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DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE PATCHES OF BOSENTAN FOR BUCCAL ADMINISTRATION

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Abstract:

Maximum of the preparations of anti-hypertensive drugs are presented within the market within the style of tablets. The disadvantage in terms of efficacy, absorption and bioavailability, undesirable side effects are because of fluctuating plasma drug level. Inability to keep up adequate drug concentrations in plasma for therapeutic effect, larger doses than those required by the cells should be administered so as to realize the therapeutic concentration. to beat all the shortcomings within the conventional tablet dosage forms, there's a desire to formulate mucoadhesive buccal patches which provides an honest advantage of easy accessibility and needle free drug application without the need of a trained personnel facilitating self-medication.

KEYWORDS- Nanoparticles, Bosentan, HPMC K-100M.

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1. INTRODUCTION:

Buccal mucosa is a horny route for systemic delivery of medication since it's relatively permeable with a fashionable blood supply. A drug may be easily applied and localized to the applying site and may be far away from there if necessary. Attempt has been ready earlier to prepare some Mucoadhesive buccal devices, through pills, films, patch, disks gels and ointments. Buccal patches are highly flexible and thus rather more readily tolerated by the patient than tablets. Patches similarly ensure more precise dosing of the drug equaled to gel and ointment. Drug delivery via the oral mucosa may be a promising route, when one wishes to attain a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there's a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating strip, which permit a rapidly dissolving drug to soak up directly into the circulation through the oral mucosa. These sorts of dosage forms are convenient for kids, elderly patients with swallowing difficulties, and within the absence of potable liquids.

2. AIM

Development and characterization of mucoadhesive Patches of Bosentan For Buccal Administration

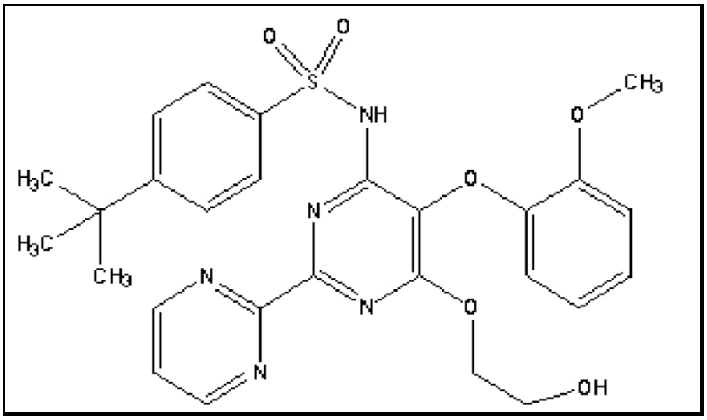
3. OBJECTIVES OF STUDY

1. Design, Development and Evaluation of mucoadhesive buccal film of Anti-hypertensive drug.
2. Preparation and evaluation of Mucoadhesive buccal film of Bosentan by solvent casting method.
3. To prepare mucoadhesive buccal film of Bosentan by using polymer HPMC-K-100M.

4. DRUG PROFILES

4.1 BOSENTAN

Table 01: Drug Profile

Structure	
IUPAC name	4-ter-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]benzene-1-sulfonamide
Molecular formula	$C_{27}H_{29}N_5O_6S$
Molecular weight	551.6g/mol
Category	Endothelin receptor antagonist
Appearance	white or almost white, crystalline powder, hygroscopic.
BCS class	Class II
Solubility	Poorly soluble in water(1.0mg/100ml)solubility increases at higher pH values(43mg/100ml at pH 7.5).Bosentan is freely soluble in acetone, acetonitrile ,chloroform and is soluble in ethanol.
Melting point	107-110^{0}C

Partition coefficient	3.1
Bioavailability	50%
Pka	5.8
Absorption	Absolute bioavailability is approximately 50% and food does not affect absorption.
Mechanism of action	Endothelin-1(ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. It displays a slightly higher affinity towards ET_A receptors than ET_B receptors.ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary and lung tissue of patients with pulmonary arterial hypertension,suggesting a pathogenic role for ET-1 in this disease.Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B.
Metabolism	Bosentan is metabolized in the liver by the cytochrome P450 enzymes CYP2C9 and CYP3A4(and possibly CYP2C19), producing three metabolites, one of which,Ro 48-5033,is pharmacologically active and may contribute 10 to 20% to the total activity of the parent compound.
Half life	Terminal elimination half-life is about 5 hours in healthy adult subjects.
Elimination	Bosentan is eliminated by biliary excretion following metabolism in the liver.Renal clearance is 4L/h(patient with pulmonary arterial hypertension)
Protein binding	Greater than 98% to plasma proteins, mainly albumin.

