International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Issue 3, 2011

Research Article

DEVELOPMENT AND EVALUATION OF MUCOADHESIVE TABLETS OF CLOTRIMAZOLE AND ITS β- CYCLODEXTRIN COMPLEX FOR THE TREATMENT OF *CANDIDIASIS*

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Received: 28 March 2011, Revised and Accepted: 29 April 2011

ABSTRACT

Clotrimazole is an antifungal agent widely used as a first line treatment for oral candidiasis. Clotrimazole is a poorly water soluble drug, so solubility is main constraints for its oral bioavailability. An attempt has been made to increase its solubility by complexation with β-cyclodextrin and then formulating mucoadhesive tablets of best formulation with β-cyclodextrin. Mucoadhesive tablet formulations were prepared by direct compression technique using various concentrations of HPMC K4M, Carbopol-934p on a 10 station pilot press using 13 mm flat faced punches (PPID, Chamunda, India). All the formulations were evaluated for weight variation, hardness, thickness, % swelling index, mucoadhesive strength and in vitro drug release of the drug in simulated saliva solution pH 6.8. In vitro drug release of clotrimazole was best explained by zero order equation and formulations F1 to F5 were found to be following anomalous diffusion and F6 was found to be following fickian diffusion. The formulations F5 showed maximum drug release for 12 h study, therefore this formulation was optimized by complexing the clotrimazole with β-cyclodextrin (1:1 molar ratio) which resulted in increase the dissolution rate of the formulation F 6. The stability studies showed that there is no decrease in the drug content of all formulations for the period of 3 months.

Keywords: Mucoadhesive tablet, Clotrimazole, β-cyclodextrin, HPMC, Carbopol 934p.

INTRODUCTION

The major disorders of the oral cavity are toothache, periodontal diseases, dental caries, bacterial and fungal infections and aphthous stomatitis. Candidiasis, commonly called yeast infection or thrush, occurs commonly in the mucous membranes of the mouth. Oral thrush refers to temporary candidiasis in the mouth of babies, whilst if occurring in the mouth or throat of adults, is a fungal infection (mycosis) of any of the Candida species, of which Candida albicans is the most common [1, 2]. Candida infections of the latter category are also referred to as candidemia and are usually confined to severely immunocompromised persons, such as cancer, transplant, and AIDS patients, whereas superficial infections of skin and mucosal membranes by Candida causing local inflammation and discomfort is common in many human populations.

Typical symptoms of candidiasis are, Sore and painful mouth with a burning tongue and altered taste. Oropharyngeal candidiasis can impair speech, nutritional intake, and quality of life. Although it affects patients who used antibiotics or corticosteroids for a long time, it is also commonly people with poor nutrition, specifically vitamin A, iron and folate deficiencies. Worldwide, 30–40 % of the 38 600 000 people in 2005 estimated to be living with HIV are in need of highly active antiretroviral therapy (HAART) on Oropharyngeal candidiasis. In Europe, North America, Mexico, Thailand, and South Africa, oral candidiasis is observed in 50–67 % of children, and is considered the most common oral manifestation of HIV infection. Oropharyngeal candidiasis occurs in up to 55 % of people with HIV infection and in over 90 % of those with advanced disease. To prevent and treat the Oral candidiasis clotrimazole is widely used as first line treatment for local effect in the mouth [3, 4].

In the present investigation an attempt has been made to develop controlled release mucoadhesive tablets containing an antifungal agent, clotrimazole to release the drug unidirectionallly in buccal cavity for extended periods of time for improvement in bioavailability, to reduce the dosing frequency and to improve the patient compliance for an effective and safe therapy of oral candidiasis. Since the drug has poor absorption window orally and highly lipophilic, therefore it was planned to improve its solubility, by forming inclusion complex with β-cyclodextrin for optimized formulation and to study the effect of hydrophilic additives like HPMC K4M, and Carbopol 934P on release rate of the drug.

MATERIALS AND METHODS

Clotrimazole was a gift sample from Unique Pharmaceutical Pvt. Ltd, (Mumbai, India). β-cyclodextrin, Carbopol 934P, talc and mannitol were obtained from Danmed Pharmaceuticals Pvt. Ltd., (Hyderabad, India). Magnesium stearate was procured from S.D. Fine chemicals limited, (Mumbai, India). Others used were of analytical reagent grade.

