Development and Characterization of Miconazole Nitrate Loaded Mucoadheshive Patches for Effective Management of Oral Candidiasis

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Abstract : Miconazole nitrate bearing patches were prepared to deliver drug in buccal cavity for local action for effective management oral candidiasis. It were prepared by solvent cast method employing the varieties of polymers ratios and then studied for their % drug entrapment efficiency, patch thickness, folding endurance, tensile strength and moisture content and uptake. The optimized formulations were further assessing for their in-vitro muco-adhesion and drug diffusion efficiency. The drug content was found 95.7±4.7%. Thickness was 0.95± 0.03 mm. Folding endurance and tensile strength of the optimized formulation BPT-9 was 214±14 and 11.8±0.3(kg/mm^2) respectively. The mucoadhesive strength was revealed 31.6±2.4 g/cm.s^2 of the optimized formulation. The drug release study was also performed to check the drug release kinetic. It was shown 60.9±3.4 % drug release from optimized formulation (BPT-9) in 24 hr. The optimized formulations were shown matrix diffusion Huguchi release kinetics.

Keywords: Drug delivery; controlled release, patches; candidiasis, mucoadhesive

1.0 INTRODUCTION

Mucoadhesive drug delivery systems play a very important role in site specific delivery of drug for local and systemic effect. Some polymers either natural or synthetic have properties to adhere on biological mucus membrane of the GIT system (Khurana et al., 2000). The bio-adhesion properties of polymers can utilize to formulate the drug delivery system that are capable to adhere on the mucus membrane and deliver drug for longer period of time in sustained manner (Nafee et al., 2003). Bioadhesive drug delivery systems are adhering on the mucus membrane by the interfacial force. These drug delivery system can be utilize to deliver drug site specifically by buccal, oral, veginal, rectal, ocular, and nasal route. Bioadhesive drug delivery system are beneficial for drugs which absorb from specific site, it can avoid first pass effect and minimize the drug loss by degradation. Candidiasis is caused by a fungus it is a type of yeast called candida. Normally it is present in oral cavity without any harmful effect but when it invade the mucosa and grow under its lining then it cause the infection. It can infect the mouth and throat. The infection caused by candida in the mouth and throat called oral thrush or orophryangeal candidiasis. Candidiasis is characterized with white patches on tongue, mouth, and throat and in the inner lining of cheeks, which result in loss of taste, pain and difficulty in eating and swallowing (Akimoto et al., 2003; Baert et al., 2012). Miconazole nitrate is a imidazole derivates has potent

antifungal activity that is used in the treatment of ring worm infection, pityriasis, vesicolor and infection caused by yeast. Miconazole nitrate is a choice of drug that can use to treatment of candidiasis in the form of oral gel or given by oral and IV route.

In the treatment of oral candidiasis, the oral gel, tablet and IV dose of antifungal drug is administered which distribute systemically in whole body and very low concentration of administered dose is reached in oral cavity that may very low for therapeutic effect. Unwanted distribution may precipitate side effect and also increase the cost and duration of treatment. In this present work, the main objective was to retain the effective drug concentration in the oral cavity to treat the infection caused by candid yeast. In it was proposed to prepare the mucoadhesive patches which that adhere to mucosa of oral cavity and release the antifungal drug in sustained manner that maintain the high concentration of drug in oral cavity for longer time.

2.0 MATERIAL AND METHODS

2.1 Material

Miconazole nitrate was purchased from Cipla Ltd. (Mumbai, India). Hydroxy propyl methyl cellulose, HPMCK15M, Poly vinyl pyrolidone (PVPK30) and Sodium carboxy methyl cellulose (NaCMC), PEG 400, Agar were purchased from Himedia pvt Ltd, Mumbai, India. Miconazole nitrate was obtained as gift sample. All other reagents were of analytical grade were purchased from Himedia Pvt Ltd and Central Drug House (CDH), Mumbai India.

