Original Article


Sara Salatin *, Pouya Darvishi, Mitra Jelvehgari *
Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract

Objective: Sumatriptan (ST) is a 5-hydroxytryptamine receptor agonist commonly suggested in the treatment of migraine and cluster headaches. However, the bioavailability of ST is generally poor because of the first-pass metabolism. The present work was undertaken to formulate gastro-retentive microparticles of ST due to enhance the pharmaceutical effect of orally administered ST.

Materials and Methods: The ST microparticles were fabricated via the ionotropic gelation technique using sodium alginate (SA) and different ratios of mucoadhesive polymers, namely, chitosan (CS), and carbopol 934P (CP). The developed microparticles were characterized by the production yield, drug loading, entrapment efficiency, size, differential scanning calorimetry (DSC), swelling index, floating capacity, ex vivo mucoadhesion effect, and in vitro drug release.

Results: The best formulations (F2 and F'2) exhibited satisfactory physicochemical characteristics. The ST microparticles were detected to be in a micrometer size range. The microparticles exhibited very good percentage of mucoadhesion compared with the SA microparticles. The prepared microparticles had a slower release pattern than the commercial tablet (P<0.05) and the drug release was extended for 8 h.

Conclusion: It may be concluded that the gastro-retentive ST microparticles have promising properties and therefore, this formulation is expected to improve migraine management in a better manner.

Keywords: Sumatriptan, Sodium alginate, Chitosan, Carbopol 934P, Mucoadhesive, Oral drug delivery.

Introduction

Migraine is a complex neurological disorder of the brain which is often accompanied with headache, gastrointestinal, neurologic, and sometime aural symptoms [1, 2]. Sumatriptan (ST) is a serotonin receptor agonist (5-hydroxytryptamine or 5-HT receptor) used to treat migraine and cluster headaches [3]. However, ST is rapidly but incompletely absorbed following oral administration (15%) because of the high first-pass metabolism [4]. On the other hand, a large number of patients suffer from nausea and vomiting during multiple migraine attacks, which may result in inadequate absorption of ST in oral therapy.

The sustained release drug delivery systems for ST can be useful to reduce dosing frequency, enhance drug oral bioavailability, minimize gastrointestinal adverse effects, and improve the effectiveness of drug in the management of migraine. However, a major problem commonly associated with the conventional sustained release drug delivery systems is a shorter mean retention time in the stomach. Moreover, traditional oral preparations lead to large fluctuations in the plasma drug level [5]. Thus, increasing the retention time of dosage form in the stomach while improving their stability in the gastric medium is an excellent strategy to bypass this problem. Various gastro-retentive drug delivery systems including expanding and swelling systems, floating drug delivery systems, mucoadhesive systems, and modified-shape systems have been proposed to improve the gastric retention time of drugs [6]. Among gastro-retentive systems, microparticles with floating and mucoadhesive capabilities have attracted large interest owing to their capacity to interact with the mucosal site, improving the retention time of drug in the stomach for a long period of time. Afterwards, the payload is slowly released at the specific time and rate from the carrier. This leads to a large concentration gradient which
allows localization and drug absorption in desired site [7, 8]. Microparticle is a term used to describe spherical and free flowing particles with diameters in the 1 to 1000 micrometer size range that enable the introduction of a pharmaceutical agent into the body as well as improve its efficacy by controlling the place, the time, and also the rate of drug release [9]. Microparticles can be formed from both natural and synthetic polymers.

The goal of this work was to develop gastro-retentive microparticles containing ST to increase the sustained release of ST in the stomach using a blend of sodium alginate (SA) with mucoadhesive chitosan (CS) or carbopol 934P (CP) in the presence of calcium ions. SA is known as a natural anionic polymer derived from brown seaweed and algae, which is used commonly as a controlled-release biodegradable polymer [10]. At acidic pH, alginate with carboxyl groups tends to shrink, thereby decreasing the rate of drug leakage from the blend microparticles. It has excellent gelation characteristics in the presence of calcium in aqueous media, forming egg box-like gel structure [11]. Therefore, it is always desirable to encapsulate both low molecular weight and macromolecular active agents. Due to hydrogel forming feature, it is capable to release loaded cargo in a pH-dependent controlled-release profile, when a SA-based formulation comes into contact with an aqueous medium [12].

