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Research Article

Formulation and Evaluation of Mucoadhesive Buccal Film Containing Drug

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Abstract: The purpose of this research was to develop sustained release mucoadhesive films of atenolol by using Hibiscus esculentus polymer & hydroxy propyl methyl cellulose. Various proportions and combinations were fabricated by using solvent casting technique. Various physico mechanical parameters like Physical appearance and surface texture, Drug content uniformity, Surface pH, Weight uniformity, Thickness uniformity, Folding endurance, In vitro drug release, Swelling Index, Mucoadhesive strength were evaluated. In-vitro residence time and Mucoadhesive strength of films was also performed using porcine buccal mucosa. All prepared formulations indicated good physical stability. The possible drug polymer interactions were studied by FTIR studies. The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. An ideal film should have the properties like pleasant taste, high stability, ease of handling and administration, no water necessary for application.
Keywords: atenolol, solvent casting technique, Hibiscus Esculentus Mucilage, HPMC.

INTRODUCTION:

The development of a novel drug delivery system for existing drug molecules not only improve the drugs performance in terms of efficacy and safety but also improve patient compliance and over all therapeutic benefit to a significant extent. A method of drug delivery in which a drug is introduced to the body across a mucous membrane which allows for the avoidance of the gastrointestinal tract and first pass liver metabolism and consequently allows the therapeutic drug to directly enter into circulation. Among the various drug delivery systems, buccal delivery system is found to be the most promising because buccal mucosa itself provides a protective covering for the underlying tissues, acting as physical barriers against toxins and micro-organisms [1].

Mucoadhesive Buccal Films:

Various mucoadhesive devices has been formulated like tablets, patches, devices, strips, ointments, gels, disks and more recently films. Films can circumvent the difficulty of the relatively short residence time of oral gels on mucosa because the gels are easily washed away by saliva. An ideal buccal film must be soft, flexible, expandable and strong enough to withstand breakage because of stress from activities in the mouth and also it possess good mucoadhesive strength so that can be retained in the mouth for the desired duration [2].

Manufacturing methods:

The following process can be used to manufacture the mouth dissolving films.

1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Solid dispersion extrusion
5) Rolling

1. Solvent casting method:

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the petriplate and dried.

2. Semisolid casting:

In semisolid casting method firstly a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate) which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added to that a gel mass is obtained. Finally the gel mass is casted in to the films or

ribbons using heat controlled drums. The thickness of the film is about 0.015 – 0.05 inches. The ratio of the acid insoluble polymers to film forming polymer should be 1:4.

3. Hot melt extrusion method:

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion. Less operation units-better content uniformity –An anhydrous process.

4. Solid dispersion extrusion:

In this method immiscible components are extrude with drug and then solid dispersion are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5. Rolling method:

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and alcohol. The film is dried on the rollers and cutter in to desired shapes and sizes other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor Water soluble hydrochloride dissolved in water to form homogenous viscous solution [2, 19].

MATERIALS:

The Formulation Drug and Excipients used are Atenolol gift sample by kopran pharmaceutical Ltd. Mumbai, Hibiscus Esculentus Mucilage by local market, Chikhli, Hydroxy Propyl Methyl Cellulose by Ozone Internation Ltd, Mumbai, Propylene Glycol by Ozone International Ltd, Mumbai, Polyvinyl Alcohol by Ozone International Ltd, Mumbai, Glycerine by Ozone Internatiol Ltd, Mumbai.

Table-1: Formulation and composition

Formulations	Atenolol API	Hibiscus Esculentus Mucilage	HPMC	Propylene glycol	PVA
F1	50mg	-	30 %	40 %	40 ml
F2	50mg	-	40 %	40 %	40 ml
F3	50mg	-	50 %	40 %	40 ml
F4	50mg	2 mg	-	40 %	40 ml
F5	50mg	2.5 mg	-	40 %	40 ml
F6	50mg	3 mg	-	40 %	40 ml
F7	50mg	1 mg	50 %	40 %	40 ml
F8	50mg	1.5 mg	60 %	40 %	40 ml
F9	50mg	2 mg	70 %	40 %	40 ml
F10	50mg	4 mg	30 %	40 %	40 ml
F11	50mg	4.5 mg	40 %	40 %	40 ml
F12	50mg	5 mg	50 %	40 %	40 ml

