FORMULATION AND EVALUATION OF POSACONAZOLE MUCOADHESIVE TABLETS

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Abstract

An attempt was made to design and develop mucoadhesive tablet formulation of posaconazole against candida albicans in immunocompromised pateints. Poorly soluble drugs are very challenging to formlate in oral mucoadhesive dosage form. Whereas lipophilic drugs, well absorbed through oral mucosa, but shows very low fluxes hence exhibit difficulty in transport across mucosa. The complexation of posaconazole with β- cyclodextrin was studied by phase solubility method which indicates the formation of complex with 1:1 stoichiometry. The muccoadhesive tablets for the delivery of posaconazole were prepared by compression using carbopol and HPMC. The assessment of buccal administration of posaconazole was analyzed by penetration through in-vitro excised goat mucosa. The results of experimented study reveals that, as there was increase in drug release rate from the tablets in solution as well as an increase in the amount of posaconazole permeated through sheep buccal mucosa. An attempt was made to study the suitability of posacanazole in buccal drug delivery system[1]

Keywords: *Posaconaole; β- Cyclodextrin; HPMC; Carbopol; Mucoadhesive.*

Introduction

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 immunocompromised 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. Oropharyngeal 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. [1]

Materials and Methods

Posaconazole was generously gifted by Ajanta Pharmaceuticals Ltd., Mumbai. β-Cyclodextrin was gifted by SA Pharmachem Pvt. Ltd., Mumbai. Hydroxypropyl methylcellulose K4M was obtained as a gift sample from Colorcon Asia Limited, Goa. Carbopol 934P was provided by Central Drug House India, ethyl cellulose (10cps), lactose DC was purchased from SD Fine Chem. Mumbai, India.

Method:

1. Formulation of inclusion complex.

Posaconazole and β-CDwere dissolved inwater and methanol. The two solutions were heated to 65^0C separately and mixed together. The mixture was cooled to 0^0C and allow to crystalized and filtered. The crystals were allowed to dry overnight.

2. Formulation of tablets.

Preparation: Mucoadhesive tablets of posaconazole were prepared byusing direct compression method. Inclusion complex powder accurately weighed 82 mg posaconazole was used for one tablet. The ingredients of formulationvizposocaconazole inclusion complex, polymers, lactose DC,talc and magnesium stearate were thoroughlymixed in mortar in geometrical proportions. The tablets were punched using suitable punching machine. Finally ethyl cellulose was used as backing layer for unidirectional release of drug.

Table-1: Formulations

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Posaconzaole inclusion complex powder	82	82	82	82	82	82	82	82	82
HPMC K4M	10	10	10	20	20	20	30	30	30
Carbopol 934P	5	10	15	5	10	15	5	10	15
Lactose DC	98.5	93.5	88.5	88.5	83.5	78.5	78.5	73.5	68.5
Magnesium stearate (2%)	3	3	3	3	3	3	3	3	3
Talc (1%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of mucoadhesive tablet of Posaconazole:

Uniformity of weight: Tablets selected randomly from each formulation was evaluated by placing it in an electronic balance. The percent deviation in weight of tablets was analyzed.

Hardness test: 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/cm^2.

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

Uniformity of drug content: Mortar and pestle were used to break the tablet into the powder. Then powered drug equivalent to 82 mg of active drug was placed in 100 ml flask. Mehtanol was used to extract the drug and sample was heated for half an hour. Finally the solution was filtered and the absorbance observed at 262 nm.

Friability test: 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.

Mucoadhesion strength:

Bioadhesive strength expressed in Newton, required for detachment of the tablet from the mucosa was determined using the fresh sheep buccal mucosa as mucosal substrate. The right pan was replaced with a lighter base [A] and on the left side a teflon ring [B] was hanged with a metallic wire [C and D]. A Teflon cylinder [E] of 1.5 cm diameter and 3 cm height was hanged with a metallic wire on the opposite side of this ring. The two sides were then balanced so that right hand side was exactly 5 g heavier than the left.Buccal mucosa hanged in upward. The tablet was attached on the mucosa by slightly moistening the surface. The balance was slowly raised upward with the help of slight rise in the weight.

Figure-1: Mucoadhesion

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.

Tablet surface pH test

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.