CS is a positively charged biopolymer derived from chitin that displays attractive benefits such as biocompatibility, strong mucoadhesiveness, and high membrane permeability. Its solubility is high in acid medium and low in base medium. The positive charge of CS makes it possible to interact with negatively charged mucus, increasing the residence time of cargo on the mucosal tissue [13]. Alginites are capable to form strong complexes with CS that can be applied to both reduce its porosity and stabilize the gel matrix. CP is an anionic polymer polymer which is widely suggested in controlled drug delivery. It has extensively been used as a useful adjuvant in the formulation development of oral mucoadhesive systems, owing to excellent swellability and biosafety. At higher pH (pKa = 6.0), the carboxylate groups on the CP backbone ionizes, causing a charge repulsion between the carboxylate anions. This provides the swelling capacity of the polymer. Notably, CP possesses many free hydroxyl groups that exhibit a great potential to form a gel [14]. Here, various batches of ST blend microparticles were formulated and evaluated in terms of physicochemical characteristics, mucoadhesion effect, and drug release.

Materials and Methods

Materials

ST, SA, CS (medium MW and deacetylation degree up to 75%), and CP were provided from Sigma-Aldrich (St. Louis, USA). HCL, glacial acetic acid, and salts for the simulated gastric fluid (SGF) were purchased from Merck (Darmstadt, Germany).

Preparation of Microparticles

The ST loaded microparticles were fabricated using the ionotropic gelation technique. The detailed composition of ST formulations is reported in the Table 1. One set of ST microparticles was prepared using SA, alone. Subsequently, six sets of ST microparticles were formulated using SA and polymers such as CS and CP. Here, calcium chloride was applied as an agent to ionically cross-link alginate.

Table 1. The formulation composition of ST microparticles.

<table>
<thead>
<tr>
<th>ST Formulation</th>
<th>ST:SA:CS Ratio</th>
<th>Cross-linked Insoluble Complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial phase</td>
<td>External phase</td>
</tr>
<tr>
<td></td>
<td>ST  Water SA</td>
<td>CS Acetic solution Calcium</td>
</tr>
<tr>
<td></td>
<td>(mg) (mL) (mg)</td>
<td>(2 %v/v) (mg)</td>
</tr>
<tr>
<td>F0</td>
<td>-</td>
<td>250 100 1200</td>
</tr>
<tr>
<td>F1</td>
<td>7.5:1</td>
<td>250 100 1200 162.5 100 1300</td>
</tr>
<tr>
<td>F2</td>
<td>15:1</td>
<td>250 100 1200 325 100 1300</td>
</tr>
<tr>
<td>F3</td>
<td>30:1</td>
<td>250 100 1200 1200 50 100 1300</td>
</tr>
</tbody>
</table>

| ST:CP Ratio | ST Water SA CP Aqueous Calcium |
|-------------|-------------------------------|-------------------------------|
|             | (mg) (mL) (mg) (mg)          |
| F’1         | 24:1 250 100 1200 50 100 1300 |
| F’2         | 48:1 250 100 1200 100 1300    |
| F’3         | 96:1 250 100 1200 200 100 1300 |

Notes: ST: Sumatriptan; SA:CS: Sodium alginate:Chitosan; SA:Sodium alginate:CP:Carbopol 934P.

SA-CS Microparticles

At first, 250 mg of ST was dissolved in 10 mL water. The aqueous internal phase containing ST was emulsified into aqueous solution of acetic acid (2 %v/v), containing SA and CS under stirring at 100 rpm. Afterwards, the primary emulsion was poured drop wise through a needle into 100 mL calcium chloride aqueous solution to obtain microparticles. Mixing was stirred at room temperature for 2h. The prepared microparticles were collected by filtration and dried at room temperature for 24 h, and subsequently stored in a desiccator until use.

SA-CP Microparticles

The aqueous internal phase containing ST (250 mg) was emulsified into aqueous solution containing SA and CP under stirring at 100 rpm. The resulting mixture was also heated uniformly to obtain a homogeneous mixture. Afterwards, the primary emulsion was poured drop wise into 100 mL of a calcium chloride solution and stirred for 2 h to form SA-CP microparticles. The prepared microparticles were collected by filtration and dried at room temperature for 24 h, and subsequently stored in a desiccator until use.