Formulation of Atenolol buccal film

Experimental work:

Phytochemical Characterization of Hibiscus Esculentus Mucilage:

1. **Molisch's test (general test for carbohydrate):** To 2-3 ml aqueous extract, add few drops of alpha-naphthol solution in alcohol shake and add conc. H_2SO_4 from side of the test tube. Violet ring formed at the junction of two liquids.
2. **Ruthenium red test:** Place powder on glass slide, add drop of ruthenium reagent observe glass slide under microscope, mucilage cells shows pink colour.
3. **Biuret test (general test for protein):** To 3 ml test solution add 4% NaOH and few drops of 1% $CuSO_4$solution. Violet or pink color appears.
4. **Iodine test (for starch):** Place a powder on slide, add a drop of iodine solution, and observe the slide under the microscope a blue color appears indicate presence of starch [3, 4].

Physico-Chemical Characterization of Hibiscus Esculentus Mucilage:

1. Solubility profile:

Solubility profile mucilage were carried out by visual inspection of mucilage powder solution with various solvent such as cold water, hot water, ethanol, methanol, isopropyl alcohol, acetone, chloroform and benzene.

2. pH of 1% solution:

The pH of the hibiscus esculentus mucilage was measured using a digital pH meter by dispersing the hibiscus esculentus mucilage in 25 ml of distilled water.

3. Loss on drying:

500 mg of hibiscus esculentus mucilage powder was weighed and placed in a clean and neat china dish. It was kept in hot air oven at 105^0 c for 1 hr. the china dish was removed from the oven and again the weight of the hibiscus esculentus mucilage powder was

determined. Loss on drying can be calculated by the following equation-

$$\% \text{ LOD} = \frac{\text{Initial weight – final weight}}{\text{Initial weight}} \times 100$$

4. Ash value:

2 gm accurately weighed air-dried powdered drug was taken in tarred crucible. Spread the drug material in fine even layer at bottom of the platinum crucible. This crucible with drug material was kept in muffle furnace for ignition at high temperature. Temperature of furnace was increased gradually up to 450^0c. The material was kept at this temperature for 6 hours till complete ignition of drug occurred, that is till complete white colored ash was obtained. Intermittent weighing was also done and heating continued till constant weight of crucible. Crucible then was taken out from muffle furnace, cooled and weighed. The total ash was calculated by subtracting the weighed of crucible with ash of drug after ignition from weighed of crucible with powdered drug before ignition. Percentage of total ash was calculated with reference to air-dried drug.

Total ash = weight of ash / weight of powder substance X 100

5. **Swelling index:**

1 gm of powder was taken into 25 ml round glass stoppered cylinder graduated over a height of 120 to 130 mm in 0.5 divisions. To this 25 ml of respective medium was added and this will shake vigorously every 10 min for 1 hr and then allowed to stand for 24 hr. the swelling index was determined using following equation.

$$SI = \frac{V2 \times 100}{V1}$$

Where; SI = swelling index, V1 = volume occupied by mucilage prior to hydration, and V2 = volume occupied by mucilage after to hydration.

6. Bulk density:

A sample of powder of mucilage 25 gm was introduced into 100 ml graduated cylinder. The volume of material was taken on graduated cylinder. The bulk density was calculated by the formula

Bulk density = weight of powder / bulk volume

7. Tapped density:

Mucilage powder was passed through a #20 sieve to break the clumps, if any. Accurately weighed 30 gm of the powder was placed in a 100 ml graduated measuring cylinder. Initial volume was observed. The tapped volume was measured to the nearest graduated unit. The tapping was repeated additional 100 times if necessary. Again the tap volume was measured to the nearest graduated unit. The same thing was done for powder blend of the tablet. The tapped density was calculated by the formula-

Tapped density = weight of powder / tapped volume

8. Compressibility index (car's index):

The compressibility index and Hausner's ratio are measures of the flow properties of a powder to be compressed. Compressibility index of mucilage powder was calculated by the formula,

$$\text{Car's compressibility index} = \frac{\text{Tapped density – Bulk density X 100}}{\text{Tapped density}}$$

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 12 to 21 % compressibility index is defined as the free flowing material.

