Development and Evaluation of Donut Matrix Tablets of Baclofen Using Mucilaginous Polymer from Portulaca oleracea Linn.

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ABSTRACT

The aim of this work was to prepare and evaluate novel mucoadhesive donut-shaped tablets of baclofen for the gastric retentive delivery of the drug. Drug release from donut-shaped tablets followed approximately zero order, owing to constant surface areas of drug release, caused by the special donut geometry. Mucilaginous polymeric extract from Portulaca oleracea Linn. leaves was used as a novel mucoadhesive agent for gastric retention purposes. This mucilage displayed superior gastric retentive and drug release properties during in vitro dissolution and ex vivo permeation compared to synthetic mucoadhesives such as Carbopol 940 (a cross-linked polycrylate polymer) and sodium carboxymethylcellulose.

ZUSAMMENFASSUNG

Entwicklung und Evaluierung von ringförmigen Baclofen-Tabletten mit Portulaca oleracea Linn.-Polymer


KEY WORDS

- Baclofen
- Donut-shaped tablet
- Gastric retention
- Mucoadhesion
- Portulaca oleracea
- Zero order drug release

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1. Introduction

Baclofen, a centrally acting muscle relaxant, acts by inhibiting polysynaptic reflexes at the spinal level by acting as an analogue at the GABA-B receptor [1]. It is widely used for the treatment of spinal cord injuries and spasticity associated with diseases like multiple sclerosis and amyotrophic lateral sclerosis [2, 3]. Traditionally, baclofen has been administered via intrathecal injection [4] that is both difficult to administer and hazardous to patients. When orally administered, there is a narrow window of absorption of baclofen in the stomach and proximal small intestine that necessitates its gastric retentive delivery [5]. The drug’s absorption is drastically reduced once it reaches the lower gastrointestinal tract [6]. Moreover, multiple administration of baclofen, as a result of its short serum half-life of 2.5–4 h [6], produces high incidence of adverse effects that range from moderate to serious neuropsychiatric manifestations, cardiovascular toxicity and gastrointestinal problems [4, 7]. Marketed oral formulations of baclofen have been limited to orally disintegrating tablets, conventional oral tablets, and instant release tablets that neither ensure site-specific baclofen delivery in the gastrointestinal tract nor sustained release of the drug [6]. This results in fluctuating plasma drug levels caused by multiple administrations enhancing the ad-
developing a gastric retentive sustained release oral delivery system of baclofen is a reasonable option from a therapeutic viewpoint.

Mucoadhesive delivery systems provide consistent gastric retentive drug delivery localized at target sites in the upper gastrointestinal tract [8, 9] and intimate contact with adherent mucus layer resulting in high drug penetration across absorptive tissue [10, 11]. Mucoadhesion of dosage forms is achieved by incorporating mucoadhesive polymers in formulations that bind with carbohydrate residues like sialic acid on functional glycoprotein components of mucus [12] through van der Waals bond, electrostatic interactions and hydrogen bond [13]. Traditionally used mucoadhesive polymers include synthetic and semi-synthetic cellulose derivatives [14], hydrogels [15, 16], thiolated polymers [17] and thermoplastic polymers [18]. Mucilages extracted from natural edible sources offer viable alternatives as novel polymeric materials for mucoadhesive drug delivery, because they preclude the drawbacks like low biocompatibility and limited biodegradability associated with many synthetic and semi-synthetic mucoadhesives [19].

Zero order drug release is rarely achieved with ordinary matrix tablet systems due to decrease in effective surface area of drug release with tablet dissolution. A novel way for ensuring zero order drug release from matrix tablets is by modifying the tablet geometry by creating one or more central donut hole(s) in the tablet running across the entire tablet thickness [20, 21]. Previous research has proved that decrease in the outer surface area of drug release during donut tablet dissolution is compensated with increase in the inner surface area, the total surface area for drug release, thus, remaining constant throughout dissolution [21, 22]. This compensation ensures constant zero order release that may help to reduce fluctuations in plasma drug levels of baclofen.

The present study aims at developing and optimizing mucoadhesive donut tablets of baclofen for sustained release gastric retentive delivery of the drug. Natural mucoadhesive mucilage extracted from Portulaca oleracea Linn. leaves has been incorporated as a novel mucoadhesive polymer and its mucoadhesive properties studied in comparison to sodium carboxymethylcellulose (SCMC) 500–800 cp and Carbopol 940. Drug release kinetics of the developed dosage form has also been studied.