Characterization of the Microparticles

Entrapment efficiency

The entrapment efficiency of microparticles was determined using an indirect method via determining the quantity of non-entrapped ST in the external aqueous solution [15]. For this, the supernatant solution was separated by 0.22 millipore filters and the entrapment efficiency of microparticles was examined via a
spectrophotometer (UV1800 Shimadzu, Kyoto, Japan) at 227 nm by the following formula:

\[
\text{Entrapment efficiency (\%)} = \left( \frac{C_0 - C_I}{C_0} \right) \times 100 \quad \text{Eq. (1)}
\]

Where, \(C_0\) is the difference between the total amount of ST used in the preparation of microparticles and the amount of ST in the supernatant solution, and \(C_I\) is the total amount of ST used.

**Morphology**

The morphology of microparticles was evaluated using a transmission electron microscope (TEM, Zeiss, Germany). Microparticles dispersion was placed on a carbon-coated copper grid and dried before test.

**Size**

The size of ST microparticles was measured via a dynamic light scattering (DLS) (Malvern, UK). Before analysis, the microparticles were dispersed into water due to obtain a homogeneous suspension.

**Swelling index**

The ST microparticles (100 mg) were transferred into a beaker containing SGF (0.1 N HCl, pH=1.2) at 37±1°C. At regular intervals (for 2 h), the weight of swollen microparticles was re-determined. Finally, the swelling index was calculated according to the following formula [16]:

\[
\text{Swelling index (\%)} = \left( \frac{W_2 - W_1}{W_1} \right) \times 100
\]

Where, \(W_1\) is the initial weight of microparticles and \(W_2\) is the weight of microparticles after exposure to the buffer solution.

**Floating time**

The floating time of ST microparticles was examined using the type II dissolution test paddle apparatus [17]. In this regard, ST microparticles (100 mg) were spread in a vessel containing 900 mL SGF and agitated at 100 rpm at 37°C. The floating time was monitored and reported as the total floating time of the microparticles.

**Ex vivo mucoadhesion strength**

The mucoadhesion strength of ST microparticles was measured using a modified balance method on the freshly excised rat stomach [18]. At first, a glass vial was inversely hanged from the left pan of a double-pan balance. The lower vial was filled with the SGF and its surface was attached (with adhesive tape) to the stomach tissue. The ST microparticles were placed on the stomach mucosa and the vials were clamped together for 2 min. The weights were gradually placed to other side of the modified balance until the two vials were separated from the stomach mucosa. The mucoadhesion strength was obtained by calculating the total weight needed to separate the blend microparticles from the stomach mucosa.

**Differential scanning calorimetry (DSC)**

The DSC analysis can be to determine the crystalline melting point and glass transition temperature of materials [19]. The thermal characteristics of pure drug, CS, CP, physical mixture of ST with polymers, and ST microparticles were investigated using a DSC60 (Shimadzu, Japan). Prior to analysis, 2 mg of the samples were weighed, sealed into the standard aluminum pans, and heated over a range of 25 to 300°C at a heating rate of 10°C/min.

**In vitro Drug Release**

The drug release of ST microparticles was evaluated by the USP rotating basket technique [20]. For this, ST microparticles were transferred into the SGF (900 mL), maintained in a water bath at 37±1°C under stirring at 100 rpm for 8 h. The samples (3 mL) were withdrawn for analysis at given time intervals and replaced with the same volume of medium. The specimens were filtered using the 0.45 µm filters and then estimated for ST concentration using a UV/Vis spectrophotometer at \(\lambda_{\text{max}}\) 227.4 nm.

**Release Kinetic**

The experimental data were evaluated using different release models like zero order, first order, Hixson Crowell, Higuchi, and Korsemeyer-Peppas due to obtain the mechanism of drug release from the developed ST microparticles.

**Histological Evaluation**

The histological changes of the un-treated stomach tissue was compared with that treated with the blend microparticles during the ex vivo mucoadhesion study. For this, the stomach tissues were transferred into neutral buffered formalin (10%). The tissues were then fixed on the glass slides. Subsequently, the sections were stained with hematoxylin and eosin (H&E), and finally examined under a light microscope.

**Data Analysis**

Analysis of variance (ANOVA) and t-test were applied to evaluate the data. A p-value less than 0.05 was investigated to be significant. Data were presented as mean ±SD (n=3).

**Results**

The goal of this study was to prepare and examine the physicochemical characteristics of the gastro-retentive microparticles of ST with the help of SA, CS, and CP polymers due to overcome drug absorption problems, reduce adverse effects, and ease of administration. Six samples with the same concentration of drug and SA as well as different ratios of polymers were prepared. The composition of ST microparticles was optimized by modifying polymers content.