9. Hausner's ratio:

It indicates the flow properties of the powder and it is measured by the ratio of tapped density to the bulk density-

Hausner's ratio = Tapped density / Bulk density

10. Angle of repose:

Angle of repose has been used as indirect method for quantifying powders flow ability, because of their relationship between inetrparticular cohesion; it was measured according to fixed funnel standing method.

$$\tan \Theta = \frac{h}{r}$$

Where; r and h are the radius and height of the powder cone, respectively.

Evaluation of Atenolol sustained release mucoadhesive films: [2, 5- 8]

1. Drug content uniformity:

Drug content uniformity was determined by dissolving the buccal film (10 mm in diameter) from each batch by homogenization in 100 ml of phosphate buffer (pH 6.8) for 6 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution at 274.1 nm using a UV spectrophotometer.

2. Surface pH:

The surface pH of the buccal films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The buccal film was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 hr at room temperature.

3. Weight uniformity:

Three films of the size 10mm diameter were weighed individually using digital balance and the average weights were calculated.

4. Thickness uniformity:

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

5. Folding endurance:

Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good film properties. This test was done on randomly selected three films from each.

6. In vitro drug release:

The Rotating paddle method was used to study the drug release from buccal films. The dissolution medium consisted of 400 ml of isotonic phosphate buffer pH 6.8. The release was performed at 37 ± 0.5 °C, at a rotation speed of 50 rpm. One side of the buccal film was attached to a glass disk with instant adhesive (cyanoacrylate). The disk was put in the bottom of the dissolution vessel so that the film remained on the upper side of the disk. Samples (1 ml) were withdrawn by using calibrated pipette at pre-determined time (1 hour) intervals and replaced with fresh buffer. The samples were filtered through 0.45 µm Whatman filter paper with appropriate dilutions with phosphate buffer pH 6.8 and were assayed spectrophotometrically at 274.1 nm.

7. Swelling Index:

Swelling Index of prepared buccal film was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows. The percentage weight and area swelling ratios was calculated from the average of three measurements using the equation. $\% S = (Xt - Xo / Xo) \times 100$ Where, Xt - weight or area of the swollen film after time t and Xo - is the original patch weight or area at zero time.

8. Mucoadhesive strength:

Mucoadhesive strength of the dosage form can be measured on the modified physical balance. The apparatus consists of a modified double beam physical balance in which the right pan is replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon block of fixed diameter and height is fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side.

This is kept in beaker filled with buffer media PH 6.8, which is then placed below right side of the balance. Goat or rat stomach mucosa can be used as a model membrane and buffer media PH 6.8 can be used as moistening fluid. The one side of the dosage form is attached to the glass slide of the right arm of the balance and then the beaker is raised slowly until contact between goat mucosa and mucoadhesive dosage form is established. A preload of 10 g is placed on the slide for 5 min (preload time) to establish adhesion bonding between mucoadhesive dosage form and goat or rat stomach mucosa. The preload and preload time are kept constant. After the completion of preload time, preload is removed from the glass slide and water is then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water is stopped when mucoadhesive dosage form is detached from the goat or rat stomach mucosa. The weight of water required to detach muco-adhesive dosage form from stomach mucosa is noted as mucoadhesive strength in grams.

Force of adhesion (N) = (Bio adhesive strength (g) × 9.81)/1000.

9. In-vitro Residence Time of H. esculentus Mucilage:

The in vitro residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml phosphate buffer pH 6.8 maintained at 37 ± 0.5^0 C. A goat intestinal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucilage film was hydrated from one surface using 15µml phosphate buffer pH 6.8 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 so that the film was completely immersed in the buffer

solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the film of mucilage from the mucosal surface was recorded.

RESULTS:

Calibration curve of Atenolol:

Standard calibration curve of Atenolol were prepared in 6.8 phosphate buffer were estimated in UV spectrophotometer. The drug absorbance in the range of 10 to 60 µg/ml concentrations was reported in table no. 9. The drug was found to obey Beers Lamberts Law in the range of 10 to 70 µg/ml.

