FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF POSACONAZOLE

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Abstract

In the development of mucoadhesive tablet of antifungal drug Posaconazole to treat oral thrush locally β-cyclodextrin used as hydrophilic matrix to improve the solubility. Posaconazole is poorly water soluble drug hence β-Cyclodextrin was used to improve the solubility and bioavailability of drug, simultaneously enhances the erosion rate of tablet. Which increases the drug release and permeation through buccal mucosa? The formation of inclusion complex of Posaconazole with β-Cyclodextrin was confirmed by phase solubility studies. Co-precipitation method was used to prepare inclusion complex of Posaconazole with β-cyclodextrin. The inclusion complex was characterized for compatibility studies. The results of compatibility studies reveal the successful complexation between Posaconazole and β-cyclodextrin. Mucoadhesive tablets of Posaconazole were prepared by direct compression method using altered concentrations of HPMC K4, Carbopol 934P and Maltose as polymers and Chitosan Polymer also used to enhance solubility. From the results concluded increase amount of polymers decreases the drug release at controlled rate. Formulation F6 was proved to most promising with the drug release time of 8hours 98.96%. Formulation F6 was subjected to stability testing at 45℃ & 75% RH and there is no significant change Observed. The outcome of the projected work is to designed mucoadhesive tablet of Posaconazole for controlled release in buccal mucosa. Posaconazole was chosen based on its indication for the treatment of oral Candidiasis refractory to other triazole derivatives

Keywords: Posaconazole, Mucoadhesive, Oral Candidiasis, β-Cyclodextrin.

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1. Introduction

As a triazole antifungal agent, Posaconazole exerts its antifungal activity through blockage of the cyto-chrome P-450 dependent enzyme, sterol 14α-demethylase, in fungi by binding to the heme cofactor located on the enzyme. This leads to the inhibition of the synthesis of ergosterol, a key component of the fungal cell membrane, and accumulation of methylated sterol precursors. This results in inhibition of fungal cell growth and ultimately, cell death [1].

Treatment:
Posaconazole tablets, oral suspension are used to prevent certain fungus (yeast) infections (eg, invasive Aspergillus or Candida infections) in patients who have a weakened immune system (e.g., hematopoietic stem cell transplant or HSCT recipients, or patients with blood cancers). Posaconazole tablets are also used to treat invasive aspergillosis. Posaconazole oral Tablets is also used to treat a fungus infection of the mouth or throat called oral thrush (candidiasis). Posaconazole oral suspension may be used as an initial treatment or after treatment with other antifungal medicines (e.g., itraconazole & fluconazole) have failed [2].

Muccoadhesive Tablets:
Oral mucosa is richly supplied with blood vessels which prove to be ideal site of administration to treat oral candidiasis locally. Moreover this route provides additional advantage over oral route to overcome the demerits of drug inactivation by first pass effect and gastrointestinal. The buccal route of administration improves the bioavailability of drug and its action locally. Oral caniddiasis of very common infection that occurs commonly in immune compromised pateints. The use of water soluble adhesive poymers to designed mucoadhesive tablet is to retain the dosage form on site of adhesion for the proposed time. Certain merits like self-medication, non-painful, improved bioavailability and decreased first pass effect proves mucoadhesive tablet as an ideal route of administration. Muccoadhesive tablet provides increase retention time of tablet on site of adhesion there by releasing the drug at a constant rate locally. Posaconazole is newer broad spectrum traiazole poorly soluble drug to treat severe fungal infections. Or pharyngeal candidiasis resistant to itraconazole and fluconazole.Due to lower bioavailability when taken orally Posaconazole is choosen as an ideal candidate to formulate as mucoadheive tablet using water soluble adhesive polymers. Hence in the proposed work to formulate and develop mucoadhesive tablet of Posaconazole by complexation with β- Cyclodextrin for the treatment of oral candidiasis [3].

Buccal Drug Delivery Systems:
Buccal drug delivery systems offer a promising route for drug delivery not only to the buccal mucosa for the treatment of oral conditions but also for systemic delivery by absorption through the mucosa to the systemic circulation at a predetermined and controlled rate. In addition, the buccal mucosa permits prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route. Buccal drug delivery allows interruptions at any time in the case of toxicity or adverse effects. It is also possible to administrate drugs to patients who have difficulties in swallowing. Carvedilol is a non-selective β-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. It also possesses antioxidant and anti-proliferative effects, which may enhance its ability to combat the deleterious effects of sympathetic nervous system activation in heart failure [4].

2. Materials And Methods

Materials:
We received Posaconazole and HPMC K4 M as a gift sample from Om Preegus Healthcare Private Limited, Sector 12, Dwarka Delhi. Chitosan, Carbopol 934P, Mannitol, Maltose Mg-Streate & Talc gift sample from Agra Public Institute of Technology & Computer Education, Artoni. All other chemicals used were of analytical grade and were used without further purification.

Preformulation Study:
Characterization of the Drug:
Organoleptic Properties:
The sample of Posaconazole was studied for organoleptic properties such as colour, odour and appearance.
Melting Point:
The melting points of Posaconazole were determined by melting point apparatus. Observed value was compared with the reported value.

Solubility:
Solubility of Posaconazole was checked in various solvents Like Methanol, Water, Dimethyl formamide, dichloromethane, ethyl or benzyl alcohol & phenolic.

UV Spectroscopy:
Preparation of 6.8 pH phosphate buffer:
Dissolve 13.872g of potassium dihydrogen phosphate and 35.084g of disodium hydrogen phosphate in sufficient water to produce 1000ml [5].

Standard Graph of Posaconazole in 6.8 pH:
The drug was analyzed by using LAB INDIA UV-1800 spectrophotometer having double beam detector configuration. Posaconazole dissolved in 50ml of phosphate buffer to produce primary stock solution having a concentration of 1mg/ml. 10ml of primary stock further diluted to 100ml to produce secondary stock solution having concentration of 100µg/ml. 0.5-3ml aliquots of the secondary stock were further diluted to 10ml to produce standard solutions having concentrations of 5-30µg/ml. The absorbance of the solutions was measured at 264nm using double beam UV-Visible spectrophotometer. The plot of absorbance vs. concentration (µg/ml) was plotted and data was subjected to linear regression analysis [Gupta KR, Wadodkar AR 2010].

Determination of Absorption maxima by UV spectrophotometer:
Solution of drug were prepared in 7.4pH buffer and scanned in the range of 200 to 400 nm using PG INSTRUMENTS UV spectrophotometer of (model No.T60), in order to determine the absorption maxima for analysis of dissolution samples. Preparation of calibration curve of Posaconazole 10mg was dissolved in 10ml of methanol by slight shaking (1000mcg/ml). 1ml of this solution was taken and made up to 10ml with 7.4pH buffer , which gives 100mcg/ ml concentration (stock solution). From the stock solution, concentrations of 5, 10, 1 5, 20, 25 and 30µg/ml in 7.4pH buffer were prepared. The absorbance of diluted solutions was measured at 264nm and a standard plot was drawn using the data obtained. The correlation coefficient was calculated [6].