**Characterization of the Microparticles**

The physicochemical characteristics of the developed formulations were exhibited in Table 2. The blend microparticles were observed to be discrete, and yellow in color as shown in Figure 1. According to the TEM analysis, microparticles were spherical. Moreover, no aggregation was observed in the aqueous dispersion (Figure 2). Herein, ST microparticles were prepared with a relatively narrow size distribution. The size of SA-CS and SA-CP microparticles was found to be in the range of 1296.15-1635.28 µ, and 1451.73-1949.84 µ, respectively. It was observed that the mean size of particles generally increased with increasing the content of polymers. It should be noted that
the size of blend microparticles was larger than that prepared with SA, alone. According to the results, an increased CS content results in a higher degree of entrapment efficiency in the formulations F1 (24.71%) to F3 (37.43%). Moreover, the entrapment efficiency increased with increasing the content of CP, so that in the formulations F’1, F’2, and F’3, the entrapment efficiency was 23.43, 26.90, and 32.97%, respectively. The swelling index of SA-CS and SA-CP based microparticles varied from 16.32 to 18.40% and 17.64 to 19.01%, respectively. On the other hand, microparticles prepared with the higher polymer exhibited the greater swelling index as compared to the microparticle with lower polymer content. After 1 h of assay, all the blend microparticles stopped floating, except the microparticles F2 and F’2 which remained dispersed for 2.13 and 2.44 h, respectively, indicating that the ratio of polymers affect the floating time. The microparticles prepared with SA polymer exhibited lower mucoadhesion strength (0.11 g/cm²) than SA-CS (0.17-0.52 g/cm²) and SA-CP (0.27-0.42 g/cm²) microparticles. More importantly, SA-based microparticles have the shortest shelf life compared to the microparticles prepared from a mixture of SA with CS (within 240 min) or CP polymer (within 120 min) (P<0.05).

Table 2. The physicochemical characterization of ST microparticles.

<table>
<thead>
<tr>
<th>ST formulation</th>
<th>Mean drug entrapped (%)±SD</th>
<th>Entrapment efficiency (%)±SD</th>
<th>Size (µm±SD)</th>
<th>Swelling index (%±SD)</th>
<th>Floating time (h±SD)</th>
<th>Mucoadhesive strength (g/cm²±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>2.20±0.12</td>
<td>25.21±1.35</td>
<td>1284.84±7.42</td>
<td>15.46±1.10</td>
<td>-</td>
<td>0.11±0.04</td>
</tr>
<tr>
<td>F1</td>
<td>2.12±1.04</td>
<td>24.71±0.45</td>
<td>1296.15±12.85</td>
<td>16.32±3.15</td>
<td>-</td>
<td>0.17±2.02</td>
</tr>
<tr>
<td>F2</td>
<td>2.58±0.06</td>
<td>31.71±0.70</td>
<td>1349.77±13.36</td>
<td>18.49±2.21</td>
<td>2.13±0.21</td>
<td>0.34±0.04</td>
</tr>
<tr>
<td>F3</td>
<td>2.75±0.99</td>
<td>37.43±1.24</td>
<td>1635.28±3.00</td>
<td>18.11±2.54</td>
<td>-</td>
<td>0.52±1.04</td>
</tr>
<tr>
<td>F’1</td>
<td>2.09±0.03</td>
<td>23.43±0.28</td>
<td>1451.73±12.12</td>
<td>17.64±4.11</td>
<td>-</td>
<td>0.27±0.05</td>
</tr>
<tr>
<td>F’2</td>
<td>2.56±0.10</td>
<td>26.90±0.90</td>
<td>1611.37±12.74</td>
<td>19.56±1.95</td>
<td>2.44±0.32</td>
<td>0.32±0.06</td>
</tr>
<tr>
<td>F’3</td>
<td>2.79±0.04</td>
<td>32.97±0.43</td>
<td>1949.84±13.58</td>
<td>19.01±3.43</td>
<td>-</td>
<td>0.42±0.04</td>
</tr>
</tbody>
</table>

Notes*: ST: Sumatriptan.

**Figure 1.** The representative photographs of SA-CS (A), and SA-CP (B) blend microparticles before and after freeze-drying.

