Formulation and Physicochemical Characterization of Buccoadhesive Microspheres Containing Diclofenac Sodium

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ABSTRACT

Purpose: The present study involves preparation and evaluation of diclofenac buccal-mucoadhesive microparticles for prolongation of buccal residence time.

Methods: The microparticles were prepared by modified double-emulsion dehydration method (O/W/O2) using sodium carboxymethylcellulose (CMC-Na) as mucoadhesive polymer. Calcium chloride was used as a cross-linking agent. Buccal-mucoadhesive microparticles with different drug to polymers ratios were prepared and characterized by encapsulation efficiency, particle size, DSC (Differential Scanning Calorimetric), flowability, degree of swelling, surface pH, mucoadhesive property and drug release studies.

Results: The best drug to polymer ratio in microparticles was 1:5 (F1). Microparticles showed loading efficiency 51.43% and mean particle size 1013.92 µm. The DSC showed stable character of drug in microparticles and revealed amorphous form. Microparticles had slower release than the commercial tablet (p<0.05). The results of mucoadhesion study showed better retention of diclofenac microparticles in mucosa (>50 min). Histopathological studies revealed no buccal mucosal damage.

Conclusion: It may be concluded that drug loaded buccal-mucoadhesive microparticles are a suitable delivery system for DS.

Introduction

Drugs supplied through the buccal route induce a quick onset of effect and enhanced bioavailability. The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage. Besides, first-pass metabolism and pre-systemic elimination in the gastrointestinal tract are avoided. Furthermore, there is a good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. Delivery of drugs is grouped into three various classes of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Choosing one over another is principally established on anatomical and permeability differences that is between the different oral mucosal areas. The permeability of the buccal mucosa is 4-4000 times larger than that of the skin. The buccal mucosa is thicker and significantly less permeable than the sublingual area. It is usually not able to supply the quick absorption and good bioavailability seen with sublingual administration. The buccal mucosa has an extent of smooth muscle (non-keratinized) and relatively immobile mucosa which makes it a more desirable region for oral transmucosal drug delivery. Thus the buccal mucosa is further suited for sustained delivery applications, delivery of less permeable molecules, and possibly peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability. Hydrogels are hydrophilic bioadhesive matrices that are able of swelling when put in aqueous medium. Usually, hydrogels are cross-linked so that they would not dissolve in the medium and would only absorb water. As water is absorbed into the matrix, chain relaxation happens and drug molecules are released through the spaces or channels within the hydrogel network.

Samaligy et al, formulated diclofenac sodium (DS) buccoadhesive discs containing CP 974, polycarbophil, PEO, SCMC-medium viscosity (SCMCMV), SCM-
ultrahigh viscosity (SCMC-UHV) or their combinations. Discs were prepared by directly compressing the polymer powder or polymer powder mixture with DS using a hydraulic press.\(^7\) Dhanaraju \textit{et al.} prepared sustained release particulate beads of CMC-Na and Na alginate with DS by the ionotropic gelation method using calcium chloride as a cross-linking agent. Beads of DS were produced with different concentrations of polymers.\(^8\) Abha \textit{et al.} formulated the buccal films of DS using PVA and HPMC.\(^5\)

DS is a non-steroidal anti-inflammatory drug (NSAID) which may cause gastro-intestinal inflammation and ulceration in long term therapy. The buccal delivery of DS prevents direct exposure to mucosa therefore decreases the probability of gastrointestinal ulceration.\(^6\) Buccal drug delivery has become important route of administration; thus when it is joined with mucoadhesive drug delivery, it can be called as transbuccal mucoadhesive drug delivery system.\(^6\) The aim of this research was to formulate the buccal disc of DS using mucoadhesive polymers like carboxymethylcellulose sodium.

Materials and Methods

Diclofenac sodium (DS), carboxymethylcellulose sodium (CMC-Na), acetone, almond oil, chloride calcium, isopropyl alcohol, buffer phosphate and buffer phosphate saline (pH 6.8) were obtained from Merck (Darmstadt, Germany). All solvents and reagents were of analytical grade.