2.2 Method

The solvent casting method was used to formulate the miconazole containg polymeric patches. The polymers HPMC K4M, HPMC K15M and sodium carboxy methyl cellulose (NaCMC), was dissolved in double distilled water. Drug (10mg) was added in the above polymeric solution. Drug and polymeric solution was stirred 1hr to form homogeneous solution at 60^{o}C. PEG 400 as a plasticizer was added after cooling of the polymeric solution. A fixed volume of solution was poured in the petri dishes (9.0 cm of radius) that were previously wetted with glycerin. All the petri dishes were kept under hot air oven at 30°C for the purpose of drying. After complete drying the patches from the petri dishes were removed and cut in the pieces of 2 cm^2 and stored in air tight container (Fang et al., El-Gendy et al 2009) .

Table 1: Formulation of patches

Formulation Code	Drug Concentration	HPMC-K15M	Na-CMC	PVA	PEG 400
BPT-1	50	600	300	200	0.15
BPT-2	**50**	**800**	**300**	**200**	**0.15**
BPT-3	50	1000	300	200	0.15

BPT-4	**50**	**800**	**400**	**200**	**0.15**
BPT-5	50	800	500	200	0.15
BPT-6	50	800	400	300	0.15
BPT-7	**50**	**800**	**400**	**400**	**0.15**
BPT-8	50	800	400	500	0.15
BPT-9	**50**	**800**	**400**	**400**	**0.20**
BPT-10	50	800	400	400	0.25

Table: 2 Characterization and optimization of prepared patches

Parameters	BPT-1	BPT-2	BPT-3	BPT-4	BPT-5	BPT-6	BPT-7	BPT-8	BPT-9	BPT-10
Drug Content (%)	89.1±4.6	92.8±6.3	92.3±4.2	93.6±5.3	93.2±4.6	93.3±6.3	94.3±4.2	94.1±5.3	95.7±4.7	93.6±5.3
Weight Uniformity (g) 2cm^2	1.15±0.03	1.35± 0.02	1.57± 0.03	1.45±0.0 5	1.55±0.06	1.65±0.03	1.65±0.05	1.75±0.03	1.65±0.04	1.65±0.05
Thickness	0.63± 0.01	0.67±0.03	0.693±0.04	0.72± 0.02	0.78± 0.02	0.83±0.03	0.89±0.03	0.93± 0.02	0.95±0.02	0.95± 0.03
Surface pH	6.7± 0.1	6.7± 0.1	6.7± 0.2	6.8± 0.2	6.8± 0.1	6.7± 0.1	6.8± 0.2	6.8± 0.2	6.8± 0.1	6.8± 0.1
Moisture absorption	3.47±0.07	3.67±0.03	3.93±0.03	3.81±0.06	3.97±0.05	3.89±0.06	3.97±0.04	3.93±0.03	3.98±0.05	4.03±0.03

3.0 CHARACTERIZATION OF PATCHES

3.1 Thickness

Thickness of prepared patches were determined by taking three patches from each formulation batch and measure the thickness using screw gauge at three place point of the patches. The average value was than calculate.

3.2 Weight uniformity

Randomly selected there patches ($2cm^2$) from each batch and weighed individually using a digital balance and the average value was calculated.

3.3 Surface pH

The surface pH of the patches was determined by swelling the patches (three patches from each batch) by keeping in the contact with PBS pH 6.8. Then pH paper was placed on the patches surface to determine the pH of of the patches surface. The average value was calculated from reading of three patches.

3.4 Moisture Content

He prepared patches of 2×2 cm^2 from each formulation were weigh and then kept in the oven at 30 ºC in order to complete drying. The patches were removed and kept again in desiccators for 24 hr and reweighed. The films were successively transferred to desiccators containing sodium nitrite at room temperature. The patches were removed from desiccators without any exposure to moisture and weight again. Percent moisture content was calculated employing the formula given below (Bazigha et al., 2011)

$$\% \text{ Moisture content } = \frac{\text{Intial Weight} - \text{Final weight}}{\text{Final Weight}} \times 100$$

3.5 Moisture absorption

Agar plate was prepared by dissolving agar (2% w/v) in previously warmed simulated saliva fluid having pH 6.8 and the solution was poured into a Petri dishes and cool at room temperature. Three patches were selected and determine their weight and then allow swelling on the agar plate (2%w/v) surface at 37±0.2ºC for 6hr and weighed the patches for % weight gain at 1 hr of time interval. The percent swelling index was calculated by following equation.

$$\% \text{ Moisture absorption } = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times \mathbf{100}$$

3.6 Folding endurance

The folding endurance was determined by taking the patches of $2cm^2$ and fold it at the same place until it break. The number of folds were count at which the patches were remain unbraked is called folding endurance. The procedure was repeated three times for each patch and value was recorded as average.