**Figure 2.** The representative TEM images of SA-CS (A), and SA-CP (B) blend microparticles.

**Figure 3.** DSC thermograms of the CaCl2 (A), ST (B), CS (C), SA (D), F0 (E), F1 (F), F2 (G), F3 (H), and physical mixture of drug and polymers (I).

**DSC**

As shown in Figures 3 and 4, the thermal profile of calcium chloride exhibited two endothermic peaks in the temperature range of 44.56-54.55°C (related to water molecule loss) and 107.57-187.29°C. The thermogram of ST exhibited an sharp peak at 177.27°C, representative of a crystalline anhydrous structure of the drug. There was no melting point in the thermogram of CS. The thermal profile of SA demonstrated an endothermic peak at about 70-140°C and also an exothermic peak at 256°C. In the case of formulations F0, F1, F2, F3, F’1, F’2, and F’3, the alginate peak probably overlaps the melting peak of drug. Therefore, degradation peak of SA was not observed at the highest temperatures. The physical mixture of formulation F2 showed a broad endothermic alginate peak at 138.69°C as well as a drug peak at around 169°C. The physical mixtures of F’2 exhibited a broad peak of alginate at about 50-120 °C and a drug peak with low intensity.
The drug release curve from the microparticles is shown in Figures 5 and 6. The commercial dosage form had a faster release profile than the blend microparticles (P<0.05). The average amount of drug release in first 30 min for formulations F0, F1, F2, and F3, was 41.30, 20.24, 12.09, and 9.75%, respectively. On the other hand, the drug released within 8h for microparticles F0, F1, F2, and F3, was 101.07, 101.25, 99.65, and 99.34%, respectively. Cumulative percentage drug release ranged between 99.73%, 97.15%, and 945.59% after 8 h for microparticles F'1, F'2, and F'3.

**Histological evaluation**

The histological examination in the treated tissue demonstrated that there was no significant difference in the mucosal and submucosal layers of stomach compared with that of the control group (Figure 7).

The optimized ST formulation was selected based on a satisfactory size, entrapment efficiency, swelling index, floating ability, mucoadhesive strength, residence time, and percentage of drug released. Here, the formulations F2 (SA:CS, 15:1) and F'2 (SA:CP, 42:1) were suggested for the further evaluations.