5. MATERIALS AND METHODS:

5.1 MATERIALS:

The following drugs, polymers, excipients and chemicals were used for the formulation and evaluation of Mucoadhesive Buccal Patch.

Table 02: List of Drug and chemicals

Name	Supplier Name
Drug.	
Bosentan	Sangrose Laboratories ,Alapuzha, India
Polymer.	
Sucralose	Yarrow chem products india.
HPMC K-100M	Yarrow chem products india.
Chemicals.	
Ethylcellulose	Yarrow chem products india.
Isopropyl alcohol	Yarrow chem products india.
Methanol	Rankem Chemical, Mumbai, India.

Following equipment's were used in study

5.2 Material and Methodology:

5.2.1 Pre-formulation study:

Pre-formulation study is the imperative pre-requisite in formulate of any drug delivery system. It gives information needed to define nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipient in dosage form.

5.2.2Melting point:

Melting point determination is prime confirmation of the drug. M. P. was determined by capillary tube method. In this method, drug whose analysis to be carried out was filled in to capillary tube and tied to the thermometer in such way that it remains dipped in a liquid paraffin bath and heat was done. The temperature range at which the drug starts melting and complete melting was noted.

5.2.3 UV-Visible Spectrophotometry:

UV-Visible Spectrophotometry was done to confirm wavelength maxima of the drug. The solution of Bosentan was scanned in UV range (200nm to 400 nm) by using UV Spectrophotometer (Shimadzu1800).

5.2.4 Infrared Spectroscopy:

FT-IR spectrum of drug was measured in solid state as potassium bromide (KBr) mixture. The pure drug was previously ground and mixed thoroughly with KBr, an Infrared transparent matrix at 1:100 (Sample: KBr) ratio, respectively. The KBr pellets were prepared by applying 10-12 metric pressure in a motorized pellet press (Kimaya engineers, India). The pellets were then scanned over a wave range of 4000-400 cm-1 and spectra was obtained by using a FTIR spectrometer-430 (Shimadzu 8400S, Japan).

5.2.5 Differential scanning calorimetry (DSC)

Melting point was determined by using differential scanning calorimetry. Thermogram for the drug was obtained using DSC (Mettler DSC 1 star system, Mettler-Toledo, Switzerland). The drug sealed in perforated aluminum pan and heated at a constant rate of 10°C/min over the temperature ranges of 30-350°C.

5.2.6 Preparation of standard calibration curve:

Calibration curve of Bosentan in pH 6.8 buffer was determined using a UV visible spectrophotometer (UV1800, Shimadzu).

5.2.7Preparation of standard stock solution:

100 mg of Bosentan was weighed and transferred into a 100 ml volumetric flask, which is then dissolved during a slight quantity of methanol and diluted with 6.8 phosphate buffer to provide a degree of 1mg/ml. 1 ml was taken from the stock solution in another volumetric flask and diluted up to 100ml to offer a stock solution 10µg/ml. More dilutions were made up of 2 to 10µg/ml with a 6.8 phosphate buffer. The absorbance was measured at 235nm.

5.2.8 Standard calibration curve of Bosentan in pH 6.8phosphate buffer solution:

Accurately weighed 10mg of Bosentan was dissolved in100ml volumetric flask containing 50 ml of methanolic phosphate buffer of pH 6.8and shaken for five min then remaining volume was made up with same buffer. the ultimate concentration obtained was 100µg/ml(stock solution). From the stock solution aliquots were prepared to induce a level range of 4-20 µg/ml. From the quality stock solution, appropriate dilutions were made to get in concentration range of 4, 8, 12, 16 and 20µg/ml. The aliquots were scanned within the wavelength range of 200-400 nm by using UV spectrophotometer. The absorbance maxima and absorbance of aliquots were recorded.

