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FORMULATION, OPTIMIZATION AND EVALUATION OF SUSTAINED RELEASE BUCCAL PATCHES OF PROPRANOLOL HYDROCHLORIDE USING NEEM GUM

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ABSTRACT

Mucoadhesive patch releasing the drug in the oral cavity at predetermined rate may present advantages over traditional dosage forms such as tablets, gels and solutions. The present study was focused on preparation and evaluation of mucoadhesive buccal patches for the controlled systemic delivery of Propranolol Hydrochloride using neem gum and hydroxypropyl methylcellulose (K100 M) as polymers in various proportions and combinations by solvent casting technique to avoid first pass hepatic metabolism. Propylene Glycol was used as plasticizer. The developed patches were evaluated for the physicochemical, mechanical and drug release characteristics like weight variation, thickness, folding endurance, tensile strength, swelling study, surface pH, mucoadhesive strength, in vitro residence time, drug content uniformity and drug release. The patches showed desired mechanical and physicochemical properties to withstand environment of oral cavity. The in-vitro release study showed that patches could deliver drug to the oral mucosa for a period of 8 h. the patches exhibited adequate stability when tested under accelerated conditions.

KEYWORDS: Mucoadhesive Buccal Patch, Propranolol Hydrochloride, Drug Release.

INTRODUCTION

Buccal drug delivery is a highly effective way to improve bioavailability. This is because the buccal mucosa has a rich blood supply which offers direct access to the systemic circulation through the external jugular vein which bypasses the drugs from the hepatic first – pass metabolism, leading to higher bioavailability. Buccal drug delivery is well accepted by patients as the buccal cavity is easily accessible for self-medication. In addition, buccal dosage forms allow drug absorption to be rapidly terminated in case of an adverse reaction. Formulations of buccal dosage forms include adhesive tablets, gels and patches of which patches are preferable, because patches have several advantages like they can overcome the problem of relatively short residence time of oral gels on mucosa as these gels are easily washed away by salivary secretion and also a patch offer greater flexibility and comfort than adhesive tablets.

Propranolol hydrochloride is widely used β blocker, in the treatment of Hypertension, Angina pectoris and Cardiac arrythmia. When administered orally, frequent dosing is needed due to short biological half-life (t1/2-3-5hrs). Secondly drug undergoes high hepatic first pass metabolism thus bioavailability is reduced to 15-23 % only. It has also been reported to cause gastrointestinal discomfort. Buccal route of drug administration may be a promising approach to overcome the above problems. Thus, the present work deals with the formulation and characterization of mucoadhesive buccal patches of propranolol hydrochloride using mucoadhesive polymers like Neem Gum.

MATERIALS AND METHODS

Propranolol hydrochloride was purchased from Yarrow Chem Products. Mumbai. Neem Gum was also purchased from Yarrow Chem Products. Mumbai. Hydroxypropyl Methylcellulose (K100 M) was procured from Research Lab Fine Chem Ltd. Mumbai and Propylene Glycol was secured from Thermosil Fine Chem Industries. Charholi. All other reagents used were of analytical grade. The patches were prepared by Solvent Casting Method.

Preparation of Mucoadhesive Buccal Patches with Backing Layer

Backing layer

Backing layers were prepared by solvent casting method. EC (5% w/v) was dissolved in a mixture of acetone and isopropyl alcohol (65:35). dibutyl phthalate

was added as the plasticizer in different concentrations and elasticity was optimized. The plasticized EC solution was poured into a petri plate of 7.5 cm internal diameter in different concentrations for optimizing thickness of backing layer on a level surface and allowed to air dry at controlled rate by covering the petri plate with an inverted funnel.

Mucoadhesive Buccal Patches

Patches were prepared by solvent casting method. Polymers were dissolved in their respective solvents, neem gum was dissolved in cold water and HPMC K100M was dissolved in water and then mixed properly, this polymeric dispersion was then stirred on magnetic stirrer for a period of 1hr to get a homogenous clear solution, followed by sonication for 15 minutes. Propylene glycol was added as plasticizer and stirring was continued for another 30 minutes. To this mixture required quantity of drug propranolol was added mixed thoroughly and kept aside for few hrs, this mixture was poured on prepared backing layer of ethyl cellulose and allowed to dry overnight. Petri plate was covered with inverted funnel to allow uniform evaporation of the solvent. The dried patches were removed and cut into 2 x 2 cm. packed in aluminium foil and stored in glass container.

Table 1: Composition of buccal patches of propranolol hydrochloride.

Ingredients	F1	F2	F3	F4	F5	F6	F7
Propranolol hydrochloride.	784 mg	784 mg	784 mg	784 mg	784 mg	784 mg	784 mg
Neem Gum	500 mg	500 mg	350 mg	350 mg	138 mg	200 mg	200 mg
HPMC K100 M	500 mg	200 mg	350 mg	138 mg	350 mg	200 mg	500 mg
Propylene Glycol	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Water	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

Evaluation of Mucoadhesive Buccal Patches

1. Organoleptic Evaluation

Prepared Patches were evaluated for appearance, colour and texture by visual inspection and touch.