Fourier Transformation Infra –Red Analysis:

Drug- Excipients compatibility studies the infra red absorption spectra of unmixed drug & with unalike ingredient were hold in the scale of four hundred thousand to four hundred cm-1 using KBr dise procedure, 1-2 milligram of material to be analyse was mixed with 300-400 mg, specified quantity of minute powder & dried KBr these sum are mainly enough to give a circle of 10-15 diameter and pellet of right strength by a hydraulic press [7].

Differential Scanning Calorimetry (DSC):

DSC method can be used as a screening tool for the detection of co-crystal formation in binary physical mixtures of drugs and co-former. Thermal analysis of posaconazole and prepared co-crystals were recorded on a DSC (Shimadzu DSC-60, Tokyo, Japan). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 10ºC/min was employed with nitrogen purging. Powder sample (5-10 mg) was filled into an aluminium pan and was subjected to heating from 0-300ºC, using an empty aluminum pan as a reference and analyzed (Rahman et al., 2011).

Micrometries Study:

Angle of Repose:

Mostly funnel was used in this method, firstly weight of the powder and it taken in a funnel, the height (h) funnel was place in a stand, after the powder is place in the funnel to freely flow, then the angle of repose of the powder is find out. Range of repose can zero degree. The angle of repose of the powder is found out the following formula [8].

$\tan \theta = h/r$

Therefore,

$\theta = \tan h/ r$

Here,

θ = angle of repose.

h = height of the pile.

r = radius of the pile base.

Bulk Density:

Bulk density was calculated by adding a known mass powder to a cylinder. The density was calculated as mass. Tapped density in this method firstly we have to weigh the known powder and then the known powder transfer in a 10ml mechanically tapping cylinder. The tapping was started until the little further volume changed was observed [9].

Calculated by following equation:

Loosen Bulk Density = Total Mass of Powder /Volume of Powder

Tapped Bulk Density = Powder Wt. / Tapped Volume

Carr's index:

Carr's index help in measuring the power need to breakdown the friction into the particle & the hopper. Carr's index > 25 % is carefully to be a sign of low flow capability, and under 15, of good flow property It can be calculated by following equation [10-11].

Carr's Index (%) = [(Total Bulk Density – Loosen Bulk Density) ×100]/TBD

Where,

TBD = Tapped Bulk Density

Hausner Ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's Ratio = Tapped density / Bulk Density

2.5. Preparation of Mucoadhesive Buccal Tablets:

The mucoadhesive buccal tablet was formulated using direct compression method. The excipients compatible with Posaconazole were used. Inclusion complex powder accurately weighed 100mg Posaconazole was used for one tablet. All ingredients passed through a sieve with mesh number 60. The required quantity was taken for the formulation and it was mixed thoroughly using a blender. The blended powder was compressed

using a compression machine (Cadmach Machinery Co. Pvt. Ltd., India) to produce the tablet (Yadav Deepak et al., 2011). Seven batches of the most suitable formulation were prepared by direct compression.

Evaluation of Posaconazole loaded Mucoadhesive Buccal Tablets:

Weight Variation:

Weight variation was define as to ensure that each of tablet carry proper amount of drug. This method was performed as, weight of 20 individual tablet using analytical balance, after that calculate the average weight of tablet, and after that calculate the individual tablet weight to the average [12].

Hardness of Drug:

Monsanto hardness tester was used to carry out the hardness test on mucoadhesive tablet. Individual tablet kept in between plungers and applying pressure until the mucoadhesive tablet crackdown into two parts completely and the reading on the scale was noted down in lb/cm2 [13].

Friability:

For the determination of friability test randomly selected mucoadhesive tablets were placed in friabilator and rotated at 25rpm for 4 minutes percent deviation in final weight loss is determined [14].

Thickness:

The vernier caliper (Pico India) device was used to determine the thickness of the mucoadhesive tablet.

Tablet Swelling Index Study:

The tablets were evaluated for rate of hydration when come in contact with phosphate buffer in petri-dishes. In different time interval for 24 hours, tablets were withdrawn from the petri-dish and weighed after removal of excess moisture from the surface [15].

Drug Content Uniformity:

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually. The powder was dissolved in 500ml of 0.1N HCl, filtered and the specific aliquots were taken and analyzed spectrophotometrically (Shimadzu, SPD-10AVP, Kyoto, Japan) at 264nm [16].

Mucoadhesion Strength:

A modified physical balance was used to measure the strength of mucoadhesive-ness. The apparatus consisted of a double beam physical balance, in which the right side has a pan, and the left side of the balance has a string that was hanged and at the bottom of the string was a suctioned glass slide. This was the place where the tablets were placed using an adhesive. The porcine buccal mucosa was placed on top of an inverted 50ml beaker which was placed inside a 500ml beaker that was filled with phosphate buffer with pH 6.8 kept at 37 ºC. The buffer amount was just enough so that it reaches the buccal mucosa surface. Exactly five gram of weight was placed on the right pan before putting the porcine buccal tablet in place.

The weight was then removed to lower the glass slide with the attached buccal tablet. The tablet was to be in contact with the porcine buccal mucosa membrane and this was not disturbed for 5 minutes. After 5 minutes, weights were added on the right side of the pan to separate the tablet from the membrane. The accumulated weight on the right side was then noted and subtracted with 5g. The value was taken as the measure for the bio-adhesive strength of the tablet [17].

The Bioadhesive force was calculated using the formula:

$N = W \times g / 1000$

Where,

N = Bioadhesive force.

W = Weight required for detachment of the tablet from the porcine buccal mucosa in grams.

g = Acceleration due to gravity at

9.81m/sec2 (Fatima et al., 2015; Lodhi et al., 2013; Prasad et al., 2010).