Experimental Methods

Method of preparation of CMC-Na microspheres

Double-emulsification method was utilized for the preparation of microspheres followed by cross-linking with calcium chloride according to published method with some modifications.\(^7\) Briefly, 1 ml of almond oil (O\(_1\), containing 50, 66.7 and 100 mg DS) was emulsified for 1-2 min in 10 ml of aqueous phase (containing 500 mg CMC-Na) by stirring at 500 rpm with magnetic stirrer. The primary emulsion (O\(_1\)/W) was poured into 50 ml light liquid paraffin oil (O\(_2\)) containing span 80 (1 %w/w) at 70°C to form O\(_1\)/W/O\(_2\) double emulsion. Different ratios of drug to polymer (1:5, 1:7.5 and 1:10) were prepared. After formation of emulsion 2 ml of CaCl\(_2\) (2M) was added dropwise under stirring at 1000 rpm for 10 min at 70°C. The mixture was rapidly cooled to 15°C and then, 50 ml of acetone was added in order to dehydrate the droplets. The particles were isolated by filtration and washing the microspheres with 3 X 30 ml aliquots of isopropyl alcohol. Microspheres were allowed to dry at room temperature.

Determination of Loading Efficiency and production yield

Loading efficiency (\%) = (actual drug content in microparticles/theoretical drug content) \times 100

The production yield of the microparticles was determined by calculating the initial weight of the raw materials and the last weight of the polymeric particles obtained to the initial weight of the raw materials. Each determination was performed in triplicate manner (Table 1).

Table 1. Effect of drug to polymer ratio on the loading efficiency, production yield and particle size of diclofenac sodium microparticles

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug : Polymer ratio</th>
<th>Production yield (%±SD)</th>
<th>Theoretical drug Content (%)</th>
<th>Mean drug Entrapped (%±SD)</th>
<th>Drug loading Efficiency (%±SD)</th>
<th>Mean particle size (µm±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(_1)</td>
<td>1:10</td>
<td>99.99 ± 3.54</td>
<td>9.09</td>
<td>4.67 ± 1.78</td>
<td>51.43 ± 4.19</td>
<td>13.92 ± 0.47</td>
</tr>
<tr>
<td>F(_2)</td>
<td>1:7.5</td>
<td>94.99 ± 6.07</td>
<td>11.77</td>
<td>5.04 ± 2.49</td>
<td>42.830 ± 7.98</td>
<td>14.01 ± 0.49</td>
</tr>
<tr>
<td>F(_3)</td>
<td>1:5</td>
<td>91.67 ± 2.48</td>
<td>16.67</td>
<td>5.15 ± 2.37</td>
<td>30.907 ± 4.73</td>
<td>8.34 ± 0.60</td>
</tr>
</tbody>
</table>

Physicochemical properties of discs

Each disc contained 200 mg of DS microspheres (with different drug to polymer ratios of 1:10, 1:7.5 and 1:5). The discs were round and flat with an average diameter of 7 ± 0.1 mm compressed with a constant compression force (2 tones). Hardness of the discs was determined for six discs using Erweka hardness tester (Erweka, Germany). Friability of the prepared discs was assessed using friability tester (Erweka, Germany).

Differential Scanning Colorimetry (DSC)

The physical state of drug in the microspheres was analyzed by Differential Scanning Calorimeter (Shimadzu, Japan). The thermograms were obtained at a scanning rate of 10 °C/min conducted over a temperature range of 25-300 °C.
Haunrer's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

\[
\text{Haunrer's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

**Surface pH**

The surface pH of the formulation was determined in order to investigate their possible side effects in vivo. An acidic or alkaline formulation will cause irritation of the mucosal membrane and hence this is an important parameter in developing a mucoadhesive dosage form. A combined glass electrode was used for determination of surface pH. pH was measured at time intervals of 15, 30, 60, 90 and 120 min. The discs were first allowed to swell by keeping them in contact with 5 ml phosphate buffer pH 6.8 for two hours in 50 ml beakers. pH was then noted by bringing the electrode near the surface of the formulation and allowing equilibrating for 1 min. The experiments were carried out in triplicate.

