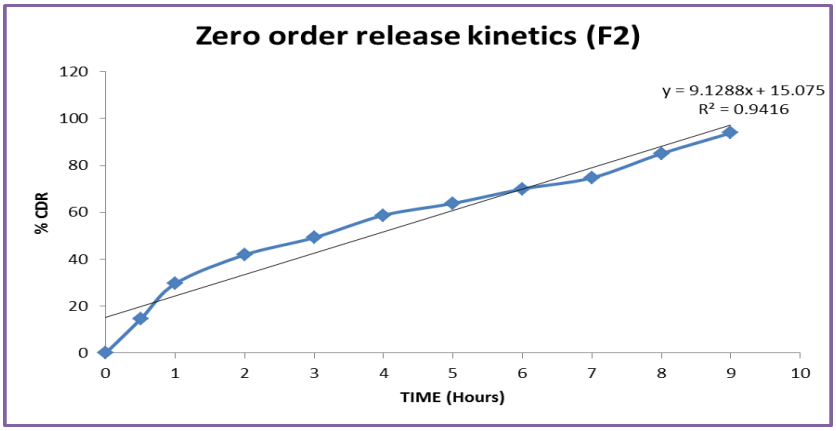

Figure 10: Graph showing Zero order release kinetics of optimized formulation F2.

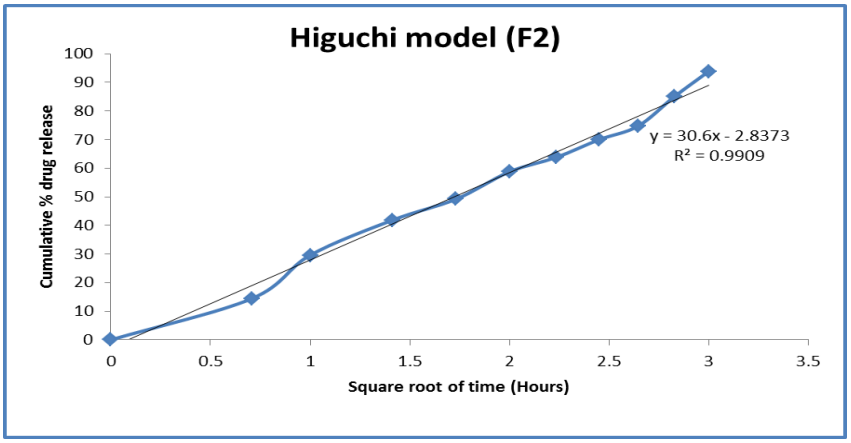

Figure 11: Graph showing Higuchi model of optimized formulation F2.

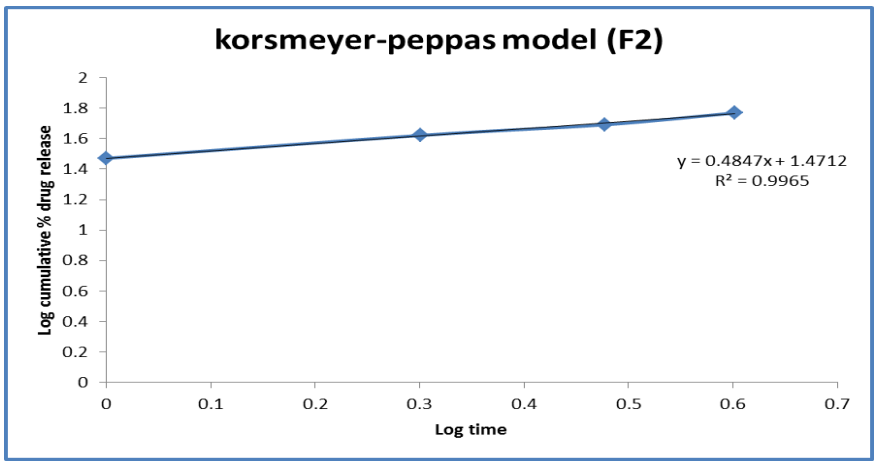

Table no.11: *In-vitro* drug release kinetic parameters of optimized formulation F2.

Formulation code	Regression coefficient	Zero order	Higuchi model	Korsmeyer-Peppas model
F2	r^2	0.941	0.990	0.991 n=0.484

The obtained regression coefficient of each kinetic was calculated and compared. The in-vitro drug release profile of optimized formula ie, F2 fitted to zero order, Higuchi and Korsmeyer-Peppas model. Regression coefficient obtained for a kinetic model such as zero order was 0.941, Higuchi model was. 990 and the korsmeyer-peppas model was 0.991. The obtained n value (0.484) from korsmeyer-peppas model indicated that drug release mechanism was found to follow non-fickian diffusion mechanism.

CONCLUSION

In this present study, bioadhesive matrix tablets of Miconazole Nitrate were formulated by using polymers such as HPMC and chitosan. Solid dispersion technique was employed to increase the solubility of poorly water soluble miconazole nitrate. Direct compression method was utilized for the formulation of bioadhesive tablets due to it's fewer formulation steps, less chance of contamination or cross contamination and easiness to meet the requirements of current good manufacturing practices. In the subsequent studies, the formulated tablets were evaluated. Among all formulation studied, formulation F2 showed better drug release over 9 hours and released 94.94% of the drug with less swelling index than other formulations. The surface pH was found to be near to neutral pH. The bioadhesive strength was found to be increased with increasing amount of chitosan and lower release rate was observed by increasing the content of HPMC. *In-vitro* drug release data were fit into the different kinetic models to explain the release kinetics of miconazole nitrate from bioadhesive matrix tablet and it was found that, they followed non-fickian diffusion mechanism. The stability study of the optimized formulation showed no significant change and fulfilled all the objectives. Thus it can be concluded that chitosan and HPMC are promising polymers for the formulation of bioadhesive matrix tablets of Miconazole Nitrate.

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