Preparation and characterization of clotrimazole -β cyclodextrin complex

Equimolar amounts (1:1 molar ratio) of clotrimazole and β cyclodextrin were weighed. Clotrimazole was dissolved in acetone and kneaded thoroughly with β cyclodextrin in a clean and dry glass mortar for 4 h. The paste formed was dried under vacuum for 4 h. Dried powder was passed through sieve # 120 and stored in a dessicator until further evaluation.

Solubility study- The solubility of both the drug and clotrimazole-β-cyclodextrin inclusion complex was determined in distilled water, methanol, ethanol and phosphate buffer pH 6.8 according to the method proposed by Diez et. al[5]. Triplicate readings were taken and average was calculated.

Differential scanning calorimetry- Differential Scanning calorimetry was used to confirm the formation of inclusion complex. DSC analysis was conducted by using (Perkin-Elmer DSC7, U.S.A.) at a heating rate of 10/ min over a 30 - 3000 C or 30 - 225º C (β-cyclodextrin or Clotrimazole) temperature range. A nitrogen purge was maintained throughout runs and base line optimization was performed before each run range 2–5 mg (3.7 mg).

Powder X-ray diffraction- The X-ray powder diffraction patterns of the samples, clotrimazole, β-cyclodextrin and clotrimazole- β-cyclodextrin inclusion complex, were measured by using Philips PW 1729/ 1710 X-ray diffractometry (Holland) with Cu as anode material, operated at a voltage of 40 kV, 30 mA. The samples were analyzed by continuous scan in the range of 5-500 at º2θ angle and the process parameters were set as scan step size of 0.020º (2θ), scan step time of 0.5 sec.

Preparation of mucoadhesive tablets - Mucoadhesive tablets were prepared by direct compression method. The blended powder was evaluated for its rheological characteristics and then compressed on 10 station pilot press using 13 mm flat faced punches to produce an approximate weight of 300 mg tablet. The composition of all formulations is shown in table 1.

Table 1: Composition of mucoadhesive tablets of clotrimazole.

Ingredients	F1	F2	F3	F4	F5	F6*
Clotrimazole (mg)	100	100	100	100	100	-
β-cyclodextrin complex equivalent to 100 mg drug	–	–	–	–	–	429
HPMC K4M (mg)	60	60	60	90	90	90
Carbopol 934P (mg)	–	60	90	60	90	90
Talc % w/w	6	6	6	6	6	13
Magnesium stearate% w/w	3	3	3	3	3	6.5
Mannitol (mg)	131	71	41	41	11	21.5
Total tablet weight (mg)	300	300	300	300	300	650

*The weight of tablet is 650 mg.

Evaluation of powder blend

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced. Angle of repose, bulk density, true density and percent compressibility index have been measured which are given in table 3.

Angle of repose

The friction forces in loose powders can be measured by angle of repose (θ). It is an indicative of flow properties of powder. The powder mixture was allowed to flow through cut stem funnel fixed to a stand at a height (h) from the plane. The angle of repose was then determined by measuring the height and radius of the heap of the powder formed.

$\theta = \tan^{-1} h / r$

Where, h = height of heap of powder/granule blend, r = radius of heap of powder blend.

Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of the powder. It was measured by pouring weighed powder into measuring cylinder and initial volume was noted. This initial volume was called the bulk volume. From this bulk density was calculated by according to formula given below. It is expressed in gm/ml and is given by

$D_b = M/V_b$

Where M is the mass of powder and V_b is bulk volume of the powder.

Tapped density (D_t)

It is the ratio of total mass of powder to the tapped volume of the powder. Volume was measured by tapping the powder in measuring cylinder for 100 times and then tapped volume was noted. It is expressed in gm/ml and is given by

$D_t = M/V_t$

Where M is the mass of powder and V_t is tapped volume of the powder.

Percentage compressibility Index

It indicates powder flow properties. It is expressed in percentage and is given by

$I = D_t - D_b/D_t \times 100$

Where I is the % compressibility index of the powder, D_t is the tapped density of the powder and D_b bulk density of the powder.

Evaluation of mucoadhesive tablets

Weight uniformity- Ten tablets were taken and weighed individually. Average weight was calculated and standard deviation was computed.

Hardness- Hardness or crushing strength of tablet was measured using Pfizer hardness tester. It is expressed in Kg/cm^2.