### 2. Materials and methods

#### 2.1 Materials

Baclofen was obtained as a gift sample from Sun Pharmaceutical Industries Ltd., India. SCMC 500–800 cp, Carbopol 940, polyvinyl pyrrolidone (PVP K30) and t alc were purchased from S.d. fine-chem Ltd., Mumbai, India. Microcrystalline cellulose was purchased from Loba Chemie, India. All other solid chemicals and solvents used were of analytical grade. Deionized double distilled water was used throughout all experimental procedures. Glassware used was of borosil grade.

#### 2.2 Extraction of mucilage from Portulaca oleracea leaves

Leaves of Portulaca oleracea Linn. (family: Portulacaceae) contain high amounts of mucilages [23] that were extracted by hot aqueous extraction [24]. The leaves were washed with water and cut into small uniform pieces. To the freshly cut pieces, approximately three volumes of water were added. The pieces were boiled on a water-bath for 5 h. The thick viscous solution was then strained through a clean muslin cloth. The filtrate was diluted with three volumes of water and allowed to settle overnight in a refrigerator. The upper clear supernatant liquid was decanted the following day. The decanted supernatant was concentrated in a rotary evaporator. The concentrate was cooled at −7°C in an air-cooled refrigerator. The upper clear supernatant liquid was decanted the following day. The decanted supernatant was concentrated in a rotary evaporator. The concentrate was cooled at −7°C in an air-cooled refrigerator. The upper clear supernatant liquid was decanted the following day.

#### 2.3 Evaluation of physical properties of mucoadhesive polymers

The pH of 1% w/v aqueous solutions of natural and synthetic mucoadhesive polymers was measured by Toshniwal pH meter. Swellability studies were conducted by dispersing 1 g of each mucoadhesive polymer in 25 ml of water with a few drops of ethanol in 50 ml graduated cylinders [25].

#### 2.4 Evaluation of mucoadhesive strength of polymers

Quantitative determination of mucoadhesive strengths of polymers was made by shear stress analysis, tensile strength studies and zeta potential measurements.

##### 2.4.1 Shear stress analysis

Shear stress is calculated as the force acting tangentially to a surface divided by the area of the surface. Shear stress measures the force that causes the mucoadhesive material to slide with respect to the mucus layer in a direction parallel to their plane of contact [13]. Shear stress analysis was conducted using a specially designed apparatus. Two smooth polished plexi glass blocks (lower and upper blocks) were selected. The lower block was fixed on a smooth glass plate, which in turn was fixed on a leveled table. To the upper block, a non-elastic thread was attached, which was passed over a pulley. At the other end of the thread, a plastic pan of negligible weight was attached for weight collection. The length of the thread from the pulley to pan was maintained at a constant value of 7 cm. Aqueous solutions of mucoadhesives at concentrations of 2.0% w/v were prepared. 0.5 ml of the prepared solution in each case was placed at the center of the fixed lower block’s top smooth surface. The upper block was then placed carefully on the lower block and pressed by the application of a constant weight of 100 g. Due care was taken to ensure uniform spreading of the polymeric solution at the interface of the smooth surfaces of the two blocks. After maintaining the application of the constant weight of 100 g for fixed time intervals of 5, 10, 15, 20 and 30 min, weights were added on the pan with gradual increments until the upper block was made to move slightly. This force was recorded as a measure of mucoadhesive strength of polymers.

##### 2.4.2 Tensile strength studies

Tensile strength is defined as the resistance provided by a material to a force tending to tear it apart in the longitudinal direction [13]. Tensile strengths of aqueous solutions of the mucoadhesives were measured...
Formulations of mucoadhesive donut tablets of baclofen.