3.7 Mucoadhesive strength

Two arm balance was used to determine the mucoadhesive strength of the prepared patches. The left arm of the balance was attached with replaced with aluminum plate hanged vertically with a wire. A plateform, at just below the plate was maintain to fix the mucosa. In order to determine the mucoadheshive strength, the mucosa and a patch were fixed on plate form and aluminium plate respectively. Cyanoacrylate adhesive was used to fix the patch at aluminium plate and mucosal membrane ($3cm^2$) at the platform respectively. The film was dipped in PBS pH 6.8 for 2 min for allowing hydration. Then the film was come in contact with mucosal membrane which was fixed on platform and applied pressure by placing 50g of weight for 5 min to adhere the patch on mucosa. Then in the pan of the right side of balance, weight of 5 gm was putted and gradually increased 5gm of weight after every at 2 min. the Weight required to detach the patch from mucosal membrane was recorded and the biodheshive strength was calculated according to formula given below (Allen et al., 2005; Khurana et al., 2000)

$$Bioadhesive\ force\ (F) = \frac{Weight\ applied\ in\ gm \times Acceleration\ due\ to\ gravity\ (g)}{Surface\ Area\ (A)}$$

3.8 Drug content

The pathes 2 cm^2 (n=3) was selected randomly from each formulation and immersed separately in 10 mL of ethanol and Sodium hydroxide (1mM solution) mixture of (50:50) and continuously stirred by magnetic stirrer for 24 hr at room temperature. The sample was withdrawn and centrifuged using mini centrifuge at 10000 rpm for 5 minute. 1 mL of the supernatant was taken in volumetric flask and volume was made upto 10 mL with methanol: water (50:50 ratio) solvent system and absorbance was taken using UV spectrophotometer.

4.0 IN VITRO RELEASE STUDY

Drug release from the patches was determined by using modified dissolution apparatus. In which a 200 ml of simulated saliva fluid was filled in 250 mL of capacity of beaker. The temperature was maintained at 37±0.5^oC by hot plate of magnatic stirrer. The prepared patch ($2cm^2$) was placed in the dissolution media and media was stirred at 50 rpm by the help of magnetic stirrer. At predetermined time interval, the sample (2mL) was

withdrawn from the receptor compartment and added the equal volume of fresh dissolution media. The samples were analyzed for drug concentration using UV spectrophotometer (Shimadzu 1700) (Funke et al., 2002).

5.0 RESULT AND DISCUSSION

The main objective of the work to prepare miconazole nitrare containing buccal patches and assess their effect against candidiasis. The patches were prepared using different proportion of of mucoadhesive polymers and other ingredients.

The prapred patches were optimized and characterized for drug content, folding endurance, tensile strength, moisture content, surface pH and mucoadhesiive strength and drug release and drug diffusion study. In the optimized formulation BPT-2, the concentration of Na-CMC and PVP was kept constant i.e. 1.5%w/v and 1.0% w/v respectively. The concentration of HPMC-K15M was 4%w/v and the concentration of plasticizer was 0.15%w/v. In the BPT-4 the concentration of Na-CMC was changed from 1.5 to 2.0%w/v and the other excipients were kept remained constant. In the formulation PBT-7, the concentration of excipients such as HPMC-K15 M, NaCMC, and PVP was 4.0%w/v, 2.0% w/v, 2.0%w/v respectively and concentration of PEG 400 was 0.2 % w/v used in the formulation. All the optimized formulation BPT-2, BPT-4, BPT-7 and BPT-9 were showed average thickness of 0.67±0.03, 0.72± 0.02, 0.89±0.03 and 0.95±0.02mm respectively. The average weight was revealed 1.35± 0.02, 1.45±0.0 5, 1.65±0.05 and 1.65±0.04 respectively for optimized formulation i.e. BPT-2, BPT-4, BPT-7 and BPT-9. It was shown that the concentration of polymer is directly proportional to the average weight and thickness of the patches. In the When the concentration of HPMC-K15M was increase from 3 to 5% w/v in the formulation of patches i.e. the patch weight was also slightly increased from 1.15±0.03 to 1.57± 0.03 g/2cm^2. The average weight of the optimized formulations (BPT-9) of the patches i.e BPT-2, BPT-4 was revealed 1.65±0.04 g/2cm^2. The thickness of the patches was also slightly increased that was revealed from 0.63± 0.01 to 0.95± 0.03. This was due to the increase in concentration of hydrophilic polymer (Table 1 and 2).