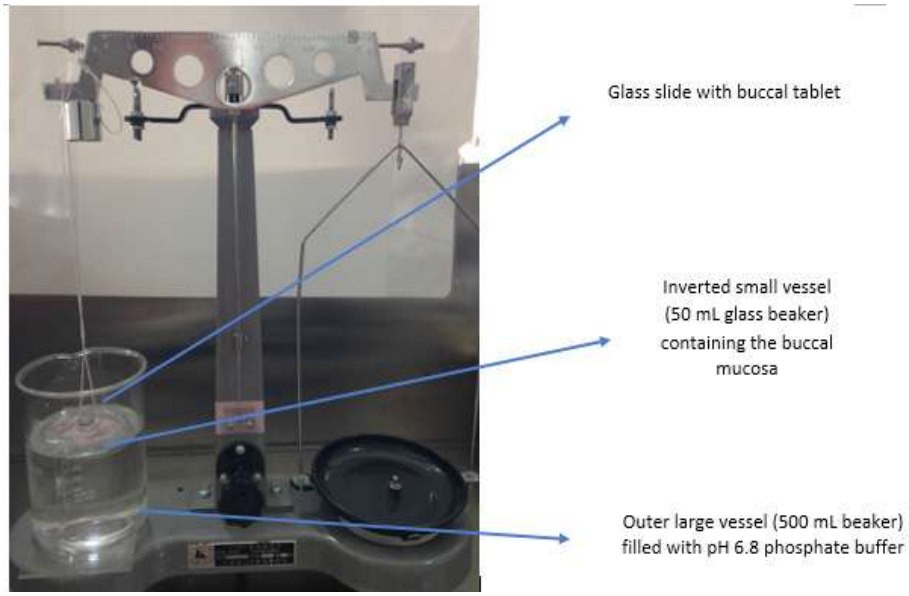

Fig.1 Modified physical balance for mucoadhesive studies

Surface pH Study:
The tablets to be evaluated were moistened in water and allowed to swell. After sometime the pH meter was to measure the surface pH of the tablet. The significance of this measurement is to avoid mucosal irritation caused by pH change [18-20].

In-Vitro Drug Release Study:
In-vitro drug release studies were tested using USP dissolution test apparatus II, the paddle type with dissolution medium of phosphate buffer with a pH of 6.8. It was performed at 37ºC + 0.5 ºC with a speed of 50 rpm. The sample at 5ml was withdrawn at time interval of 15, 30, 45, 60, 90, 120, 150, 180 minutes and was replaced with 5ml of fresh phosphate buffer. The amount of Posaconazole was determined at 264nm using UV spectrophotometer (Vikram et al., 2012; Yadav Deepak et al., 2011).

Stability:
The tablets were stored for 3 months and the samples were tested after a period of 30, 60, and 90 days (Yadav Deepak et al., 2011). The samples were analyzed using the quality control tests such as Hardness, Friability, Drug Content Uniformity, Mucoadhesive strength and Drug release.

Preformulation Study:

Organoleptic Properties:

Table.1: Identification tests of Posaconazole

Parameter	**Reported value**	**Observed value**
Appearance	Crystalline	Crystalline
Colour	White	White
Odour	Odourless	Unpleasant

Melting Point:
The melting point was determined by melting point apparatus and the melting point was found to be.

Table.2: Melting point of Posaconazole

Parameter	**Standard**	**Observed**
Melting Point	170℃-172℃	169-171℃

Solubility:

Solubility of Posaconazole was checked in various solvents.

Table.3: Determination of drug solubility in various solvents

S. No.	Solvent	Descriptive Term
1	Methanol	Soluble
2	Water	Slightly Soluble
3	Dimethyl Formamide	Soluble
4	Dichloromethane	Soluble
5	Benzyl alcohol	Poorly Soluble
6	Phenolic	Poorly Soluble

UV Spectroscopy:

The absorbance for various concentrations measured at 264nm is as follows:

Table.4: Standard Graph of Posaconazole in 6.8 pH Phosphate Buffer Solution

S. No.	Conc. (µg/ml)	Abs. at 264nm
1	0	0
2	5	0.308
3	10	0.382
4	15	0.454
5	20	0.564
6	25	0.622
7	30	0.748

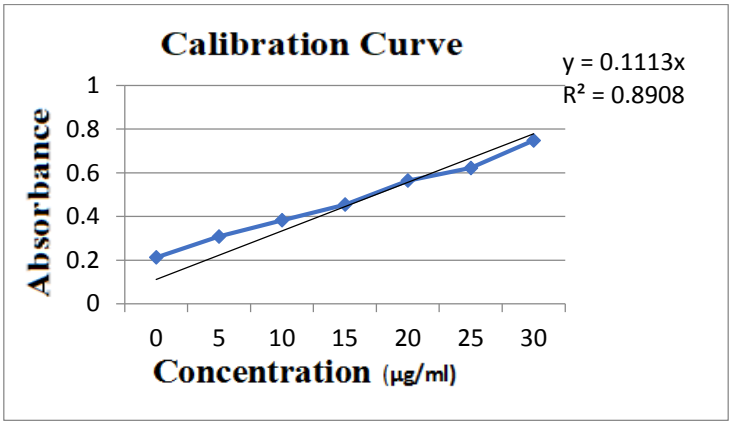

Fig.2: Standard Graph of Posaconazole in 6.8 pH Phosphate Buffer Solution

Determination of Absorption Maximum (λmax) of Posaconazole:

Determination of Posaconazole λ-max was done for accurate quantitative assessment of drug dissolution rate.

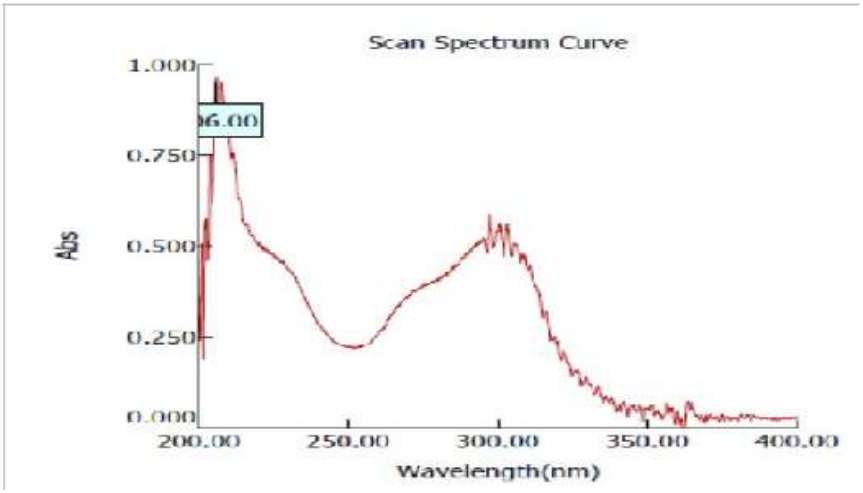

Fig.3: Absorption Maximum (λmax) of Posaconazole

Standard Calibration Curve of Posaconazole:

Table.5: Calibration curve of Posaconazole

S. No.	Conc. (µg/ml)	Abs. 264nm
1	0	0
2	5	0.310
3	10	0.390
4	15	0.490
5	20	0.550
6	25	0.668
7	30	0.724

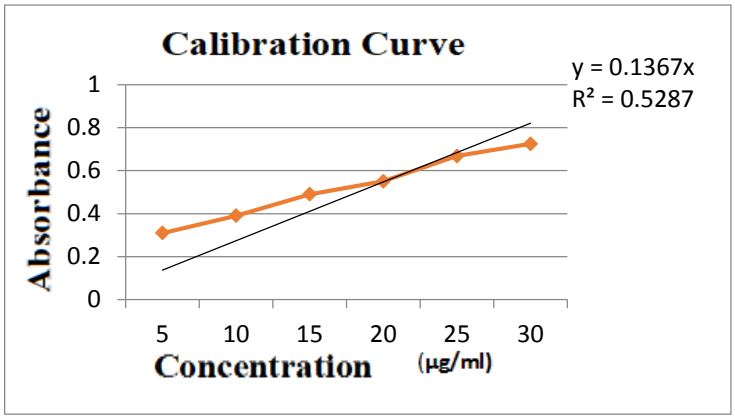

Fig.4: Calibration Curve of Posaconazole in 7.4pH buffer

FTIR Study:

IR Spectra of Pure Drug:

The FTIR spectrums of Pure Drug with different polymers were used in formulation was showed in Figures.

