To study of drug for mucoadhesive buccal drug delivery system.

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Abstract:

Nebivolol is cardio selective β-blocker used in the management of hypertension. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Nebivolol undergoes extensive metabolism in the liver after its oral administration and resulting in to a very poor (approximately 12%) bioavailability. Oral administration of nebivolol can also cause gastrointestinal disturbance and abdominal or stomach pain etc. So in order to improve the bioavailability, efficacy and to minimize the side effects associated with oral administration, we planned to prepare mucoadhesive buccal films of Nebivolol. In the present piece of research work, nebivolol buccal films were prepared using mucoadhesive polymers like HPMC k 15, EC & PVP K 30 by solvent casting technique. Buccal films were characterized for number of parameters like physical appearance & surface texture, weight uniformity, thickness, folding endurance, swelling index, mucoadhesive strength, surface pH, drug–excipient interaction study, drug content uniformity and *In- vitro* drug release study.*In- vitro* drug release studies showed better results at the end of 8th hrs. The release profile of the all formulations were subjected to various kinetic equations like Highuchi diffusion equation ($Q=Kt^{1/2}$) and Peppas exponential equation ($Q=Kt^{n}$). The regression coefficient value of this equation are very nearer to one (1) suggesting that plots are fairly linear and slope value of the Peppas equation is more than one (>1) in all the cases suggesting that the drug was released by diffusion mechanism following super case-II transport. From the result and conclusion of the research work we can summarize that nebivolol can be delivered via buccal route bypassing metabolism in gut and liver and improving the systematic Bioavailability.

Keywords: Nebivolol HCL, Buccal Films, Evaluations, *In-vitro* drug release.

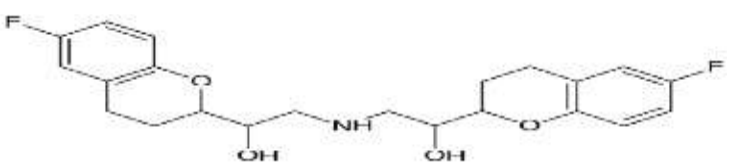
Introduction :

The oral route is the most preferred route of drug delivery as it is convenient, inexpensive and versatile. However, drug delivery by this route has certain disadvantages such as first-pass metabolism by the liver and gastrointestinal enzymatic degradation of the drug. Therefore, other transmucosal routes such as nasal, rectal, vaginal, ocular and oral mucosae are being considered as alternatives to conventional oral dosage forms for drug delivery to avoid the above disadvantages associated with conventional oral delivery (i.e., tablets, capsules, syrups, etc.). Of these routes of delivery, the buccal oral mucosa has emerged as one of the target sites for administration of drugs in a wide variety of dosage forms, particularly for those drugs targeted for local delivery in the oral cavity and systemic absorption. The buccal route of drug delivery provides the opportunity for drug absorption through the buccal epithelial lining of the oral cavity (mucosa of the cheek) for it to exhibit its action locally or systemically. The non-invasive nature of administration, ease and convenience of administration, precise localization and increased permeability of the buccal mucosa compared to other transepithelial routes makes this a promising route of delivery. Also, the rich supply of blood vessels and lymphatics in the buccal mucosa results in rapid onset of drug action for those that have the requisite physicochemical profile.

Method and materials:

Drug profile : 1. Nebivolol hydrochloride

Structure-



Molecular formula: C_{22} H_{25} F_2 NO_4. HCL**, Molecular weight:** 441.90

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Materials:

Table no. 01: list of materials

Sr. No.	Materials	Property	Source
1.	Nebivolol HCL	Pure Drug	Yarrow Chem product, Mumbai.
2.	Hydroxypropyl methyl cellulose k 15	Film former	LOBA Chemie PVT.LTD Mumbai.
3.	Ethyl cellulose	Film Former	OTTO kemi, Mumbai.
4.	PVP k- 30	Film Former	Research Lab fine Chem Industries, Mumbai.
5.	Propylene glycol	Plasticizer	S. d. fine. CHEM Limited Mumbai.
6.	Sodium hydroxide	Used in the preparation of Buffer	MEHER CHEM, Mumbai.
7.	Potassium dihydrogen Orthophosphate		HiMedia lab pvt. Ltd , Mumbai.
8.	Ethanol	Solvent	LOBA Chemie PVT.LTD Mumbai.

Table no.02: list of Equipment

Sr. no	Instrument	Manufacturer
1.	UV Visible spectrophotometer	Shimadzu (UV 1800)
2.	Digital balance	Sartorius
3.	Digital pH Meter	Systronics
4.	Sonicator	Remi R8C life care Equipment pvt. Ltd. Mumbai.
5.	In vitro diffusion apparatus (Franz diffusion cell)	Molded
6.	Mechanical stirrer	Remi motors, Ahmadabad.
7.	Magnetic stirrer	Remi motors, Ahmadabad.
8.	FTIR spectrophotometer	Bruker
9.	Digital melting point apparatus	CL 725/726,Microcontrollerbased melting point apparatus
8.	Screw Guage	Remi motors, Ahmadabad.
9.	USP Disintegration apparatus	Inco Instruments, Mumbai.