**Discussion**

Nowadays, due to various limitations of many drugs like poor stability and low bioavailability novel systems have been on focus for efficient drug delivery. A desirable delivery system should be developed in such a way to give an appropriate level of active agent, provide a suitable location in the body, minimize side-effects, and improve patient compliance [21]. In recent years, particulate carrier systems have attracted much interest.
for targeted delivery of drugs to the desired gastrointestinal regions [22, 23]. The use of gastro-retentive microparticulate systems is a promising strategy for drugs that is absorbed from the stomach, drugs with narrow therapeutic windows, and also drugs that are unstable at alkaline pH [24]. Here, gastro-retentive ST microparticles have been formulated using the ionotropic gelation method by polymers such as SA, CS, and CP that would allow the sustained drug release. The recent works reported which the size distribution of microparticles formulated by the ionic gelation technique is significantly affected via the polymer’s concentration [25]. Increasing the polymer-to-drug ratio increases the relative viscosity and therefore prevents the dispersion phase from splitting into smaller particles due to the increased interfacial viscosity [26]. The size of microparticles was affected by the viscous dispersion that was obtained when SA was mixed with CS or CP polymer [27]. The migration of ST within the aqueous phase consequently results in decreased loading of drug into the microparticles. The presence of calcium ions on the microparticles surface leads to the formation of multiple attachment points in the gel matrix and drug deposition. The entrapment efficiency of microparticles was detected to increase by increasing the concentration of polymer. This phenomenon can be related to the highly viscous dispersion that was obtained when SA was mixed with higher concentration of polymers [28]. On the other hand, high viscosity of the organic phase limits drug diffusion from the inner phase to the outer phase, causing a larger drug entrapment inside the microparticles. Therefore, the drug is fully loaded into the microparticles and less drug is absorbed on the microparticles surface. Swelling index is a critical property for gastro-retentive microparticulate systems, since this parameter exhibits a direct impact on floating/drug release. Moreover, the swelling aids the mucoadhesive properties of microparticles. It was observed that the swelling index of blend microparticles decreased by increasing the concentration of CS and CP. This phenomenon can be attributed to the decreased cross-linking capacity. The particle swelling, can enhance the drug permeability [29]. The floating ability is a key factor of gastro-retentive microparticles, allowing them to float above the gastric fluid. The swellable or gel forming materials are commonly used as excipients in floating dosage forms. These systems have a tendency to float in the stomach, thereby increasing the retention time of the system in the gastrointestinal tract. All the ST microparticles floated immediately on the SGF, and the floating lag time was zero. The absence of floating lag time is necessary to prevent microparticles quick gastric transition from the stomach into the intestine. The size of microparticles also has a critical effect on the floating ability. The smaller microparticles possess a density lower than gastric medium compared with the larger particles of similar composition [30]. Mucoadhesion is described as attractive interaction between a mucoadhesive material and mucosal surface. The surface charge is a key factor that determine the mucoadhesion strength and retention time of the carrier at the mucosal site. The mucoadhesive polymers are subjected to wetting, swelling, and diffusion into the mucosal or epithelial surface. Polymers having suitable molecular weights form strong cross-linked interactions with the mucosal tissue [31]. The SA and CP-based microparticles exhibited a lower mucoadhesion in SGF (pH = 1.2) compared to the CS-based microparticles. More importantly, SA-based microparticles have the shortest shelf life compared to microparticles prepared from a mixture of SA with CS or CP polymer. Because of cationic nature, CS is an excellent mucoadhesive polymer [32]. On the other hand, rapid wetting of the CP polymer leads to slower swelling of the microparticles and faster separation of the formulations from the mucosa [33]. The DSC analysis confirmed the drug did not retain its crystalline state in the microparticles and became amorphous, or the drug has been dissolved in the polymers. In the early hours of release, microparticles composed of SA and CS or CP exhibited a slower release than SA microparticles. The initial burst release from pure SA based microparticles is high owing to the rapid breakdown of particles in the dissolution medium. The release profiles of the drug from the blend microparticles depend on the characteristics of the polymers [34]. The alginate of the polyelectrolyte complex continues to absorb and swell, causing in the release of more drug. The rate of drug diffusion from the polymeric matrix affects the profile of drug release. In all the prepared formulations, a near-linear dissolution behavior was detected. Here, the rate of drug release decreased by increasing the amount of polymer [26]. The density of the microparticles increases as the CS or CP concentration increases, suggesting that the microparticles formed at higher polymer concentrations are more compact than those prepared at low concentration. At optimum concentration of polymer, a large amount of calcium ions can cross-link with the alginate. Similarly, Nochodchi and coworkers [35] demonstrated that a strong gel matrix is obtained as there is more calcium to bind. This structure leads to a reduction in the rate of drug release. It was reported that SA-CS complex could be more stable in the SGF and in medium having calcium chelators. The pH-sensitive behavior of the SA-CS microparticles can be related to the pH-dependent nature of alginate and CS. At an acidic pH, the carboxylic groups on the alginate backbone are transformed into alginic acid form and the amino groups of CS become protonated. Carbomers are extensively employed in the preparation of controlled release hydrogels. Hydrogels are polymeric networks that are capable of absorbing water, swelling, and adhesion to the epithelium of mucous cells. The open pores of water-swollen hydrogel can mediate the release of drug trapped between the chains of polymeric network [36]. More importantly, as the particle size is increased, surface area decreases; this in turn might contribute to a slowdown in the drug release rate as a depot effect. Biocompatibility of the developed microparticles was confirmed in histological evaluation, using rat stomach tissue, as a model for gastric-mucoadhesive drug delivery.

**Conclusion**

The development of novel vehicles that have based on natural and synthetic polymeric materials are extensively emerging to pharmaceutical fields. Here, gastro-retentive blend microparticles loaded with ST were prepared by the ionotropic gelation. The optimized ST formulations (F2 and F’2) were selected based on a satisfactory size, entrapment efficiency, swelling index, floating ability, mucoadhesive strength, residence time, and percentage
of drug released. The drug release of all the six formulations was slower than the formulations prepared with SA and commercial tablets. These results exhibited that the blend microparticles of SA, and CS or CP are more effective in improving the bioavailability of ST.

Acknowledgements
The authors would like to acknowledge the financial support received from the Faculty of Pharmacy at Tabriz University of Medical Sciences [Grant No. 63454].

Competing Interests
The authors declare no competing interests.

References