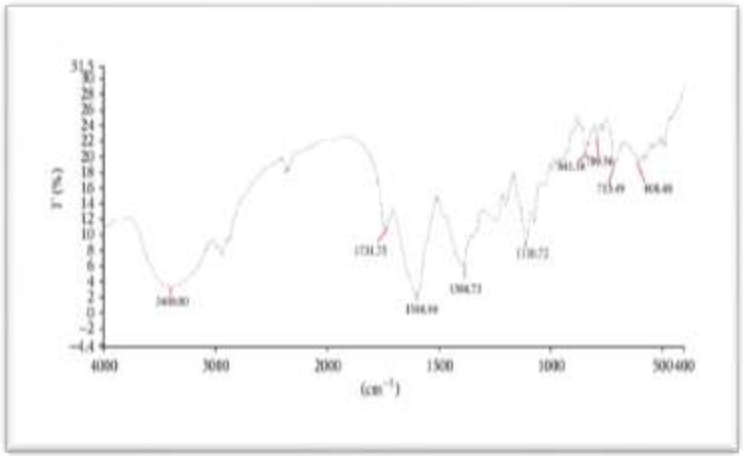

Fig.5: FTIR spectrum of Posaconazole

Table.6: Interpretation of IR spectra of pure drug

S. No.	Functional Group	Range (cm-1)	Observed Frequency (cm-1)
1	O=C= stretching	1690-1760	1710.25
2	C_4H_4O stretching	1700-1680	1410.85
3	C-H bend Alkane	1500-1378	1298.64
4	C-O-C stretching	1060-1650	1256.78
5	C-F Bending	1060-1760	1108.40
6	C-H Aromatic Bending	610-1260	720.58

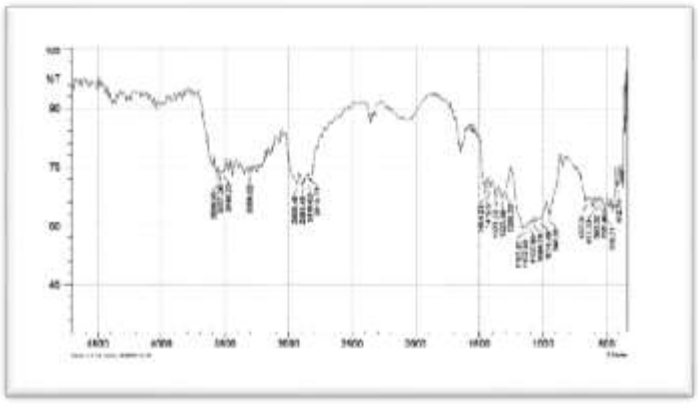

Fig.6: FTIR spectrum of pure drug + HPMC K4M

Table.7: Interpretation of IR Spectra of Pure Drug + HPMC K4M Polymer

S. No.	Functional Group	Observed Frequency (cm-1)
1	O=C= stretching	1708.20
2	C_4H_4O stretching	1410.80
3	C-H bend Alkane	1296.64
4	C-O-C stretching	1250.56
5	C-F Bending	1107.39
6	C-H Aromatic Bending	720.56

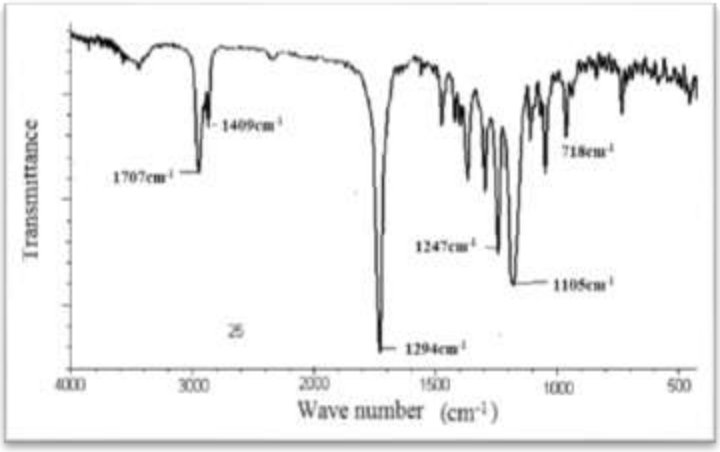

Fig.7: FTIR spectrum of pure drug + Chitosan

Table.8: Interpretation Spectra of Pure Drug + Chitosan

S. No.	Functional Group	Observed Frequency (cm-1)
1	O=C= stretching	1707.19
2	C_4H_4O stretching	1409.86
3	C-H bend Alkane	1294.60
4	C-O-C stretching	1247.27
5	C-F Bending	1105.36
6	C-H Aromatic Bending	718.54

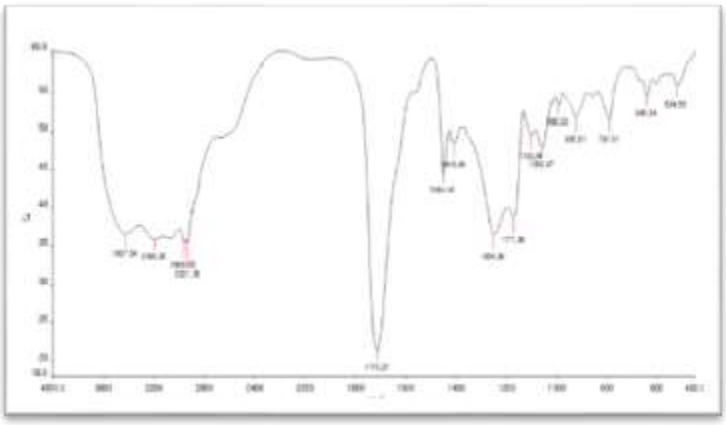

Fig.8: FTIR spectrum of Carbopol 934P

Table.9: Interpretation Spectra of Pure Drug + Carbopol 934P

S. No.	Functional Group	Observed Frequency (cm-1)
1	O=C= stretching	1707.17
2	C_4H_4O stretching	1409.84
3	C-H bend Alkane	1290.59
4	C-O-C stretching	1232.05
5	C-F Bending	1107.28
6	C-H Aromatic Bending	715.42