❖ **METHODOLOGY-**

1.Assay determination by liquid chromatoghaphy :

Chromatographic system: A stainless steel column 25 cm × 4.6 cm packed with porous silica with chemically bonded phenyl groups (5µm), Mobile phase: a mixture of 28 volumes of acetonitrile, 72 volumes of a buffer solution prepared by dissolving 3.4 g of tetrabutylammonium hydrogen sulphate in 1000 ml of water and 0.3 volume of diethyl amine, Flow rate: 1ml per min, Spectrophotometer set at 282 nm, Injection volume: 20 µl, Test

solution: Dissolve 35 mg of substance under examination in 5 ml of acetonitrile and dilute to 50 m with the mobile phase. Dilute 10 ml of this solution to 100 ml with the mobile phase.
Reference solution : Dissolve 35 mg off nebivolol HCL RS in 5 ml of acetonitrile and dilute to 50 m with the mobile phase. Dilute 10 ml of this solution to 100 ml with the mobile phase.

2. Construction of calibration curve in methanol:

Standard calibration curve of nebivolol: The standard calibration curve for nebivolol was prepared using methanol.**Standard solution:** 1oo mg of nebivolol was dissolved in 100 ml methanol to give a concentration of mg/ ml (1000 µg/ml)

Stock Solution: From standard solution was taken 1 ml of solution and diluted with methanol to 50 ml to produce the 20 µg/ml concentration. From the solution aliquots of 4, 6, 8 and 10, 20 µg/ml of stock solution were pipetted out in 10 ml volumetric flask. The volume was made up with methanol to produce concentrations as 4, 8, 12, 16 and 20 µg/ml of nebivolol respectively. The absorbances of prepared solution of nebivolol were measured at 282 nm in Shimadzu UV/visible 1700 spectrophotometer against methanol as blank. The absorbance data for standard calibration curve in methanol is given in (Table no 10). The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 4 to 20 µg/ml

3. Construction of calibration curve in phosphate buffer

Standard calibration curve of nebivolol:

The standard calibration curve for nebivolol was prepared usingphosphate buffer pH 6.8.**,Standard solution:**10 mg of nebivolol was dissolved in 10 ml methanol to give a concentration of 1 mg/ ml (1000 µg/ml).**Stock Solution:** From standard solution was taken 1 ml of solution and diluted with 50 ml of phosphate buffer of pH 6.8 to produce the 20 µg/ml concentration. From the solution aliquots of 4, 6, 8 and 10, 20 µg/ml of stock solution were pipetted out in 10 ml volumetric flask. The volume was made up to with buffer to produce concentration as 4, 6, 8, 10, and 20 µg/ml of nebivolol respectively. The absorbances of prepared solution of nebivolol was measured at 282 nm in Shimadzu UV/visible 1700 spectrophotometer against phosphate buffer pH 6.8 as blank.
The absorbance data for standard calibration curve is given in (Table no.11))The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 4 to20 µg/ml.

4. preparation of blank buccal films [59]

Matrix type Mucoadhesive buccal patches composed of different ratios of polymers with drug were prepared by solvent casting method. Accurately weighed quantities of polymers, solvent system, and Penetration enhancer. In 5 ml mixture of chloroform and methanol (1:1) were dissolved, different concentrations of polymers, plasticizer and penetration enhancer on magnetic stirrer until clear solution obtained. Solution was then casted into petridishes then kept aside at room temperature for 24 Hrs .After drying films were removed with the help of sharp blade and kept in desiccator for 24 hrs then cut into pieces of the desired shape and size.

Table no.03: Formulation Details of Blank Films

Formulation Details	Polymer & its concentration (% w/v)				Plasticizer* conc. (% w/w)	Remarks
	HPMC	EC	PVP	EUDRAGIT	Propylene Glycol	
F_1	150	150	--	--	30%	+++
F_2	150	--	150	--	30%	+++
F_3	120	180	--	--	30%	+++
F_4	150	--	--	150	30%	++
F_5	--	150	--	150	30%	+
F_6	180	120	--	--	30%	+++
F_7	----	----	180	120	30%	+
F_8	120	----	180	--	30%	+++
F_9	120	----	--	180	30%	++
F_{10}	180	--	120	--	30%	+++
F_{11}	200	100	---	--	30%	+++
F_{12}	---	100	--	200	30	+
F_{13}	200	--	100	---	30	+++

F_{14}	100	200	----	----	30	+++
F_{15}	100	----	200	--	30%	+++

d) Preparation of nebivolol buccal films (Drug Incorporated films) [60].

Table No.04 The detailed composition of the nebivolol films

Formulation Code	Polymer Concentration (%w/v)			Plasticizer* Concentration (%w/w)
	HPMC K 15	EC	PVP K 30	Propylene Glycol
BFN_1	180	-	120	30
BFN_2	180	120	-	30
BFN_3	120	-	180	30
BFN_4	250	-	50	30
BFN_5	200	-	100	30
BFN_6	150	-	150	30
BFN_7	120	180	-	30
BFN_8	200	100	-	30
BFN_9	100	200	-	30
BFN_{10}	150	150	-	30

e) Evaluation of nebivolol buccal films [61-66]

The nebivolol buccal films were evaluated for the following properties:

1.Physical properties- Physical appearance and surface texture, Weight uniformity, Thickness uniformity, Folding endurance, Swelling index, Surface pHs.