Thickness- Thickness of tablet was measured using Vernier calipers. Three tablets were selected at random from each batch. It is expressed in mm.

Friability- Percentage friability of the tablet was determined by using Rouch friabilator.

Swelling studies[6,7]- The degree of swelling of mucoadhesive polymer is an important factor affecting adhesive. For conducting study, three tablets were weighed individually (W1) and immersed in a petridishes containing simulated saliva fluid (pH 6.75) for predetermined times (0.25, 0.5, 1, 2, 4, 8 h). After immersion tablets were wiped off by the excess surface water by the use of filter paper and weighed (W2). The percent swelling index was calculated by using the following formula and results were summarized in table 5.

% Swelling Index = [W2- W1] / W2 x 100

Where, W1 is the initial weight of the tablet, W2 is the weight of the tablet after the particular swelling time interval.

Surface pH- The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence an attempt has been made to keep surface pH close to the neutral pH. Three tablets were allowed to swell for four h in distilled water and pH was found out by placing the electrode of pH meter just in contact with the surface of the tablets. Average of three readings was computed.

Drug content uniformity- Randomly ten tablets from each batch were weighed accurately and powdered; the equivalent weight of 100 mg of clotrimazole was taken and made the volume up to 100 ml with methanol in 100 ml volumetric flask and kept aside with constant shaking for 24 h to extract the total drug present in the tablet. Then the solution was filtered and the volume was made with methanol and analyzed for drug content at λmax of 262 nm. Averages of triplicate readings were taken.

Determination of *in vitro* Mucoadhesion strength[8]

Mucoadhesive strength of the tablets was conducted on modified physical balance. The apparatus consists of a modified double beam physical balance in which the left pan was replaced with a brass wire, to which a polypropylene disc was hanged. Another propylene disc of cm height and cm diameter was placed right below the suspended disc upon the base of the balance. The right pan was replaced with a lighter pan so that, the left pan weighs 9.5 gm more than the right pan. The lower polypropylene block was intended to hold the mucosal tissue of goat cheek pouch and to be placed in a beaker containing simulated saliva solution pH 6.75. Goat cheek pouch was obtained from abattoir house was kept in a sterile container containing buffer solution of pH 6.75 until further use. Then goat cheek pouch was carefully excised, without removing connective and adipose tissue and washed with simulated saliva solution. Immediately afterwards the membrane was placed over the surface of lower polypropylene cylinder and secured. Then assembly was placed into beaker containing simulated saliva solution pH 6.75 at 37 ± 2°C and tablet was stuck to the lower surface of polypropylene cylinder with a standard cynoacrylate adhesive. The exposed part of the tablet was wetted with a drop of simulated saliva solution, and then a weight of 10 g was placed

above the expanded cap, left for 10 minutes to bind tablet with mucin and the weight was removed. The weights on the right hand side were slowly added in an increment of 0.5 g till the tablet separates from the mucosal surface/ membrane. The weight required for complete detachment is noted (W1) (W1-9.5G)) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more tablets. Average was computed and recorded.

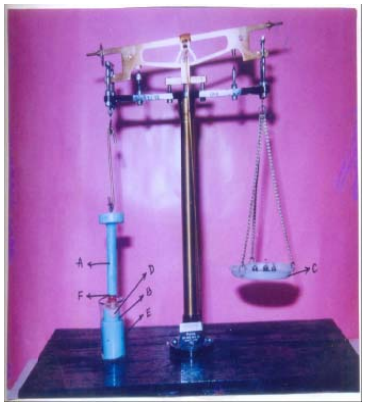

Fig. 1: Mucoadhesive test assembly

Where, A- polypropylene disc, B- Teflon block, C- Right pan, D- mucosal tissue of goat cheek pouch, E- beaker containing simulated saliva solution pH 6.75, F- Mucoadhesive tablet.

In vitro release study[9]**-** In vitro dissolution studies were carried out in USP XXIV type II apparatus (Electrolab, Mumbai) under sink conditions. The dissolution medium was 500 ml simulated saliva solution pH 6.75 at 37 ± 0.5°C with stirring speed of 100 rpm for 12 h. The samples were withdrawn at 0, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11and 12 hrs. 1ml of samples were withdrawn at intervals and replaced by equivalent amount of fresh dissolution medium. The amount of drug released in the dissolution medium was analyzed by Ultra violet (UV) spectrophotometer at 262 nm. Drug released in cumulative percentage from different formulations versus time were compared which is given in figure 4.

