Int. J. Pharm. Med. Res. 2014; 2(5):140-144 **ISSN: 2347-7008**

International Journal of Pharmaceutical and Medicinal Research

Journal homepage: **www.ijpmr.org**

Research Article

Development and Evaluation of Bisoprolol Loaded Biolayers using Biomaterial obtained from fruit pulp of *Citrus maxima*

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ARTICLE INFO:

Article history:
Received: 13 September, 2014
Received in revised form:
01 October, 2014
Accepted: 22 October, 2014
Available online: 30 October, 2014

Keywords:
Biolayers
Biopolymers
Bisoprolol
Citrus maxima

ABSTRACT

In the present research work biomaterial from the fruit pulp skin of *C. maxima was* isolated and evaluated for its film forming capacity. *C. maxima* was isolated by an economic method and subjected to various physical evaluation parameters. The biomaterial was subjected to spectral studies like IR, 1H NMR and DSC analysis. Bisoprolol loaded biolayers were prepared using the isolated biomaterial and other co- processing agents. The prepared biolayers were evaluated for their film parameters and subjected to in-vitro drug release studies. The results were compared with the standard HPMC film. The experimental results revealed that the prepared biolayers possessed good folding endurance with appreciable release characteristics. The best film formulation was BC6 with percentage cumulative drug release of 92.73% over 35 minutes. Hence it clearly indicated that the isolated biomaterial possessed inbuilt filmability.

1. Introduction

The *Citrus maximum belongs* to the family *Rutaceae*. The fruit of *C. maxima* consist of carbohydrates, vitamin c and fat. Medicinally, decoctions of the leaves, flowers, fruits and seeds have properties, which can treat coughs, fevers and gastric disorders. Fruit has alkanizing effect on blood, is a purgative, antibacterial and cleansing agent. The leaves are used for medicinal infusions. Decoctions of leaves, flowers and rind are given for their sedative effects in cases of epilepsy and convulsive coughing. The hot leaf decoction is administered on swellings and ulcers. The rind has pectin used in ointments for burns. The biomaterial obtained from *C. maxima* can be used in pharmaceutical formulation due to its edibility, biodegradability and biocompatibility**[1]**.

Bisoprolol belongs to a class of drugs called beta- adrenergic receptor blocking agents. Bisoprolol is used for treating high blood pressure and angina. Bisoprolol prevents the neurotransmitters norepinephrine and epinephrine from binding to beta receptors on nerves. Beta blockers reduce heart rate and the force with which the heart contracts and reduce blood pressure by dilating blood vessels but may constrict air passages by stimulating the muscles that surround the air passages**[2]**. The aim of our research work was to isolate a biomaterial from *C. maxima* fruit pulp skin and evaluate its film forming ability by making biolayers using bisoprolol as the model drug.

2. Materials and methods

The fresh *C. maxima* fruits were collected from plants growing in local area of Dehradun, India. Acetone was procured from SD fine chemicals (Mumbai, India). All other chemicals used were of analytical grade. HPMC were purchased from SD fine Specialties Pvt. Ltd., Mumbai.

Isolation of biomaterial

Initially fruit pulp of *C. maxima* was separated, skin was removed and minced with double distilled water and filtered. It was then treated with acetone and refrigerated for 12 hours. It was centrifuged at 3000 rpm for 30 mins, dried in dessicator for 24 hours and finally passed through 120 mesh sieve to get uniform size particles. The percentage yield of isolated biomaterial was calculated**[3,5]**.

Characterization of isolated biomaterial

The isolated biomaterial was subjected for various physical tests like colour, odour, solubility, colour changing point, viscosity and surface tension**[4,6]**. It was also subjected for IR spectral analysis in order to determine the functional groups present in the isolated biomaterial. Further the biomaterial was subjected to 1H NMR and differential scanning calorimetry (DSC).

Formulation of biolayers using the isolated biomaterial

The isolated biomaterial was used for formulating biolayers using bisoprolol as the drug. six different film formulations i.e. BC1, BC2, BC3, BC4, BC5 and BC6 were prepared using biopolymer & bisoprolol in six different ratios by solvent casting method (Table 1).

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Initially, the isolated biomaterial was dissolved in distilled water with constant stirring on a magnetic stirrer. Dextrose and xylitol were added as flexicizer for the formulation of biolayers. SLS was added as a dispersing initiator. Bisoprolol solution was prepared separately and added to the biomaterial solution containing dextrose and xylitol. This mixture was then transferred into petriplates uniformly and solvent was allowed to evaporate in a controlled manner. Dried biolayers were carefully scraped out and cut into films of 1 cm^2 **[7,8]**.