The pH of the prepared patches also determine because the high and low pH can cause irritation on administration. The pH of the surface of all the formulation was found similar as pH of the saliva. It is not possible that the formulation cause irritation to mucosa. The pH of the formulation was found 6.7±0.1 to 6.8±0.1 which shown slightly acidic which found compatible with oral mucosal membrane.

The folding endurance and tensile strength were determined to check the flexibility of the patches. The folding endurance was revealed 174± 14, 198±18, 192±09 and 214±14 respectively for BPT-2, BPT-4, BPT-7 and BPT-9 and The 4.8 ± 0.6, 5.5 ± 0.4, 8.5±0.6 and 11.8±0.3 respectively for BPT-2, BPT-4, BPT-7 and BPT-9 respectively for the optimized formulation (Fig. 1 and 2) Incease in the folding endurance and tensile strength also depends upon the concentration of polymer used in the formulation. In case of PBT-9, it shows high tensile strength and folding endurance because it contain higher concentration of plastisizer. The flexibility of the patches was increase due to the increasing the concentration of plastisizer.

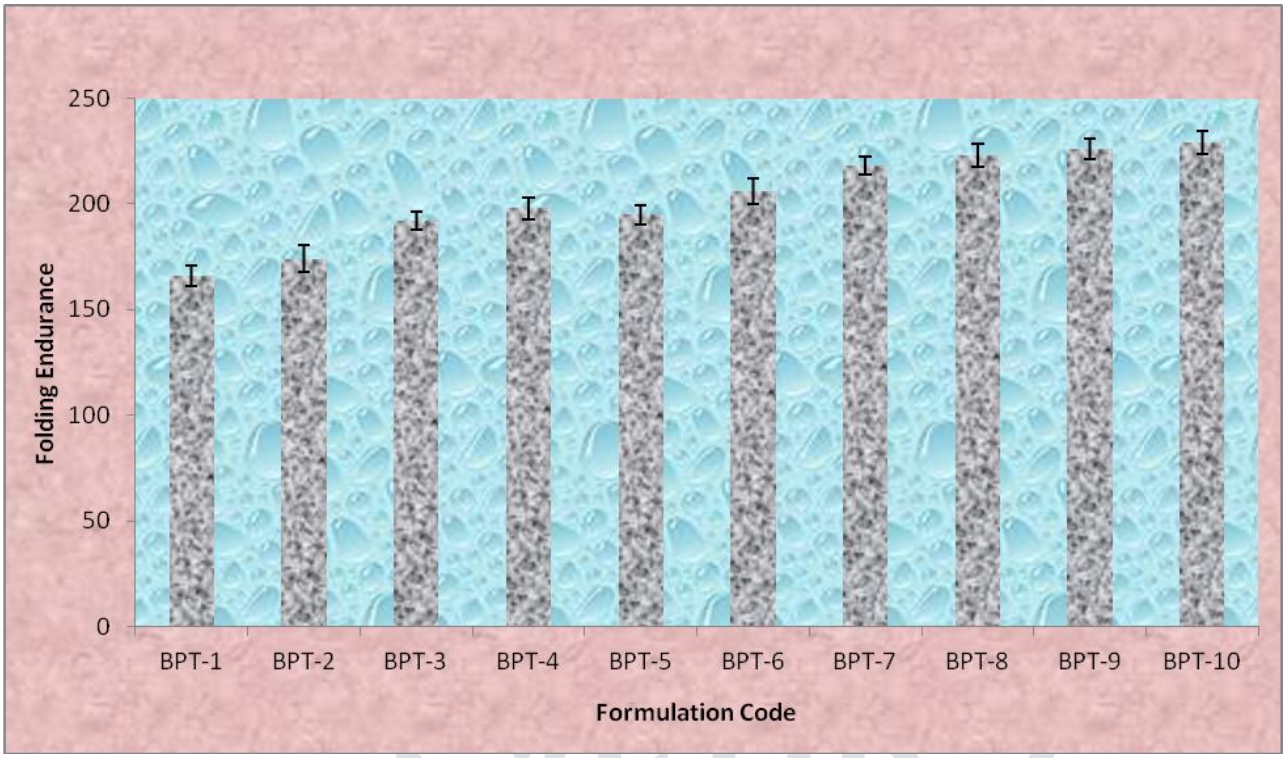

Figure:1 folding endurance of different formulations (n=3)