In vitro drug release kinetics - In the present work, data obtained from in vitro release studies were fitted to various kinetic equations to find the mechanism of drug release from the controlled release mucoadhesive tablets.

Zero order equation- The rate of release of drug can be described mathematically as follows:

Rate of release = dCs/ dt = k ---------- (1)

Where, Cs = Concentration of drug present in the matrix, K = proportionality factor i.e., reaction rate constant, t = time.

Since Cs is a constant, x- amount of drug released is described as

dx/dt = k ---------- (2)

Integration of equation

X = kt + Constant ---------- (3)

A plot of 'x'Vs't' results in a straight line with a slope = k

The value of k would indicate the amount drug released per unit time and the intercept of the line at time 0 is equal to constant to the equation.

Korsemeyer's equation[10]**-** It is a simple empirical equation to describe general solute behavior from controlled release polymer matrices:

$Mt / M\infty = K \times tn$

Where, $Mt / M\infty$ = fraction of drug released, K= kinetic constant, t = release time, n = the diffusional exponent for drug release.

Stability studies[11,12] **-**The stability studies of formulated tablets were carried out at temperature of 40°C/75% relative humidity (RH) for 3 months, to investigate the influence of temperature and relative humidity on the drug content.

RESULTS AND DISCUSSION

Solubility study

The solubility of clotrimazole and its β-cyclodextrin complex, in various solvents like water, ethanol, methanol and pH 6.8 phosphate buffers was found to be 0.076 mg/mL in distilled water, 91.66 mg/mL in ethanol and 100.29 mg/mL in methanol, 0.102 mg/mL in pH 6.8. The solubility of clotrimazole- β-cyclodextrin, 1:1 molar ratio, in water was found to be 0.657 mg/mL, which is almost 8.6 times increase of solubility than in water as shown in table 2.

Table 2: Solubility of clotrimazole and clotrimazole β-cyclodextrin inclusion complex

Water (mg/ml)		Ethanol (mg/ml)	Methanol (mg/ml)	Phosphate buffer pH 6.8 (mg/ml)
Drug	Drug:β-cyclodextrin complex (1:1 molar ratio)	Drug	Drug	Drug
0.076	0.657	91.66	100.29	0.102

Differential scanning calorimetry

The DSC thermograms (fig 2) of clotrimazole and β-cyclodextrin shows a characteristic, sharp, endothermic fusion peak at 149.47ºC corresponding to its melting point (Area of peak = 86 553.675 mJ and enthalpy ΔH = 144.237 J/g) and a broad endothermic peak at 117.44ºC respectively. The thermogram of clotrimazole- β-cyclodextrin complex shows persistence of the β-cyclodextrin peak but is shifted to a lower temperature ~105ºC, and the endothermic peak of clotrimazole has diminished in its size (Area of the peak = 112.78 mJ) and the enthalpy has reduced (ΔH= 30.464 J/g). This indicates that, even though not attributable to inclusion complex but certainly shows a stronger interaction between clotrimazole and β-cyclodextrin in solid state[13].

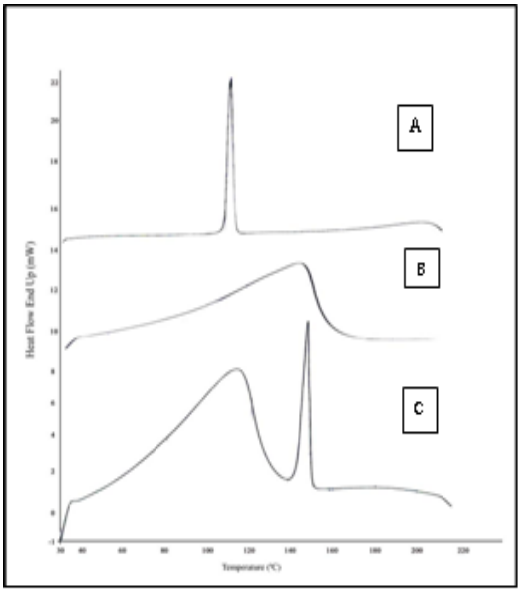

Fig. 2: DSC Thermograms of A) Clotrimazole, B) β-Cyclodextrin and C) Clotrimazole-β-Cyclodextrin complex

Powder X-ray diffraction

The X ray diffraction patterns of clotrimazole and β-cyclodextrin indicate that's both is in its crystalline form. The kneaded clotrimazole β-cyclodextrin complex exhibits significant diminution (fig 3) of the diffraction peaks, suggesting that the complex is less crystalline. This reduction in its crystallanity is attributed to the kneading treatment, is clearly evident for pure β-cyclodextrin while clotrimazole does not show this effect. It is also evident that heights of the diffraction peaks of complex have reduced indicating reduction degree of crystallanity in the case solid inclusion complex[14].