Table 1: Formulation of bisoprolol loaded biolayers using the biomaterial

Ingredients	BC1	BC2	BC3	BC4	BC5	BC6
Bisoprolol(mg)	100	100	100	100	100	100
Biopolymer(mg)	50	100	200	300	400	500
Dextrose (mg)	100	100	100	100	100	100
Xylitol(mg)	100	100	100	100	100	100
SLS(%)	0.5	0.5	0.5	0.5	0.5	0.5
Water(ml)	10	10	10	10	10	10

Evaluation of film formulations

The prepared bisoprolol loaded biolayers were evaluated for the parameters namely weight, thickness, folding endurance, surface pH, tensile strength, elongation, moisture uptake and content uniformity **[8,9]**. The mean of three readings was determined for each parameter.

In-vitro drug release studies

The *in- vitro* drug release studies of prepared biolayers were carried out by using a in house fabricated dissolution apparatus which contains 500 ml beaker filled with 300ml water. A 20ml screw cap glass vial was placed in beaker. Each having 10ml of 7.4 pH phosphate buffer solutions and film of 1cm^2 area. The magnetic bead was incorporated into it. The whole assembly was kept on magnetic stirrer set at 50 rpm and maintained at 37± 0.2°C. Samples were withdrawn at regular intervals till 35 minutes and replaced by fresh buffer. Six assemblies were used in the same manner. The samples were analyzed by Shimadzu 1800 UV-Visible Spectrophotometer at λ max 222 nm. % Cumulative drug release was calculated. It was compared with standard film of HPMC polymer **[8,10]**.

3. Results and discussion

Physical evaluation parameters of isolated biomaterial

Our experimental results revealed that the isolated biomaterial was light brown powder with a colour changing point of 227° C and percentage yield 25%. It was soluble in water, slightly soluble in chloroform and insoluble in alcohol. It 1% solution showed viscosity 2.8 cp and surface tension 76.54 dyne/cm.

Spectral analysis of isolated biomaterial

IR spectroscopy of the isolated biomaterial revealed peaks at 2928.07cm^{-1} (C-H-Alkanes stretching), 1741.80 cm^{-1} (C=O aldehyde carboxylic acids), 1621.24 cm^{-1}(C-N Amines stretching)(Figure 1). The presence of OH and COOH groups in IR spectrum confirmed the polymeric nature of the biomaterial.1H NMR spectra of *C.maxima* biomaterial is showed in (Figure 2).The DSC curve of *C.maxima* showed glass transition temperature 133.15°C. Peak height was observed at 21.6949 mW, area was found to be 2653.214 mJ. The value of delta H was 265.3214J/g (Figure 3).