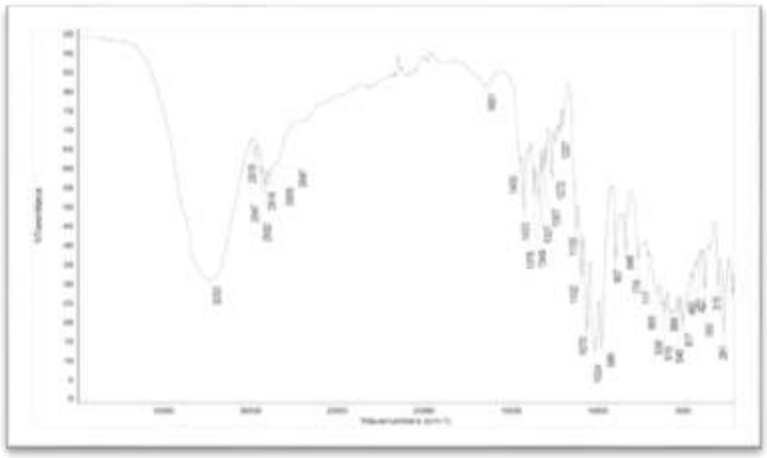

Fig.9: FTIR spectrum of Posaconazole + Maltose

Table.10: Interpretation Spectra of Pure Drug + Maltose

S. No.	Functional Group	Observed Frequency (cm-1)
1	O=C= stretching	1705.15 CM^{-1}
2	C_4H_4O stretching	1408.83 CM^{-1}
3	C-H bend Alkane	1288.55 CM^{-1}
4	C-O-C stretching	1230.01 CM^{-1}
5	C-F Bending	1102.20 CM^{-1}
6	C-H Aromatic Bending	710.36CM^{-1}

Discussion of FTIR Spectrum:
The IR spectrum of the formulation showed that there was no significant evidence for interaction between drug and the polymer. Peaks of both drugs as well as formulation were observed are same. So this clearly suggest that the drug has not undergone any interaction with the polymer in the formulation, as there was no any shift in the positions of the characteristic absorption bands of drug in the formulation.

Differential Scanning Calorimetry (DSC):
A little amount of sample, between 1 and 15 mg, was put into a temperature-controlled DSC cell inside of a closed crucible. As a benchmark, a second crucible without a sample was employed. To characterize phase transitions and cure processes as a function of temperature, a typical DSC test involves heating and cooling the sample at a regulated steady rate while monitoring the heat flow. More complex investigations can use isothermal mode and several heating and cooling steps. Weak transitions can be identified and overlapping thermal events can be distinguished using modulated DSC, which applies a temperature modulation approach.

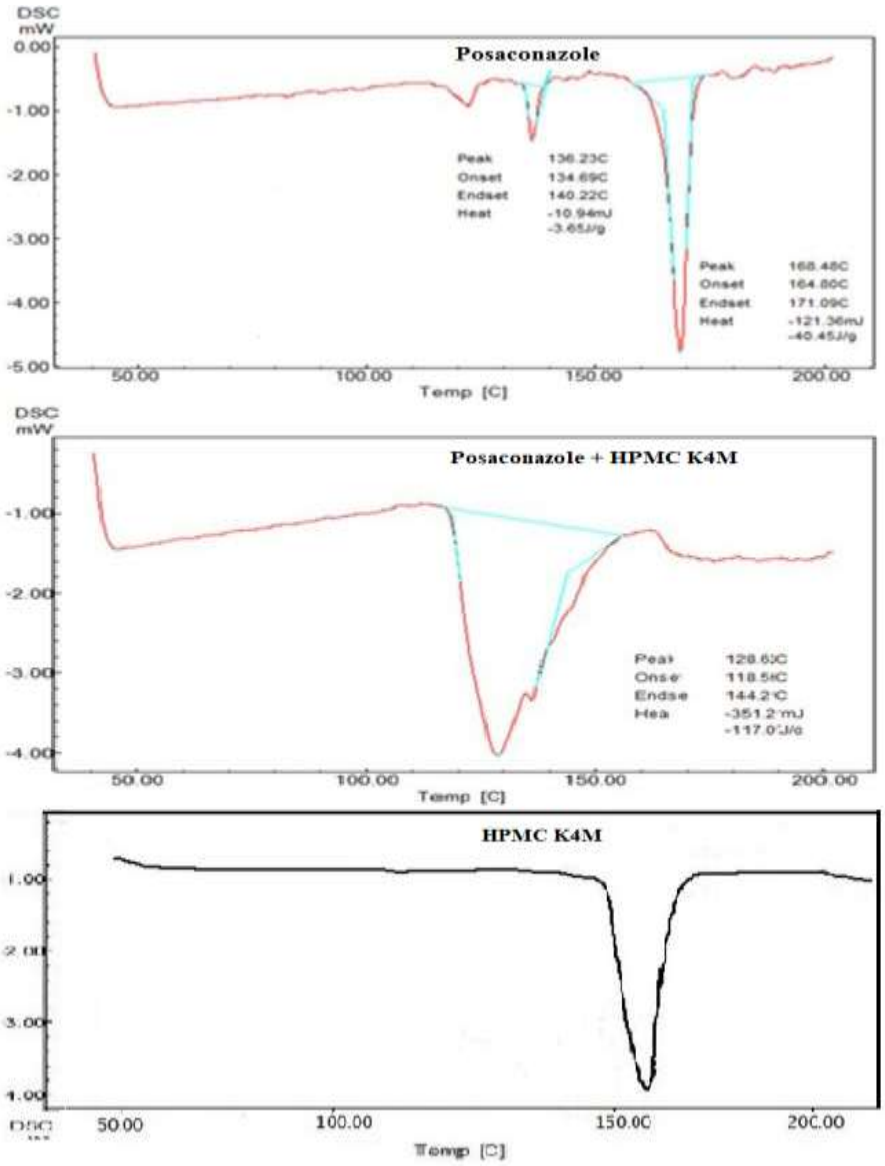

Fig.10: DSC thermo grams of Posaconazole and HPMC K4M

3. Discussion:

DSC gives an accurate temperature for the onset of melting. DSC thermo grams of Posaconazole and HPMC K4M were shown in Fig.10. Posaconazole showed an endothermic peak at 168.48 °C corresponding to its melting point while the Polymer showed a peak at 128.62 °C. The endothermic peak of co-crystals was found to be different the drug and Polymer, that confirms the formation of a new phase.