Evaluation of powder blend

Angle of repose

The angle of repose for the entire formulations (F1 to F6) blend was found to be in the range 29.05° to 31.99 ° before adding glidents and similarly studies were conducted after adding glidents showed reduced angle of repose in the range 25.64º and 29.86º.

Percentage compressibility Index

Compressibility index was found to be in the range of 11.56 % to 14.73 %. All formulations showed good flow properties which are given in table 3.

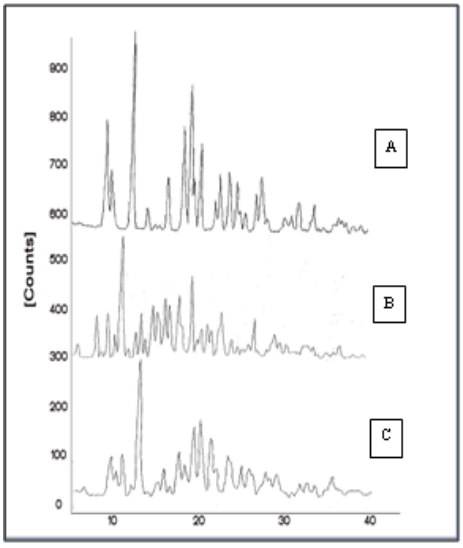

Fig. 3: Powder X-ray diffraction patterns of A) Clotrimazole, B) β-Cyclodextrin and C) Clotrimazole-β-Cyclodextrin complex.

Table 3: Flow properties of prepared mucoadhesive tablets of clotrimazole

F code	Compressibility index (%)	True density gm/ml	Bulk density gm/ml	Angle of repose (θº)	
				Before adding glidents	After adding glidents
F1	11.56	0.360	0.318	29.95	26.39
F2	12.9	0.383	0.330	29.05	26.74
F3	13.53	0.404	0.346	29.65	25.84
F4	14.73	0.371	0.315	30.75	26.56
F5	12.96	0.357	0.310	30.19	26.56
F6	13.5	0.557	0.468	31.99	29.86

Evaluation of mucoadhesive tablets

Prepared controlled release mucoadhesive tablets were then evaluated for various physical properties like swelling studies, surface pH, drug content uniformity, in vitro mucoadhesive strength, friability, thickness, hardness, weight variation and all the observations are summarized in table 4.

Weight variation- The weight of the formulated tablets of clotrimazole (F1 to F5) was found to be uniform with low standard deviation values from 284.75 ± 2.64 mg to 294.5 ± 2.34 mg and the weight formulated tablets of the clotrimazole β-cyclodextrin complex (F6) was found to be 669.1 ± 2.98 mg. The prepared formulations comply with the weight variation test as per IP. The results are given in table 4.

Thickness- The thickness of the tablets was found to be uniform, between 2.03 ± 0.084 mm to 2.57 ± 0.018 mm for (F1 to F5) and 5.75 ± 0.06 mm for F6.

Hardness- The hardness of the tablets was found to be F1 through F6 was found to be 3.24 ± 0.185 Kg/cm^2 to 4.22 ± 0.17 Kg/cm^2 which indicating good binding and satisfactory strength of tablets to withstand stress during transportation and also may offer good adhesion to mucosa.

Friability test- The percent friability for formulations (F1 to F5) was found to be 0.52 % to 0.98 % and 1.23 % (F6). The % friability was less than 1% for all formulations except formulation F6 ensuring that tablets were mechanically stable.

Drug content- The maximum drug content for all formulations was found to be 99.14 ± 0.35 mg and minimum drug content from all formulations was found to be 95.87 ± 0.31 mg. The results were within pharmacopoeial limits.