5.2.9 Solubility of Bosentan

Saturation solubility is defined because the maximum quantity of a compound (solute) that may be dissolved in certain quantity of a selected solvent at a specified temperature. The saturation solubility of pure drug Bosentan resolve in several buffer solutions pH 1.2, 6.8 phosphate buffer and H2O at 37°C ± 0.5°C. The weigh accurately 10 mg of pure drug was added in separate vial containing 5 ml of above pH buffer separately and continually shaken into mechanical orbital shaker (Remi mechanical shaking incubator, Bombay) up to 48 hrs. After 48 hrs samples were withdrawn and filtered through a 0.22 µm membrane filter (Millipore, India). The solutions were analyzed by using UV spectrophotometer at 235 nm, which was the absorption maxima determined earlier and drug concentrations were calculated.

5.3 Formulation of Buccal Patch (Solvent Casting Method)

5.3.1Method of Preparation of Mucoadhesive Buccal Patch

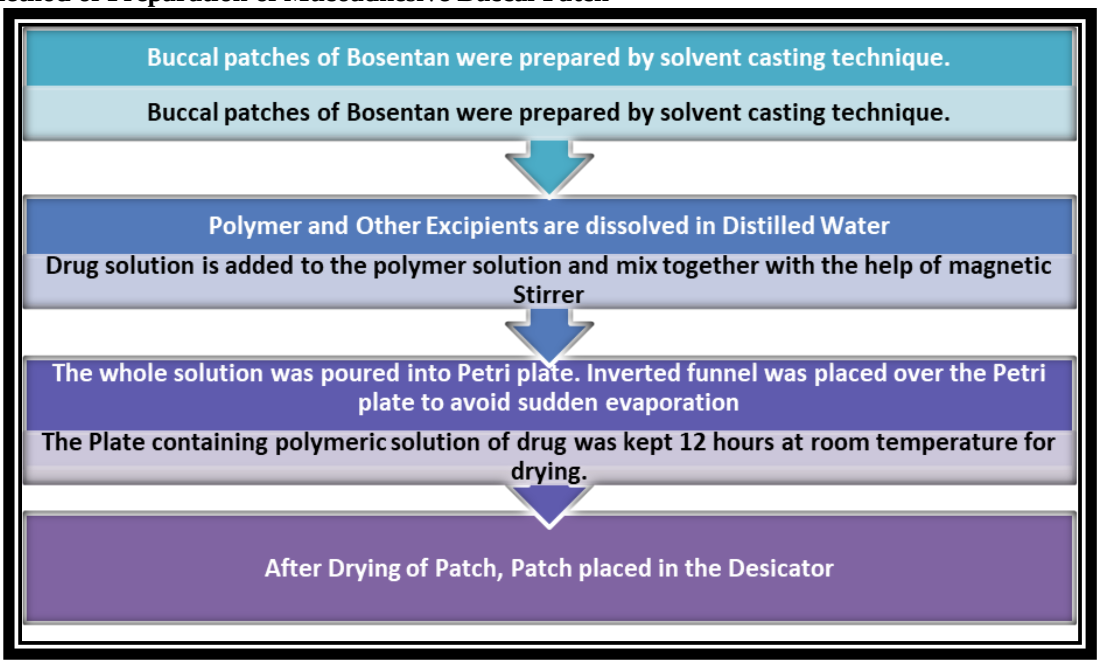


Figure 1: Method of preparation of Mucoadhesive Buccal Patch

Mucoadhesive buccal patches equipped thru solvent casting technique. The drug and potassium were dissolved in 10ml of water containing acid and sucralose by stirring on a magnetic stirrer for 1 h .A 10ml solution of jackfruit gum in water was kept aside for 1 day to make a transparent solution. HPMC K-100M was dissolved in 10 ml of acetone and added to the above solution. After stirring mix the drug and polymer solution stirred for 11 h. the answer was then poured into a 9cmglass Petri dish and allowed to dry at 400C in an oven. an answer of 500mg of ethylcellulose and 0.2 ml dibutyl phthalate in 10ml of acetone was poured to the Petri dish to create a backing layer. it had been air-dried , far away from the Petri dish, packed in tin foil, and stored in an exceedingly desiccator.

Table 03: Composition of Mucoadhesive Buccal Patch

Sr no	Ingredients	Formulation batch				
		F1	F2	F3	F4	F5
1	Bosentan	296.39mg	296.39mg	296.39mg	296.39mg	296.39mg
2	HPMC K-100M	250ml	250ml	250ml	250ml	250ml
3	Citric Acid	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
4	Sucralose	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
5	Propylene glycol	1ml	1ml	1ml	1ml	1ml
6	Dist.water	10ml	10ml	10ml	10ml	10ml

Polymer HPMC K-100M are utilized in the various concentration and various batches are prepared.