In vitro Dissolution studies

In vitro dissolution studies of buccal tablets of Posaconazole were carried out in USP TDT 06P tablet dissolution test apparatus-II, employing a paddle stirrer at 50 rpm using 900ml of pH 6.8 Phosphate buffer + 0.5% w/v SLS solution at 37 ±0.5ºC as dissolution medium. One tablet was used in each test. The samples were analyzed for drug release by measuring the absorbance at 262 nm using UV-Visible spectrophotometer after suitable dilutions.

Drug Permeation studies

Franz diffusion cell was used to carry out the study of drug permeation throught mucosal. Diffusion cells consist of two units, one containing the (Phosphate buffer) and the other containing glycol (receptor unit), separated by mucosal membrane. Hot plate was used to provide the constant heat to the assembly along with constant stirring. The tablet under test was kept in donor unit in contact with the receptor unit. The rate of diffusion was evaluated after 10 hours through mucosa.after specified amount of time the sample from receptor unit was analyzed for drug content by using UV spectrophotometer at 262nm.

Stability studies

Formulation F1 was found to be promising with all aspects of evaluation, hence performed stability studies at temperature of 40^0 C at 75 % RH, over a period of three months. kept in stability chamber maintained at $40^0 \pm 1^0$C & 75 % RH.

Figure-2: Drug permeation test

Results and discussion

The aim of this work was to develop a tablet for the buccal delivery of the poorly water-soluble drug Posaconazole, for that solubilization of Posaconazole by complexation with β-Cyclodextrin and then delivery via buccal mucosa using mucoadhesive tablets of Posaconazole to release drug at mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. To achieve optimum mucoadhesion HPMC K4M and Carbapol were used as polymers of choice.Whereas unidirectional release of drug from the tablet surface was designed by using ethyl cellulose as backing polymer.

.**Physiochemical Properties:**

The powder flow improved by the addition of lubricant in the formulation and exhibit excellent flow properties. Monsanto's hardnesstester was used to evaluate hardness of posaconazolemucoadhesive tablet and were found to be in the range of 4.10 to 4.61 kg/cm^2. Thickness was measured by Vernier caliper found to in the range of 2.6 to 3.0mm. The friability of tablet was observed in the range of 0.25 to 0.67 %. The tablets were evaluated for weight variations and percentagedeviation from mean weights were found to be in limits.

Swelling Index and Surrface pH:

In-vitro evaluation of water uptake by the surface of tablet were found to be significant to avoid changes in mechanical properties of final formulations. The swelling indices of the tablets were found to be parameters which affects the release of the drug from the tablet.The swelling indices of the formulations were found in order, $F_9>F_8>F_7>F_6>F_5>F_4>F_3>F_2>F_1$. The surface pH was found to be in the neutral range and ideal for minimal mucosal irritation.

Mucoadhesive Strength Measurement:-

Carbopol is an important polymer for mucoadhesion of the tablet to the mucosal linings. Hence the strength required to detach the tablet from mucosa is taken as mucoadhesion strength and the time noted as mucoadhesion time.Mucoadhesion strength decreased in the order: $F_9>F_6>F_3>F_8>F_5>F_2>F_7>F_4>F_1$. The mucoadhesion strength was due to interaction of bonds with mucin. Optimal mucoadhesion is achived by using combination of HMPC and carbapol.

Table -2: Evaluation of formulations

Formula-tion code	Mean Hardness Kg/cm^2	Thickness (mm)	Friability % w/w	Average weight (mg)	Mean drug content %±SD	SI ± SD (after 6 hrs)	Mucoadh esion (time of detachment hrs)	Tablet Suface pH
F_1	4.30	2.9	0.43	199.58	99.89 ± 1.30	20.74	>12	7.13
F_2	4.43	2.7	0.51	197.37	97.12 ± 1.12	31.31	>12	6.82
F_3	4.40	2.8	0.73	201.62	99.90 ± 0.71	49.35	>12	7.12
F_4	4.39	3.5	0.68	202.38	98.77 ± 0.08	57.52	> 12	6.97

F_5	4.30	3.2	0.73	200.89	99.14 ± 1.35	68.31	> 12	7.58
F_6	4.46	3.3	0.69	198.12	97.36 ± 0.68	72.36	> 12	6.23
F_7	4.38	3.8	0.72	201.08	98.09 ± 1.13	85.30	>12	6.15
F_8	4.50	2.9	0.68	200.56	97.39 ± 0.87	90.48	>12	6.78
F_9	4.39	3.5	0.69	199.94	97.87 ± 0.15	93.85	> 12	6.18

In vitro drug release study:
The dissolution test performed by using conventional dissolution test apparatus with pH 6.8 Phosphate buffer + 0.5% w/v SLS. Increased concentration of polymer reduces the drug release from the tablet. From the nine batches, formulation F_1 to F_2 have released 98to 100% drug in 10 hours. β-CD improves the drug release and solubility of posaconazole from the tablet. HPMC K4M and carbopol 934P responsible for controlled release of drug at predetermined rate. Among nine batches Formulation F1 has shown promising results.