2. Mechanical properties-Mucoadhesive strength, *In- vitro* residence time

3.Evaluation of nebivolol buccal films for Drug content uniformity

i)Physical appearance and surface texture of film:

These parameters were checked simply with visual inspection of patches and evaluation of texture by feel or touch.

ii) Weight uniformity:

Three films of 10mm diameter each of every batch were weighed individually using Shimadzu digital balance and the average weight was calculated.

iii) Thickness uniformity:

The thickness of the films was measured using screw gauge with a least count of 0.01mm at three different spots of the films and the average thickness was calculated.

iv) Folding endurance:

The flexibility of films can be measured quantitative in terms of folding endurance; folding endurance of the films was determined by repeatedly folding a small strip of the films at the same place till it broke. The number of times films could be folded at the same place without breaking gives the value of folding endurance and the procedure was repeated for three times.

v) Swelling index:

A buccal film of 10 mm diameter was weighed on a pre- weighed cover slip, the initial weight of the film was recorded (W_0) and then it was kept in a petridish containing 5 ml of phosphate buffer pH 6.8.kept it for 8hrs and excess of water was carefully removed and swollen films were re-weighed (W_t). The experiment was repeated three times. Then the percentage swelling was calculated by following formula

$$\% S = \frac{W_t - W_0}{W_0} \times 100$$

vi) Surface PH:

The film was allowed to come in contact with 1ml of phosphate buffer for 1-3 min then the surface pH was measured using pH meter and the procedure was repeated for three times.

vii) *Ex- vivo* Mucoadhesive strength:

Fresh sheep buccal mucosa was obtained from a local slaughterhouse; the mucosal membrane was separated by removing the underlining fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer (IPB) solution of 6.8 pH at 37^0C. Mucoadhesive strength of the film ware measured on modified physical balance.

viii) *In- vitro* residence time of films:

The *in-vitro* residence time was determined using a locally modified USP disintegration test apparatus (Photograph-2). A segment of sheep buccal mucosa of 3 cm long was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive films were hydrated from one surface using 15 µl IPB and then the hydrated surface was brought into contact with the mucosal membrane.

The glass slab was vertically fixed to the apparatus and allowed to move up and down in 800 ml isotonic phosphate buffer pH 6.8 (IPB) maintained at 37^0 C, so that the film was completely immersed in the buffer solution at the lowest point and was out at highest point. The time taken for the complete erosion or detachment of the films from the mucosal surface was recorded (mean of triplicate determinations) in table No.

ix) Drug-excipient interaction study of films:

There is always a possibility of drug-excipient interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipient interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug nebivolol and polymer.

x) In vitro permeation study:

Preparation of egg membrane from egg:

Place fresh egg in distilled water, pour Conc HCl on it keep it for 3 to 4 hrs so that outer thick layer precipitates and is converted into thin membrane. Remove the yellowish material by making a small cut on the membrane. Soak this membrane for a period of 24 hrs in phosphate buffer pH 6.8 The in vitro buccal permeation study of nebivolol buccal film(patch) through egg membrane was performed using Franz diffusion cell at 37 ºC ± 0.2ºC. Freshly egg membrane was mounted between the donor and receptor compartments.

Procedure:

1.Fill the receptor compartment with diffusion media (Phosphate buffer pH 6.8).

2. Place the egg membrane above the receptor compartment, no bubble should from between the fluid and egg membrane.

3.The film 20mm was placed on egg membrane towards donor compartment and compartments were clamped together and Stir the diffusion fluid by using magnetic stirrer at 50 rpm.

4. Remove 1ml sample from receptor compartment through sampling port with the help of pipette at predetermined intervals and replaced with fresh phosphate buffer solution to maintain sink condition.

5. Dilute the withdrawn 1ml sample with phosphate buffer pH 6.8 up to 10 ml using 10 ml volumetric flask

6. Measure the absorbance at 282 nm by UV spectrophotometer and determine the % cdr by using equation of standard calibration curve.

Result and Discussion-

Table no.05 : Standard calibration data of nebivolol in methanol at 282 nm.

Sr.No	Conc (mcg/ml)	Absorbance ± SD
1	0	0 ± 0.00
2	4	0.056 ± 0.00102
3	8	0.096 ± 0.0095
4	12	0.144 ± 0.01184
5	16	0.192 ± 0.00784
6	20	0.23 ± 0.00429

Fig no 01: Standard calibration data curve of nebivolol in methanol at 280 nm.

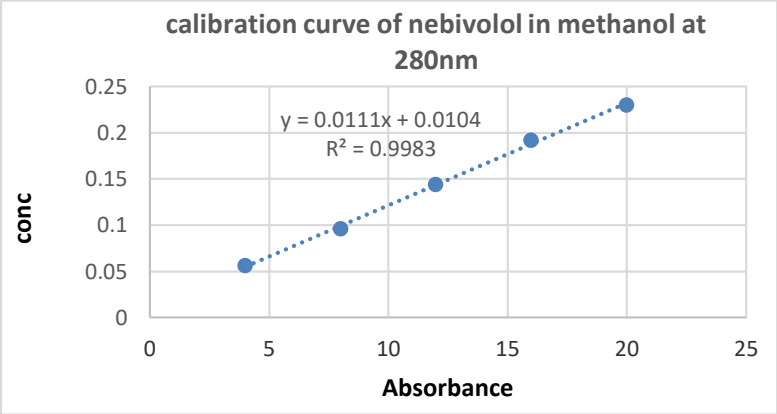

Table no.06: Standard calibration data of nebivolol in phosphate buffer (pH 6.8) at 282nm.

