FORMULATION AND IN VITRO EVALUATION OF CATECHIN MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT

The aim of the present work is to investigate the formulation of catechin buccal patches for controlled release. The half life of catechin is 3 hrs. Catechin has many good pharmacological action which required prolonged drug release and to avoid degradation of drug in GIT. The buccal patches were prepared by solvent casting method using chitosan. The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH and in vitro diffusion study using Franz diffusion cell. The optimized patch of 2% chitosan and Marrigold extract exhibit in vitro release of 54% through cellophane membrane. The patches were stable at a temperature range of 2-30°C.

KEYWORDS: catechin, buccal patch, diffusion, in vitro.

INTRODUCTION

The catechin has a half life of 3 hrs and shows a bio availability of less than 5 percentages. The catechin has low bio availability and high first pass metabolism, the buccal release formulation has its own significance for improving the systemic concentration. The polymer used in this investigation are chitosan. Chitosan is a natural bio compatible and bio degradable polymer, extensively used in the development of mucoadhesive buccal drug delivery. Chitosan as a biodegradable polymer has proved its ability as the safest and efficient material for the development of novel drug delivery system for various drug molecules. Due to its inherent properties this is one of the preferred polymer for the formulation developers. Chitosan has an excellent film forming ability and better muco adhesive property. the mucoadhesive property of chitosan either due to its ability to form secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of...
chitosan and the negatively charged mucin. Apart from this chitosan has a cell binding and membrane permeation activity. So in this investigation, an attempt has been made to develop a mucoadhesive bucal patches of Catechin by using chitosan, thus expecting a modified release characteristics of the drug.

MATERIALS AND METHODS

Catechin, HPMC, CMC was obtained as a gift sample from KTPL, Chennai, chitosan was obtained from Balaji chemicals, Gujarat. All other reagents and chemicals were of analytical or pharmaceutical grade.

Isolation of Oleoresin- Extraction

The water from the raw material was removed and then dried in a drier for 8 to 10 hour under controlled conditions at a temperature lower than 60-65°C to a moisture level of 8% to 10%. The dried flowers are powdered to a particle size of 0.5 mm and then extracted. Of the solvents, hexane, acetone, ether, isopropyl ether, methylenechloride, 1, 2- dichloroethane, chloroform, hexane- acetone and hexane- acetone-toluene; hexane was found to be the efficient solvent (Verghese.J 1998b) for better yield of xanthophylls. The powdered marigold flowers were then packed in a column and were eluted using analytical grade hexane under mild conditions (30°C, for 15 min). The extract (miscella) so obtained was distilled, under controlled conditions until the desired quantity of the solvent in the oleoresin was achieved. In order to prevent the degradation of xanthophylls, 0.1 to 0.3 % of ethoxyquin was mixed to the final product with stirring at a temperature less than 45°C. Purified mainly by phase partition, by using petroleum ether and aqueous methanol (90%) or ethylene dichloride (EDC). The product obtained after extraction was then washed with EDC. The solvent was removed and dried.

Preparation of catechin buccal patches

Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent. The buccal mucoadhesive films of polyphenols were prepared using chitason, sodium carboxyl methyl cellulose and Hydroxy propyl methyl cellulose E15 cps polymers by casting method. HPMC polymer (1000 mg), Marigold extract, Poly ethylene glycol (PEG 600) and sodium CMC was weighed accurately and placed in 5 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 minutes for swelling of polymer. Further 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then 1ml of MDC was added to the polymer solution. The drug (polyphenol)
solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a magnetic stirrer. Finally 1 ml of distilled water added and stirred well. The glass mould of size 5 × 3 cm² was placed over a flat surface. The drug-polymer mixture was poured into the glass mould. The mould was kept in hot air oven for 1 hour at 50°C for drying and sudden evaporation. After this period, an inverted funnel was placed over the mould overnight to remove the remaining solvent. The film was removed from the mould, packed in wax paper, and stored in a desiccator.

**Folding Endurance**[^4][^5]

Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

**Patch thickness**[^6]

The thickness of the buccal patch was measured by using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

**Weight variation**

Ten patches of 1 cm² were weighed individually and average of those patches measured.