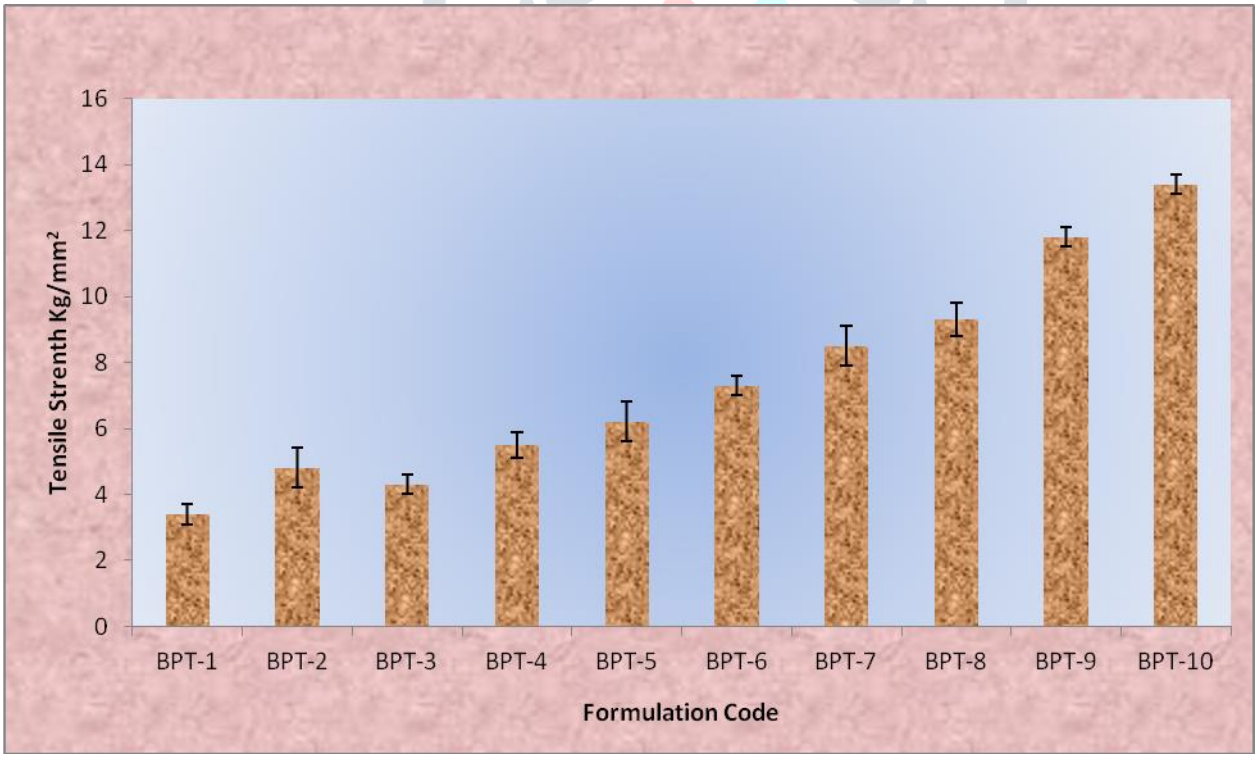

Figure 2:Tensile strength of different formulations (n=3)

Swelling of the patches support effective mucoadhesiveness as well as prolonged drug release

As the concentration of hydrophilic polymer was increase the swelling behavior of the patches was also increase due to increase in absorption capacity of water of used polymers. The moisture content was revealed 1.32±0.02%, 1.43±0.01%, 1.58±0.01%, 1.67±0.01 % and moisture uptake was 3.67±0.03, 3.81±0.06, 3.97±0.04

and 3.98±0.05 respectively for the optimized formulation i.e. BPT-2 and BPT-4, BPT-7 and BPT-9 (Table 2 and Figure 4). The polymer has the capacity to absorb the water. The increase in the moisture content and moisture uptake of the formulation is due to the higher concentration of polymer in the formulation.