Sr.No	Conc (mcg/ml)	Absorbance with ± SD
1	0	0± 0.00
2	4	0.067 ± 0.0024
3	8	0.097 ± 0.00345
4	12	0.144 ±0.00348
5	16	0.183 ± 0.00495
6	20	0.273 ± 0.00733

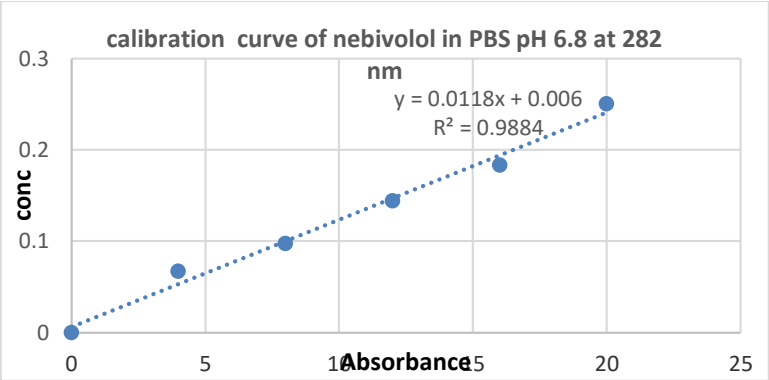

Fig no.02: Standard calibration data curve of nebivolol in phosphate buffer pH 6.8 at 282nm

PREFORMULATION STUDIES

Table no.07-Physicochemical parameters of Nebivolol:

Melting point	PKa	Partition Coefficient	Solubility	Assay
220-222 ^{0}C.	9.6	0.16	Soluble in methanol, , dimethylsulfoxide, Sparingly soluble in Ethanol, very slightly soluble in hexane	Determined by Liquid Chromatography and the nebivolol drug 98% pure

Drug-excipients compatibility studies

Table no-8: FT-IR spectrum and values

SR NO	IR SPECTRUM	GROUPS	PEAKS (Cm^{-1})	STRECHING / DEFORMATION
1.	NEBIVOLOL HCL	OH	3562	STRECHING
		CH_2	2964	STRECHING
		C=O	1664	STRECHING
		NH	1502	STRECHING
		C-O	1037	STRECHING
		R_2C = CHR	833	STRECHING
		CO	1247	STRECHING
2.	PHYSICAL MIXTURE OF PURE DRUG AND HPMC	CO	1240	STRECHING
		CH_2	2970	STRECHING
		C=O	1766	STRECHING
		R_2 C=CHR	830	STRECHING
		C-O	1030	STRECHING
		OH	3558	STRECHING
3.	PHYSICAL MIXTURE OF PURE DRUG AND PVP K 30	CH_2	2964	STRECHING
		C-O	1035	STRECHING
		R_2C = CHR	835	STRECHING
4.	PHYSICAL MIXTURE OF PURE DRUG AND EC	CH_2	2930	STRECHING
		C-H	2830	STRECHING
		C=O	1750	STRECHING

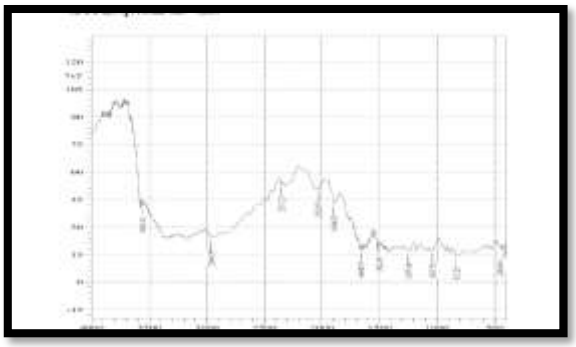

Fig no : 03. I R Spectrums Of Pure Nebivolol Drug

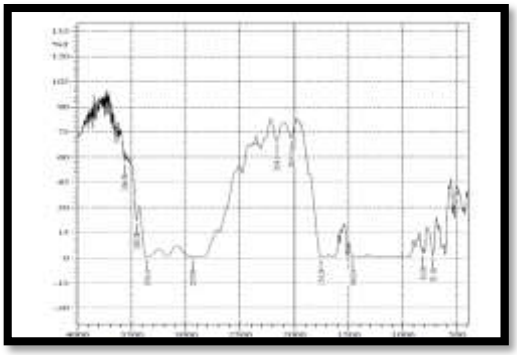

Fig no : 04 I R Spectrum Of Physical Mixture Of Pure Drug and HPMC K 15

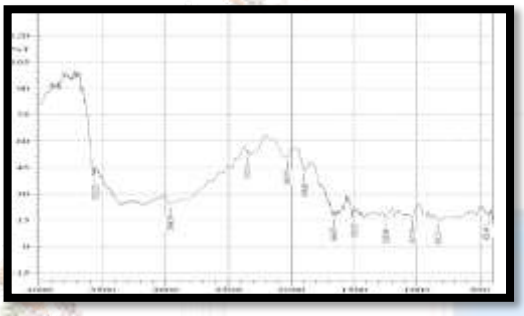

Fig no: 05 I R Spectrum Of Physical Mixture Of Pure Drug And EC

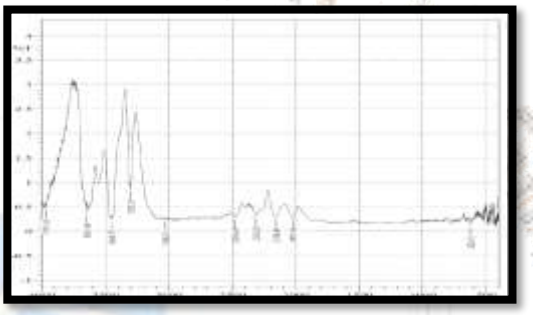

Fig no.06: I R Spectrum Of Physical Mixture Of Pure Drug And PVP

Result of weight uniformity

Table- no 9: Weight uniformity of various nebivolol buccal films prepared using polymers.