5.4 Evaluation of Buccal Patch

5.4.1 Physical appearance

Physical appearance performed by visual inspection of patches and evaluation of texture by feel or touch.

5.4.2 Weight variation test

The patch size of 2×2 cm2 was cut. the burden of every patch was taken and therefore the weight variation was calculated.

5.4.3 Thickness

The thickness of patches were measured employing a screw gauge at different positions of the patch and also the mean was calculated.

5.4.4 Surface pH

For the determination of surface pH, three films of every formulation were placed on the agar plate and allowed to swell for 2h. The pH paper was located over it and a mean of 3 interpretations was noted.

5.4.5 Folding endurance

Folding endurance of patches was measured by frequently folding one patch at the identical place until it broke or folded up to 300 times manually. the quantity of times the patch may well be folded at the identical place with none breaking gave the result.

Goat buccal mucosa was fixed inside the beaker above 2.5 cm from the underside using cyanoacrylate glue. The patch was then pasted on to the mucosa by a lightweight force by fingertip for 30 s. The beaker was full of 500ml of 6.8 solution maintained at 370C±10C and was stirred at 50rpm for 6h.Then, the time taken by the patch to detach from the buccal mucosa was calculated as mucoadhesion time.

5.4.6 Drug content

Patches were dissolved in 5ml ethyl alcohol and 2ml of dichloromethane by homogenization for 5h with occasional shaking and diluted to 50ml with H2O. it absolutely was then filtered to get rid of insoluble residue from the filtrate.1ml was taken and was diluted to 10ml with pH 6.8 buffer. Using ultraviolet spectrophotometer absorbance was measured at 235nm.

5.4.7 In-vitro dissolution study:

The study was performed using the rotating paddle apparatus, maintained at 37±0.50C, with a speed of fifty rpm. Buffer pH of 6.8 was used as a dissolution medium. By cyanoacrylate glue, the support layer of the patch sticks to a glass slide. Then, it had been placed at the underside of the vessel. 5ml sample was withdrawn at predetermined time intervals and replaced with fresh medium. After appropriate dilution, it had been filtered and analyzed by UV spectrophotometer at 235nm.

5.4.8 Stability study

5ml human saliva was taken in a very Petri dish and patches were placed over it. Then, it absolutely was kept in a very temperature-controlled oven at 370C ±0.20C for 8h. An explicit time intervals, morphological, and physical changes like appearance, color, and shape were observed.

6. RESULTS:

6.1 Preformulation Study

6.1.1 Identification and conformation of drug Bosentan:

Confirmation of the drug was carried out by using UV spectroscopy, Infrared spectroscopy and Differential scanning calorimeter (DSC).

6.1.2. Melting point:

Melting point of the medication was determined by capillary method. The melting point was found to be in reference with the literature, hence the sample is authentic.