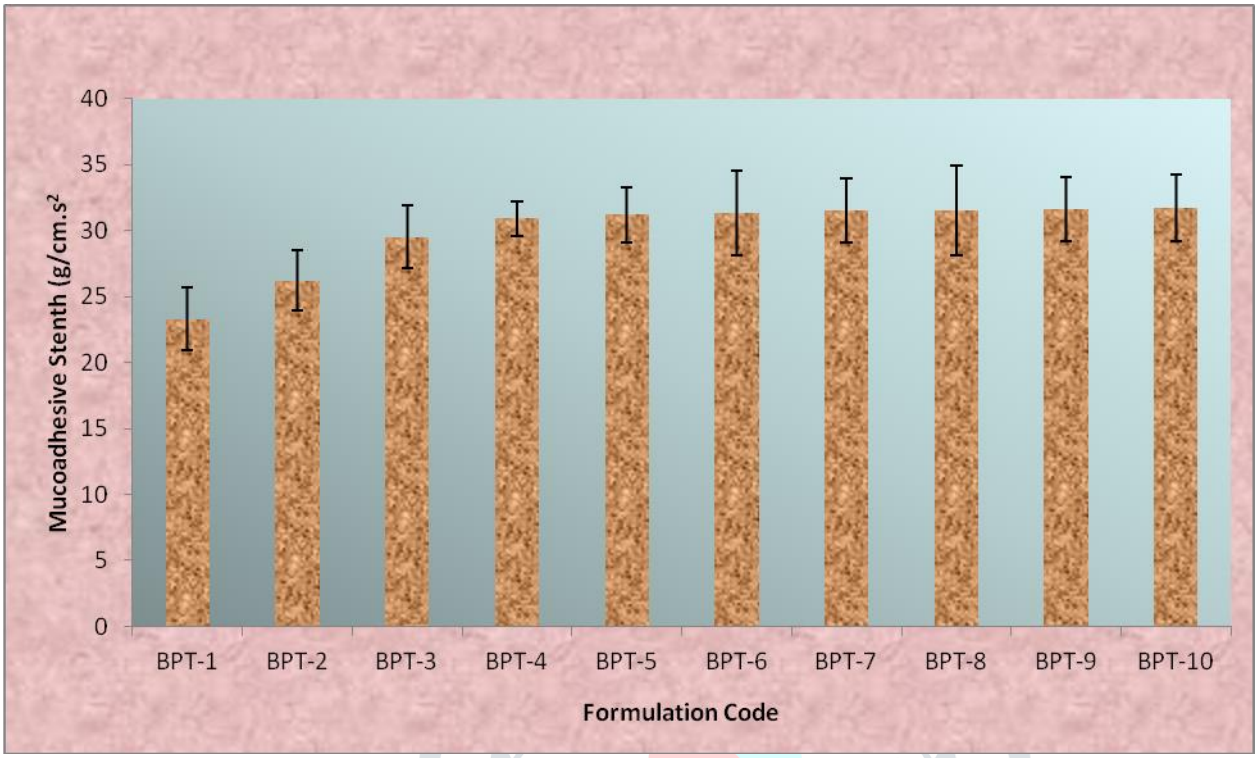

Figure 3:Mucoadhesive strength of different formulations (n=3)

The drug content was determined for all the prepared patches, it was show the uniformity in dose in the patches. Drug content was found slightly increase when increase the concentration of polymer. It was found 92.8±6.3%, 93.6±5.3%, 95.3±4.2 and 95.7±4.7 respectively for BPT-2, BPT-4, BPT-7 and BPT-9. The drug content was increase when increasing the concentration of polymers. The polymer has capacity to entrapped drug molecules in their matrix until at saturation. The uniform distribution of drug in polymer matrix was shown the uniformity of dose in the patches.