Formulation Code	Weight of film (mg)			Average mg ± SD
BF1	7	6	6	6.33 ± 0.277
BF 2	13	14	15	14.00 ± 100
BF 3	11.8	10	11	11.33 ±0.477
BF 4	13.8	13.7	12.9	13.33 ± 0.577
BF 5	17.6	18.1	18.3	18.00 ± 0.608
BF 6	16.8	17	16.5	16.435 ± 0.693
BF 7	15.3	14.8	14.8	14.96 ± 0.598
BF 8	16.8	17	16.5	16.43 ± 0.638
BF 9	10.8	10.7	10.9	10.85 ± 0.393
BF 10	11.6	11.1	11.3	11.4±0.460

Result of Thickness

Table no 10: Thickness of various nebivolol buccal films prepared using polymers.

Formulation Code	Thickness of film (mm)			Average thickness ± SD
BF1	0.061	0.080	0.075	0.072 ± .0098
BF 2	0.17	0.15	0.15	0.156 ± 0.0152
BF 3	0.09	0.12	0.12	0.12±0.0115
BF 4	0.12	0.14	0.15	0.136 ± 0.0152
BF 5	0.23	0.25	0.26	0.243 ± 0.0208
BF 6	0.25	0.26	0.28	0.203± 0.0378
BF 7	0.15	0.14	0.15	0.126 ± 0.012
BF 8	0.22	0.21	0.20	0.20 ± 0.024
BF 9	0.19	0.20	0.19	0.19± 0.0192
BF 10	0.15	0.16	0.18	0.16 ± 0.037

Result of Folding Endurance

Table no 11: Folding endurance of various Nebivolol buccal films prepared using polymers.

Formulation code	Folding in durance			Average folding endurance ± SD
BF 1	310	290	298	299 ±2.964
BF 2	280	270	260	270 ± 2.764
BF 3	301	302	304	302 ± 4.1633
BF 4	302	301	302	302 ± 3.6055
BF 5	301	302	300	310 ± 3.6055
BF 6	304	302	304	304 ± 3.741
BF 7	260	270	275	268 ± 2.6075
BF 8	302	304	304	304 ± 3.1733
BF 9	290	280	260	276 ± 2.8075
BF 10	265	268	265	265 ± 2.5166

Result of Swelling Index

Table no 12: Swelling Index of various Nebivolol buckle films prepared using polymer

Formulation code	Swelling index of film (%)			Average index % ± SD
BF1	24.87	23.56	24.98	24.47 ± 1.971
BF 2	30.45	30.56	31.87	30.96 ± 2.450
BF 3	34.87	35.56	36.43	35.93± 2.966
BF 4	40.87	41.23	40.76	40.95 ± 3.246
BF 5	46.65	48.98	48.64	48.09 ± 4.168
BF 6	40.23	41.12	41.24	41.19 ± 3.960
BF 7	31.06	30.98	32.45	31.10 ± 2.531
BF 8	35.78	36.43	36.00	36.02 ± 2.943
BF 9	30.09	30.78	30.98	30.61 ± 2.493
BF 10	37.06	35.23	34.23	35.50 ± 2.951

Table no 13 : Surface pH of various Nebivolol buccal films prepared using polymers.

Formulation code	Surface pH			Average surface pH ± SD
BF 1	6.50	6.52	6.51	6.51 ± 0.205
BF 2	6.71	6.70	6.71	6.71 ± 0.255
BF 3	6.78	7.20	6.84	6.64 ± 0.227
BF 4	7.10	6.26	6.46	6.90 ± 0.438
BF 5	6.79	6.80	6.81	6.82 ± 0.420
BF 6	6.82	6.88	6.86	6.83 ± 0.428
BF 7	6.60	6.59	6.61	6. 61 ± 0.268
BF 8	6.70	6.71	6.71	6.71± 0.284
BF 9	6.64	6.60	6.70	6.66 ± 0.252
BF 10	6.68	6.67	6.68	6.68 ± 0.255

Result of Mucoadhesive Strength

Table no 14: Mucoadhesive strength of various nebivolol buccal films prepared using polymers.

Sr no	Mucoadhesive strength (mg)			Average mucoadhesive strength ± SD
BF 1	2.7	2.8	2.7	2.7 ± 0.125
BF 2	3.7	3.5	3.6	3.6 ± 0.225
BF 3	2.8	2.7	2.6	2.75 ± 0.135
BF 4	4.8	4.7	4.8	4.76 ± 0.357
BF 5	5.0	5.1	5.0	5.0 ± 0.453
BF 6	4.8	4.6	4.4	4.2 ± 0.315
BF 7	3.2	3.3	3.1	3.2 ± 0.200
BF 8	4.9	4.8	4.9	4.9 ± 0.365
BF 9	3.9	4.0	4.1	4.0 ± 0.305
BF 10	4.0	4.1	4.1	4.1 ± 0.313

Result of *In- vitro* Residence Time.

Table no15: *In- vitro residence* time of various nebivolol buccal films prepared using polymer

Sr no	*In vitro- residence* time(Hrs)			Average residence time ± SD
BF 1	2.05	2.15	2.11	2.10 ± 0.1502
BF 2	2.32	2.25	2.28	2.27 ± 0.1617
BF 3	3.24	3.22	3.27	3.23 ± 0.2606
BF 4	4.14	4.25	4.21	4.23 ± 0.3026
BF 5	5.21	5.44	5.41	5.35 ± 0.4332
BF 6	4.45	4.51	4.47	4.49 ± 0.3551
BF 7	2.37	2.35	2.38	2.36 ± 0.14041
BF 8	3.45	3.52	3.45	3.48 ± 0.2985
BF 9	4.50	4.51	4.58	4.54 ± 0.3604
BF 10	4.02	4.06	4.04	4.03 ± 0.3405

Result of Drug Content Uniformity

Table no 16: Drug content uniformity of various nebivolol Buccal films prepared using polymers.