In vitro mucoadhesive strength- The maximum mucoadhesive strength of all the formulations (F1 to F6) was found to be 43.32 ± 1.69 gm and minimum mucoadhesive strength was found to be 27.61 ± 0.82 gm. It indicates that as the content of HPMC K4M or Carbopol was increased the mucoadhesive strength was found to be increased. Similarly in formulation F6 the presence of β-cyclodextrin complex does not influences the mucoadhesive strength of tablets.

Surface ph- The surface pH of all formulations was found to 6.14 ± 0.007 to 7.05 ± 0.071. The acceptable pH of the saliva in the range of

5-7 and surface pH of all the tablets was within limits. Hence, formulations may not produce any irritation to the buccal mucosa.

Table 4: Evaluation of physical characteristics of mucoadhesive tablets containing clotrimazole

F code	Weight mg±SD	Hardness Kg/cm²±SD	Thickness mm±SD	Friability (%)	Drug content mg±SD	Bioadhesive strength gm±SD	Surface pH±SD
F1	293.1±2.04	3.18±0.13	2.57±0.01	0.92	99.14±0.35	27.61±0.82	6.53±0.03
F2	286.5±2.19	3.24±0.18	2.25±0.02	0.76	97.28±0.41	31.46±1.94	6.61±0.10
F3	288.3±1.88	3.52±0.07	2.29±0.02	0.52	95.87±0.31	32.44±1.54	6.69±0.04
F4	288.8±2.37	3.66±0.18	2.33±0.05	0.68	96.54±0.28	35.20±2.02	6.58±0.04
F5	284.7±2.64	3.38±0.01	2.33±0.07	0.59	97.68±0.23	43.32±1.69	6.65±0.07
F6	669.1±2.98	4.22±0.17	5.75±0.06	1.23	96.69±0.59	43.15±1.67	7.05±0.07

SD- standard deviation, where n = 3

Swelling studies- Appropriate swelling behavior of buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion. The % swelling index of all formulations was found to in the range of 16.65 % to 77.05 % for 8h. Swelling studies indicate that the swelling index of the (F6) was found to be higher followed by F5 > F3 > F4 > F2 > F1. Swelling of tablets increases with time due to increase in content of either HPMC or Carbopol as shown in table 5.

Table 5: Swelling studies for different formulations of clotrimazole mucoadhesive tablet.

F code	% swelling index					
	0.25 h	0.5 h	1 h	2 h	4 h	8 h
F1	16.65	25.62	32.99	38.37	54.41	66.96
F2	17.06	28.27	35.53	42.51	56.21	68.93
F3	17.88	28.56	36.00	42.60	57.17	69.47
F4	18.84	27.96	37.27	43.43	56.99	69.34
F5	21.22	30.37	38.77	45.16	57.84	70.34
F6	16.36	31.87	40.92	48.32	71.84	77.05

In vitro drug release study- The in vitro drug release studies were carried out in USP XXIV type II apparatus for all formulations (F1 to F6). The tablet was observed to be intact but swollen for all formulations up to 12 h and erosion of smaller particles was started after 5 h up to 12 h for all formulations. The results of drug release studies are indicate that a polymer concentration has substantial effect on drug release from the tablets as shown in figure 4. The in vitro cumulative amount of drug release for formulations F1, F2, F3, F4 and F5 at 12 h showed 62.80 %, 65.09%, 66.57 %, 64.60 %, and 70.53 % respectively. The concentration of Carbopol 934P has greater effect on drug release than concentration HPMC K4M, which may be due to lesser permeability of former. This finding is in favor of investigation done to study the effect of levels of HPMC K4M and Carbopol 934P on release profile of clotrimazole from the swellable matrices.

The overall data on in vitro dissolution studies closely indicated that, the formulation F5 was found to be the best with high percentage of drug release. Therefore formulation F5 was selected to formulate formulation F6 with clotrimazole: β-cyclodextrin complex (1:1) molar ratio showed 87.67% of the drug released in 12 hrs. By incorporating β-cyclodextrin the amount of drug release was found to be increased in formulation F6 as shown in figure 4, which indicates that these formulations are capable of achieving the objective of this investigation.