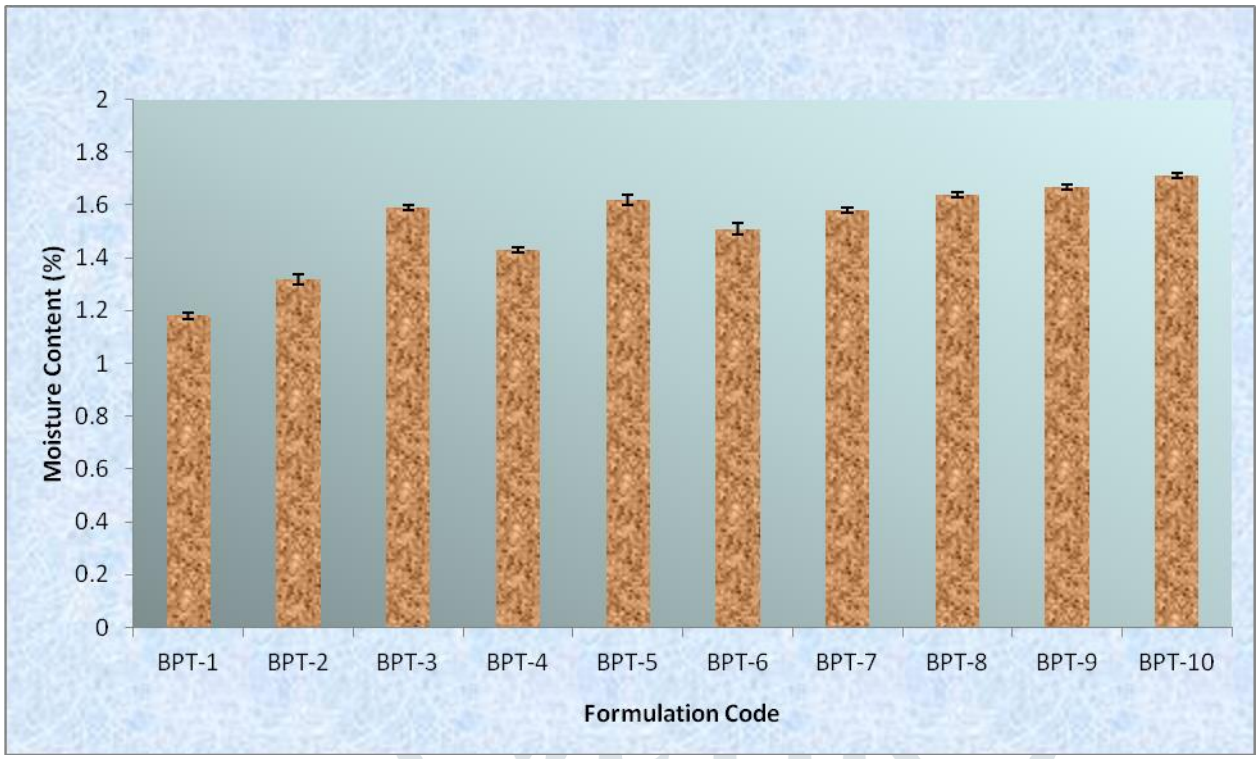

Figure 4:Moisture content of different formulations (n=3)

Drug release behavior of drug from patches is generally depends upon the type and concentration of polymer that was used to formulate. Drug release was start within 15 min of the dissolution. And approx 10% of drug was found released from prepared patches within 30 min. This was due to the drug readily dissolve which was presented on outer surface or layer of the patches or due to present of erodible, hydrophilic polymer in the patches. When a hydrophilic polymer is dissolve then it creates pores or channels in the patches result in fast dissolution. After some times the dissolution was found in sustained manner and it was due to the formation of diffusion layer and swelling of the patches. The 50 % of drug was release in 8-9hr. The drug release was found 70.4±3.9, 67.5±3.4, 65.2±3.1 and 60.9±3.4 respectively from optimized formulation BPT-2, BPT-4, BPT-7 and BPT-9 in 24 hr (figure 5). The drug release data were analyse for the release kinetic model and it was observed that all the optimized formulation were showed matrix diffusion Higuchi release kinetic model (table 3).

In mucoadhesion study, the mucoadhesive force was found to be 31.6±2.4 g/cm.s^2 and the mucoadhesive
The result obtained from all the study was concluded that miconazole nitrate loaded buccal patches can be uses for the oral and oesiofagal candiadiasis. Patches can be release the drug in sustained manner and maintain the drug concentration in effected area for longer time that will manage candidiasis effectively.

