

Development and evaluation of mucoadhesive buccal patches of miconazole nitrate by using tamarind gum and HPMC

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ABSTRACT

Miconazole nitrate (MN) is a broad-spectrum antifungal agent that has been extensively applied for the management of dermal, buccal and vaginal candidiasis. In this study, Mucoadhesive patches were prepared with tamarind gum and HPMC. Mucoadhesive patches containing 10 mg miconazole nitrate were evaluated. The patches were evaluated with respect to their in vitro drug release, mucoadhesive strength, folding endurance, buccal residence time, convenient bioadhesion, acceptable elasticity, swelling and surface pH were obtained. The FT-IR spectroscopy revealed no interaction between drug and polymer and compare the evaluation parameter between tamarind gum and HPMC. Thus the tamarind gum could be a promising vehicle for the fabrication of buccal patches.

Keywords: Miconazole nitrate, Tamarind gum and HPMC.

INTRODUCTION

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. The systems contact with the absorption surface resulting in a better absorption, and also prolong residence time at the site of application to permit once or twice daily dosing. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery than the intravenous route.¹

Miconazole nitrate (MN) is a broad-spectrum antifungal agent that has been extensively applied for the management of dermal, buccal and vaginal candidiasis. Several buccal drug delivery devices containing miconazole were developed such as chewing gum, oral gel and bioadhesive

buccal tablets³. The main aim in the present study was to develop buccal mucoadhesive patch to ensure satisfactory miconazole level in the mouth for prolonged periods.

Tamarind powder is derived from the seeds of *Tamarindus indica* Linn, a common and most important tree of India and South East Asia. Tamarind powder polysaccharide has xyloglucan and glucose backbone with xylose and galactose decoration as side chains⁷. Refined Tamarind gum and tamarind cmc is used as a thickening, stabilizing and gelling agent in the food industry, particularly in Japan where it is a permitted food additive. The polysaccharide is composed of (1→4)-β-D-glucan backbone substituted with side chains of α-D-xylopyranose and β-D-galactopyranosyl (1 to 2)-α-D-xylopyranose linked (1→ 6) to glucose residues. The glucose, xylose and galactose units are present in the ratio of 2.8:2.25:1.0.⁷⁻⁸ In India, it is one of the cheapest gums available and excellent stability over the acid pH range.⁹ Tamarind polysaccharide has the ability to form the gels in the presence of sugar or alcohol. The molecular weight of the polysaccharide is reported to the range from 115,000 to 2,500,000 Da.¹⁰

Tamarind is as a viscosity enhancer showing mucomimetic, mucoadhesive, bioadhesive activities.¹¹ and noncarcinogenic, biocompatible and has high drug holding capacity. These led to its application as excipient in hydrophilic drug delivery system.¹²⁻¹⁴

MATERIALS AND METHODS

Materials

Miconazole nitrate was obtained as a gift sample from Praniti drug pvt ltd; Ankaleshwar Tamarind gum was obtained as a gift sample from Bhavna gum udyog, Gujrat .and HPMC was Purchased from Jinendra Scientific, Jalgoan. Other chemicals were of analytical grade.

Methods

Preparation of buccal patch by using HPMC and tamarind gum

1. By using HPMC

Buccal patches of Miconazole nitrate were prepared by solvent casting technique using film forming polymers HPMC polymer dissolved in 3 ml of ethanol. The beaker containing polymer and ethanol was kept aside for 5 min for swelling of the polymer. Further 3 ml of ethanol was added to the above polymer solution and the dispersion was stirred. Then Dibutyl phthalate as was added to the polymer solution. Simultaneously Miconazole nitrate was accurately weighed and dissolved in 1 ml of ethanol in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5×3 cm² was placed over a flat surface. The whole solution was poured into the glass mould. Inverted funnel was placed over the mould to avoid sudden evaporation. The mould containing polymeric solution of drug was kept 12 hours at room temperature for drying. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds. They were covered with wax paper and preserved in desiccators till the evaluation tests were performed.