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Bac</th>
<th>SCMC</th>
<th>Carb</th>
<th>PO</th>
<th>EC</th>
<th>MCC</th>
<th>Tale</th>
<th>Mg St</th>
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<tr>
<td>F1</td>
<td>10.0</td>
<td>35.0</td>
<td></td>
<td>15.0</td>
<td>35.0</td>
<td>3.0</td>
<td>2.0</td>
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<tr>
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<td>3.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>10.0</td>
<td>45.0</td>
<td></td>
<td>15.0</td>
<td>25.0</td>
<td>3.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>10.0</td>
<td></td>
<td>35.0</td>
<td>15.0</td>
<td>35.0</td>
<td>3.0</td>
<td>2.0</td>
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</tr>
<tr>
<td>F5</td>
<td>10.0</td>
<td></td>
<td>40.0</td>
<td>15.0</td>
<td>30.0</td>
<td>3.0</td>
<td>2.0</td>
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</tr>
<tr>
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<td></td>
<td>45.0</td>
<td>15.0</td>
<td>25.0</td>
<td>3.0</td>
<td>2.0</td>
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<tr>
<td>F7</td>
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<td></td>
<td>35.0</td>
<td>15.0</td>
<td>35.0</td>
<td>3.0</td>
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<tr>
<td>F8</td>
<td>10.0</td>
<td></td>
<td></td>
<td>40.0</td>
<td>15.0</td>
<td>30.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>F9</td>
<td>10.0</td>
<td></td>
<td></td>
<td>45.0</td>
<td>15.0</td>
<td>25.0</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

All values in percentages. Bac: baclofen; Carb: Carbopol 940; PO: Portulaca oleracea leaf mucilage; EC: ethyl cellulose; MCC: microcrystalline cellulose; Mg St: magnesium stearate.

by the Park and Robinson method [26]. Gastric mucus, scraped from freshly excised porcine gastric mucus tissue, was separated from adhering adipose layers and kept in lactated Ringer’s solution. 2.0% w/v aqueous solution of each polymer was tested for tensile strength, under a load of 10 g at varying time durations. Force necessary for detaching the polymer from the mucosal surfaces was then recorded.

2.4.3 Zeta potential measurements

The potential associated with the “shear plane” of an electrical double layer is known as zeta potential or electrophoretic potential that may be defined as the potential between the tightly bound surface liquid barrier or the “shear plane” of a dispersed particle and the bulk phase of the solution. Mucus of the gastrointestinal tract contains functional groups and moieties like sialic acid and sulfates that are negatively charged. Thus, more positively charged polymers have greater affinity to interact with mucus lining. Hence, the determination of the charges of the mucus layer and the mucoadhesive polymers has been proposed as a method to study mucoadhesive strength of polymers [27]. Freshly excised porcine gastric mucus was defatted and mucosal homogenates were prepared in pH 1.2 acid buffer at concentration of 0.05% w/v. Mucoadhesive polymer solutions of concentrations of 0.05% w/v were prepared in pH 1.2 acid buffer. The zeta potentials of the finely dispersed mucus suspensions and polymer suspensions were measured with Zetasizer Nano ZS (0.6 nm to 6 μm) using DTS software (Malvern Instrument Limited, GB) using M3-PALS technology. The zeta potentials were measured in triplicate.

2.5 Preparation of mucoadhesive donut tablets of baclofen

The compositions of formulation batches are provided in Table 1. Accurately weighed amounts of baclofen, mucoadhesive polymers (SCMC 500–800 cp in formulation batches F1 to F3, Carbopol 940 in batches F4 to F6 and P. oleracea leaf mucilage in batches F7 to F9), ethyl cellulose, microcrystalline cellulose (directly compressible diluent), magnesium stearate (lubricant) and talc (lubricant and glidant) were sieved through 200-mesh screen to break possible lumps and blended following the geometric dilution method. The powder mixes were compressed into final tablets on a ten-station rotary tablet machine (Rimek Mini Press L Karnavati) using concave punches of 8.0 mm diameter, with special modification for donut holing. Tablet holes had diameters of 3 mm. The average final weight of a mucoadhesive donut tablet was 250 mg.

2.6 In vitro evaluation of tablets

2.6.1 Physical characterization of tablets

The tablets of each batch were evaluated for tablet weight variation (Precisa XB 600 M-C Digital Balance), hardness (Monsanto Hardness Tester), thickness (Digimatic Caliper, Mitutoyo Corporation) and friability (Friabilator, USP Electrolab EF-2).

2.6.2 Drug content of tablets

Twenty tablets of each batch were powdered in a clean mortar. An amount of powder equivalent to 25 mg of baclofen was taken and extracted with 100 ml of 0.1 M hydrochloric acid and sonicated for 10 min. The solution was filtered, diluted with 0.1 M hydrochloric acid, and assayed by UV/Visible spectrophotometer (Jasco V-550) at 266 nm (absorption maxima of baclofen).