**Swelling Studies**

Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of buccoadhesive discs was evaluated by placing the discs after weighting (W₁) in phosphate buffer solution pH 6.8 at 37°C. Swelling was measured at time intervals of 15, 30, 60, 90 and 120 min. The disc was removed from the beaker and excess surface water was removed carefully using the filter paper. The swollen disc was then weighed again (W₂) and the swelling index was calculated.

\[
\text{Swelling index} = \frac{W₂ - W₁}{W₁} \times 100
\]

**Ex vivo mucoadhesion time**

Male Wistar rats (260±30 g) were used in this study. The animals were given food and water ad libitum. They were housed in the Animal House of Tabriz University of Medical Sciences at a controlled ambient temperature of 25±2 °C with 50±10% relative humidity and a 12-h light/ 12-h dark cycle. The present study was performed in accordance with Guide for the Care and Use of Laboratory Animals of Tabriz University of Medical Sciences, Tabriz-Iran (National Institutes of Health Publication No 85-23, revised 1985). The selected batch was subjected to ex vivo mucoadhesion test. The disintegration medium was composed of 900 ml phosphate buffer pH 7.4 maintained at 37°C. An abdominal segment of rat, 3 cm long, was glued to the surface of a glass slab, vertically attached to the disintegration apparatus (Erweka, Germany). The mucoadhesive discs were hydrated from one surface and then were brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the disc was completely immersed in the buffer solution at the lowest point and was out of solution at the highest point. The time necessary for complete erosion or detachment of the discs from the mucosal surface was recorded. The experiment was carried out in triplicate.

**Permeation studies**

The in vitro study of DS permeation through the mucosal area of rat abdominal was performed using a Franz diffusion cell at 37 ± 0.2°C. Mucosa was obtained from mucosal area of rat in animal center. Freshly obtained rat mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The discs were placed on the mucosa and the compartments clamped together. The donor compartment was filled with 3 ml simulated saliva, pH 6.8 (sodium chloride 4.50 g, potassium chloride 0.30 g, sodium sulfate 0.30 g, ammonium acetate 0.40 g, urea 0.20 g, lactic acid 3 g, and distilled water up to 1,000 mL, adjusting pH of the solution to 6.8 by 1 M NaOH solution). The receptor compartment was filled with 22-25 ml phosphate buffer pH 7.4 and by stirring with a magnetic bead at 700 RPM. 3ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 224 nm.

**Bioadhesion strength**

The tensile strength required to detach the bioadhesive discs from the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled. The device was mainly composed of a two-arm balance. The mucoadhesive forces of discs were determined by means of the mucoadhesive force-measuring device, using tissue cut from mucosal area abdominal of rat. The pieces of mucosa were stored frozen in phosphate buffer pH 7.4, thawed to room temperature before use. At the time of testing, a section of mucosa was secured to the upper glass vial (C) using a cyanoacrylate adhesive (E). The diameter of each exposed mucosal membrane was 1.5 cm. The vials were equilibrated and maintained at 37°C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). To exposed tissue on this vial, a constant amount of discs (D) was applied. The height of the vial was adjusted so that the discs could adhere to the mucosal tissues of both vials. Immediately, a constant force of 0.5 N was applied for 2 minutes to ensure intimate contact between the tissues and the samples. The vial was then moved upwards at constant speed, it was connected to the balance. Weights were added at a constant rate to the pan on the other side of the modified balance of the used device until the two vials were separated. During measurement, 150 μl of phosphate buffer, (pH 6.8) was evenly spread onto the surface of the test membrane. The bioadhesive force, expressed as the detachment stress in g/cm², was determined from the minimal weights that detached the tissues from the surface of each formulation using the following equation.

\[
\text{Bioadhesion force} = \frac{W}{A} \times \text{stress in g/cm}^2
\]
Detachment Stress \( (g/cm^2) = \frac{m}{A} \)

Where \( m \) is the weight added to the balance in grams and \( A \) is the area of tissue exposed. Measurements were repeated thrice for each of the discs. All the above three experiments were conducted in triplicates.