In-vitro Drug permeation study of formulation F_1
The drug permeation is directly proportional to the drug release from the mucoadhesive tablet and bioavailability. The formulation F1 shows slow and steady drug permeation rate i.e. 78% in 10 hours.The addition of β- Cyclodextrin results in the improved drug permeation rate.β-Cyclodextrin used to improve the permeation and helps to carry the drug from aqueous media towards the lipophilic mucosal barrier.Posaconazole and β-Cyclodextrincomplex didn't penetrate the mucosa only it releases the free drug by establishing equilibrium.

Stability Studies
Formulation $F_1$was chosen to perform the stability testing and stored at 45±1°C for 3 months. The samples were analyzed the changes in physiochemical properties and appearance for specified time of intervals for 3 months. The formulation F_1did not showed significant changes hence proved to be stable throughout the period.

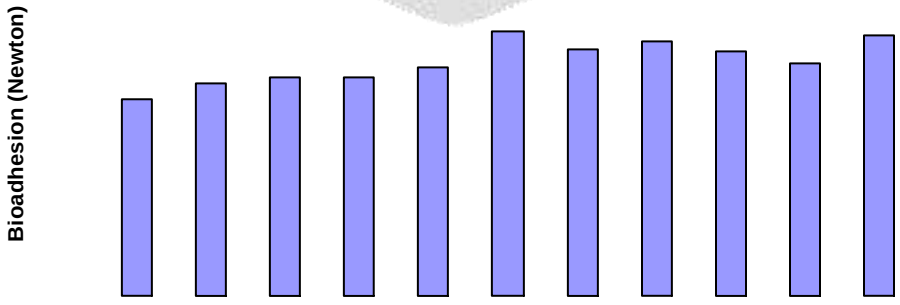

Figure- 3: Bioadhesive strength

measurement of Formulations

Table-3: Bioadhesive Strength

measurement.

FORMULATION CODE	BIOADHESIVE STRENGTH
	[Newton] [Mean, n=3]
F1	0.2902
F2	0.3129
F3	0.3608
F4	0.3820
F5	0.3949
F6	0.3581
F7	0.3228
F8	0.3919
F9	0.3400

Table-4: In-vitro Drug permeation study of formulation F_1

.	**Cumulative Percentage of Drug permeated across sheep buccal mucosa ±SD**										
FORMU L-ATION	**0.5 hr**	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**7 hr**	**8 hr**	**9 hr**	**10 hr**
F_1	12.12±1.30	16.36±1.18	21.32±1.09	27.10±1.13	31.81±1.31	35.91±1.08	46.66±1.36	58.66±1.36	69.87±1.22	75.55±1.67	79.47±2.11