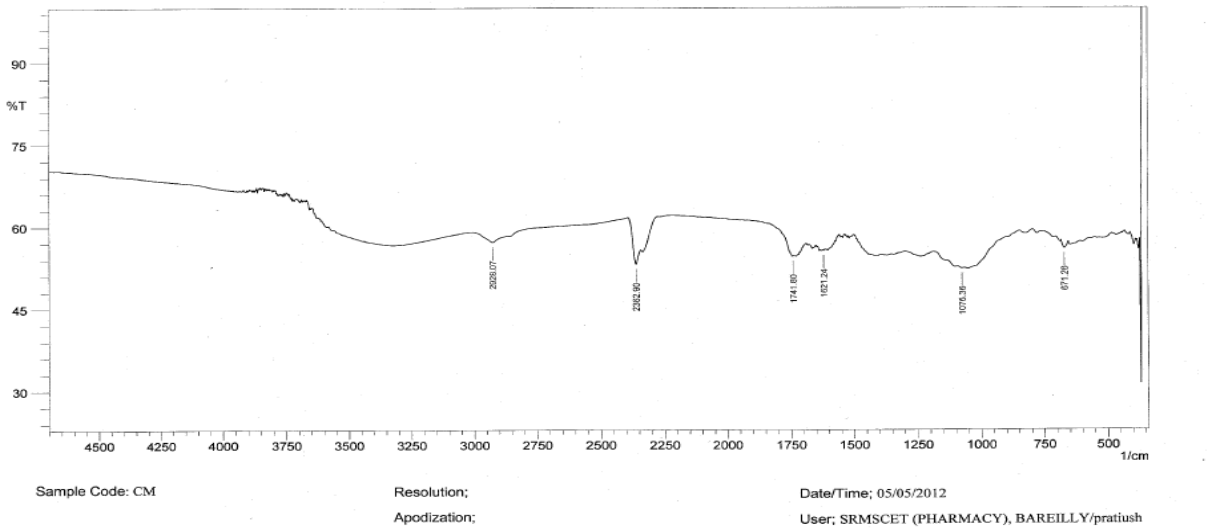

Figure 1: IR Spectra of Citrus maxima biomaterial

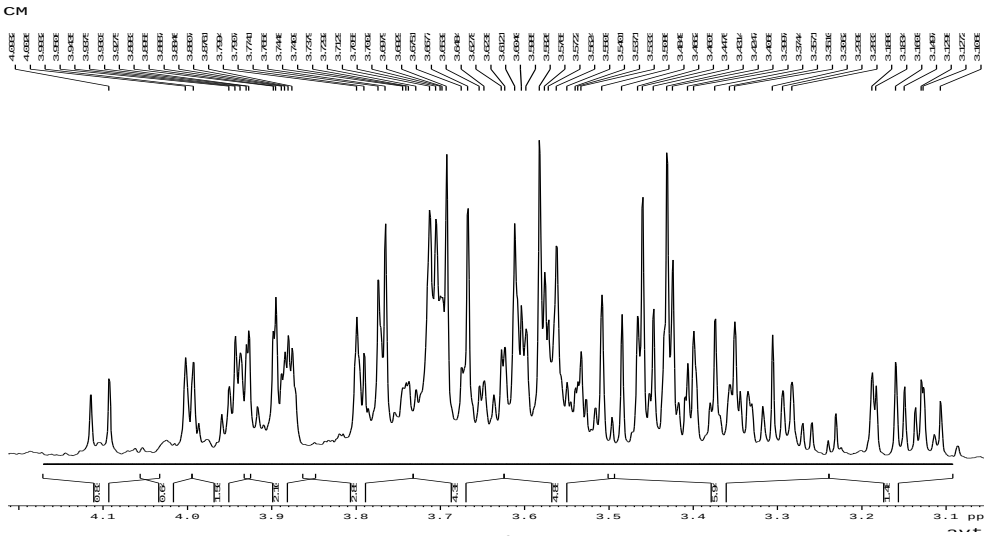

Figure 2: 1H NMR Spectra of Citrus maxima biomaterial

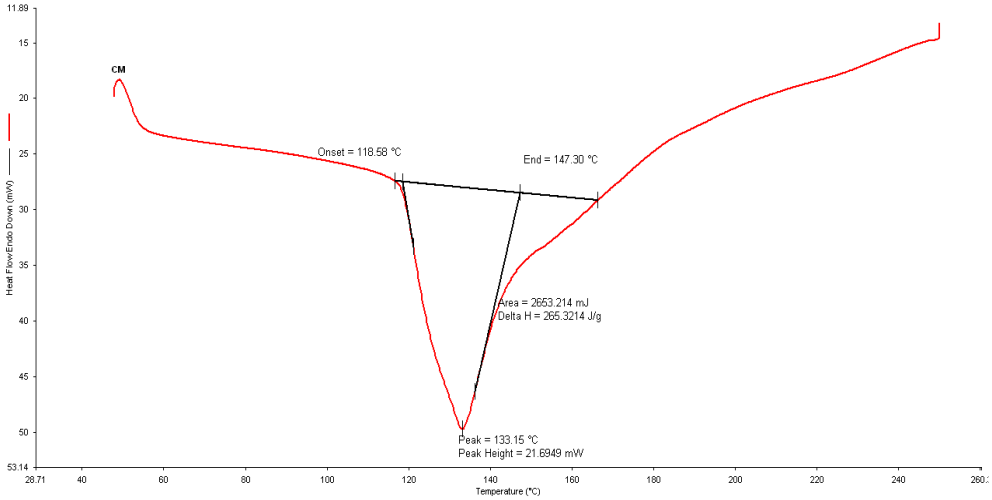

Figure 3: DSC curve of Citrus maxima biomaterial

Formulation and evaluation of biolayers using the biomaterial

Six biolayers were successfully prepared from Citrus maxima biomaterial in the ratio of drug: biomaterial 1:0.5, 1:1, 1:2, 1:3, 1:4 and 1:5 respectively. The weight of prepared bisoprolol loaded biolayers of biomaterial varied from 46.08±0.04 mg to 70.46±0.55 mg for BC1 to BC6. The thickness of biolayers of biomaterial ranges from 0.25±0.02 mm to 0.72±0.01 mm. The maximum folding endurance was obtained for biolayer BC6 (156.67±0.57). The measured surface pH for all batches was found near to neutral pH (Table 2).The film formulations showed maximum tensile strength for BC6. The percent elongation ranged from 5.43±0.28 % to 7.80±0.07 %. All the biolayers showed % moisture uptake in the range13.34±0.11 to10.13±0.08. The film formulation BC6 showed maximum content uniformity(Table 3).