Micrometry Study:

Table.11: Evaluation of Powders for Posaconazole

Formulation Code	**Carr's index (%)**	**Angle of Repose**
F1	24.15±1.9	28.20±0.52

F2	21.36±0.6	26.36±1.06
F3	20.50±1.2	30.86±0.48
F4	28.68±0.8	28.25±1.10
F5	26.09±0.7	27.54±0.12
F6	19.50±0.8	29.74±0.64
F7	24.16±0.6	31.46±0.60

Values are expressed as mean ±SD (n=3)

Discussion:

The physical mixtures for Posaconazole Powder are evaluated with respect to Carr's index values are found 19.50±0.8 to 28.68±0.8% and Angle of repose was found b/w 27.54±0.12 to 31.46±0.60 the powder of all batches excellent to poor flow ability and compressibility.

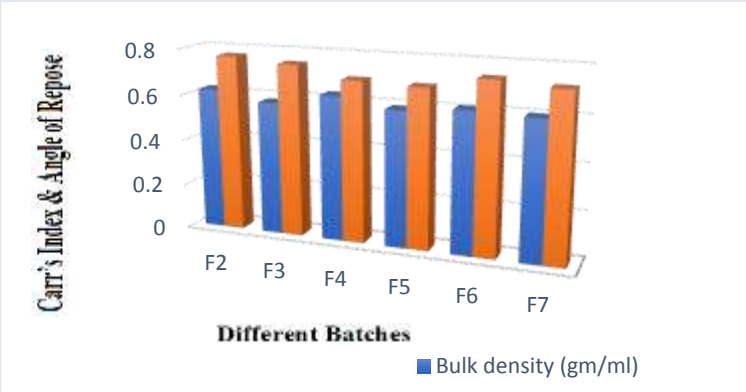

Fig.11: Powder Evaluated with respect to Angle of repose & Carr's index

Table.12: Evaluation of Powders for Posaconazole

Formulation Code	**Bulk density (gm/ml)**	**Tapped density (gm/cc)**	**Hausner's ratio**
F1	0.64±0.68	0.78±0.54	1.25±0.14
F2	0.62±0.51	0.77±1.06	1.19±0.18
F3	0.58±0.44	0.75±0.99	1.26±0.23
F4	0.63±1.22	0.70±1.05	1.40±0.20
F5	0.59±0.78	0.69±0.02	1.29±0.18
F6	0.61±0.56	0.74±0.89	1.34±0.13
F7	0.60±0.52	0.72±0.79	1.30±0.13

Values are expressed as mean ±SD (n=3)

Discussion:

Bulk density ratio 0.58±0.44 to 0.64±0.68 and Tapped density ratio 0.69±0.02 to 0.78±0.54 & Hausner ratio is found to be 1.19±0.18 to 1.40±0.20 for all the batches indicating that possible and poor flow properties.

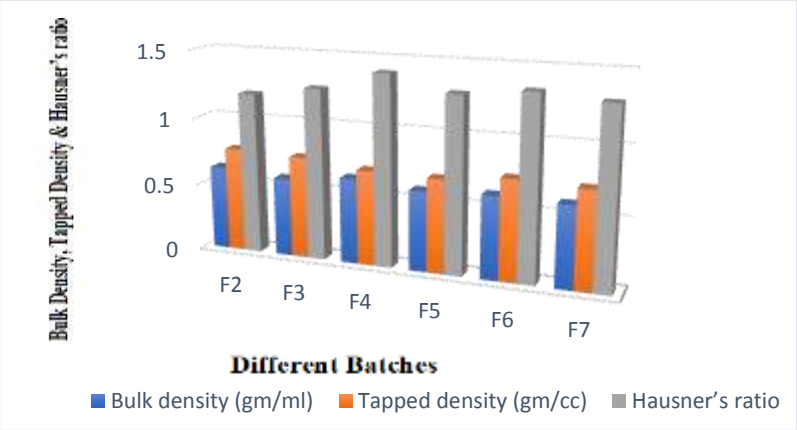

Fig.12: Powder Evaluated with respect to Bulk, Tapped Density & Hausners Ratio

Preparation:

Table.13: Preparation of Mucoadhesive Buccal Tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Posaconazole	100mg	100mg	100mg	100mg	100mg	100mg	100mg
2	HPMC K4M	15	20	25	15	20	25	15
3	Chitosan	5	10	15	5	10	15	5
4	Carbopol 934P	10	15	20	10	15	20	10
5	Maltose	10	15	20	10	15	20	10
	Mg-Stearate	2	2	2	3	3	3	2
6	Talc	1.5	1.5	1.5	1.5	1.5	2.0	1.5

Evaluation Parameters:

Table.15: Evaluation of Compressed Posaconazole Loaded Mucoadhesive Buccal Tablets

Formulation Code	Hardness (Kg/cm2)	Thickness in (mm)	Friability (%)
F1	3.60±0.35	2.72±0.22	0.31±0.22
F2	3.10±0.50	2.24±0.12	0.44±0.13
F3	2.98±0.61	2.76±0.03	0.68±0.13
F4	4.03±0.68	2.78±0.02	0.52±0.21
F5	4.15±0.36	2.42±0.06	0.58±0.14
F6	4.25±0.20	2.76±0.14	0.74±0.14
F7	3.86±0.20	2.79±0.04	0.68±0.14

Values are intimate as design ± SD (n = 3)

Discussion:

The Hardness ratio was found 3.60±0.35 to 3.86±0.20 and Thickness ratio 2.72±0.22 to 2.79±0.04 & Friability ratio is found to be 0.31±0.22 to 0.68±0.14 for all the batches indicating that possible evaluation properties.

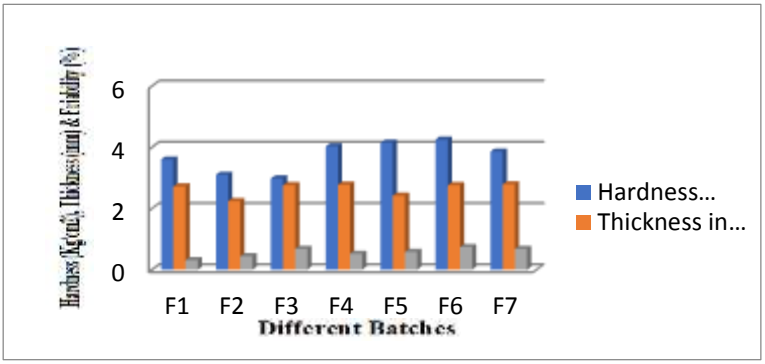

Fig.13: A Diagrammatically Representation of Hardness, Thickness & Friability

Table.14: Evaluation Parameters of Wt. Variation & Tablet SIS

Formulation Code	**Weight variation Average wt in (mg)**	**Tablet Swelling Index Study**
F1	186.42	24.86
F2	190.51	34.76
F3	200.48	48.90
F4	196.47	60.98
F5	202.48	75.46
F6	198.50	88.96
F7	199.26	94.46

Values are intimate as design ± SD (n = 3)

Discussion:

The Weight variation was found 186.42 to 199.26 and Tablet Swelling Index ratio 24.86 to 94.46 for all the batches indicating that possible evaluation properties.