S.r no.	Drug content			Average drug content ± SD
BF 1	73.68	75.88	76.95	75.17 ± 0.2780
BF 2	88.71	88.51	88.75	88.66± 0.4679
BF 3	85.41	88.07	85.69	86.09 ±0.3353
BF 4	87.99	87.86	89.27	88.05± 0.4641
BF 5	90.41	89.41	90.34	90.05 ± 0.6775
BF 6	86.76	88.03	88.68	87.49 ± 0.3566
BF 7	77.24	78.00	77.32	77.20 ± 0.2920
BF 8	79.41	82.10	80.10	80.53 ±0.5291
BF 9	86.76	86.44	87.30	87.13 ± 0.3381
BF 10	82.24	83.24	83.24	83.24 ± 0.3842

Result of *In-vitro* release of buccal film.

Table no 16: *In -vitro* release data Nebivolol Buccal film BF 1

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.00±0.000	2.000±0.000
1	1.000	0.000	8.3280±0.52	0.920±0.007	91.67±0.195	1.962±0.001
2	1.414	0.301	18.853±0.34	1.257±0.007	81.15±0.343	1.9092±0.002
3	1.732	0.477	27.223±0.57	1.4348±0.010	72.78±0.571	1.8620±0.003
4	2.000	0.602	34.951±0.34	1.543±0.005	65.05 ±0.343	1.813±0.002
5	2.236	0.698	49.358±0.69	1.693±0.010	50.65±0.690	1.7045±0.004
6	2.449	0.778	53.0508±0.50	1.724±0.006	46.95±0.503	1.6716±0.003
7	2.648	0.845	68.145±0.19	1.833±0.002	31.86±0.186	1.5032±0.001
8	2.828	0.903	73.246±0.32	1.864±0.003	26.76±0.319	1.4274±0.002

Table no 17 : *In -vitro* release data Nebivolol Buccal film BF 2

Time (Hrs)	√t	og t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	7.838±0.19	0.789±0.014	92.16±0.195	1.9645±0.001
2	1.414	0.301	17.432±0.33	1.241±0.017	82.57.390±0.333	1.916±0.002
3	1.732	0.477	24.056±0.33	1.381±0.013	75.95±0.333	1.880±0.002
4	2.000	0.602	31.798±0.19	1.502±0.006	68.21±0.198	1.838±0.001
5	2.236	0.698	43.516±0.39	1.638±0.010	56.49±0.390	1.7519±0.002
6	2.449	0.778	53.657±0.52	1.729±0.011	46.35±0.524	1.6660±0.003
7	2.645	0.841	65.941±0.31	1.819±0.006	34.06±0.319	1.5322±0.002
8	3.162	0.903	72.875±0.34	1.862±0.005	27.13±0.348	1.433±0.002

Table no 18: *In - vitro* release data Nebivolol Buccal film BF 3

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	4.841±0.19	0.684±0.014	95.14±0.195	1.978±0.001
2	1.414	0.301	11.448±0.34	1.055±0.014	88.56±0.343	1.947±0.002
3	1.732	0.477	22.149±0.18	1.345±0.006	80.28±0.184	1.9046±0.001
4	2.000	0.602	30.551±0.20	1.484±0.004	77.83±0.201	1.8913±0.001
5	2.236	0.699	43.422±0.34	1.635±0.006	56.58±0.348	1.7526±0.002
6	2.449	0.778	50.504±0.49	1.699±0.007	50.50±0.499	1.735±0.003
7	2.645	0.845	65.301±0.68	1.821±0.008	34.7±0.681	1.540±0.005
8	2.8284	).903	71.049±0.31	1.8515±0.003	28.96±0.314	1.4617±0.002

Table no 19: *In - vitro* release data Nebivolol Buccal film BF 4

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	6.8394±0.39	0.832±0.036	93.17±0.390	1.9692±0.002
2	1.414	0.301	16.428±0.38	1.215±0.015	83.58±0.385	1.922±0.002
3	1.732	0.477	26.320±0.20	1.420±0.006	73.68±0.206	1.8673±0.001
4	2.000	0.602	33.651±0.20	1.526±0.004	66.35±0.204	1.8218±0.001
5	2.236	0.699	46.596±0.21	1.6829±0.004	53.41±0.215	1.7276±0.001
6	2.449	0.778	53.516±0.17	1.728±0.003	46.49±0.170	1.6673±0.001
7	2.647	0.845	62.012±0.32	1.792±0.005	37.99±0.324	1.579±0.002
8	2.828	0.903	73.778±0.34	1.867±0.004	26.23±0.348	1.4187±0.002

Table no: 20 ***In -vitro* release data Nebivolol Buccal film BF 5**

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	9.906±0.19	0.9958±0.012	90.09±0.195	1.9546±0.001
2	1.414	0.301	16.792±0.33	1.225±0.014	83.21±0.333	1.9201±0.002
3	1.732	0.477	29.055±0.33	1.463±0.010	70.95±0.333	1.8509±0.002
4	2.000	0.602	38.358±0.20	1.583±0.005	61.65±0.201	1.7899±0.001
5	2.236	0.699	49.311±0.52	1.692±0.009	50.69±0.527	1.7049±0.003
6	2.449	0.778	61.022±0.36	1.838±0.005	38.98±0.362	1.5908±0.002
7	2.645	0.8451	72.5591±0.18	1.860±0.002	27.45±0.190	1.4385±0.001
8	2.824	0.9030	86.568±0.19	1.937±0.002	13.44±0.195	1.128±0.001