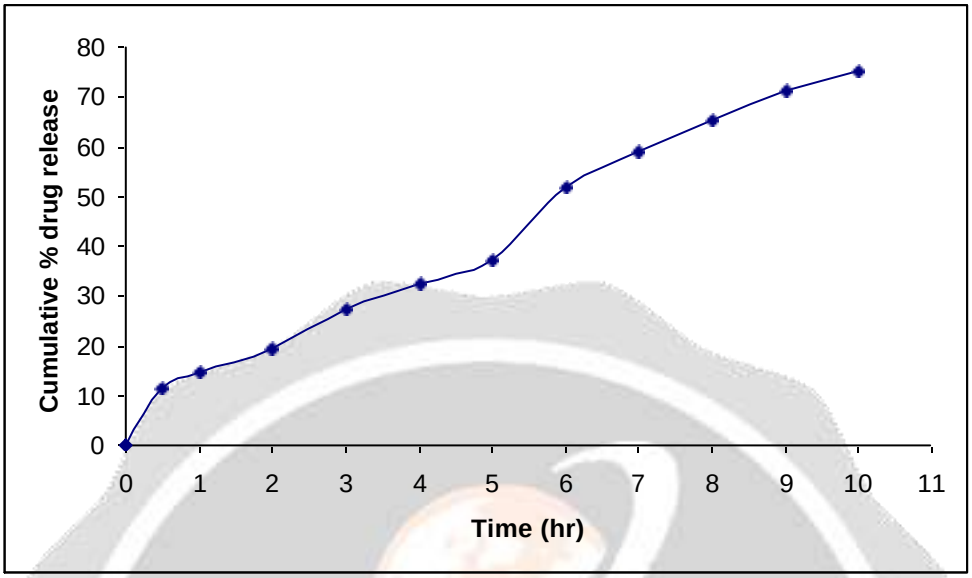

Figure -4: Cumulative Percent Drug permeated across sheep buccal mucosa Vs Time Plots (Zero Order) of formulations F_1

Table-5: In-vitro Drug release

	Cumulative Percentage of Drug released ±SD										
FORMUL-ATION	0.5 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr	9 hr	10 hr
F_1	10.13±1.15	15.10±1.45	28.52±1.69	40.69±1.18	51.33±1.33	62.70±1.12	73.22±1.12	88.62±1.11	96.01±1.21	99.10±1.33	99.89
F_2	09.33±1.22	14.81±1.33	25.51±1.15	35.30±1.33	46.55±1.33	59.14±1.01	68.28±0.13	76.12±1.24	86.98±1.32	90.13±1.66	94.16±1.70
F_3	08.33±1.11	13.28±1.26	27.90±1.12	33.22±1.22	41.22±1.11	49.28±1.43	58.22±1.11	65.19±1.77	71.22±1.21	77.16±1.32	85.21±1.22
F_4	09.13±1.22	13.38±1.44	19.20±0.56	27.63±1.69	39.41±1.43	43.39±1.55	57.33±0.46	63.23±1.54	69.18±1.74	78.31±1.33	83.48±1.32
F_5	07.52 ±1.22	13.31±0.73	22.02±1.12	30.41±1.98	36.61±1.22	43.52±1.24	51.73±1.23	59.82±0.44	63.12±0.63	70.59±1.66	79.00±1.01
F_6	10.71±1.09	13.24±1.52	19.55±1.53	27.08±1.08	36.15±1.15	40.16±1.66	48.41±0.56	55.70±1.30	61.90±0.31	69.68±0.30	73.20±1.24
F_7	12.91±1.24	17.31±0.98	23.41±0.23	31.62± 1.86	35.55± 1.91	41.63± 1.41	47.18± 1.14	53.59 ± 0.55	60.38± 1.56	65.18± 1.06	71.19± 1.99
F_8	11.45± 1.23	17.53± 1.57	23.38 ±1.79	31.38± 1.33	38.65± 0.46	48.78± 1.25	53.08± 0.52	59.08± 1.33	63.29± 2.16	69.32± 0.65	78.56± 1.23
F_9	09.05± 1.47	11.29 ±1.98	19.85± 1.82	25.32± 0.53	29.50± 1.21	36.54± 1.07	46.62± 1.23	58.64± 1.51	68.71±0.43	72.63± 1.57	79.81±0.52

data of formulations

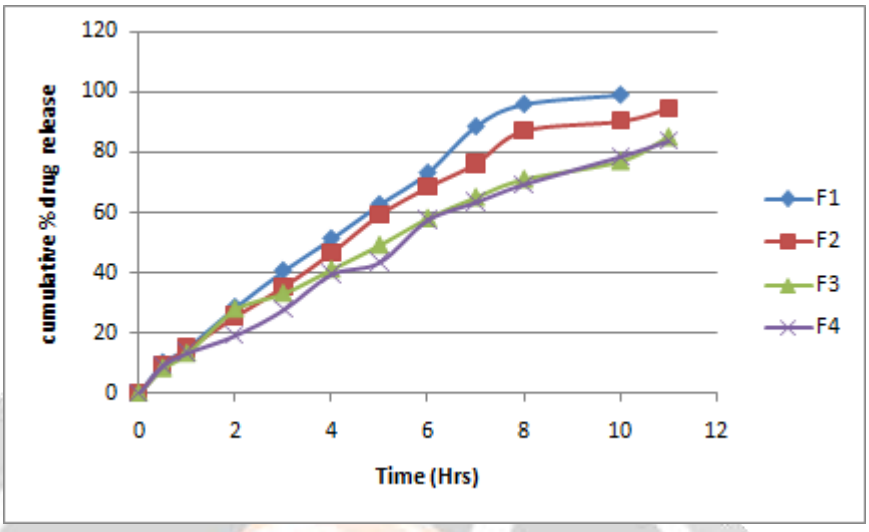

Figure -5: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of formulations F1,F2,F3& F4