2. By using Tamarind gum

Miconazole nitrate buccal patch prepared in two steps in first Gel of Tamarind gum was prepared according to the method of cross linking of Tamarind gum with epichlorhydrin.^[22] Tamarind gum and sodium hydroxide (1N, 54°C) were mixed thoroughly and epichlorhydrin

was slowly added with continuous homogenization (15 min). Then the formed gel was diluted with water. , the miconazole nitrate was added to the gel and mixed properly. After required amount of Dibutyl phthalate as plasticizer were added as mentioned in the formula. The patches were prepared using solvent casting technique. The metal rings having diameter of 4.5 cm and thickness 0.5 cm were used for holding the polymer solution on aluminum foil. The resulting gel was poured in the ring and dried at 50°C at an oven. After drying the patch was taken out from the metal ring and cut into circular shapes and stored in desiccators. and amount of loaded miconazole nitrate (i.e. 10 mg) were kept constant for all formulation including the optimized formulations

Evaluation of Buccal Patches

Film Weight

For evaluation of film weight, three films of (2×2cm²) from each formulation were taken and weighed individually on a digital balance

Thickness

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five patches.

Uniformity of weight of the patches

Patches sizes of 1x1 cm² were cut. The weights of five patches were taken and the weight variation was calculated.

Drug Content

The patches were tested for the content uniformity. A patch of size 1×1 cm² was cut and placed in a beaker. Ten ml of a 0.1 N hydrochloric acid solution was added. The contents were stirred in a cyclo-mixer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 220 nm

Swelling Index

Weight and area increase due to swelling were measured

Weight increase due to swelling: A drug-loaded patch of 1x1 cm² was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.8 was added. After every five min, the cover slip was removed and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch

Area increase due to swelling: A drug loaded patch size of 1x1 cm² was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. 50 ml of phosphate buffer, pH 6.8, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated.

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \times 100$$

Where, W1 is the weight of buccal patch before dipping into Beaker and W2 is the weight of buccal patch after dipping in beaker and wiped.

In vitro residence time

The in vitro residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8 isotonic phosphate buffer (IPB) maintained at 37 °C. A segment of rabbit intestinal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using pH 6.8 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded.

In Vitro Release

The USP 24 dissolution apparatus type 1 was used. Patches were fixed to the central shaft using cyanoacrylate adhesive. The dissolution medium consisted of 900 ml pH 6.8 phosphate buffer. The release was performed at 37 ± 0.5 °C with a rotation speed 50 rpm. At predetermined time intervals, the remaining patch was removed from the dissolution flask and assayed for the amount of drug remaining using two-phase titration technique. The release study was carried out for 24 h. One patch was used for each interval. The percent MN released was determined by difference. The data presented were the mean of three determinations. Miconazole nitrate was assayed using a two-phase titration. The medicated patch was placed in a 100-ml beaker and soaked with 10 ml distilled water till complete disintegration. Then, 10 ml of 1M sulphuric acid, 25 ml of dichloromethane and 1ml of dimethyl yellow (as indicator) were added. The mixture was titrated 0.01M sodium dodecyl sulphate solution with vigorous magnetic stirring until a colour change from yellow to pink was observed in the organic phase at the end-point. The upper aqueous layer remained colourless throughout the titration. A reagent blank prepared in the same way was titrated and any necessary corrections were calculated. The sensitivity and linearity of the assay were checked over a concentration range from 1 to 30mg ($y = 0.281x$; $r^2 = 0.9999$). Inter-day precision ($n = 9$) at the concentration of 5mg had a coefficient of variation of 2.55%.

Surface pH Determination:

The surface pH was determined by using combined glass electrode. The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.8 ± 0.1) for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of close to the neutral pH.

Mucoadhesive Strength

The strength of bond between the patch and mucosal membrane (excised from sheep buccal mucosa) was determined using tensile experiments on a specially fabricated assembly. The sheep buccal mucosa was used as model membrane and isotonic phosphate buffer pH 6.8 was used as the moistening fluid. The sheep buccal mucosa was stuck onto inner surface of the petri dish using suitable glue such that a mucosal surface faces upwards. Then the phosphate buffer pH 6.8 was added into petri dish such that the buffer was contacted with the mucosal membrane. Two sides of balance were made equal before study, by keeping a 5 g weight on the left side. A petri dish containing mucosal membrane was kept below the right-hand setup of the balance. The

test dummy films were stuck on to lower flat side of hanging glass assembly. The surface of mucosa was blotted with Whatmann filter paper no. 42. Two mL of phosphate buffer pH 6.8 was added to the mucosal surface and 5 g weight from the left pan was removed. This lowered the glass assembly along with film over the membrane with weight of 5 g. This was kept undisturbed for 3 min. Then the weights on the left hand side were slowly added till the patch just separated from the membrane surface. The excess weight on the left pan that is total weight minus 5 g was taken as adhesive strength.