Table 04: Melting point of the drug by capillary method

Sample	Melting point(Found)	Melting point(Reported)
Drug	107°C	110.0°C

6.1.3 UV spectroscopy:

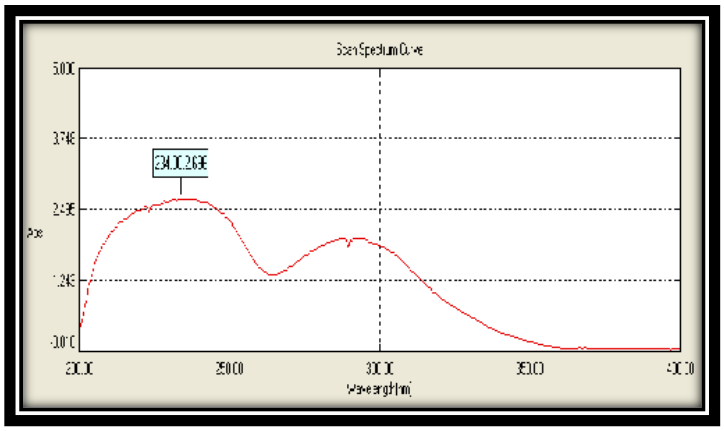


Figure 2: UV Spectrum of Bosentan

6.1.4 Infrared Spectroscopy:

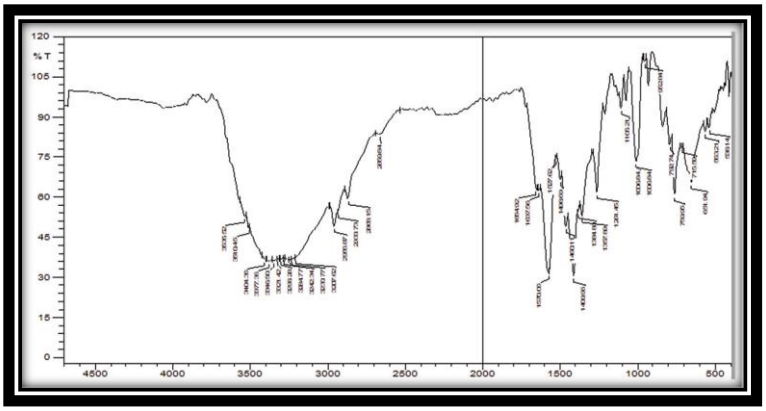


Figure 3: FTIR spectrum of Bosentan

6.1.5. Differential Scanning Calorimetry (DSC):

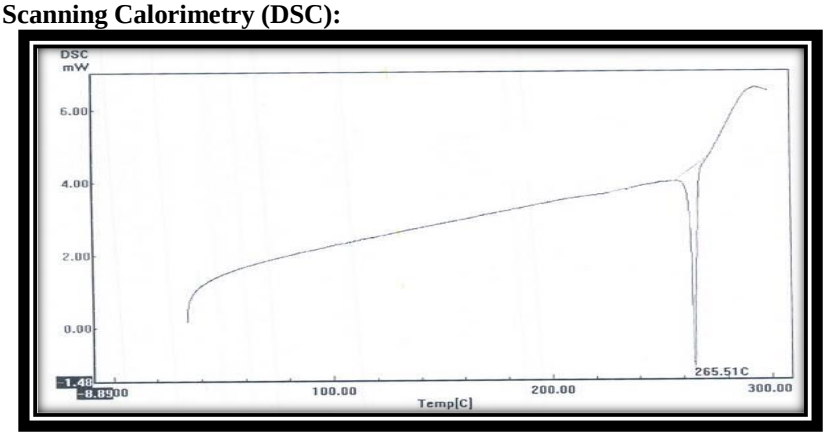


Figure 4: DSC Thermogram of Bosentan

6.1.6 Standard calibration curve of Bosentan in pH 6.8 buffer

Table 05: calibration curve Absorbance of Bosentan

Conc. (µg/ml)	Absorbance (nm)
0	0
2	0.1097
4	0.2245
6	0.3377
8	0.4297
10	0.5531

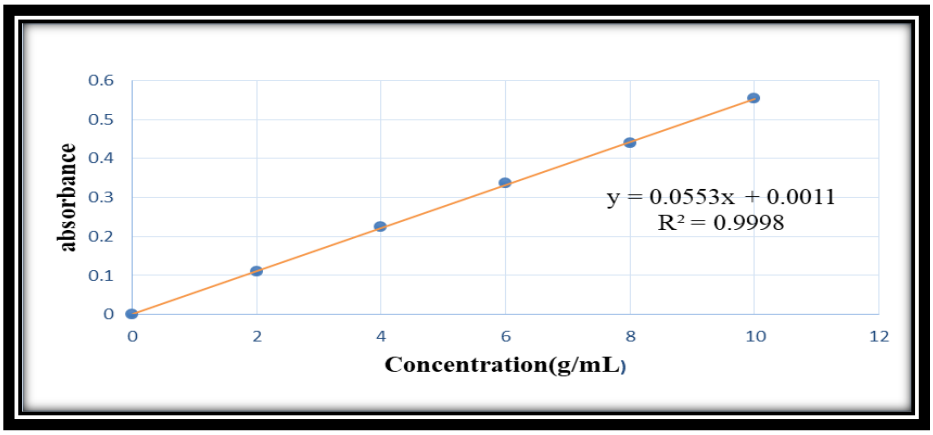


Figure 5: Standard calibration curve of Bosentan in pH 6.8 buffer

6.1.7 Solubility of Bosentan:

Table 06 Bosentan solubility

Media	Saturation Solubility (mcg/ml)
1.2 pH	0.02±0.02
6.8 pH	0.15±0.02
Distilled water	0.02±0.01