Table no: 21 *In-vitro* release data Nebivolol Buccal film BF 6

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	8.490±0.19	0.9242±0.012	91.51±0.195	1.9614±0.001
2	1.414	0.301	19.348±0.33	1.286±0.014	80.66±0.333	1.9066±0.002
3	1.732	0.477	26.752±0.33	1.427±0.010	73.25±0.333	1.8648±0.002
4	2.000	0.602	39.251±0.20	1.593±0.005	60.75±0.201	1.7835±0.001
5	2.236	0.699	49.637±0.52	1.695±0.009	50.37±0.527	1.7021±0.003
6	2.449	0.778	63.963±0.36	1.805±0.005	36.04±0.362	1.5567±0.002
7	2.645	0.845	72.046±0.18	1.857±0.002	27.96±0.190	1.4465±0.001
8	2.824	0.903	80.801±0.19	1.9030±0.002	1.92±0.195	1.2833±0.001

Table no: 22 *In-vitro* release data Nebivolol Buccal film BF 7

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	6.839±0.19	0.834±0.014	93.17±0.195	1.9692±0.001
2	1.414	0.301	13.874±0.34	1.142±0.014	86.13±0.343	1.9351±0.002
3	1.732	0.477	23.934±0.20	1.378±0.005	76.06±0.209	1.8811±0.001
4	2.000	0.602	30.969±0.31	1.490±0.007	69.04±0.319	1.8391±0.002
5	2.236	0.699	37.009±0.18	1.568±0.003	63.00±0.190	1.7993±0.001
6	2.449	0.778	48.351±0.33	1.684±0.004	51.65±0.333	1.7130±0.002
7	2.645	0.851	54.007±0.18	1.732±0.002	45.93±0.187	1.6620±0.001
8	2.828	0.9030	68.078±0.34	1.8325±0.004	31.93±0.343	1.5041±0.003

Table no: 23 *In- vitro* release data Nebivolol Buccal film BF 8

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.000	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	6.603±0.338	0.819±0.018	93.39±0.338	1.970±0.002
2	1.414	0.301	16.961±0.203	1.229±0.007	83.04±0.203	1.919±0.001
3	1.732	0.477	23.530±0.181	1.371±0.004	76.47±0.181	1.883±0.001
4	2.000	0.602	30.316±1.026	1.481±0.020	69.69±1.026	1.843±0.006
5	2.236	0.699	41.050±0.918	1.6133±0.014	58.95±0.918	1.770±0.006
6	2.449	0.778	53.718±0.148	1.730±0.002	46.29±0.148	1.665±0.001
7	2.645	0.851	64.358±0.326	1.756±0.004	35.65±0.326	1.5520±0.002
8	2.828	0.9030	79.270±0.305	1.898±0.003	20.73±0.305	1.316±0.002

Table no: 24 *In- vitro* release data Nebivolol Buccal film BF 9

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	6.6036±0.39	0.819±0.036	93.39±0.390	1.970±0.002
2	1.414	0.301	13.867±0.38	1.141±0.015	86.14±0.385	1.935±0.002
3	1.732	0.477	23.220±0.20	1.365±0.006	76.78±0.206	1.885±0.001
4	2.000	0.602	34.480±0.20	1.537±0.004	65.52±0.204	1.816±0.001
5	2.236	0.699	46.751±0.21	1.669±0.004	53.25±0.215	1.726±0.001
6	2.449	0.778	54.156±0.17	1.733±0.003	45.85±0.170	1.661±0.001
7	2.647	0.845	65.039±0.32	1.813±0.005	34.97±0.324	1.543±0.002
8	2.828	0.903	72.181±0.34	1.858±0.004	27.82±0.348	1.444±0.002

Table no: 25 *In- vitro* release data Nebivolol Buccal film BF 10

Time (Hrs)	√t	log t	% Cumulative drug release	Log % cumulative drug release	% cumulative drug retained	Log % cumulative drug retained
0	0.000	0.000	0.000±0.00	0.000±0.000	100.000±0.000	2.000±0.000
1	1.000	0.000	6.883±0.39	0.837±0.036	93.12±0.390	1.969±0.002
2	1.414	0.301	16.232±0.38	1.210±0.015	83.77±0.385	1.923±0.002
3	1.732	0.477	26.124±0.20	1.4169±0.006	73.88±0.206	1.868±0.001
4	2.000	0.602	33.456±0.20	1.524±0.004	66.55±0.204	1.823±0.001
5	2.236	0.699	46.403±0.21	1.663±0.004	53.6±0.215	1.729±0.001
6	2.449	0.778	53.320±0.17	1.726±0.003	46.68±0.170	1.669±0.001
7	2.647	0.845	64.176±0.32	1.8238±0.005	35.83±0.324	1.554±0.002
8	2.828	0.903	70.583±0.34	1.848±0.004	29.42±0.348	1.4686±0.002