RESULTS AND DISCUSSION

Thickness:

All the patches have uniform thickness throughout. Standard deviation of all the patches ranged from 0.0062 to 0.0421.

Weight Uniformity

The average weight of patch was reported in Table no.2 and calculated by using ten patches of sizes 1.128 cm diameter for standard deviation. The weight of buccal patch ranges from 0.02844-0.04638

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when comparison was made between dummy films and drug loaded films.

Surface pH: The surface pH of all formulations was the neutral pH and hence no mucosal Irritation was expected and ultimately achieved patient compliance.

In vitro release: The release data of Miconazole nitrate from all the patches were given in Fig.1. It indicates that the drug release was highest in Tamarind gum. Data of the in vitro release were fit into different equations and kinetic models to explain the release kinetics of Miconazole nitrate from the buccal patches.

Drug-Polymer Compatibility

IR spectra of Miconazole nitrate and Tamarind gum polymers are shown in Figure 1. It observed were not affected which indicated that there was no interaction between Miconazole nitrate and polymers.

Mucoadhesive Strength

The mucoadhesive strength of different formulations was determined. All the formulations showed good mucoadhesive strength. Among the formulations F3 showed maximum mucoadhesive strength while formulation F2 showed less mucoadhesive strength (Table 2).

Table1. Composition of different buccal mucoadhesive formulations

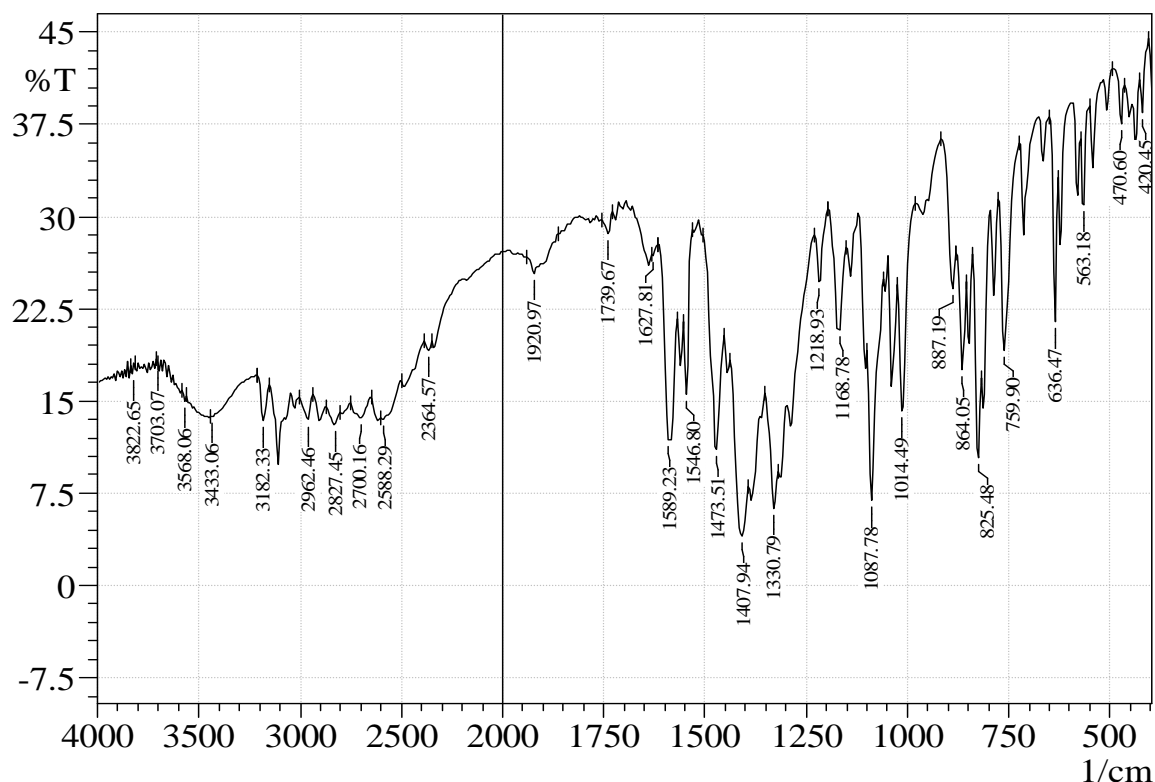
Formulations	I	II	III	IV	V	VI
Miconazole nitrate(mg)	10	10	10	10	10	10
Tamarind gum(mg)	200	150	100	-	-	-
NaoH(ml)	0.5	0.5	0.5	0.5	0.5	
HPMC(mg)	-	-	-	200	150	100
Epichlorhydrin	30	20	10	-	-	-
Dibutyl phthalate(mg)	200	400	600	200	400	600
Oleic acid(mg)	100	100	100	100	100	100
Ethanol (ml)	-	-	-	6	6	6