6.2 Combability Study

6.2.1 Fourier Transform Infrared (FT-IR) Spectroscopy:

Drug excipient interaction study

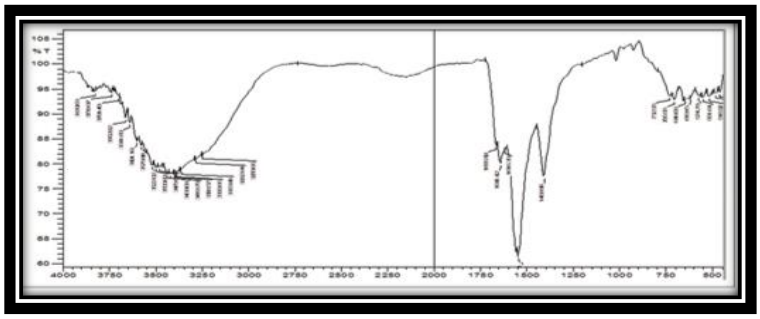


Figure 6: Drug + Polymer IR Spectrum

Table 07: IR Ranges of Drug and Polymer

Drug peak	HPMC	Drug+ HPMC	Interaction
1666.40	3419.79	1709.89	No interaction
1641.42	3398.57	1699.28	
1616.36	3363.86	1681.93	
1408.96	3282.84	1641	

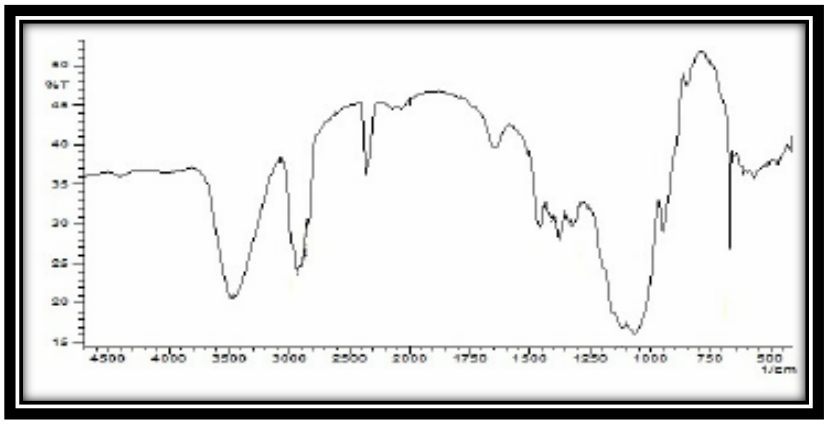


Figure 7: Overlay of FTIR spectra of Drug, Polymer and Physical mix

Table 08: IR ranges of Drug excipient (physical mixture)

Drug peaks (cm^{-1})	Drug+Exipients peaks (physical mixture) (cm^{-1})	Interaction
1666,1641,1616,1400, 732,706,648,619 ,574,551,516	3830,3730,3701,3662,364 3601,3579,3522,3495,3433, 3419,3393,3330	**No interaction**

FTIR spectra of Overlay of pure drug and physical mixture are shown in Figure 6and their interpretation in Table 6 From FTIR interpretation it can be concluded that there was no drug-polymer interaction

5.3 Physical Appearance And Surface Texture

Physical appearance and Surface texture of patches prepared using different concentration of HPMC.

Table 09: Physical appearance and surface texture of Buccal Patch

Formulation code	Appeance	Surface texture
F1	White	Smooth
F2	White	Smooth
F3	Yellowish white	Smooth
F4	White	Smooth
F5	White	Smooth

6.4 Weight Uniformity:

Drug loaded Patch was tested for uniformity of weight and the results are given in the table: 9. the weight of all the prepared batches was found to quite uniform.

Table 10: Weight uniformlity of Buccal Patch

Formulation code	Weight of Patchs (mg)
F1	88.97 ± 0.17
F2	93.74 ± 0.26
F3	97.12 ±0.33
F4	100.24± 0.25
F5	103.41 ± 0.41

6.5 Thickness Uniformity:

The thicknesses of drug-loaded Patch were measured with the help of electronic vernier Caliper. The mean values are shown in the table 12.