Table-2: Reading of Calibration curve of Atenolol

Sr. No.	Concentration (µg)	Absorbance
1	0	0
2	10	0.131
3	20	0.227
4	30	0.40
5	40	0.50
6	50	0.632
7	60	0.722

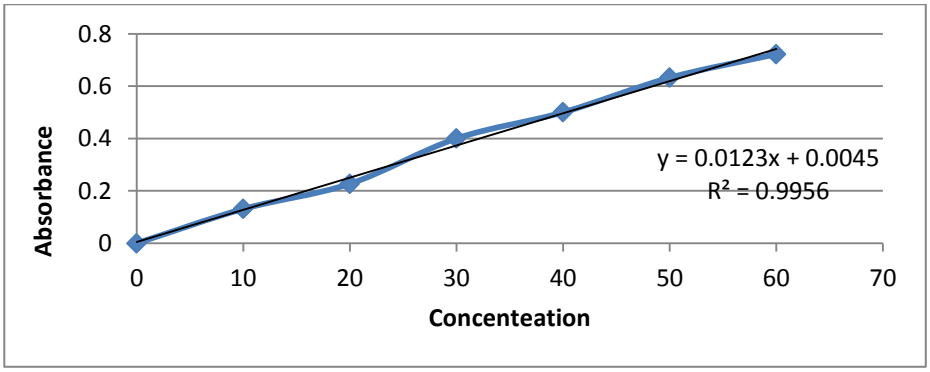

Fig-1: Standard calibration curve of Atenolol in 6.8 phosphate buffer

Table-3: Physiochemical tests of Hibiscus Esculentus Mucilage

Sr. no.	Tests	Observation	Inferences
1	Molish test	Violet ring at junction between two liquids	Carbohydrate may present
2	Ruthenium red test	Pink colour	Mucilage present
3	Iodine test	No blue colour	Starch may absent
4	Biuret test	Blue colour	Protein may present

Table-4: Physicochemical Characterization of H. Esculentus Mucilage

Sr. no	Parameter	Observed value
1	Solubility profile	
	Cold water	Swell to form gel
	Hot water	Soluble
	Methanol	Insoluble
	Ethanol	Insoluble
	Acetone	Insoluble
	Isopropyl alcohol	Insoluble
	Chloroform	Insoluble
	Benzene	Insoluble
2	pH of 1% solution	7
3	% LOD	9.00%
4	Ash value	5.50%
5	Swelling index	12%
6	Bulk density	0.48gm/cc
7	Tapped density	0.5gm/cc
8	Car's index	10
9	Hausner's ratio	1.04
10	Angle of repose	27^0

Table-5: Physicochemical characteristics of formulations

Formulation code	Weight uniformity (mg)	pH of films	Content uniformity (%)	Thickness uniformity (mm)	Folding endurance
F1	24±0.26	6.8±1.2	92.9±0.77	0.80±0.02	>220
F2	24±0.30	6.9±1.9	98.7±1.4	0.82±0.01	>220
F3	25±0.19	7.2±0.2	96.6±1.6	0.85±0.04	>220
F4	25±0.15	6.5±1.1	104.40±1.7	0.93±0.2	>220
F5	27±0.42	6.6±0.3	97.6±1.3	0.82±0.13	>220
F6	27±0.37	6.8±0.6	101.3±1.4	0.80±0.23	>220
F7	25±0.41	7.3±0.5	95.2±1.3	0.81±0.08	>220
F8	25±0.32	6.9±0.7	97.3±0.99	0.84±0.03	>220
F9	26±0.27	7.0±0.8	99.97±1.2	0.70±0.02	>220
F10	27±0.33	7.6±1.6	96.22±1.3	0.75±0.08	>220
F11	27±0.31	7.5±1.5	104.2±1.8	1.04±0.13	>220
F12	28±0.29	7.7±1.6	103.2±1.3	1.07±0.17	>220