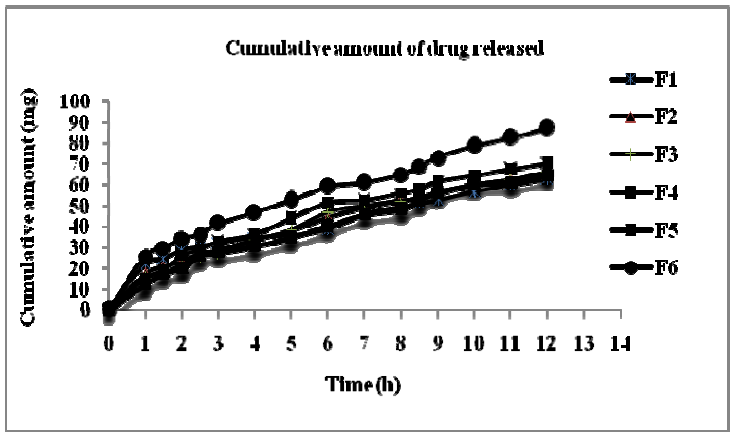

Fig. 4: Drug release profile for controlled release mucoadhesive tablets of clotrimazole

Kinetic treatment to dissolution data- Dissolution data from the batches was fitted to zero order and Korsemeyer Peppas model and the results are shown in table 6. The value of release exponent (n) was found to be a polymers used and the physicochemical properties of the drug molecule itself. It was found that in vitro drug release of clotrimazole in all the formulations was best explained by zero order equation, as the plots showed highest regression correlation coefficient (r) and followed by Korsemeyer Peppas model. A good compliance with zero order equation (average=0.99) indicates that drug release from all formulations were nearly

independent of drug concentration in tablets. The next best fit was Korsemeyer Peppas model (average=0.99). The calculated diffusion exponent (n) were found between 0.41 to 0.64 which indicates a combination of diffusion and swelling controlled release mechanism and drug release was highly influenced by swelling and gradual erosion of the tablets. It was concluded in a study that formulations (F1 to F5) exhibited anomalous (non fickian) diffusion and formulation F6 exhibited Fickian diffusion.

Stability studies- The stability studies were carried out for all formulations according to ICH guidelines at temperature of 40°C with 75 % relative humidity (RH) for 3 months. The results showed that there was no considerable difference in drug content as shown in table 7.

CONCLUSION

The current studies are aimed at successful development and optimization of mucoadhesive tablets of clotrimazole for the local treatment of oral candidiasis with high regulation of the release rate. Based on the in vitro dissolution studies, it was found that formulation (F5) showed maximum drug release in 12 hrs. Therefore this formulation was optimized by complexing the clotrimazole with β-cyclodextrin (1:1 molar ratio) which was resulted in increase the dissolution rate of the formulation (F6).

Table 6: Drug release kinetic parameters for controlled release mucoadhesive tablets of clotrimazole

Formulation	Zero order plot	Korsemeyers Peppa's plot		Mechanism of drug release
	r	n	r	
F1	0.990	0.41	0.983	anomalous (non fickian) diffusion
F2	0.988	0.56	0.997	anomalous (non fickian) diffusion
F3	0.980	0.62	0.997	anomalous (non fickian) diffusion
F4	0.986	0.64	0.996	anomalous (non fickian) diffusion
F5	0.970	0.61	0.995	anomalous (non fickian) diffusion
F6	0.992	0.5	0.995	fickian diffusion

Table 7: Data of stability studies of mucoadhesive tablet formulations at 40°C / 75% RH

Time in days	F1	F2	F3	F4	F5	F6
	DC (mg)	DC (mg)	DC (mg)	DC (mg)	DC (mg)	DC (mg)
0	99.14	97.28	95.87	96.54	97.68	97.68
1	98.68	97.10	95.26	95.78	97.36	96.68
3	97.89	96.69	95.02	95.26	97.01	96.00
7	97.36	96.05	94.87	95.00	96.65	95.69
15	96.89	95.85	94.12	94.58	96.05	95.12
30	96.02	94.75	94.03	94.01	95.69	94.13
45	95.56	94.25	93.45	93.85	95.00	93.01
60	95.01	94.00	93.01	93.10	94.12	92.56
90	94.58	93.45	92.16	92.25	93.00	91.36

Stability studies were performed for all formulations as per ICH guidelines, for drug content. The formulations showed no significant variations in the drug content and they were stable for specified time period. It was concluded that the mucoadhesive controlled release tablets of clotrimazole may be a good choice to bypass the extensive hepatic first pass metabolism with clotrimazole alone tablets and clotrimazole with β-cyclodextrin to improve the bioavailability of drug through buccal mucosa.

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