Table 2: Characteristics of buccal mucoadhesive patches

formulation	Thickness (mm)	Swelling		Content Uniformity	Folding endurance	Weight Uniformity (mg)	Surface pH	Muco adhesive strength	In vitro Residence Time(min)
		% Weight Increase After 30 min	% Area Increase After 30 min						
F1	0.299	778.25	58.52	89.12	>300	13.17	6.5±0.25	40.92	245 ± 12
F2	0.264	754.29	47.25	88.75	>300	13.29	6.9±0.17	38.22	259 ± 4
F3	0.261	751.56	46.36	86.92	>300	15.05	6.2±0.25	39.88	244 ± 11
F4	0.213	322.14	31.25	82.51	>300	23.28	6.24±0.25	30.14	162 ± 5
F5	0.209	354.24	29.44	80.46	>300	24.44	6.19±0.25	30.36	97 ± 9
F6	0.200	349.25	29.69	83.53	>300	19.17	6.20±0.25	28.59	175 ± 2

Table no 3: Kinetic parameters of all formulations

formulation	Zero order	First order	matrix	Peppas	Hix.Crow
F1	0.9702	0.9702	0.9612	0.9924	0.9702
F2	0.9736	0.9736	0.9659	0.9948	0.9736
F3	0.9780	0.9780	0.9550	0.9937	0.9780
F4	0.9663	0.9663	0.9773	0.9958	0.9663
F5	0.9464	0.9464	0.9759	0.9934	0.9464
F6	0.9001	0.9001	0.9880	0.9829	0.9001

Figure 1. FTIR of a) Miconazole nitrate pure b) Tamarind gum
a)