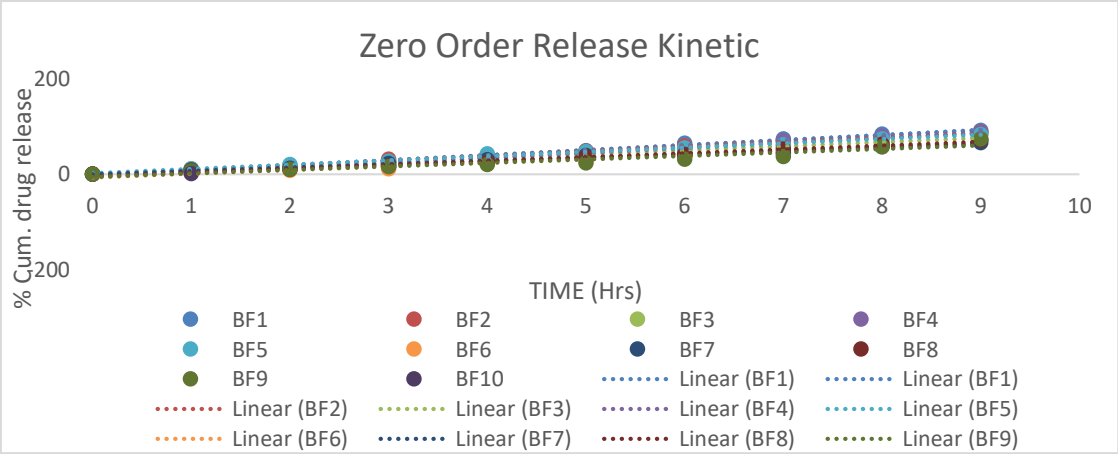

Fig no 7: Comparative In vitro release data Nebivolol Buccal film according to zero order Kinetics.

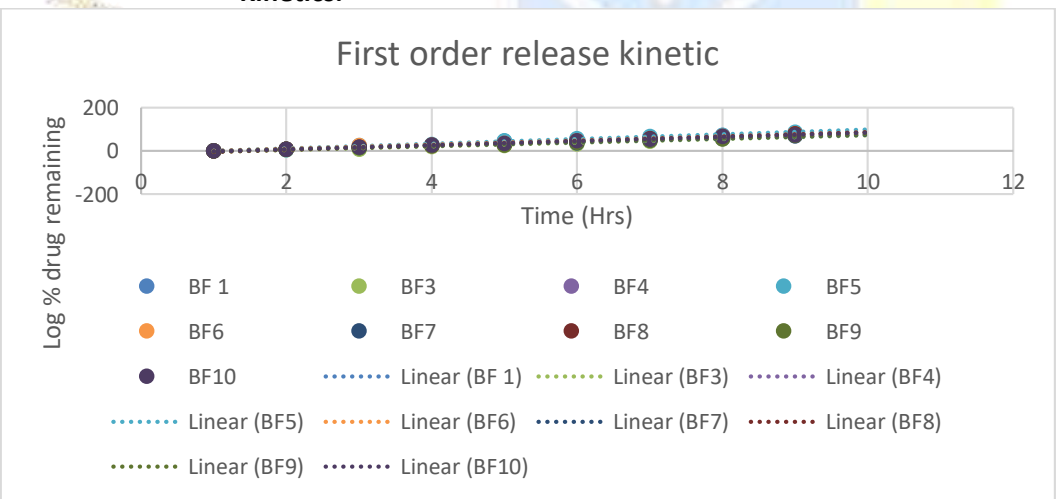

Fig no 8: Comparative In vitro release data Nebivolol Buccal film according to Peppas model.

Table no- 29 : Regression co-efficient (R^2) values of different kinetic models for Nebivolol Buccal film

Formulation code	Regression coefficient values				Slope values of Peppas exponential plots
	zero	first	Higuchi diffusion plots	Peppas exponential plots	
BF1	0.9897	0.9616	0.9107	0.7604	1.564
BF 2	0.9826	0.9527	0.9939	0.8407	1.645
BF3	0.9598	0.9349	0.9582	0.8701	1.580
BF4	0.9009	0.9657	0.9148	0.8373	1.657
BF5	0.9825	0.9246	0.9895	0.7556	1.575
BF6	0.9879	0.911	0.9889	0.745	1.585
BF7	0.9942	0.9519	0.9944	0.7944	1.526
BF8	0.9890	0.907	0.9893	0.8088	1.507
BF9	0.9868	0.922	0.9878	0.8082	1.508
BF 10	0.947	0.9667	0.9472	0.7854	1.545

Coclusion:

Many drugs are there with compromised oral bioavailability due to metabolism in the gut as well as in the liver. Considerable increase in the oral bioavailability can be obtained by avoiding drug exposure wall to gut and liver. One such promising drug delivery to deliver the drug to buccal mucosa. When absorbed from buccal mucosa, drug directly enters the systemic circulation bypassing metabolism in the gut and liver. Nebivolol is cardioselactive β-blocker used in the management of hypertension. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Nebivolol undergoes extensive metabolism in the liver after its oral administration resulting into a very poor (approximately 12%) bioavailability. In order to increase bioavailability we prepared mucoadhesive buccal films of Nebivolol by using combination of three polymers, namely HPMC k 15, PVP K30 and Ethyl Cellulose. The prepared films were evaluated for number of parameters like physical appearance and surface texture, weight uniformity, thickness of the films, folding endurance, swelling index, mucoadhesive strength, in vitro residence, drug–excipient interaction study, content uniformity and in vitro drug release study. From the result of various evaluation parameters, we can summarize- The films were completely dried, The films prepared were elegant in appearance with smooth surface,The films prepared were of uniform weight, The films were of uniform Thickness, The films had good flexibility.The films showed uniform swelling index, The films were of uniform surface pH,The films showed uniform and good mucoadhesive strength, There was no drug-excipient interaction between the drug and excipients used in the formulation, The drug was distributed throughout the film uniformly .

From the result of the research work we can summarize that nebivolol can be delivered successfully via buccal route through mucoadhesive buccal film.

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