Table 11: Thickness of Buccal Patch

Formulation code	Thickness of Buccal Patchs (mm)
F1	0.11 ± 0.04
F2	0.11 ± 0.03
F3	0.13 ± 0.01
F4	0.14 ±0.05
F5	0.16 ± 0.06

6.6 Surface pH:

The surface pH of drug loaded Patch were measured with the help of the electronic pH meter.

Table 12: Surface pH of Buccal Patch

Formulation code	pH of Buccal Patchs
F1	**6.11** ± 0.14
F2	**6.30** ± 0.05
F3	**6.28**± 0.09
F4	**6.26**± 0.12
F5	**6.20**± 0.16

6.7 Folding Endurance>

Table 13: Folding endurance of buccal Patch

Formulation code	Folding endurance
F1	**275**
F2	**293**
F3	**>300**
F4	**>300**
F5	**>300**

6.8 Mucoadhesion Time

Table 14: Mucoadhesive time of Buccal Patch

Formulation code	Mucoadhesive time (min)
F1	296
F2	189
F3	130
F4	268
F5	147

6.9 Drug Content Uniformity:

The content uniformity test is commonly employed for unit dosage forms. In order to make sure about the uniform dispersion of drug in Patch, the drug content was carried out. The drug content was analyzed at 239 nm by using suitable blank.

Table 15: Drug Present in the Buccal Patch

Formulation code	Drug present (%)
F1	86.36
F2	85.55
F3	89.23
F4	86.96
F5	92.45

6.10 In-Vitro Drug Release Study:

The Veggo VDA-6D USP eight station dissolution apparatus was used throughout the study. The dissolution study was performed by using basket type setting where, one Patch of each batches was fixed inside the basket.

Table 16: In-vitro Drug release of Buccal Patch

Time (h)	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	10.41	11.87	8.28	9.96	8.25
1	12.17	12.96	12.74	14.23	12.21
2	13.96	14.89	15.36	15.89	16.36
3	16.67	15.29	16.34	20.25	23.96
4	17.73	17.87	16.99	26.36	27.85
5	19.69	18.89	27.23	28.41	29.56
6	20.46	20.12	33.23	40.36	34.47

Table 17: In-vitro Drug Release After 6 hours

Formulation code	In vitro % drug release after 6 hours
F1	61.74
F2	58.44
F3	60.79
F4	62.74
F5	59.26

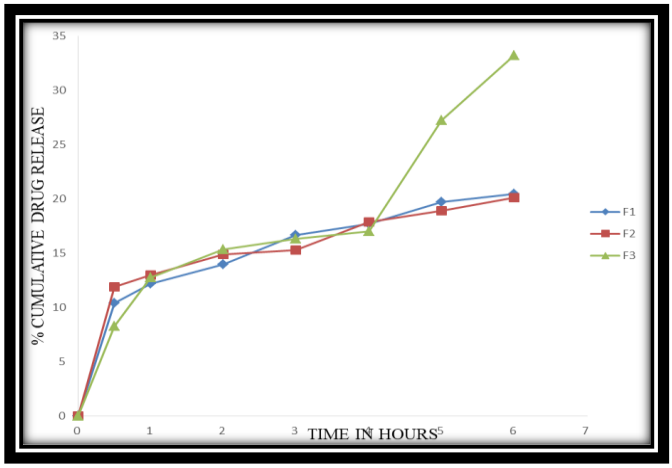


Figure 8: Grapical representation of in-vitro release study of formulation batches of F1,F2 and F3

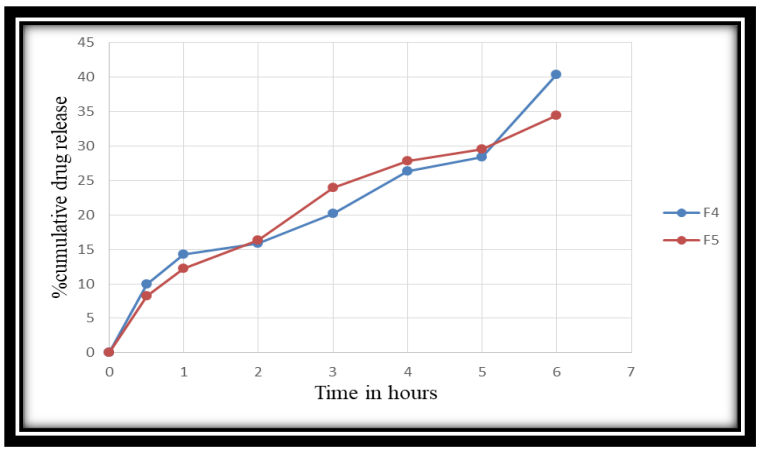


Figure 9: Graphical representation of In-vitro Drug release study of different formulation of F4.