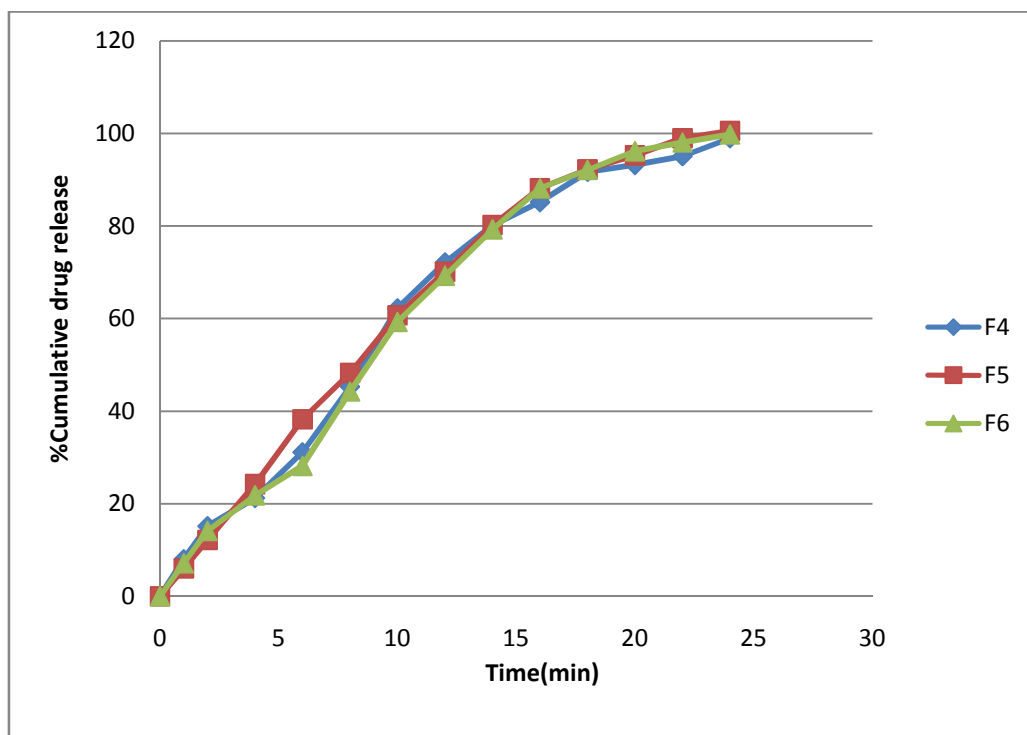
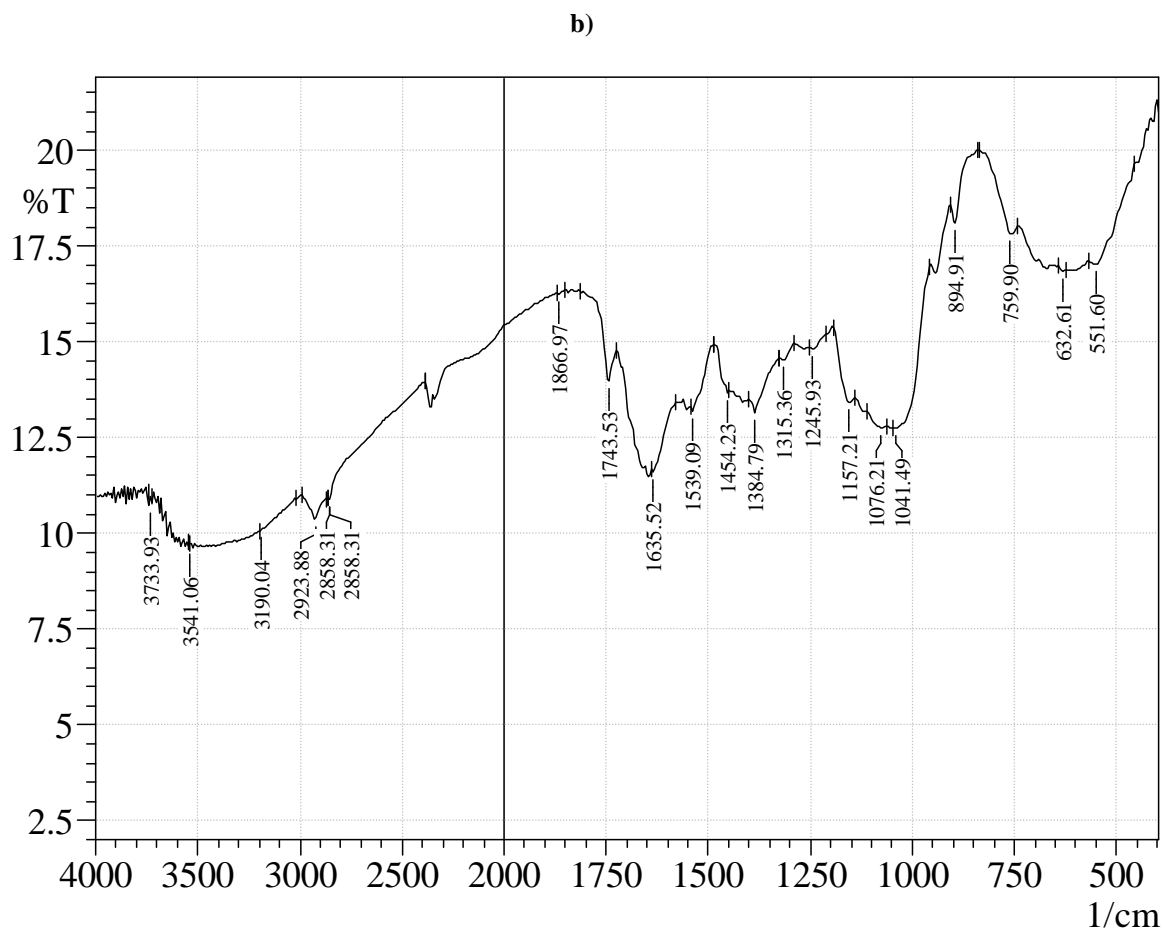