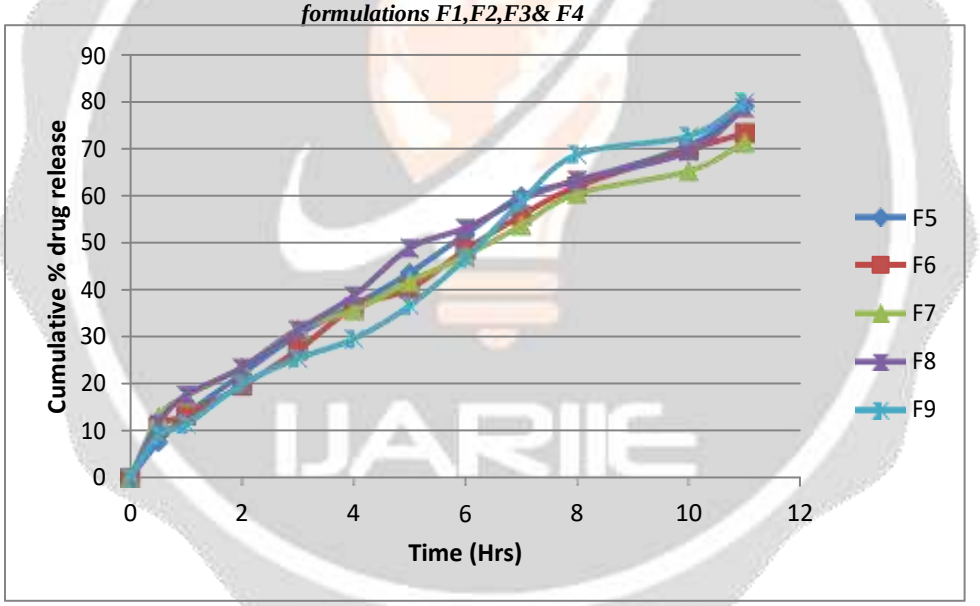

Figure -6: Cumulative Percent Drug Released Vs Time (Zero Order) of formulations F_5, F_6, F_7, F_8, and F_9 Table - 6: Kinetic Data of Formulations

FORMULATION	CORRELATION COEFFICIENT [R]			
	Zero Order	First Order	Higuchi's Equation	Peppas Equation
F_1	0.9812	0.1322	0.9169	0.8550
F_2	0.9713	0.1425	0.9695	0.9214
F_3	0.9556	0.1258	0.9865	0.9586
F_4	0.9875	0.1789	0.9789	0.9248
F_5	0.9689	0.8896	0.9556	0.8756

F_6	0.9856	0.1475	0.9755	0.8147
F_7	0.9332	0.1586	0.9758	0.8456
F_8	0.9875	0.1458	0.9778	0.8796
F_9	0.9478	0.1245	0.9875	0.8147

Table – 7: Dissolution and Swelling Index Parameter

Formulation code	Variable level in coded form		$t_{50\%}$ (hours)	$t_{70\%}$ (hours)	SI (after 6 hours)	Cumulative percent drug release in 10 hours
	X_1	X_2				
F_1	-1	-1	4.1	4.9	20.74	99.89
F_2	-1	0	4.3	5.5	31.31	94.16
F_3	-1	+1	5.3	7.3	49.35	85.25
F_4	0	-1	5.8	7.3	57.52	83.48
F_5	0	0	4.9	8.2	68.31	79.00
F_6	0	+1	5.3	7.5	72.36	73.20
F_7	1	-1	5.9	8.0	85.30	71.19
F_8	1	0	6.0	8.7	90.48	78.56
F_9	1	+1	6.5	8.6	93.85	79.81

Table - 8: In vitro Release Data of the Stability Formulation (F_1)