2. Weight and thickness of the patches.

The average weight of 5 samples of each formulation were determined by weighing individually on a Digital Balance. 5 samples of each formulation were taken, and the thickness was measured using micrometer screw gauge at three different locations, and the mean thicknesses were calculated.

3. Folding endurance

The folding endurance was determined by repeatedly folding one patch at the same place till it broke or folded up to 250 times without breaking. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance.

4. Tensile strength and % Elongation

Dried patch samples were cut into uniform strips (2 x 2 cm). Two pieces of cardboard (1 cm × 2.5 cm) were attached to the upper and the lower end of the patch using cyanoacrylate resin adhesive. Attaching the patch to the cardboard facilitates clamping it to the jaws of the modified device used for tensile strength (TS) measurement, thus preventing pressure on the patches and slipping prior to or during application. The modified device contains a rectangular frame with two jaws made up of aluminium. One jaw is stationary in the front and the other one is movable and can be pulled by loading weights on the pan attached with string to the movable part. The patch on the cardboard was clamped between the two jaws of the device positioned at a distance of 3 cm. The weights were gradually added to the pan till the patch was broken. The weight necessary to break the patch was noted as breaking force and the simultaneous distance travelled by the pointer on the graph paper indicated the elongation at break (E/B).

TS and percent elongation can be obtained by following formula

$$Tensile\ strength = \frac{force\ at\ break}{\text{cross sectional area of sample}}$$

$$\%\ Elongation = \frac{\text{increase in length}}{\text{original length}} * 100$$

5. Swelling study

The swelling ratio was measured by placing the patches on the surface of 2% agar plates. Agar plates were, then, incubated at 37°C, and the patches were weighed at every hour for 3 hours after incubation. Finally, the swelling index was calculated as:

Swelling index (%) = (Wt – W0) / W

Where, W0 is the initial weight, and Wt is the weight of swelled patch after the incubation for time t.

6. Surface pH.

Patches were left to swell for 3 h on agar plate prepared by dissolving 2% (m/v) agar in simulated human saliva (SHS; NaCl [0.126 g], KCl [0.964 g], KSCN [0.189 g], KH2 PO4 [0.655 g], and urea [0.200 g] in 100 ml of distilled water) under stirring and then pouring the solution into a Petri dish until gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch.

7. Mucoadhesive strength.

Freshly excised buccal mucosa of an adult goat was used as a model membrane for the measurement of bioadhesive strength. Fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by

removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer pH 6.8 at 37°C. Bioadhesive strength of patch (n = 3) was measured on a modified two-arm physical balance. The pan at the left arm of the balance was detached and to the lever of the left arm, was hung a vertical thread, which had a rubber stopper tied to its end, hanging downward. The patch to be tested was adhered to the downward facing side of the rubber stopper. Goat buccal mucosa was tied onto the open mouth of a glass vial filled with isotonic phosphate buffer. The vial was fitted in the center of a glass beaker filled with SHS (pH 6.8, 37°C ± 1°C). The apparatus was set such that the vial (mucosal membrane tied on it, facing upward) lies exactly below the rubber stopper (patch adhered onto it, facing downward). The rubber stopper was lowered so as to make the patch come in contact with the membrane. After facilitating the contact between the two, weight was put on the right limb of balance and increased gradually until the patch got detached from the buccal mucosa. The weight (gram force) required to detach the patch from the mucosal surface gave the measure of detachment stress.

8. In vitro residence time

The ex vivo bioadhesion time was ascertained (n = 3) after application of the patches onto freshly cut goat buccal mucosa. The fresh goat buccal mucosa was fixed in the inner side of the beaker, above 2.5 cm from the bottom, with cyanoacrylate glue. One side of each patch was wetted with one drop of isotonic phosphate buffer pH 6.8 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 s. The beaker was filled with 500 ml of phosphate buffer pH 6.8 and was kept at 37°C ± 1. After 2 min, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored up to 6 h. The time required for the patch to detach from the sheep buccal mucosa was recorded as the mucoadhesion time.

9. Drug content uniformity

patches of each formulation were taken in separate 100ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for few hrs. solutions were filtered, diluted and analysed at 290 nm in UV. Average of drug contents of three patches was taken as final reading.

