Mucoadhesive patches for the delivery of carvedilol were prepared using chitosan, a cationic polymer. Solvent casting technique was used for the purpose of preparation of buccal patches. Different physico-chemical properties like content uniformity, thickness, surface pH, radial swelling, residence time and bioadhesive force were determined. In-vitro drug release was carried out in USP dissolution apparatus. For in-vitro residence time, all patches, except C-2 (2% m/v chitosan) remained attached to the mucosal surface till complete erosion. Maximum bioadhesion was recorded for C-1 (1% m/v chitosan), followed by the C-3 (3% m/v chitosan), then C-2 (2% m/v chitosan). The in-vitro drug release within 1 h from C-1, C-2 and C-3 patches was 10.96%, 15.42% and 12.32% respectively, and after 8 h it was found 37.77%, 50.23%, and 42.87% respectively. Non-storage patches released 50.23% after 8 h, whereas patches stored for 4 months released 40.1% drug in the same period.

**Keywords:** Carvedilol, Buccal patches, Mucoadhesion, Drug release, Ageing

**INTRODUCTION**

Retentive Buccal mucoadhesive formulation may prove to be a viable alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Buccal delivery of drug provides an alternative to the oral route of drug administration. In recent years, delivery of therapeutic agent through various trans-mucosal routes gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration.

Buccal mucosa is an attractive route for systemic delivery of drugs since it is relatively permeable with a rich blood supply. A drug can be easily applied and localized to the application site and can be removed from there if necessary. Attempt has been made earlier to formulate various Mucoadhesive buccal devices, including tablets, films, patches, disks gels and ointments. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gel and ointment. In the present study, the bioadhesive polymer chitosan was used for the preparation of buccal patches. A wide variety of pharmaceutical applications for chitosan have been reported over the last two decade due to its bioadhesion and trans-mucosal drug transport properties. Carvedilol is a β-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many others cardiovascular disorders. In this study, we attempted to formulate Mucoadhesive patches, which would release the drug in a sustained manner using chitosan as mucoadhesive polymer. In addition, the effect of ageing on the mucoadhesive characteristic and the in-vitro release pattern of a selected patch were investigated.

**MATERIALS AND METHODS**

Carvedilol (Aurobindo Pharma Ltd. Medak), Chitosan (Sigma-aldrich, Mumbai), Glacial acetic acid (Qualigens fine chemicals, Mumbai), poly vinyl pyrrolidone (Qualigens fine chemicals, Mumbai) were used. Other chemicals were of analytical grade.

**Preparation of buccal patches**

The buccal patches of Chitosan, containing carvedilol were prepared by dissolving 1, 2, 3 % (m/V) of chitosan in 1.5% glacial acetic acid at room temperature and stirrer for 12 h. To improve elastic and film forming properties of the patches, PVP (1% m/V) was added in all the preparations. PVP was first dissolved in a small volume of distilled water, and then added to the solution of polymer. Glycerol as Plasticizer 5% (V/V) was added in all formulations. The resultant viscous solution was filtered and filtrate was left to stand until all air bubbles disappear. The solution was poured into a clean, dry, glass petri dish and left to dry at room temperature. The dried films were carefully removed from the petri dish, checked for any imperfection or bubbles and cut into 10mm diameter patches. The samples were packed in aluminium foil and stored in a glass container maintained at room temperature.

Patches containing Carvedilol were prepared by dissolving the calculated amount of drug in 20 ml distilled water. The drug solution was added to the polymer solution under stirring (Table-1).

<table>
<thead>
<tr>
<th>Composition</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan (%) m/V</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PVP (%) m/V</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glycerol (v/v)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Evaluation of patches**

**Weight and patch thickness**

Assessment of weight and thickness was done on ten patches by using electronics balance and screw gauge. The mean and standard deviation were calculated.

**Content uniformity**

The drug loaded patch was allowed to dissolved in 100mL phosphate buffer, pH 6.8. The amount of Carvedilol in the patch was measured spectrophotometrically at λmax = 285 nm (n = 5).

**Folding endurance**

For the determination of Folding endurance the patches were folded repeatedly at the same place till it broken or folded up to 300 times, which is considered to reveal good film properties. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

**Surface pH**

Patches were left to swell for 1 h on the surface of agar plate, prepared by dissolving 2% (m/V) agar in warmed phosphate buffer of pH 6.8 under stirring and then set a side till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three reading was recorded.
Radial swelling

Radial swelling was determined by diameter method. After determination of the original patch diameter, the patch was allowed to swell on the surface of an agar plate kept in an incubator maintained at 37°C. Measurement of the diameter of the swollen patch was done at one hour intervals for 6 h. Radial swelling was calculated from the following equation:

\[ S_D(\%) = \left( \frac{D_t - D_0}{D_0} \right) \times 100 \]

Where \( S_D(\%) \) is the percent swelling, \( D_t \) is the diameter of the swollen patch after time \( t \), and \( D_0 \) is the original diameter of the patch at time zero.13

Residence time

The in vitro residence time was determined by a locally modified USP disintegration apparatus using phosphate buffer of pH 6.8 maintained at 37±0.5°C as medium. A segment of rabbit intestinal mucosa was glued to the surface of glass slab, vertically attached to the platform. The patch surface was moistened with 10 µL of phosphate buffer and left for 20 s for initial hydration. On the right pan, a constant weight of 5 g was added at 2 min interval, until the hydrated patch was brought into contact with the mucosal surface. The total weight required for complete detachment of the patch was recorded and the bioadhesion force was calculated per unit area of the patch as follows:

\[ F = \frac{(W_s \times g)}{A} \]

where \( F \) is the bioadhesion force (kg m⁻¹s⁻²), \( W_s \) is the mass applied (g), \( g \) is the acceleration due to gravity (cm s⁻²), \( A \) is the surface of the patch (cm²). The bioadhesion force data reported represent the mean of three determinations.15