**Surface pH**[^7][^8][^9]

Buccal patches were left to swell for 1 hour on the surface of 2% agar plate, it was allowed to stand until it is solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

**% Swelling Index**[^10][^11]

The developed buccal patches were cut in to small sizes of 1.5 cm diameter. This patch was placed on the surface of 2% agar plate and the diameter at different time intervals where taken up to 5 hrs and the percentage swelling index was calculated using the formula,

\[
\% \text{SD} = \frac{D_t - D_o}{D_o} \times 100
\]

Where, \% SD = % swelling by diameter method \(D_t\) = diameter of swollen patch after time \(t\), \(D_o\) = original patch diameter.
% Moisture content$^{[4,5]}$

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by the formula:

\[
\text{% Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]

Tensile Strength$^{[12,13]}$

**Instrument:** The apparatus was locally assembled and was a modification of the apparatus applied by Parodi et al. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane.

**Tensile strength,** \( T = \text{Mg/Bt Dynes/cm}^2 \)

\( T = \frac{\text{force at break}}{\text{initial cross-sectional area of sample}}. \)

Where,

\( M = \text{mass in grams}, \ g = \text{acceleration due to gravity 980 cm/sec}^2, \ B = \text{breadth of the specimen in cm}, \ t = \text{thickness of sample in cm}. \)

% Drug content$^{[14,15,16]}$

Prepared buccal patch was dissolved in 100ml of Phosphate buffer solution (PBS) of pH 6.8 using a magnetic stirrer for 12 hours and then sonicated for 30 minutes. The solution was centrifuged and then filtered. The drug content determination was done by using UV spectroscopy at 223 nm.

In vitro diffusion study$^{[17,18]}$

In vitro diffusion study was performed by using modified franz diffusion cell across cellophane membrane. Phosphate buffer solution (PBS) of pH 6.8 was used as medium for diffusion study. Patches of dimension 2x2cm$^2$ were placed on the membrane, which was placed between donor and receptor compartment of franz diffusion cell. Cellophane membrane was brought in contact with PBS of pH 6.8 filled in receptor compartment. Temperature was maintained at 37ºC with stirring at 50 rpm using magnetic bead stirrer. 1ml of sample was withdrawn from receptor compartment at pre-determined interval and was replaced with fresh PBS of pH 6.8. With suitable dilution, samples were measured for
absorbance at 730nm using UV visible spectrophotometer. Using 20-200μl of gallic acid as standard were dispensed into triplicate sets of 25ml volumetric flasks. 500μl of Folin Ciocalteau (diluted 1:1 with water) reagent followed by 100μl of 30% Na2CO3 were added to the flasks and mixed. The volume is made up to 25 ml mark by distilled water and allowed to react at room temperature for 30 min. The blue color developed is read against reagent blank at 730 nm in a Shimadzu UV-VIS (UV-2450) spectrophotometer. The gallic acid concentration was plotted against absorbance.

**Stability study**\(^{[19,20]}\)

Stability studies were performed in accordance with ICH guidelines for accelerated stability testing. Patches (2x2 cm\(^2\)) were wrapped individually in aluminium foil and maintained at refrigerated temperature (4±20C), room temperature (30±20C) and oven temperature (450C and 75 % RH) for a period of 1 month. Changes in the appearance and drug content of the stored patches were investigated after storage period.

**RESULTS AND DISCUSSION**

The results of evaluations were summarized in table (Table No.2). The developed chitosan patches were smooth and flexible. All the characteristics such as folding endurance, thickness average weight, % swelling index, moisture content, tensile strength and % drug content were increased with increase in concentration. The reason behind this is, at higher concentration the more polymer chain with flexible nature may be available, which resulted in higher folding endurance value.\(^{[22]}\) It was already proved by the researchers that, the thickness, average weight, % swelling index, moisture content and tensile strength will increases with increase in concentration of polymer.\(^{[23,24]}\) The surface pH value indicating that the patches may not produce any irritation to oral mucosa and safer for application.\(^{[25]}\) The % drug content was higher with F2, this may be due to higher entrapment efficacy of chitosan polymer at higher concentration.\(^{[24]}\)

The diffusion data obtained for the buccal patches containing catechin with different concentrations of chitosan and MG extract were closely assessed. The % drug diffused was plotted against time (Table No.3). The % drug diffused from formulation F1 and F2 were found to be 33.84 % and 58.73 % respectively after 6 hours diffusion (Table No.3). From the data it can be assumed that the %drug diffused from formulation F2 containing MG extract and chitosan had approximately 15% greater release than formulation F1. When MG extract combines with the optimum level of polymer, there may be a possibility of good initial burst
release as well as better diffusion profile for a drug such as catechin. This may be a possibility for improved release profile of formulation F2. Apart from this, chitosan possess inherent permeation enhancing property, which might have resulted in a synergistic effect with MG extract incorporated in formulation for improved release properties of chitosan based buccal patch.\textsuperscript{[26]} After good initial burst release from F2, good controlled release profile was maintained for the entire duration of investigation. This may be due to the natural polymeric structure of chitosan which might have been reflected in F2 with 2\% chitosan.