10. Drug release

The drug release study from the patches was carried out using a USP 23 Type-2 rotating paddle dissolution test apparatus (Electrolab). 500 ml of phosphate buffer solution (pH 6.8) at 37°C ± 5°C was used as the dissolution medium with a stirring rate of 50 rpm. A patch of 2 x 2 cm diameter was fixed onto a glass disc with the help of cyanoacrylate adhesive. The disc was put at the bottom of the dissolution vessel such that the patch remained on the upper side of the disc. Samples (5 ml) were withdrawn at a predetermined time interval of 1 Hr and replaced with an equal volume of dissolution medium. The samples were filtered through a 0.45 mm filter and appropriately diluted with water and assayed spectrophotometrically at 290 nm. The experiment was performed in triplicate and average values were reported.

RESULTS AND DISCUSSIONS

1. Organoleptic Evaluation

Prepared patches of Propranolol Hydrochloride were found to be smooth, colourless with good flexibility and showed no visible imperfection.

2. Weight and Thickness of the patch

Physicochemical characteristics of the formulated patches are shown in [Table 3]. The prepared patches were Based on the quantities of the polymers, Neem Gum and HPMC K100M, the thickness, as well as the weight of different patches were found to be varying. The patch thickness was observed to be in the range of 0.20 ± 0.06 mm to 0.25 ± 0.05 mm and weight was found to be in the range of 70 ± 1 mg to 134 ± 2 mg. It was observed that as the percent of the polymers increased, thickness and weight also increased, as more amount of polymer resulted in the thickness as well as the weight of patches.

3. Folding endurance

All the patches had the satisfactory folding endurance of >250. The range of folding endurance study ensured flexibility of these formulated buccal patches.

4. Tensile strength measurement

The Tensile Strength of the patches varied between 2.33 ± 0.32 and 2.83 ± 0.20 kg/mm and E/B was between 30 ± 5 and 50 ±2% [Table 4]. The observed results revealed that TS increased with an increase in polymer concentration. Prepared patches showed acceptable Tensile strength among which formulations F1 and F2 showed highest TS ,all patches were found to be strong that can withstand mechanical disturbances in mouth.

5. Swelling study

Swelling study Swelling behaviour was assessed by measuring equilibrium degree of swelling by the weight method. The swelling profile of all the formulations, as shown in Table No7 revealed that the swelling index of the patches increased with an increase in the polymer concentration as well as with the HPMC viscosity. SI ranges from 17±1.2 to 28±0.72%.Formulation F1 showed highest swelling as concentration of neem gum and HPMC present in it is highest.

6. Surface pH determination

Acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers. The surface pH of the patches ranged between 6.39 ± 0.15 and 6.83 ± 0.11. The results were found to be close to neutral in all the formulations, and this means that they have less potential to irritate the buccal mucosa.

7. Mucoadhesive strength

All patches showed appreciable bioadhesive detachment stress, which ranged between 152 ± 3.25 and 168 ± 3.25 [Table 4] indicating a potential of sustaining the stay and enhancing contact with buccal mucosa. Formulation F1 showed highest mucoadhesive strength as it contains more amount of Neem Gum which is used as mucoadhesive polymer whereas F2 showed less mucoadhesive strength as amount of Neem Gum in it was less. Hence it was concluded that mucoadhesive strength depends on amount of mucoadhesive polymer (Neem Gum) used.

8. In vitro residence time

The ex vivo bioadhesion time (residence time) of the patches varied from 330± 2 to 390 ± 2 min [Table 4]. It was observed that a gradual increase in the residence time occurred with a concomitant increase in the polymer viscosity. The observation can be assigned to the inherent property of the polymer Neem Gum and HPMC that although showing significantly higher swelling is less water affined and hence tends to retain its structure better. In addition, increased viscosity led to formation of surface gel that maintained its structural integrity for a longer period of time, thereby resulting in increased residence time.

9. Drug content uniformity

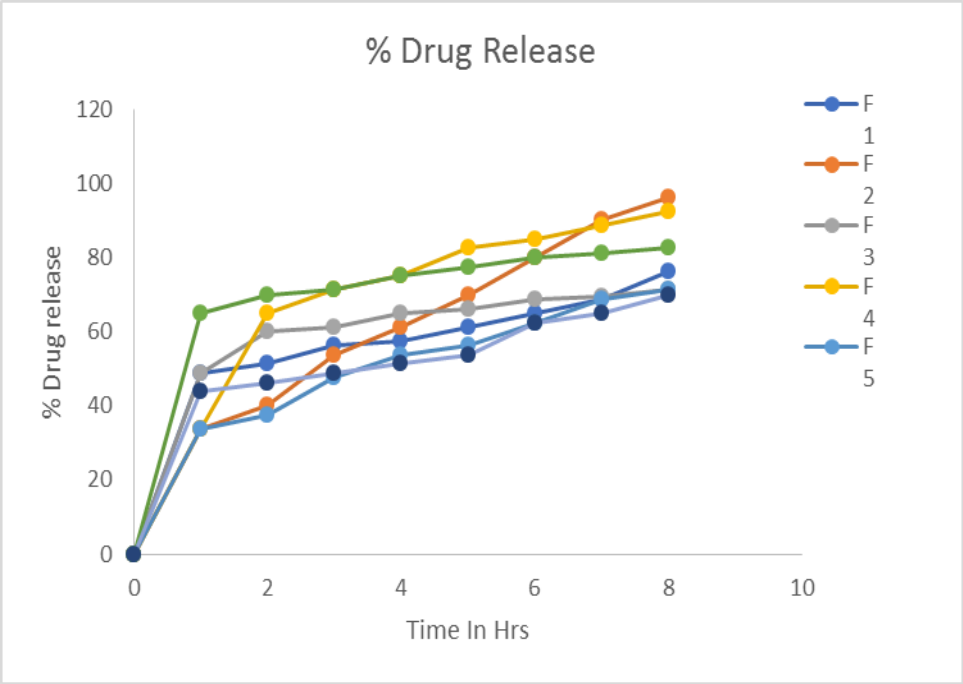
The drug content (%) in all formulations varied between the ranges of 91.25±0.25% to 96.5±1.0 %. This indicates that the drug dispersed uniformly throughout the polymeric patches.