**Histopathological Evaluation of mucosa**

Histopathological effects of mucoadhesive discs were evaluated. The tissue was fixed with 10% formalin, routinely processed, and embedded in paraffin. Paraffin sections were cut on glass slides and stained with hematoxylin and eosin. Any damage to tissue was recorded by a light microscope.

**In vitro release Studies**

In order to carry out In-vitro release studies dissolution test apparatus type II (USP) rotating paddle method was used. The studies were carried out for all formulation combination in triplicate, using 900 ml (37°C, 100 rpm) of isotonic phosphate buffer (pH 6.8) as the dissolution medium. An aliquot of 5ml sample was withdrawn at 0.25, 0.5, 1, 2, 3, 4 hours intervals and similar volume was replaced with fresh phosphate buffer (pH 6.8) maintained at same temperature. Samples were then analyzed under 224 nm with UV spectrophotometer.

### Results

**Physicochemical Properties of microparticles/discs**

Mucoadhesive buccal discs of DS were prepared using CMC-Na as a matrix. The discs were characterized for their physical characteristics (Table 1). The production yield of the beads was increases with the increase in the concentration of drug. A lower drug entrapment was observed with increasing concentration of CMC-Na. This is in accordance with the results previously reported on DS beads.\(^9\) This phenomenon could be due to the difficulty of formation of microspheres due to the high concentration of hydrophilic polymer (F\(_1\), 1:10 drug to polymer ratio).\(^10\) Particle analysis of microspheres prepared is shown in Table 1. An increase in polymers ratio from 1:5 to 1:10 results in a significant effect on the mean particle size of microspheres. The analysis of data showed that all obtained microparticles followed a log-probability distribution.

Angle of repose of microspheres was between 29.745° to 33.693°, indicating poor flow property for microspheres (Table 2). DS showed an amorphous state (Figure 1). Pure DS exhibits a melting exotherm around 281°C (Figure 1). CMC-Na showed wide endothermic peak in rang of 50-120°C and calcium chloride demonstrated abrupt or drastic change in the thermal behavior at 47.48 °C. It is obvious from thermograms that the DSC curves of physical mixtures of drug with polymer and the microparticle formulations are almost the same.

### Table 1. Flowability Characteristics of microparticle formulations, physicochemical characteristics of disc formulations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Formulation code</th>
<th>F(_1)</th>
<th>F(_2)</th>
<th>F(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug : Polymer ratio</td>
<td></td>
<td>1:10</td>
<td>1:5</td>
<td>1:5</td>
</tr>
<tr>
<td>Bulk density (g/cm(^2)± SD)</td>
<td></td>
<td>0.187±0.01</td>
<td>0.232±0.00</td>
<td>0.191±0.00</td>
</tr>
<tr>
<td>Tapped density (g/cm(^2)± SD)</td>
<td></td>
<td>0.287±0.02</td>
<td>0.408±0.00</td>
<td>0.283±0.01</td>
</tr>
<tr>
<td>Carr’s index (%±SD)</td>
<td></td>
<td>34.78±0.00</td>
<td>43.18±0.01</td>
<td>32.57±0.00</td>
</tr>
<tr>
<td>Hausner ratio (±SD)</td>
<td></td>
<td>1.53±0.00</td>
<td>1.76±0.01</td>
<td>1.48±0.00</td>
</tr>
<tr>
<td>Angle of repose (°±SD)</td>
<td></td>
<td>29.745±0.22</td>
<td>31.820±1.14</td>
<td>33.690±0.56</td>
</tr>
<tr>
<td>Weight variation (mg ± SD)</td>
<td></td>
<td>194±3.63</td>
<td>193±4.13</td>
<td>190±6.25</td>
</tr>
<tr>
<td>Hardness (N ± SD)</td>
<td></td>
<td>14.99±0.72</td>
<td>19.28±2.14</td>
<td>16.19±0.83</td>
</tr>
<tr>
<td>Friability (%±SD)</td>
<td></td>
<td>6.15±0.43</td>
<td>5.01±1.63</td>
<td>6.42±0.85</td>
</tr>
<tr>
<td>Content uniformity (%±SD)</td>
<td></td>
<td>97.19±0.47</td>
<td>94.00±0.47</td>
<td>91.29±0.85</td>
</tr>
<tr>
<td>*pH surface (±SD)</td>
<td></td>
<td>5.95±0.01</td>
<td>5.13±0.01</td>
<td>5.96±0.01</td>
</tr>
<tr>
<td>*Swelling (%±SD)</td>
<td></td>
<td>76.47±3.55</td>
<td>94.74±2.24</td>
<td>111.11±4.43</td>
</tr>
<tr>
<td>Mucoadhesive strength (g/cm(^2)±SD)</td>
<td></td>
<td>8.95±0.53</td>
<td>7.89±0.69</td>
<td>5.88±0.15</td>
</tr>
<tr>
<td>Residence time (min±SD)</td>
<td></td>
<td>53.43±0.93</td>
<td>51.51±0.19</td>
<td>50.69±5.67</td>
</tr>
</tbody>
</table>