2.6.3 Tablet dissolution studies

Studies on drug release from donut tablets were conducted in pH 1.2 acid medium at 75 rpm and 37.0 ± 0.5°C. 900 ml dissolution medium was used per tablet. For the in vitro release studies, USP Dissolution Apparatus II (Electrolab TDT-08L, USP XX111) was used. Five ml aliquots were withdrawn from the baskets with subsequent replenishments using fresh dissolution medium, each time. For the first hour, aliquots were withdrawn at 2, 15, 30 and 60 min with subsequent replenishments. Thereafter, aliquots were withdrawn at intervals of 1 h. The samples were assayed using UV/Visible Spectrophotometer (Jasco V-550) at 266 nm without any dilutions.

2.6.4 Drug release kinetics

Dissolution data of tablets were fit to zero order (linear fit), as well as transformed for other kinetics such as first order, Higuchi, Korsmeyer–Peppas and Hixon-Crowell kinetic models. The R² values of each model were compared for all formulation batches. The model for which the R² value was the closest to 1.00 was considered as the predominant model for drug release, as that indicated closest clustering of data points on linear regression line with least square minimization. From Korsmeyer–Peppas plots, n values were obtained (n = slopes of the plots) that indicated the predominance of either erosion or diffusion on drug release. As Korsmeyer constant (k) can sometimes be a misleading parameter while comparing release profiles, mean dissolution time (MDT) was used as a kinetic drug release parameter [28]:

\[
\text{MDT} = \frac{(n \times k^{-1/n})}{(n + 1)}
\]
2.6.5 Evaluation of mucoadhesive strengths of tablets

Forces of detachment necessary to separate the mucoadhesive donut tablets from mucosal surfaces indicate the strength of mucoadhesion achieved with the prepared dosage forms. Freshly excised porcine gastrointestinal mucus was defatted and kept in lactated Ringer’s solution till further use. The mucoadhesive strength of each tablet was then determined [29]. The mucoadhesive strength of tablets was deduced from the minimum weights (in gm) necessary to detach the tablets from the mucus surfaces.

2.6.6 Ex vivo permeation studies

In mucoadhesive delivery of drugs, drug release from dosage forms is a function of both drug dissolution and transmucosal drug permeation. Ex vivo permeation studies were conducted on the tablet batches to analyze drug permeation. Ex vivo permeation studies were conducted in the Frantz Diffusion Cell [30] containing pH 1.2 acid buffer (at 37 ± 0.5 °C, 50 ± 5 rpm) through freshly excised and defatted porcine gastric mucus. Drug permeation fluxes (J) across experimental porcine gastric mucus were compared [31].

2.6.7 Histological studies

Histological experiments were conducted to examine changes in the histology of the gastric mucous membranes post ex vivo permeation studies. After the completion of the ex vivo permeation, the mucoadhesive donut tablets were carefully removed from the mucus samples using forceps. The post-permeation mucous membranes were then sectioned and fixed in 10% formalin solution. The finely sectioned mucus layers were carefully placed on clean glass slides, stained with eosin and hematoxylin and examined under light Olympus CKX41 microscope (Olympus Optical Co. Ltd, Tokyo, Japan). The photographs were taken by Olympus SC 35 camera. As control, unused porcine gastric mucosa was taken and sectioned, fixed, stained and observed similarly.

3. Results and discussion

3.1 Evaluation of P. oleracea mucilage

P. oleracea leaf mucilage has a complex arabinogalactan structure similar to Gum Arabic and contains d-galactosel-arabinosegalacturonic acid-d-xylose: l-rhamnose at a ratio of 40:20:5:1:31 [23]. Because of the presence of high amounts of edible carbohydrates, mucilage extract is expected to show good mucoadhesive properties. Strong mucoadhesive interactions might be formed with sialic acid and other carbohydrate residues of mucin [12]. Carbohydrates in P. oleracea leaf mucilage were isolated by hot aqueous extraction process followed by organic solvent precipitation following established procedure [32]. The yield was calculated to be 3.89% w/w of P. oleracea leaves.