Table 2: Evaluation parameters of bisoprolol loaded biolayer of Citrus maxima

Formulation	Wt.Uniformity (mg)	Thickness (mm)	Folding endurance	Surface pH
BC1	46.08±0.04	0.25±0.02	116±0.57	6.9±0.16
BC2	51.04±0.06	0.32±0.15	123±1.15	6.6±0.15
BC3	57.13±0.13	0.42±0.01	139±1.52	6.8±0.13
BC4	63.13±0.02	0.56±0.02	143±0.57	6.7±0.14
BC5	67.80±0.49	0.63±0.01	149±1.52	6.8±0.13
BC6	70.46±0.55	0.72±0.01	156±0.57	6.8±0.15

Table 3: Additional evaluation parameters of bisoprolol loaded biolayers of Citrus maxima

Formulation	Tensile strength	Elongation (%)	Moisture uptake (%)	Content uniformity (%)
BC1	93.20±0.47	5.43±0.28	13.34±0.11	73.03±0.12
BC2	98±0.21	5.87±0.11	12.45±0.11	80.71±0.44
BC3	109.64±0.91	6.37±0.07	12.44±0.21	81.6±0.38
BC4	116.66±0.95	6.62±0.13	11.16±0.07	86.14±0.04
BC5	120.84±0.57	7.19±0.11	10.20±0.11	90.69±0.30
BC6	135.54±0.87	7.80±0.72	10.13±0.08	94.56±0.67

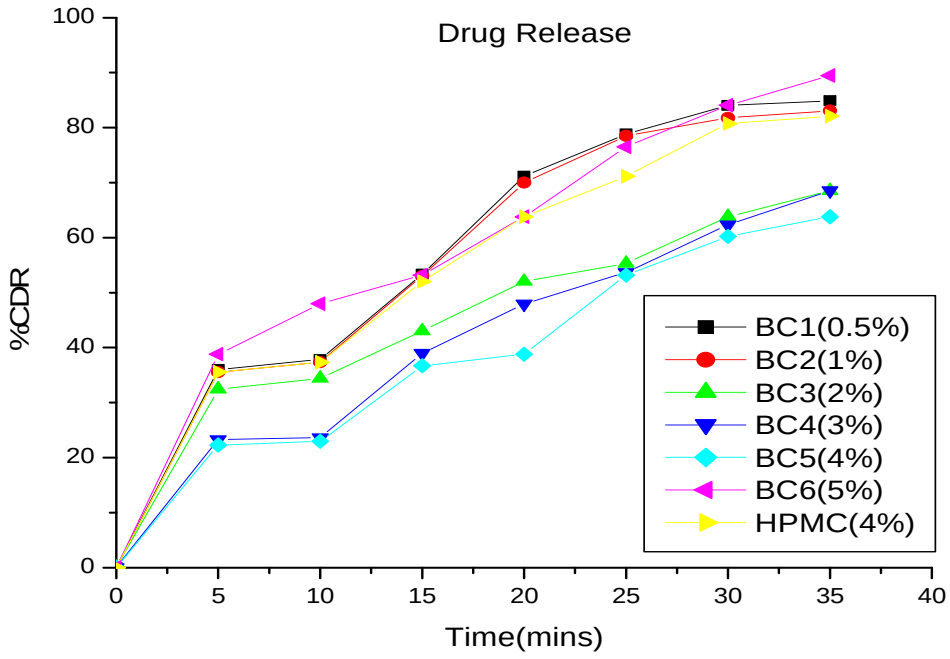

Figure 4: *In-vitro* drug release of bisoprolol loaded biolayers of *Citrus maxima*

The percentage release of film formulations containing bisoprolol drug and Citrus maxima bio-polymer (0.5, 1, 2, 3, 4, 5 %) was found to be in the order BC6> BC5> BC4 > BC3 >BC2 > BC1. The maximum drug release was observed for BC6 formulation was 92.73 %, which was comparable to HPMC film (Figure 4).

4. Conclusion

In the present study the biolayers were prepared using Citrus maxima biomaterial that exhibited appreciable folding endurance. The in vitro studies confirmed that the biolayers prepared using isolated biomaterial showed a good release profile in a controlled manner. Hence this natural biomaterial can act as a promising excipient for formulating film formulations. Moreover the biomaterial has been isolated from an edible source, it can prove an effective alternative to conventional polymers.

Acknowledgement

We are thankful to SRMSCET(Pharmacy), Bareilly, U.P for providing IR spectral analysis, Dibrugarh University, Assam for providing DSC analysis and SAIF, Punjab University, Chandigarh for providing 1H NMR of the isolated biomaterial.

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Source of support: Nil, Conflict of interest: None Declared