* Results of pH and swelling index was determined after 2h in phosphate buffer (pH=6.8).

All formulations consisted of 91.29-97.19% drug content, 14.99-19.28 N hardness, and 5.01-6.42% friability (Table 2).

The results revealed that all microsphere formulations swelled rapidly when immersed in 0.2 M phosphate buffer (pH 6.8). The swelling percent of different microparticle formulations was found to follow the rank order of 31.58±1.61% (F\(_3\)), 33.33±2.013% (F\(_1\)) and 41.18±1.72% (F\(_2\)). After 2 h of incubation swelling percent was observed to be 76.47±3.55% (F\(_1\)), 94.74±2.24% (F\(_2\)) and 111.11±4.43% (F\(_3\)), respectively (Table 2).
The surface pH of all the discs was within the range of salivary pH (5.13-5.96). No significant difference was found in surface pH of different discs (Table 2). The in vitro mucosal residence time in phosphate buffer (pH 6.8) varied for microparticles from 0 to 120 min (Table 2). Microparticles showed high mucoadhesion and did not dissolve in 0.2 M phosphate buffer (pH 6.8) for about 2 h.

The results of in vitro bioadhesive strength study are shown in the Table 2. The bioadhesion characteristics were affected by the concentration of the bioadhesive polymers. F1 Formulation containing 1:10 ratio (drug:polymer) showed the highest mucoadhesive property (8.95±0.53 g/cm²).

**In vitro release**

The release profiles for all microparticles are illustrated in Figure 4. In order to have better comparison between the dissolution profiles, dissolution efficiency, \( t_{50\%} \), \( Q_{0.5} \) and \( Q_2 \) were calculated. Microparticles with high loading efficiency or high drug entrapment showed faster dissolution rate. This could be due to lower level of polymers corresponding to higher level of the drug in the formulation (F3, 1:5 drug to polymer ratio) which resulted in a decrease in the drug release rate \( p<0.05 \).

As more drugs are released from the microparticles, more channels and pores are probably produced, contributing to faster drug release rates. Figure 4 and Table 3 show that the initial drug releases for the microparticle formulations are high. The release of drug from microparticles (\( t_{50\%}=90.34-124.41 \) min) was slower than the release of drug from commercial tablet (\( t_{50\%}=78.93 \) min) \( (p>0.05) \). However, a significant difference was observed between the percentages of drug released at 2 hours \( (Rel_2) \) between discs and commercial tablet \( (p>0.05) \). There was a significant difference between dissolution profiles of commercial tablets and microparticles. During dissolution, CMC-Na containing microparticles swelled forming a gel layer on the exposed beads surfaces.
The release of DS from CMC Na beads was slow (Figure 4), because of the formation of a loose network of CMC which dissociates and disintegrates slowly in phosphate buffer. With an increase in DS concentration, the interaction between the polymer and drug increased with the formation of a closer network, which showed a decrease in the diffusion of drug from the beads. The reason for the burst release (Rel < 0.05)