The pH of 1% w/w aqueous solution of P. oleracea mucilage was found to be approximately 3.14, and, thus close to the acidic pH of the stomach (pH 1 to 3). This ensures that gastric mucosal irritation, if at all, will be low. Of the synthetic mucoadhesives evaluated, SCMC had a basic pH of 7.19, while Carbopol 940 had an acidic pH of 2.63. Swollen volume of 1 g P. oleracea mucilage was 9.75 ml while those of SCMC and Carbopol were 8.34 ml and 13.14 ml, respectively. Polymeric swelling is an important criterion in mucoadhesion. Generally, better swelling might be correlated with superior mucoadhesive properties [32]. However, in this case, a very high swelling rate is undesirable, as that can close the donut holes of tablets. This will affect the steady drug release that we want to achieve with the donut geometry. P. oleracea mucilage showed optimum swelling indicating its suitability for our studies.

In Fig. 1, the detachment forces of 2% w/v mucoadhesive solutions measured by the shear stress method are shown. In Fig. 2, tensile stress results on porcine gastric mucus are provided. The results of shear and tensile stress analyses indicate that the mucoadhesive properties of P. oleracea mucilage are somewhat superior as compared to SCMC. These results correlated with the greater swelling volume achieved with P. oleracea than SCMC. The average shear strength of P. oleracea mucilage also exceeds that of Carbopol, especially at higher polymer concentrations and greater contact times (Fig. 1), but experiments with excised mucus (Fig. 2) indicated much superior mucoadhesion of the natural mucilage than Carbopol. Thus, experiments with biological substrates underlined the hypothesis that very high swelling rates of polymers do not necessarily result in superior mucoadhesion. This is because at high swelling, the polymer surfaces tend to be more slippery that can compromise mucoadhesion [33]. In fact, the mucoadhesion achieved with Carbopol was almost similar to that of SCMC, even though polymeric swelling of the former was almost ~58% higher than the latter.

Zeta potential of porcine stomach mucus homogenate in pH 1.2 acid buffer was found to be –23.12 mV. High negative zeta potential of gastric mucus homogenate was probably due to the presence of sialic acid and sulfate residues in glycoprotein component of mucin [12]. Zeta potentials of polymer dispersions (0.05% w/v in pH 1.2 acid buffer) were –11.28 mV for P. oleracea mucilage, –14.36 mV for Carbopol 940 and –17.35 mV for SCMC 500–800 cp. Of the polymer dispersions, SCMC had the lowest zeta potential owing to its strong anionic nature. The values of zeta potential...
Fig. 2: Detachment forces of mucoadhesive polymer solutions (2.0 % w/v) using porcine gastric mucus tissue.

Fig. 3: Effect of donut hole size on drug release from tablets.

measurements in pH 1.2 acid buffer correlated with the mucoadhesive strength of the polymers (P. oleracea mucilage > Carbopol 940 > SMC 500 – 800 cp). The polymer with the highest zeta potential (P. oleracea mucilage) with respect to gastric mucus homogenate had the strongest mucoadhesive potential as indicated by the detachment forces (Fig. 1 and 2). This was due to stronger electrostatic interactions between charged species of mucin and polymer.

3.2 Optimizing the donut geometry
Drug release from donut tablets generally followed a steady linear release (aka approaching zero order). Previous studies have indicated that 2-hole or 3-hole tablets would result in more linear drug release compared to single hole donuts [34, 35]. However, having 2 or 3 holes would substantially reduce the drug-carrying space of tablets [22]. Moreover, release from multi-holed tablets would be extremely fast that will negate the sustained release necessary in our case.

Size of donut hole is an important parameter in determining the extent to which drug release would follow zero order kinetics. In our research, tablets with 3 mm hole diameters ensured zero order release for ~95 % of the release duration. Smaller donut holes resulted in closure of holes during tablet dissolution due to polymer swelling. On the contrary, tablets with holes exceeding 3 mm diameters released drugs very rapid. Interestingly, zero order R2 was drastically reduced when the hole diameter was 4 mm or higher, indicating deviation from the linear model. So, the optimized hole diameter for 8 mm donut tablets was ~ 3 mm. In Fig. 3, the effects of the hole size on drug release have been shown.