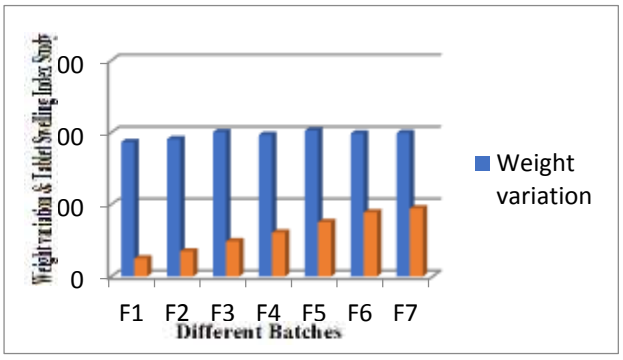

Fig.14: A Diagrammatically Representation of Wt. Variation, Tablet Swelling Index Study

Table.15: Evaluation Parameters of pH surface & M.S

Formulation Code	**Surface pH Study**	**Mucoadhesion Strength**
F1	7.01	>11

F2	6.90	>10
F3	6.70	>14
F4	7.16	>13
F5	7.30	>15
F6	7.04	>13
F7	6.56	>10

Values are intimate as design ± SD (n = 3)

Discussion:

The Surface pH was found 7.01 to 6.56 and Mucoadhesion Strength ratio >11 to >10 for all the batches indicating that possible evaluation properties.

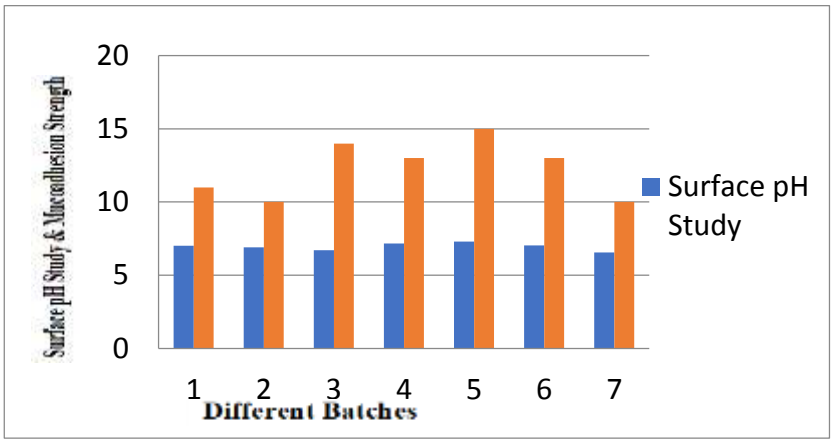

Fig.15: A Diagrammatically Representation of Surface pH Study & Mucoadhesion Strength

Table.16: Evaluation Parameters of Drug Content

Formulation Code	**Drug Content Uniformity**
F1	96.56±1.20
F2	97.86±1.90
F3	98.24±1.86
F4	96.78±1.35
F5	97.96±1.25
F6	99.86±1.18
F7	98.76±1.18

Values are intimate as design ± SD (n = 3)

Discussion:

The Drug Content Uniformity was found 96.56±1.20 to 98.76±1.18 for all the batches indicating that possible evaluation properties.

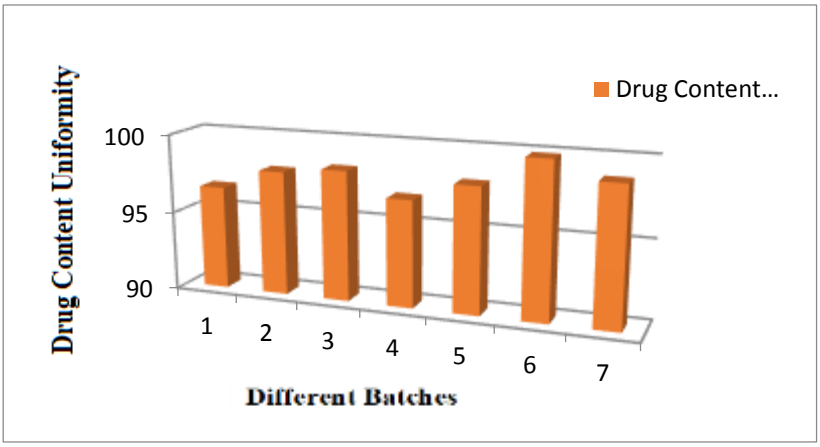

Fig.16: A Diagrammatically Representation of Drug Content Uniformity

In-Vitro Drug Release Studies:

Table.17: Release studies F1-F7

Time/Hrs	**% Release Drug**						
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0.5	41.75±2.4	40.30±0.28	46.65±0.24	46.04±0.96	47.40±0.72	48.42±1.30	42.42±1.30
1	46.56±2.2	45.55±0.99	54.46±0.48	52.52±1.33	56.85±0.88	57.78±1.25	54.78±1.25
2	51.78±2.3	54.04±0.90	59.52±0.76	63.13±1.28	60.58±1.24	63.47±1.20	60.47±1.20
3	59.25±0.2	60.56±0.36	65.32±0.82	69.49±1.22	67.44±1.45	75.89±1.18	72.89±1.18
4	66.52±0.5	69.78±1.25	76.70±0.91	72.21±0.98	77.98±1.20	87.45±0.78	82.45±0.94
5	76.48±0.8	78.65±1.09	79.46±0.52	78.16±0.88	80.43±1.40	92.25±1.77	88.45±0.76
6	84.89±0.3	85.44±1.17	86.24±0.78	88.29±0.68	88.78±1.48	95.67±1.57	94.45±1.24
8	92.34±0.9	93.13±1.18	90.76±0.34	94.90±0.48	96.38±1.26	98.96±0.82	97.45±1.82

Point are communicate as mean ±standard deviation (n = 3)

Discussion:

Formulations F1 to F7 of the in vitro drug release investigation were successfully finished. When compared to another formulation, Formulation F6's medication release time of 8 hours for 98.96% of patients was shown to be the most effective.