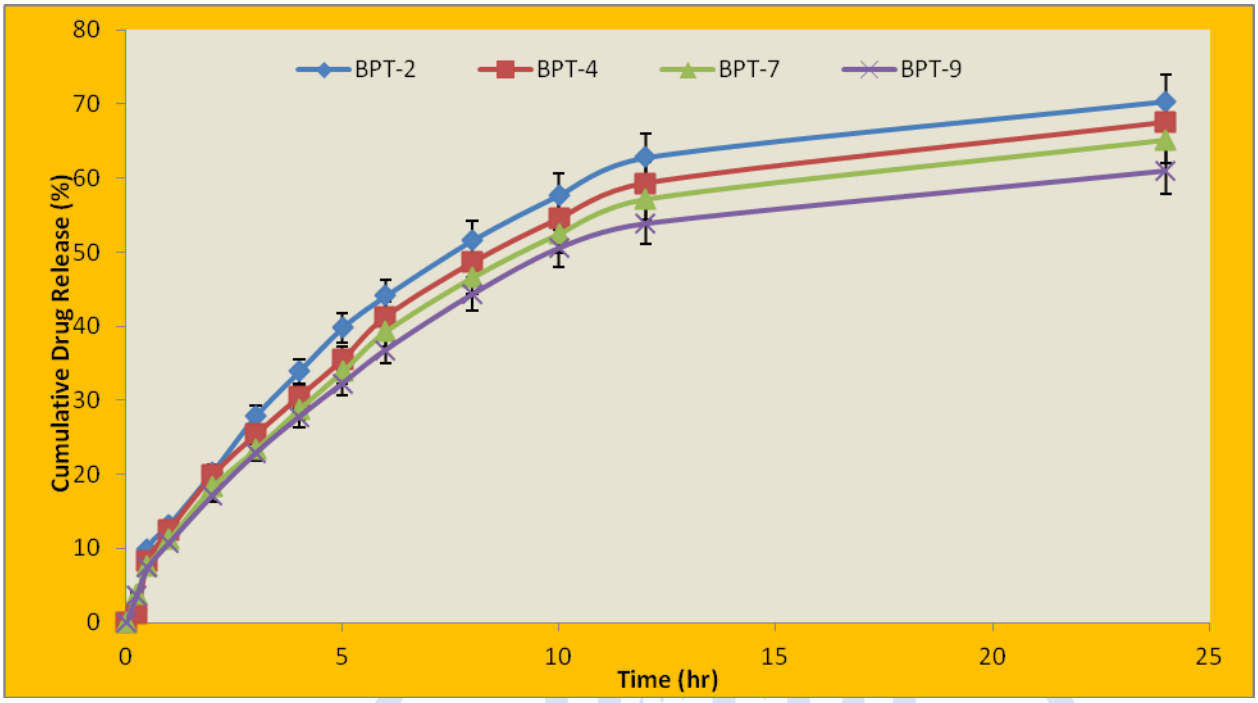

Figure 5: Cumulative % drug release from optimized formulation

Table 3:Kinetic Models and Regression coefficient

S.NO	Equation	Regression Coefficient (R^2)			
		BPT-2	**BPT-4**	**BPT-7**	**BPT-9**
1	Zero- Order	0.9403	0.9432	0.9509	0.9448
2	First-Order	0.9917	0.9878	0.9895	0.9843
3	Higuchi	0.9987	0.9946	0.9925	0.9967
4	Korsmeyer	0.999	0.9953	0.9959	0.9933
5	Hixson Crowell	0.6763	0.9763	0.9737	0.9792

6.0 CONCLUSION

Mucoadhesive patches containing miconazole nitrate using different polymers such as HPMC, PVA, PEG and NaCMC showed significant mucoadhesiveness. The optimized patches were revealed uniformity in dose, weight, thikness and other characteristics. The prepared patches showed matrix diffusion Higuchi release kinetics. On the basis of all the data, the prepared patches can be used for the treatment of oral cadidiasis.

7.0 Declaration of interest

We declare that we have no conflict of interest.

8.0 References

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