10. In vitro drug release study

The in vitro drug release profiles of bioadhesive patches are shown in Table 3. Drug release from Propranolol Hydrochloride patches ranges from 33.75 to 65 % after 1 hour and 70 to 96.25 % after 8 hours. It could be concluded from the results that the patches containing lesser concentration of the polymer gave a faster release of the drug. The rate of drug release decreased substantially on increasing the concentration of Neem Gum and HPMC. Formulation F2 showed highest release in 8 hours and was selected as optimized batch.

Table 2: In vitro Drug Release of mucoadhesive buccal patches of Propranolol Hydrochloride.

Time In Hrs	F1	F2	F3	F4	F5	F6	F7
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	48.75	33.75	48.75	58.75	33.75	65	43.75
2	51.25	40	60	65	37.5	70	46.25
3	56.25	53.75	61.25	71.25	47.5	71.25	48.75
4	57.5	61.25	65	75	53.75	75	51.25
5	61.25	70	66.25	82.5	56.25	77.5	53.75
6	65	80	68.75	85	62.5	80	62.5
7	68.75	90	69.5	88.75	68.75	81.25	65
8	76.25	96.25	71.25	92.5	71.25	82.5	70



Graph 1: Comparative Drug Release Profile of formulations F1 to F7.

Table 3: Evaluation of different mucoadhesive buccal patches of Propranolol Hydrochloride.

Batch Code	Weight (mg)± SD *	Thickness (mm)± SD*	Folding endurance ±SD *	Surface pH ±SD *	Drug content (%)± SD *
F1	134±1	0.24±0.06	>250	6.52±011	92.5±0.50
F2	94±3	0.21±0.04	>250	6.44±0.13	96.5±1.0
F3	109±3	0.24±0.02	>250	6.62±0.11	95±1.0
F4	70±2	0.20±0.004	>250	6.83±0.14	92.75±0.25
F5	78±2	0.21±0.005	>250	6.60±0.16	91.25±0.25
F6	70±2	0.21±0.005	>250	6.53±0.16	93.75±0.50
F7	91±2	0.24±0.004	>250	6.39±0.14	92.5±0.50

*(n=3)

Table 4: Evaluation of different mucoadhesive buccal patches of Propranolol Hydrochloride.

Batch Code	Swelling Index (%) ± SD*	Tensile Strength (kg/mm) ± SD*	Elongation at Break (%) ± SD*	Mucoadhesive Strength (gms) ± SD*	Residence Time (min) ± SD*
F1	28±0.72	2.83±0.20	30±5	168±3.25	390±2
F2	24±1.0	2.80±0.20	40±3	165±2.84	345±3
F3	23±0.76	2.5±0.35	40±3	165±3.20	350±2
F4	17±1.5	2.55±0.20	45±2	152±3.25	340±2
F5	17±1.2	2.47±0.20	40±4	155±3.0	340±1
F6	17±1.5	2.33±0.32	50±2	144±2.47	330±2
F7	27±0.65	2.5±0.40	30±3	163±2.08	345±1

*(n=3)

CONCLUSION

In the present study, an attempt has been made to develop a novel mucoadhesive drug delivery system in the form of the buccal patches for the release of Propranolol Hydrochloride in a unidirectional manner, to maintain constant therapeutic levels of the drug and for long time. Although all buccal patches exhibited satisfactory results, best results were obtained with optimized formulation F2 containing Neem Gum and HPMC K100 M in 1:0.75 ratios. The above study concluded that the possibility of the making of mucoadhesive drug delivery system for Propranolol which will be more efficacious and acceptable than conventional drug delivery of Propranolol Hydrochloride and also having satisfactory controlled release profile which may provide an increased therapeutic efficacy.

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