In vitro release study

The release study was carried out in a USP dissolution apparatus type 1, slightly modified in order to overcome the small volume of the dissolution medium. The dissolution medium was 50 mL phosphate buffer, pH 6.8, maintained at 37±0.5°C and kept in a glass beaker fixed inside the dissolution flask. The patch was fixed to the central axis, which rotates at 50 rpm. Filtered samples (2 ml) were manually collected at intervals of 1, 2, 3, 4, 5, 6, 7, and 8 h. The samples were compensated with equal volume of phosphate buffer kept at the same temperature. The concentration of the drug release in the medium was assayed spectrophotometrically at 285 nm after suitable dilution with the dissolution medium when necessary. The experiment was carried out in triplicate.16

Ageing:

Optimized drug loaded patches were subjected to accelerated stability testing. Patches were kept in an incubator maintained at 37±0.5°C and 75±0.5 RH for 4 months. Changes in the appearance, residence time, release behaviour and drug content of the stored buccal patches were investigated after 1, 2, 3, and 4 months. The data presented were the mean of three determinations.17

RESULTS AND DISCUSSION

The results of Physical Characteristics of patches containing individual concentration of polymer are shown in Table 2. The patches were 10 mm in diameter, and 1.01±0.01 to 1.07±0.02 mm in thickness. The weight ranged from 117±0.15 to 123±0.22 mg. The surface pH of all formulations was nearer to neutral (7±7) and hence no mucosal irritation was expected. The recorded folding endurance of the patch was >300 times. Assessment of the swelling behaviour was done by measuring radial swelling. C-1 patches showed high radial swelling, followed by C-3 and then C-2; the recorded swelling values after 6 h were 51.8±0.78, 92.9±0.01 and 87.0±0.11% respectively. For in vitro residence time, all patches, except C-2, remained attached to the mucosal surface till complete erosion. C-3 patches showed convenient duration for complete erosion (2.7 h), longer duration was recorded for C-1 (10.0 h). C-2 patches retained their integrity during the study time (12 h) without detachment. Maximum bioadhesion was recorded for C-1 (65.60 x 10² kg m⁻³²), followed by the C-3 (50.76 x 10² kg m⁻³²), then C-2 (45.34 x 10² kg m⁻³²).

No correlation was found between the bioadhesion force and residence time of the polymer. It seems that highly bioadhesive polymers do not necessarily reside longer on the mucosal surface. In the patches containing Carvedilol radial swelling was more as compare to the plain patches because the presence of drug would modify the way water is bound to or taken up by the polymer. In addition, the presence of a water soluble drug might improve the surface wetting of the matrix.

The release profile of Carvedilol patches is shown in Fig.1. The extent of Carvedilol release within 1 h from C-1, C-2 and C-3 patches was 10.96%, 15.42% and 12.32% respectively, and after 8 h it was found 37.77%, 50.23% and 42.87% respectively.

Chitosan patches containing 10 mg Carvedilol were subjected to 4-months storage at 37±0.5°C and 75±0.5 RH and found that they exhibit excellent drug content over the storage period. The folding endurance test revealed good flexibility and elastic properties. However, a delay in the residence time of the storage patches was noticed (Table 3). The percent Carvedilol released versus time demonstrates a decrease in the amount of drug released with time. Non-storage patches released 50.23% after 8 h, whereas patches stored for 4 months released 40.1% drug in the same period. The decrease in release during storage may be a direct consequence of the reduced erosion rate of the patches.

### Table 2: Characteristics of mucoadhesive patches containing 2% (m/V) Carvedilol

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content Uniformity (%)</td>
<td>95.44</td>
<td>97.20</td>
<td>98.75</td>
</tr>
<tr>
<td>Patch thickness (mm)</td>
<td>1.02±0.01</td>
<td>1.01±0.01</td>
<td>1.07±0.02</td>
</tr>
<tr>
<td>Patch weight (mg)</td>
<td>123±0.22</td>
<td>117±0.15</td>
<td>119±0.19</td>
</tr>
<tr>
<td>Surface pH</td>
<td>≥7</td>
<td>≥7</td>
<td>≥7</td>
</tr>
<tr>
<td>Folding endurance</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Radial swelling (6 h)</td>
<td>51.8±0.78</td>
<td>92.9±0.01</td>
<td>87.0±0.11</td>
</tr>
<tr>
<td>Residence time (h)</td>
<td>10.0±0.01</td>
<td>12.0±1.1</td>
<td>2.7±0.12</td>
</tr>
<tr>
<td>Bioadhesion force (x10² kg m⁻³²)</td>
<td>48.27±0.42</td>
<td>53.34±0.7</td>
<td>76.82±0.72</td>
</tr>
<tr>
<td>% Release</td>
<td>after 1 h</td>
<td>10.96±0.78</td>
<td>15.42±0.12</td>
</tr>
<tr>
<td></td>
<td>after 8 h</td>
<td>37.77±0.17</td>
<td>50.23±1.20</td>
</tr>
</tbody>
</table>

Verma et al.

Duration properties of the chitosan patches but affected the extent of drug and released the drug for 8 h. Ageing did not affect the elastic properties of the chitosan patches but affected the extent of drug release, this may be attributed to changes in the crystal habit of the drug.

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REFERENCES