Mucoadhesive donut tablets were prepared by the direct compression method as the compressibility of powder mixes for all formulation batches was found to be good. The average weight of the tablets was 248.87 ± 0.07 mg (n = 20). Average hardness was 5.13 ± 0.13 kg/cm² (n = 10) and average crown-to-crown thickness of the tablets was 5.23 ± 0.02 mm (n = 20). The average friability was 0.23 ± 0.07 % (n = 20). Compressibility was determined by evaluating compressibility indices of powders that ranged between 12.6 and 18.9 %. Compressibility index values of less than 15 % indicate excellent compressibility, while values up to 25 % indicate reasonable compressive properties [36]. Microcrystalline cellulose (MCC) was used as the diluent due to its excellent direct compression properties [37]. In our tablets, the effect of baclofen loading was studied at three levels: 5, 10 and 15 % for the individual polymer system. A 10 % baclofen loading in tablets provided the most linear drug release and essentially followed zero order kinetics (Table 2). A 5 % loading resulted in shorter release duration, while 15 % loading in tablets led to marked deviation of the release from linearity. As a twice-daily formulation is aimed at, 10 % (w/w) loading was used in all formulations. Drug content of the prepared donut tablets ranged between 97.65 % and 101.11 %.

The prepared tablets were subjected to the mucoadhesive strength determination analysis, using porcine gastric mucus tissue (Table 3). The superior mucoadhesive strength of P. oleracea mucilage compared to the synthetic polymers was clearly visible in our studies. For each polymer system, mucoadhesion of the donut tablets increased with increasing mucoadhesive polymer levels.

3.3 Drug release studies
After the release of baclofen from conventional oral tablets, the drug’s dissolution in both gastric and intestinal fluids is fast [6]. This occurs even though baclofen’s aqueous solubility is very low at room temperature [6]. But this low aqueous solubility corresponds to the unionized form of the drug. Baclofen possesses both amino and carboxylic acid groups, and as such, exhibits amphoteric properties with two dissociation constants, pKₐ1 = 9.6 (corresponding to amino moiety) and pKₐ2 = 3.8 (corresponding to carboxylic moiety). At pH 7, the solubility of the drug is very low as it exists in
zwitterionic form at its isoelectric point. But, in acidic pH of the stomach or in the basic pH of intestine, the drug is ionized and solubility increases [38]. So, the fast drug dissolution after release from conventional tablets adds to the drug’s short action. We, thus, need to slow the release rate as once released, baclofen’s dissolution will be rapid in gastric pH. Mucoadhesive polymers possess release retardant property and can be expected to slow down baclofen release. However, to ensure sustained release, we added hydrophobic ethyl cellulose at the same levels in all batches as an additional release retardant.

In Table 4, the in vitro tablet dissolution parameters are provided. Release was faster from SCMC batches (F1–F3), while P. oleracea mucilage caused prolonged drug release (especially formulations F8 and F9). Factor “n” of the Korsmeyer-Peppas model indicates release mechanism depending on aspect ratio of tablets, i.e. the ratio of diameter to thickness of tablets [39]. Interpretation of n values is as follows: 0.43–0.5 = Fickian (Case I) diffusion, 0.5 – 0.89 = anomalous diffusion, 0.89 – 1 = predominant erosion, 1 = pure erosion (case II) and > 1 = super case II [40]. In most of our formulation batches, the release followed the super case II mechanism with n > 1 (Table 4). MDT is a measure of release-retarding capacity of polymers, a higher MDT indicating better retarding efficacy [41]. At higher levels of mucoadhesive polymers, MDT levels were found to be higher (Table 4) indicating that these polymers had good release-retarding properties. Carbopol was found to be a better retardant than SCMC with higher MDT values. This was probably due to the formation of a glassy matrix caused by microgel cross-linking of Carbopol in aqueous medium. Highest MDT values of P. oleracea mucilage among the three mucoadhesives indicated the superior release-retardant efficacy of this mucilage over the synthetic alternatives. The in vitro drug release profiles from mucoadhesive donut tablets are shown in Fig. 4.

As drug release from mucoadhesive tablets is a function of both tablet dissolution and drug permeation.