6.11 Stability Study

The optimized formulation F4 was evaluated at the time interval of 60 days for the all the parameters like Appearance, Weight, Thickness, % and drug content. The observations of stability studies of optimized formulation F4 are shown in given table did not show any significant change in these parameters after stability studies. This confirms the stored Patch formulation were stable for the storage period.

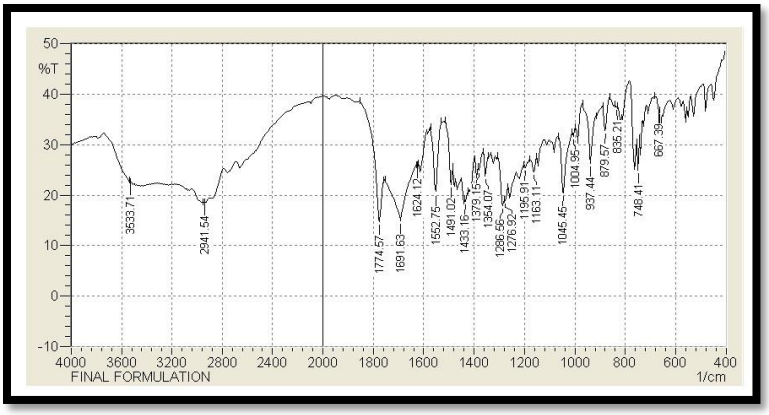


Figure 10. FTIR spectrum of F4 Batch

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Table 18: Stability Study

Time	Colour change	Thickness	Change in pH	Collapsing
0	No Change	0.16	No Change	No Change
1	No Change	0.17	No Change	No Change
2	No Change	0.20	No Change	No Change
4	No Change	0.22	No Change	No Change
6	No Change	0.25	No Change	No Change
8	No Change	0.26	No Change	No Change

7. SUMMARY

The goal was to design and evaluate buccal mucoadhesive patches of Bosentan by solvent casting method using HPMC polymer. The film were evaluated for physical appearance and surface texture, thickness, drug content uniformity, swelling index, mucoadhesive time and in vitro drug release study. Buccal patches of Bosentan were prepared to retain in oral cavity thus increase bioavailability, reduces drug waste and side effect like gastric irritation and nausea and also facilitate administration to patients suffering from nausea or vomiting and with and upper gastrointestinal tract disease or surgery which affects GIT absorption and having difficulty in swallowing oral medication. Buccal drug distribution has recently become an main route of drug administration, many bioadhesive mucosal dose forms are actuality established. The formulations were prepared by using polymers such as HPMC K-100M and by the utilization of plasticizer (Propylene Glycol) by solvent casting method. In the present study, the film was prepared by using different polymeric concentration as well as the concentration of plasticizer 5 and 10%. All the formulations were subjected to various evaluation parameters like compatibility studies, thickness, uniformity weight, content uniformity, percentage moisture loss, DSC and IR. In vitro drug release study was carried out on all the prepared formulations. In FT-IR study the drug estimation carried out, it shows the drug was pure. In UV-Spectroscopy the drug estimation carried out, as per literature survey the λ max was found to be 235 nm, it shows the drug was pure.The thermo grams of Bosentan exhibited endothermic peak at 200-210^{0}c The DSC thermo grams of physical mixture as well as film showed identical peaks corresponding to pure drug. The average thickness of the film ranges from 0.5 mm to 0.7 mm. The thickness of film not much varies when the concentration of polymer changed.

8. CONCLUSION:

In this study, Oral mucoadhesive buccal film were prepared using polymer HPMC K-100M and by solvent casting method. It was detected that concentration of polymer effects the creation of film and dissolution time of the preparations. Preparation of Mucoadhesive buccal film by solvent casting method showed higher release of drug as comparing with the others method. Different evaluation parameter like thickness, weight uniformity, folding endurance, surface pH, mucoadhesive time has been performed. In order to know the release pattern of drugs from prepared formulation, in-vitro drug release studies were carried out. Formulation F5 shows the higher amount of drug release. And by according to obtained results can be concluded that batch F4 is optimized batch prepared by solvent casting technique, which showed desired results.

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