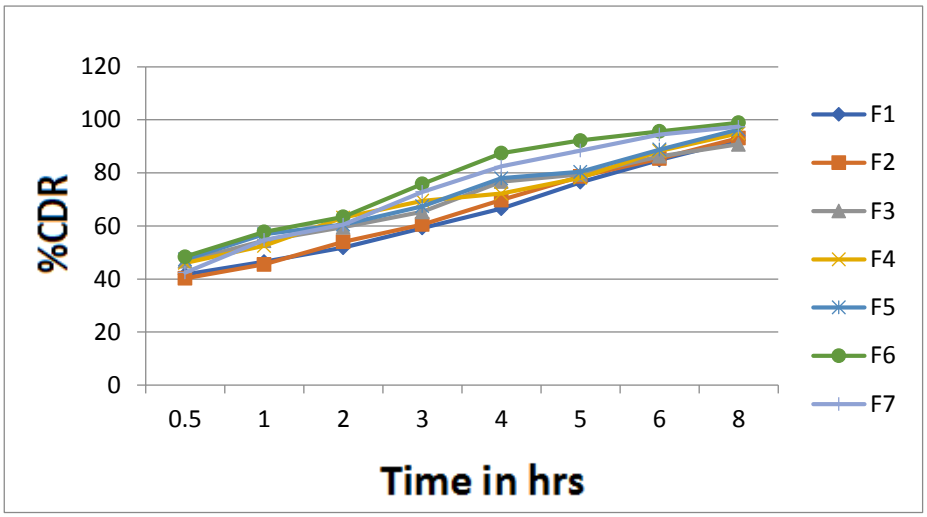

Fig.17: A Diagrammatically Representation of % Release Drug

Stability Studies:

Formulation F6 was deemed to be the best of the seven formulations based on the findings. Thus, stability experiments were conducted on formulation F6. Percentage yield, Drug content and in vitro drug release were measured for each month up to three months for Formulation F6. Results are reported in Table.20.

Table.18: Stability Study for Best Formulation F6

S. No.	Parameters	Initial	1 Month	2Month	3Month
2	Hardness	4.25±0.20	4.25±0.20	4.25±0.18	4.25±0.17
3	Friability	0.74±0.14	0.74±0.14	0.74±0.14	0.74±0.15
4	In-Vitro Drug Release	98.96±0.82	98.90±0.76	98.68±0.22	98.10±0.34
5	Drug Content Uniformity	99.86±1.18	99.81±1.12	99.10±1.09	98.90±1.11
6	Mucoadhesive strength	>13	>13	>12.5	>12

Discussion:

The duration of stability studies of the Formulation 6, there is no major variation, the minor variation found in Hardness, Friability and In vitro drug release, Drug Content Uniformity & Mucoadhesive strength that is adjustable, All data evaluated according to ICH guidelines at 40±2°C/75±5% RH for 90 days.

4. Conclusion

In the development of mucoadhesive tablet of antifungal drug Posaconazole to treat oral thrush locally β-cyclodextrin used as hydrophilic matrix to improve the solubility. Posaconazole is poorly water soluble drug hence β-Cyclodextrin was used to improve the solubility and bioavailability of drug, simultaneously enhances the erosion rate of tablet. Which increases the drug release and permeation through buccal mucosa? The formation of inclusion complex of Posaconazole with β-Cyclodextrin was confirmed by phase solubility studies. Co-precipitation method was used to prepare inclusion

complex of Posaconazole with β-cyclodextrin. The inclusion complex was characterized for compatibility studies. The results of compatibility studies reveal the successful complexation between Posaconazole and β-cyclodextrin. Mucoadhesive tablets of Posaconazole were prepared by direct compression method using altered concentrations of HPMC K4, Carbopol 934P and Maltose as polymers and Chitosan Polymer also used to enhance solubility. From the results concluded increase amount of polymers decreases the drug release at controlled rate. Formulation F6 was proved to most promising with the drug release time of 8hours 98.96%. Formulation F6 was subjected to stability testing at 45℃ & 75% RH and there is no significant change Observed. The outcome of the projected work is to designed mucoadhesive tablet of Posaconazole for controlled release in buccal mucosa. Posaconazole was chosen based on its indication for the treatment of oral Candidiasis refractory to other triazole derivatives.

5. References:

Seager, H., Drug delivery products and Zydis fast dissolving dosage form, 1998, 50, 375-382.

Bongomin F, Gago S, Oladele R, Denning D. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. J Fungi (Basel) 2017; 3: 57.

Gupta P, Gautam P, Rai N, Kumar N. An emerging hope to combat Candida albicans: plantbased therapeutics. Biotechnol Int 2012; 5: 85-114.

Calderone RA, Clancy CJ, editors. Candida and Candidiasis. Washington: American Society of Microbiology Press. 2012.

Hani U, Hosakote G, Vaghela R, Osmani RA, Shrivastava A. Candidiasis: a fungal infection-current challenges and progress in prevention and treatment. Infect Disord Drug Targets 2015; 15: 42-52.

Berkow EL, Lockhart SR. Fluconazole resistance in Candida species: a current perspective. Infect Drug Resist 2017; 10: 237-45.

Han Y, Ulrich M, Cutler J. Candida albicans mannan extract-protein conjugates induce a protective immune response against experimental candidiasis. J Infect Dis 1999; 179: 1477-84.

Cateau E, Rodier MH, Imbert C. Candidoses associées aux cathéters: Quelle place pour les verrous antifongiques [Could antifungal lock be useful in the management of candiasis linked with catheters] Med Sci (Paris) 2012; 28: 740-5.

Madhu P. Oral candidiasis. Int J Pharm Sci Invent 2013; 2: 3-6.

Guessous-Idrissi N, Essari A, Abdallaoui S, Youssouf M. Première identification de Candida dubliniensis au centre hospitalier universitaire Ibn Rochd de Casablanca, Maroc. J Mycol Med 2007; 17: 77-81.

Eggimann P, Que YA, Revelly J P, Pagani JL. Preventing invasive Candida infections. Where could we do better? J Hosp Infect 2015; 89: 302-8.

Seleem D, Pardi V, Mendonça Murata R. Review of flavonoids: a diverse group of natural compounds with anti-Candida albicans activity in vitro. Arch Oral Biol 2017; 76: 76-83.

Barnes PD, Marr KA. Aspergillosis: spectrum of disease, diagnosis & treatment external icon. Infect Dis Clin North Am. 2006 Sep; 20 (3):545-61.

Singh N, Bhalodiya NH. Allergic fungal sinusitis (AFS)–earlier diagnosis and management external icon. J Laryngol Otol. 2005 Nov; 119 (11):875-81.

Mario Jug and Mira Becirevic-Lacan. Influence of hydroxypropyl cyclodextrin complexation on piroxicamrelease from buccoadhesive tablets. Er. J. Pharm. Sci. 2004;21: 251–260.

Priyanka R, Murthy RS. Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: a potential approach for delivery of drugs having high first-pass metabolism. Drug Delivery 2013; 20:224-35.

Ranganathan T, Sudhakar Y, Chetty M. Buccal drug delivery from carvedilol polymeric mucoadhesive film. J Pharm Res 201; 4:3897-901.

Concetta G, Ayensu II, John JT. Development and characterization of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules. Int J Pharm 2012; 428:143–51.

Shirsand S, Suresh S, Keshavshetti G, Swamy P, Reddy PVP. Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using the simplex design method. Int J Pharma Investig 2012; 2:34-41.

Vamshi VY, Ramesh G, Chandrasekhar K, Bhanoji Rao ME, Madhusudan Rao Yamsani. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm 2007; 57:185–97.