### Table 2

<table>
<thead>
<tr>
<th>Mucoadhesive level in donut tablet</th>
<th>Drug load (% w/w)</th>
<th>Cumulative percent drug released (%)</th>
<th>Drug release duration (h)</th>
<th>R² (zero order)</th>
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<tbody>
<tr>
<td>SCMC 500 – 800 cp (40 % loading)</td>
<td>5</td>
<td>99.60 ± 3.89</td>
<td>7</td>
<td>0.97 ± 0.02</td>
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<td>10</td>
<td>99.71 ± 2.46</td>
<td>11</td>
<td>0.99 ± 0.07</td>
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<tr>
<td></td>
<td>15</td>
<td>97.84 ± 3.21</td>
<td>14</td>
<td>0.97 ± 0.03</td>
</tr>
<tr>
<td>Carboxpol 940 (40 % loading)</td>
<td>5</td>
<td>98.20 ± 3.96</td>
<td>7</td>
<td>0.96 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>98.66 ± 3.67</td>
<td>12</td>
<td>0.99 ± 0.03</td>
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<tr>
<td></td>
<td>15</td>
<td>94.91 ± 3.86</td>
<td>14</td>
<td>0.97 ± 0.10</td>
</tr>
<tr>
<td>P. oleracea (40 % loading)</td>
<td>5</td>
<td>96.90 ± 4.11</td>
<td>8</td>
<td>0.98 ± 0.09</td>
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<td></td>
<td>10</td>
<td>95.80 ± 3.66</td>
<td>12</td>
<td>0.99 ± 0.05</td>
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<td></td>
<td>15</td>
<td>99.31 ± 3.65</td>
<td>15</td>
<td>0.96 ± 0.05</td>
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### Table 3

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Mucoadhesive strength of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight of detachment (g)</td>
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<td>21.9 ± 2.31</td>
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<td>F2</td>
<td>23.9 ± 1.36</td>
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<td>F3</td>
<td>25.1 ± 1.59</td>
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<td>30.3 ± 2.71</td>
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<tr>
<td>F9</td>
<td>33.1 ± 1.87</td>
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</table>

Fig. 4: In vitro drug release from mucoadhesive donut tablets of baclofen.
Für Ihre Anzeigenplanung die nächsten Termine:

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Anzeigenschluss:

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11.1.2011
Schwerpunkte
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across the mucosa, *ex vivo* permeation studies are necessary for mucoadhesive tablets. In Table 5, the diffusion parameters of permeation studies are. Drug permeation from SCMC tablets (F1 – F3) lasted typically about 9 to 10 h. Polymers with higher retarding efficacies like Carbopol and *P. oleracea* mucilage resulted in more prolonged permeation of drug across mucus. For *P. oleracea* mucilage, drug flux, which indicates the rate of permeation, was about 0.2 – 0.25 μg/(mm² × min), which was less compared to the other two polymers. This again indicated greater retarding efficacy of this mucilage. In general, for all polymers, flux decreased with increase in mucoadhesive polymer levels at constant ethyl cellulose loadings. Histological studies indicated that no significant morphological alterations in porcine mucus sections occurred as a result of mucoadhesive drug delivery (Fig. 5A – D). Taking into consideration mucoadhesion, *in vitro* drug dissolution and *ex vivo* permeation, formulation F9 was the best for getting prolonged release of baclofen.

### Table 4

*In vitro* tablet dissolution parameters (*n* = 3).