Discussion

Hydrogels are three dimensionally cross-linked polymer chains with capacity to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. As water is absorbed into the matrix,chain relaxation occurs and drug molecules inside matrix are released through the spaces or channels within the hydrogel network through the dissolution and/or the disintegration of the matrix.

The influence of drug on the swelling properties of polymer is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules plays an important role in the matrix integrity of the swollen hydrophilic cellulose matrices. The amount and properties of the incorporated drug determine matrix integrity. Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs. The effect of DS on the swelling behaviour and the residence time of various mucoadhesive polymer was also observed (Table 2).

The comparative percentage swelling for various formulations was in order of F3 > F2 > F1. CMC-Na containing beads showed high percent swelling due to presence of more hydroxyl group in the CMC-Na molecules. The weight of these formulations was increased to the extent of 30 to 110% from the initial value within 2 h (Table 2). Although the marked increase in surface area during swelling can promote drug release but the increase in diffusion path length of the drug may paradoxically delay the release. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the buccal discs was determined to optimize both safety as well as drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal/salivary pH as possible. Increase in the ratio of polymer increased bio-adhesive strength of formulation. The incorporation of the drug induced significant reduction of the residence time of various formulations. As the particle swells, the matrix experiences intra-matrix swelling force which promotes disintegration and leaching of the drug leaving behind a highly porous matrix. Water influx weakens the network integrity of the polymer, thus influencing structural resistance of the swollen matrices, which in turn results in pronounced erosion of the lose gel layer. DS, with logP value of 1.13, exhibits low permeability through buccal mucosa. Similar to the other studies the obtained results showed that generally an increase in the ratio of drug to polymer ratio resulted in a reduction in release of DS from discs (Table 3 and Figure 2).

Cellular membrane was intact and no damage was observed to the treated rat mucosa (was used in the disintegration test). Thus, formulation containing microparticles appeared to be safe with respect to buccal administration (Figure 3).

The ionic interactions between calcium ion and negatively charged polymer (CMC-Na) might have been reduced at pH 6.8, forming a loose network with induced porous surface. In pH 6.8 phosphate buffer, slow dissociation of the CMC membrane may occur leading to drug release with a burst effect.

The release of DS from CMC-Na beads was slow (Figure 4), because of the formation of a loose network of CMC which dissociates and disintegrates slowly in phosphate buffer. With an increase in DS concentration, the interaction between the polymer and drug increased with the formation of a closer network, which showed a decrease in the diffusion of drug from the beads. The reason for the burst release (Rel < 0.05)
could be due to the presence of some DS particles close to the surface of the microspheres. When water-soluble drugs don’t have a tendency to migrate to the non-polar medium (liquid paraffin), thereby drug did not concentrate at the surface of the microspheres and did not induce the burst effect. The pores present in CMC-Na polymer act as a channels for the entrance of the liquid medium through the microparticles wall, causing it to swell. Hydrogen bonding between the hydroxyl groups of the carboxylic moiety and the carbonyl oxygen of ester group increases the degree of solidity of the polymer and decreases its porosity and permeability. Thus, by varying the ratio of drug to polymer the release rate of DS can be controlled.

According to the obtained results, Carr’s (compressibility) index was greater than 25, indicating poor flow characterizes. The DSC thermograms showed amorphous character of drug in the drug loaded microparticles.

**Conclusion**

Sustained release diclofenac loaded buccal-mucoadhesive microparticles with prolonged buccal residence time was designed. From the obtained results it may be concluded that the proposed drug loaded CMC-Na buccoadhesive microparticles could be suitable for diclofenac delivery.

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**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**