Time (Hrs)	Cumulative* Percent of Drug Released ± SD at 45 ± 1^0C	
	1st Day	**90th Day**
01	12.15±1.24	11.55±1.35
02	19.00±1.25	15.75±1.97
03	25.31±1.30	26.99±1.08
04	33.15±1.20	35.49±1.42
05	49.54±1.25	51.88±0.76
06	60.10±1.12	63.56±1.58
07	79.12±1.42	83.25±1.90
08	85.12±1.33	89.12±1.84
09	92.01±1.31	95.15±1.68
10	97.99±1.21	98.18±1.36

*Average of three determinations

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 solublility. 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 reveals the successful complexation between posaconazole and β-cyclodextrin. Direct compression method was used to prepare the mucoadhesive tablets of posaconazole using HPMC, carbapol and ethyl cellulose.From the results concluded increase amount of polymers decreases the drug release at controlled rate. The formulations were followed zero order kinetics by Most of the designed formulations of Posaconazole buccal tablets displayed zero order release kinetics by non – Fickian diffusion mechanism. Formulation f1 was proved to most promising with the drug release time of 10hours 99.41%.Formulation F1 was subjected to stability testing at 45^0C & 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.

References

1. Mario Jug and Mira Becirevic-Lacan. Influence ofhydroxypropyl-_-cyclodextrin complexation on piroxicamrelease from buccoadhesive tablets. Er. J. Pharm. Sci. 2004;21: 251–260.
2. Narendra C et al. Development of three layered buccalcompact containing metoprolol tartrate by statisticaloptimization technique. Int. J. Pharm. 2005:304:102-114.
3. Esclusa-Diaz M T. et al. Characterization and in vitrodissolutionbehaviour of ketoconazole / b-and 2- hydroxypropyl-b-cyclodextrin inclusion compounds. Int. J.Pharm. 1996; 143: 203-210.
4. Vergnaud JM. Liquid transport controlled release processes inpolymeric materials: Application to oral dosage forms. Int. JPharm. 1993; 90:89-94.
5. Shoufeng Li et. al. Statistical optimization of gastric floatingsystem for oral controlled delivery of calcium. AAPS Pharm.Sci. Tech. 2001; 2(1): 10-16.
6. Munasur A.P. et al. Statistical optimisation of themucoadhesivity and
7. characterisation of multipolymericpropranolol matrices for buccal therapy. Int. J Pharm. 2006;323: 43–51.
8. Higuchi T., Connors K.A., Phase-solubility techniques, Adv.Anal.Chem.Instr., 4, 117-122, (1965).
9. Swami PV, Kinagi MB, Biradar SS, GadaSN,Shilpa H. Design and evaluation of buccalbilayer tablets of granisetron hydrochloride. IntJPharmSci Res 2010; 1(8):104-110.
10. 9. Satyabrata B, Ellaiah P, Mohanty C, Murthy KVR,Bibhusan P, Kumar PS. Design and invitroevaluation of mucoadhesive buccal tablets ofperindopril prepared by sintering technique. IntJPharmTech Res 2010; 2(3):1810-23.
11. Indian pharmacopoeia. Delhi. The IndianPharmacopoeia Composition. 2007; p: 731-34.
12. Derle D, Joshi O, Pawar A, Patel J, JagadaleA.Formulation and evaluation of buccoadhesivebi-layer tablet of propranalol hydrochloride. IntJPharmSci 2009; 1(1):206-12.

13. Emami J, Varshosaz J, Saljoughian N. DARU 2008;16(2):60-9.23) Vaidya VM, Manvar JV, Mahjan NM, SakarkarDM. Design and invitro evaluation ofmucoadhesive buccal tablets of terbutalinesulphate.Int J PharmTech Res 2009;1(3):588-97.
14. Guda A, Gudas GK, Bingi M, DebnathS,Rajesham VV. Design and evaluation ofcontrolledrelasemucoadhesive buccal tabletsoflisinopril. Int J Pharm Res 2010;2(4):24-7.
15. Rowe RC, Sheskey PJ, Weller PJ. Handbook ofpharmaceuticalexcepients.4th ed. UK.Pharmaceutical press.2003; p.89, 297, 97, 283.
16. Senthil A, Narayanaswamy VB, Ajit I, GalgeDS,Bhosale RS. Mucoadhesive microspheres.IndJResAyur 2011; 2(1):55-9.5) Hao J, Heng PWS.Buccal delivery systems.DrugDevInd Pharm. 2003;29(8):821-32