Fig. 2 *In vitro* release of Miconazole nitrate from patches 1 to 3

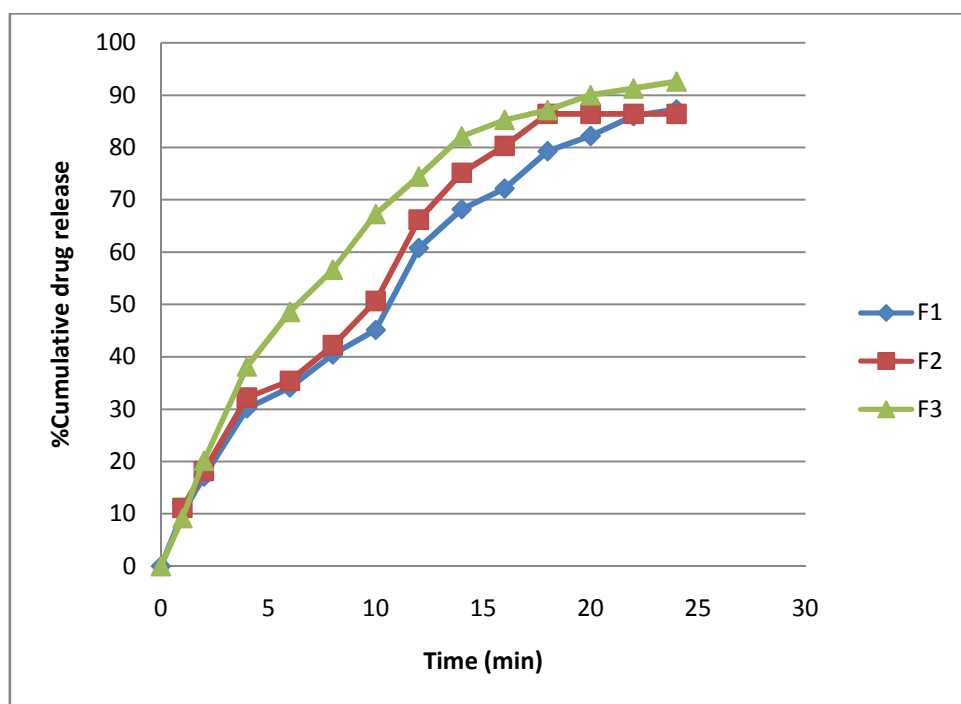


Fig. 3 *In vitro* release of Miconazole nitrate from patches 4 to 6

CONCLUSION

Mucoadhesive patches containing miconazole nitrate using tamarind gum and HPMC polymers showed satisfactory mucoadhesive characteristics. Tamarind patches improved uniform and effective miconazole levels *in vitro* without being drastically influenced by ageing. The optimized batch F1 and F3, Miconazole nitrate buccal mucoadhesive patches gave a reasonable *in vitro* residence time 244 ± 11 min and 245 ± 12 min, which is important for prolonging the adhesion of the patch with the buccal mucosa, thus improving the overall therapy of muscle spasticity. The batches F1 and F3 provided a controlled and prolonged *in vitro* release of Miconazole nitrate (for 24hr). This would be important for better patient compliance because of the decrease in the frequency of administration. Additionally, it may avoid the tolerance formation of Miconazole nitrate. The prepared dosage form was found to stable at room temperature after performing stability testing for 1month. In future, pharmacokinetics studies will be carried out to assess efficacy of buccal mucoadhesive patch of Miconazole nitrate. Hence The optimised formulation were found to be between F1 to F 3.

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