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Drug release duration (h)</th>
<th>Cumulative percent drug released (%)</th>
<th>R²</th>
<th>Rel Mech</th>
<th>Rel Order</th>
<th>MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zero</td>
<td>First</td>
<td>Higuchi</td>
<td>Kors</td>
<td>Hixon</td>
</tr>
<tr>
<td>F1</td>
<td>9</td>
<td>99.99 ± 0.060</td>
<td>0.872 ± 0.057</td>
<td>0.939 ± 0.054</td>
<td>0.986 ± 0.077</td>
<td>0.867 ± 0.071</td>
</tr>
<tr>
<td>F2</td>
<td>10</td>
<td>99.47 ± 0.059</td>
<td>0.802 ± 0.067</td>
<td>0.963 ± 0.082</td>
<td>0.988 ± 0.106</td>
<td>0.887 ± 0.084</td>
</tr>
<tr>
<td>F3</td>
<td>11</td>
<td>99.85 ± 0.063</td>
<td>0.728 ± 0.089</td>
<td>0.947 ± 0.100</td>
<td>0.987 ± 0.045</td>
<td>0.906 ± 0.054</td>
</tr>
<tr>
<td>F4</td>
<td>11</td>
<td>99.92 ± 0.058</td>
<td>0.863 ± 0.053</td>
<td>0.955 ± 0.066</td>
<td>0.982 ± 0.055</td>
<td>0.885 ± 0.047</td>
</tr>
<tr>
<td>F5</td>
<td>11</td>
<td>97.64 ± 0.064</td>
<td>0.894 ± 0.047</td>
<td>0.963 ± 0.041</td>
<td>0.987 ± 0.018</td>
<td>0.879 ± 0.061</td>
</tr>
<tr>
<td>F6</td>
<td>12</td>
<td>95.97 ± 0.061</td>
<td>0.901 ± 0.036</td>
<td>0.960 ± 0.049</td>
<td>0.990 ± 0.061</td>
<td>0.908 ± 0.067</td>
</tr>
<tr>
<td>F7</td>
<td>10</td>
<td>99.21 ± 0.045</td>
<td>0.876 ± 0.045</td>
<td>0.976 ± 0.073</td>
<td>0.994 ± 0.084</td>
<td>0.866 ± 0.053</td>
</tr>
<tr>
<td>F8</td>
<td>12</td>
<td>99.83 ± 0.048</td>
<td>0.779 ± 0.036</td>
<td>0.968 ± 0.034</td>
<td>0.978 ± 0.062</td>
<td>0.865 ± 0.050</td>
</tr>
<tr>
<td>F9</td>
<td>12</td>
<td>93.95 ± 0.048</td>
<td>0.934 ± 0.072</td>
<td>0.947 ± 0.024</td>
<td>0.963 ± 0.054</td>
<td>0.890 ± 0.047</td>
</tr>
</tbody>
</table>

Notations: Kors: Korsmeyer-Peppas kinetic model; MDT: mean dissolution time of tablets; Ero: predominant erosion; SCI: super case II release.

### Table 5

*Ex vivo* permeation parameters of mucoadhesive donut tablets (*n* = 3).

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Duration of drug permeation (h)</th>
<th>Mean cumulative percent drug permeated (%)</th>
<th>Flux μg/(mm² × min)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>9</td>
<td>99.27</td>
<td>0.3008</td>
<td>0.9631</td>
</tr>
<tr>
<td>F2</td>
<td>9</td>
<td>98.53</td>
<td>0.2757</td>
<td>0.9702</td>
</tr>
<tr>
<td>F3</td>
<td>10</td>
<td>99.04</td>
<td>0.2573</td>
<td>0.9777</td>
</tr>
<tr>
<td>F4</td>
<td>9</td>
<td>98.23</td>
<td>0.2774</td>
<td>0.9835</td>
</tr>
<tr>
<td>F5</td>
<td>10</td>
<td>99.19</td>
<td>0.2604</td>
<td>0.9895</td>
</tr>
<tr>
<td>F6</td>
<td>12</td>
<td>99.55</td>
<td>0.2171</td>
<td>0.9834</td>
</tr>
<tr>
<td>F7</td>
<td>11</td>
<td>98.59</td>
<td>0.2411</td>
<td>0.9707</td>
</tr>
<tr>
<td>F8</td>
<td>12</td>
<td>98.02</td>
<td>0.2313</td>
<td>0.9882</td>
</tr>
<tr>
<td>F9</td>
<td>12</td>
<td>95.97</td>
<td>0.2086</td>
<td>0.9921</td>
</tr>
</tbody>
</table>
Through our research, we prepared and evaluated a novel mucoadhesive donut-shaped tablet for the gastric retentive delivery of baclofen. This controlled release delivery system ensured prolonged baclofen delivery that followed linear release kinetics. Such a delivery was intended to maximize the drug’s efficacy by promoting its absorption from the absorption window in the stomach and, thus, reduce its toxicity. A novel mucoadhesive from Portulaca oleracea leaf mucilage was extracted and evaluated in comparison with standard synthetic mucoadhesives. High MDT values during tablet dissolution and low flux across porcine mucus tissues indicated good release-retardant potential of this polymeric mucilage. Further, force of detachment studies and zeta potential evaluations indicated the superior mucoadhesive properties of the mucilage compared to SCMC and Carbopol.

4. Conclusion

REFERENCES