Table-6: In-vitro drug dissolution study of F1 and F6

Formulation-ns	F1	F2	F3	F4	F5	F6
Time in hrs						
0	0	0	0	0	0	0
1	20.5±0.09	21.5±0.35	17.5±0.88	18.75±1.62	22.91±0.41	24.16±0.51
2	27.08±0.21	28.31±0.38	26.66±0.81	22.95±1.43	27.08±0.42	30±0.48
3	34.08±0.27	34.06±0.42	35.83±0.87	26.66±1.55	29.0±0.45	31.66±0.44
4	42.58±0.29	40.83±0.47	43.33±0.83	34.16±0.89	32.5±0.42	35.41±0.42
5	49.08±0.25	45.83±0.41	46.25±0.86	40.41±0.90	50.83±0.43	55.83±0.42
6	57.08±0.21	52.5±0.43	48.75±0.88	57.08±0.99	61.66±0.44	61.16±0.49
7	63.75±0.22	60.0±0.55	67.83±0.83	70.41±0.91	73.33±0.51	78.83±0.59

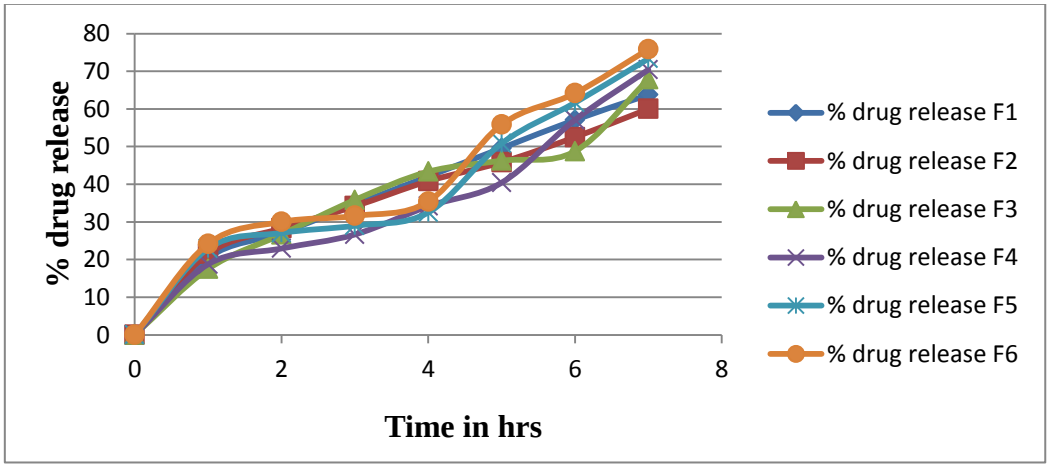

Fig-2: In-vitro drug dissolution study of F1 and F6

Table-7: In-vitro Drug Dissolution Study of of F7 and F12

Formulations	F7	F8	F9	F10	F11	F12
Time in hrs						
0	0	0	0	0	0	0
1	30.41±1.7	27.08±0.88	36.33±0.31	23.75±0.52	25.83±0.84	25.83±0.87
2	37.08±1.5	35.41±0.85	45.83±0.54	30.16±0.55	35.5±0.74	33.75±0.87
3	41.25±0.77	42.5±1.6	55.25±0.72	37.08±0.51	42.5±0.75	40.16±1.5
4	49.16±0.72	52.5±1.5	67.66±1.25	46.25±1.5	50.83±0.78	49.16±1.7
5	57.5±0.59	67.66±1.7	75.83±1.33	55.09±0.99	57.33±0.79	58.75±1.9
6	67.5±0.33	75.83±1.8	88.16±1.4	62.5±1.4	65.66±0.81	67.5±0.95
7	78.83±0.38	85.66±0.88	94.56±0.68	70.83±0.88	72.50±0.83	74.16±1.6