Accelerated stability studies were performed in accordance with ICH guidelines with necessary modifications. The studies were carried out to verify the changes in physical characteristics such as color, thickness, folding endurance and pH along with changes in \% drug content at three different conditions of higher temperature (45±2\textdegree C), room temperature (30±2\textdegree C), and refrigeration temperature (4±2\textdegree C). After the completion of one month, formulation F1 with 1\% chitosan had 98.90±0.05\% of drug content reported at room temperature, with a minor decrease during the storage at refrigeration temperature of 4 ± 2\textdegree C. But when the drug content was estimated for F1 at oven temperature, the drug content dropped significantly to 73.30±0.05\%. Similar drop in \% drug content were observed in case of formulation F2 when kept at higher temperature. Loss in \% drug content was found to be minimum in case of formulation of F2 with MG extract. (Table No.4).

Table 1: Composition of formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation code</th>
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<tbody>
<tr>
<td></td>
<td>F1</td>
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<tr>
<td>Catechin</td>
<td>25 mg</td>
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<tr>
<td>Chitosan(%) in acetic acid 1%</td>
<td>1 %</td>
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<tr>
<td>MG extract</td>
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<td>PEG 600</td>
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Table 2: Characterization of developed formulations

<table>
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<tr>
<th>FORMULATION CODE</th>
<th>F1</th>
<th>F2</th>
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</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>smooth</td>
<td>smooth</td>
</tr>
<tr>
<td>Texture</td>
<td>flexible</td>
<td>flexible</td>
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<tr>
<td>Folding endurance</td>
<td>290±2</td>
<td>280±2</td>
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<tr>
<td>Thickness(mm)</td>
<td>6±0.1</td>
<td>7±0.2</td>
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<tr>
<td>Average weight (mg)</td>
<td>10.8</td>
<td>11.3</td>
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<td>Surface pH</td>
<td>6.6</td>
<td>6.7</td>
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<tr>
<td>welling index(after 5 hours)</td>
<td>17</td>
<td>20</td>
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<tr>
<td>% Moisture content</td>
<td>1.4</td>
<td>1.8</td>
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<tr>
<td>Tensile strength (Kg/cm2)</td>
<td>17±0.02</td>
<td>19±0.03</td>
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<tr>
<td>% Drug content</td>
<td>96.05</td>
<td>98.79</td>
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Table 3: Comparison of % drug diffused from formulation F1 and F2

<table>
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<tr>
<th>Time (hrs)</th>
<th>% Drug diffused</th>
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<tr>
<td>0</td>
<td>0</td>
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<td>0.5</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>50.31</td>
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<tr>
<td>6</td>
<td>33.84</td>
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</table>

Table 4: Stability study data of developed formulation F1- F2

<table>
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<tr>
<th>Formulation code</th>
<th>Physical appearance</th>
<th>% Drug content</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>4±2°C</td>
<td>30±2°C</td>
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<tr>
<td>F1</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>F2</td>
<td>+</td>
<td>+</td>
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CONCLUSION
This investigation established the effectiveness of chitosan as a polymer to develop buccal patches containing Catechin. The results shown that buccal patches developed using chitosan were showing excellent characteristics which was ideally required for buccal patches,. More or less the patches were stable at varying conditions. In vitro diffusion profile of Catechin from chitosan was showing good initial burst release along with excellent controlled release profile for 12 hours duration. Based on investigation results, it may be suggested that 2% is the optimum concentration to develop a good buccal patch containing Catechin. Design and development of such buccal patches may be highly beneficial which can deliver drug up to a period of 12hrs duration. Hence application of buccal patches may ensure sufficient level of Catechin in the body to necessary antioxidant effect.

REFERENCES