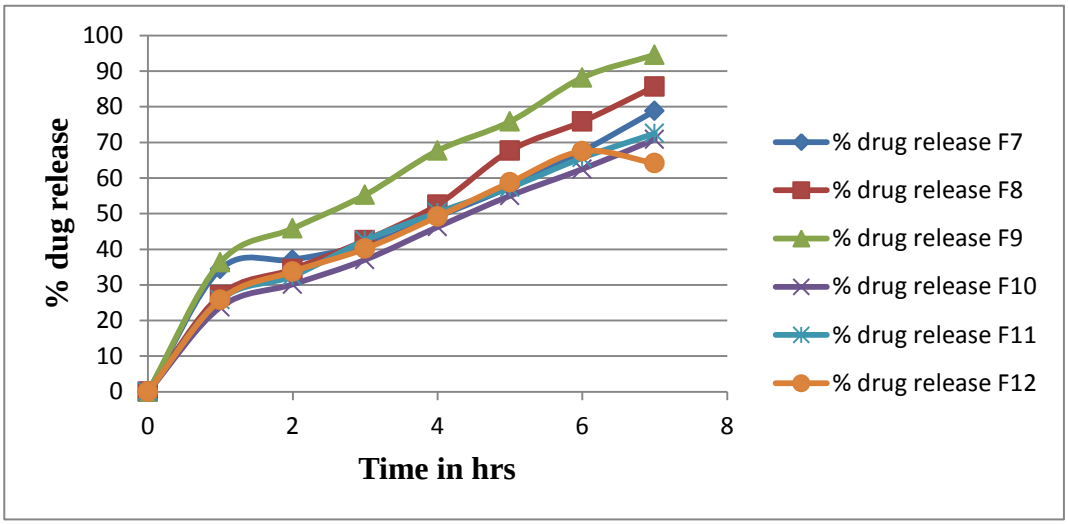

Fig-3: In-vitro Drug Dissolution Study of of F7 and F12

Table-8: Swelling Index of Formulations

Formulation code	Swelling Index (% wt. increases after 1 hr)
F1	15.07±1.30
F2	15.86±0.47
F3	16.93±2.31
F4	14.46±0.86
F5	16.57±3.2
F6	15.01±1.8
F7	16.07±1.4
F8	16.88±0.88
F9	16.22±0.99
F10	18.55±1.22
F11	15.86±1.15
F12	22.18±1.61

Table-9: Detachment weight in gm of Formulation

Formulation code	Detachment weight in gm
F1	9.8
F2	10.2
F3	12.6
F4	12.06
F5	11.3
F6	11.9
F7	8.65
F8	8.26
F9	8.06
F10	12.06
F11	15.28
F12	17.38

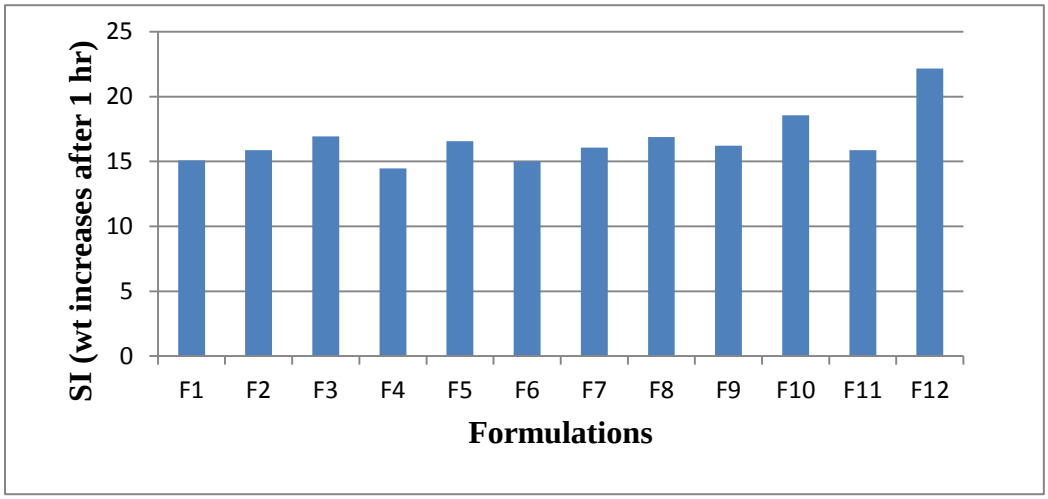

Fig-4: Swelling Index of Formulations

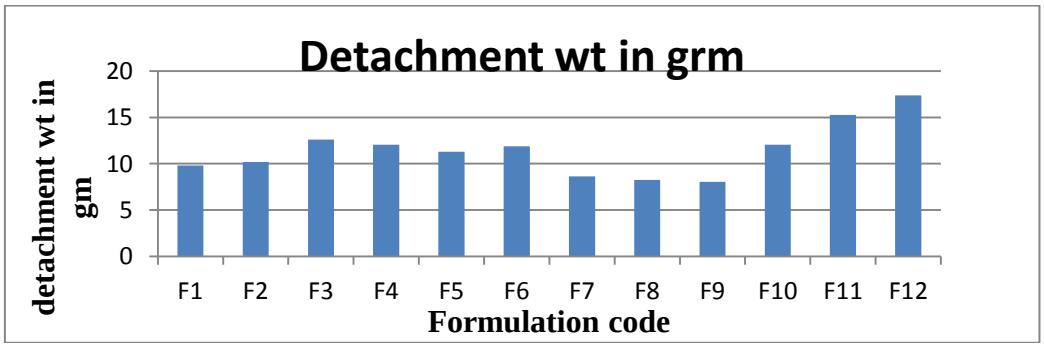

Fig-5: Detachment weight of Formulations

Fig-10: In-vitro residence time of Atenolol containing mucoadhesive buccal films

Sr. No.	Concentration of mucoadhesive agent		Residence time in (Hrs.)
1	H. esculentus Mucilage & HPMC	F1	4.5
		F2	4.3
		F3	5.3
		F4	6.2
		F5	5.2
		F6	7.2
		F7	6
		F8	7.5
		F9	8.0
		F10	6.2
		F11	5.5
		F12	6.1

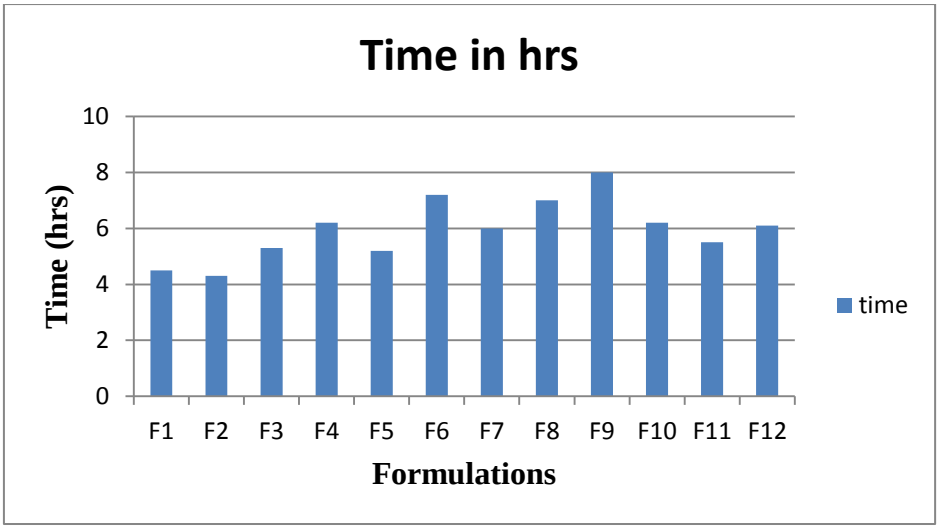

Fig-6: Resistance time of mucoadhesive Film

The sustained release mucoadhesive films of atenolol were prepared along with other additives by solvent casting method. A total number of twelve formulations were prepared and evaluated. The following are the significant results obtained. In the preformulation studies the drug excipient compatibility study of the blend were assessed by evaluating the FTIR spectra and UV scan of the API**.** The percentage drug content of sustained release mucoadhesive films of atenolol in all the formulations were found satisfactorily. Among all the twelve formulations, F9 was of good quality and mucoadhesive strength formulations.

CONCLUSION:

In the present work, sustained release mucoadhesive films of Atenolol were prepared by solvent casting method.

1. IR study is used for the identification of the drug Atenolol, Polymer Hibiscus esculentus, and Hydroxypropyl methyl cellulose and drug complex it also reveals that the drug is pure, no drug interactions.
2. The prepared films of Atenolol were clear and Whitish color. The scanning electron photomicrograph of the film at 1000 X magnification showed smooth surface with some little pores and without any scratches.
3. Formulated films gives satisfactorily result for various physicochemical evaluation of films like physical appearance, and surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, drug content uniformity, In-vitro disintegration time, in vivo drug release. The low value of standard deviation for average weight and drug content of the prepared films indicate weight and drug content uniformity within the batches prepared.
4. Based on the in vitro release time it was found that formulation F9 having quite more drug release than the other formulations.
5. It was observed from the results that F9 formulation showed maximum dissolution rate.

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