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Abstract
The Journal of Drug Delivery Science and Technology is abstracted or indexed in Chemical Abstracts, Current Contents/Life Sciences, International Pharmaceutical Abstracts, Pascal.
γ-scintigraphic evaluation of enteric-coated capsules containing chitosan-brilliant blue gel beads as hydrophilic model for colon drug delivery

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In the present study, a suitable enteric-coated capsule containing brilliant blue-chitosan beads was prepared and investigated by means of γ-scintigraphy for colon drug delivery. Chitosan brilliant blue gel beads were prepared by dropping drug-containing solution of chitosan into triply phosphate solution using ion complexation method. Moreover, effects of different variables were investigated using 2 factorial design experiments. It was shown that concentration of chitosan and triply phosphate, as well as, drug-polymer weight ratio had significant effects on drug entrapment and brilliant blue release from the beads. Moreover, decreasing drug solubility in the external phase has caused a significant increase in drug loading. Release data was studied kinetically and the drug release from chitosan beads was indicated to be a non-Fickian transport. It seemed that diffusion and/or relaxation of the polymer chains controlled the transport. γ-scintigraphy has shown that the gastric emptying of the enteric-coated capsule containing chitosan beads occurred at 37 ± 10 min under fasting condition. Small intestinal transit time in men was determined to be 228 ± 35 min; subsequently, the arrival time in the colon was 266 ± 41 min on average post-administration.

Keywords: Chitosan – B ads – Colon – Scintigraphy – Brilliant blue – Release.

In recent years, colon drug delivery has been considered as a desirable site of absorption for hydrophilic macromolecular drugs. Colonic drug delivery is intended either for local or systemic therapies. The colon has been determined as an ideal site for protein and peptide absorption [1]. The acidic and enzymatic degradations are two major problems in oral administration of protein and peptide drugs; however, by targeting the delivery system to colon, it is determined that proteolytic degradation can be minimized [2]. Recent studies have determined that polymeric compounds are useful carriers for drug targeting and absorption of high molecular weight drugs [3, 4].

Chitosan, a natural poly- (amino-saccharide), with similar structure to glycosamine, is a non-toxic, biocompatible and biodegradable polymer [5]. In addition, chitosan appears to be economically attractive because chitin is the second most abundant biopolymer in nature after cellulose [6]. Chitosan can be used as a suitable carrier for controlled drug delivery systems. Several studies have been done in the past by many researchers to extend the retention of the dosage forms in stomach by administration of chitosan [7]. Due to its wide application in chemical and biochemical fields of research, chitosan has become an important biomaterial in recent years. It has been shown that the derivatives of chitosan may enhance the penetration of macromolecules across the intestinal barrier [8]. Several alkylated chitosans including diethyl methyl chitosan have been reported for drug delivery purposes [9].

Spherical gel beads, prepared by crosslinking between oppositely charged macromolecules such as chitosan and negatively charged molecules such as triply phosphate (TPP), has received a lot of attention as a drug delivery vehicle for controlled-release formulations [10]. Nigalaye et al. [11] prepared sustained-release tablets of theophylline containing a hydrocolloidal matrix system of chitosan, carboxymethyl cellulose and citric acid. They demonstrated that chitosan formed an insoluble non-erosive type matrix at concentrations above 50% of total tablet weight; while, a fast releasing matrix system was obtained at concentrations lower than 33%. Moreover, Aydin and Akbuga [12] prepared chitosan beads for the delivery of salmon calcitonin. It was determined that controlled-release chitosan beads containing salmon calcitonin was prepared successfully by gelling the cationic polysaccharide with the anionic counterion.

Shu and Zhu [14] reported a novel approach to prepare TPP/chitosan beads for controlled-release drug delivery. Their studies have shown that the TPP/chitosan beads prepared by this novel method had stronger, more homogeneous structure. An alternative approach to the preparation of chitosan beads was reported by Murata et al. [13]. In this study, sodium alginate was used instead of glutaraldehyde for better cross-linking. Studies have shown that the polyelectrolyte complexation occurs not only between chitosan and TPP but also between chitosan and alginate which may protect the gel matrix from environmental conditions. Szer and Akbuga [15] examined various materials such as drug concentration, type and concentration of chitosan, pH value of TPP solution, volume of internal and external phase, gelation time and drying condition on chitosan beads.

γ-scintigraphy has been used for evaluation of in vivo characteristics of colonic delivery systems based on pH dependent polymers [16], pectin [17] and guar gum [18]. 99mTc is the most widely used radionuclide in γ-scintigraphy due to its short half-life, low energy and easy availability. 99mTc is usually ligated with different tagging agents such as Tc-dihylenetriaminopenta-acetic acid(DTPA) in order to make it non-absorbable by the gastrointestinal tract when used in drug delivery systems. 99mTc (DTPA), as a tracer in γ-scintigraphy, is a suitable agent for the evaluation of colon specific drug delivery systems [16].

Certain pH sensitive polymers, with a charged moiety, can be used as coating agents to protect contents of tablets, capsules or
beads from gastric fluid and therefore, can be used for colon targeting. Methylacrylate acid methyl metacrylate copolymers, (Eudragit S100), dissolves at pH above 7.6; therefore, it is a suitable coating agent for colon drug delivery systems. The main aim of the present study was to investigate variables that can affect loading and release of brilliant blue as a hydrophilic model from coated capsules for colon drug delivery.

1. MATERIALS AND METHODS

1. Materials

Chitosan (98% deacetylated, viscosity of 1% w/v solution, 204 mPa.s) was gravitationally provided by Primex Iceland. Triplyphosphate and brilliant blue were purchased from Sigma (Vienna, Austria). Eudragit S100 was gravitationally provided by Rohn GmbH (Darmstadt, Germany) and other chemicals and solvents were of pharmaceutical or analytical reagent grade, and used as received.

2. Equipment

Spectrophotometer (Shimadzu 1201, Japan), pH-meter (Corning 120, UK), freeze driber (Reward Edwards High Vacuum 30P2, T.S. 1114, UK) and γ-camera (Genesys, ADAC model, Dual head, USA) were used in this study.

3. Methods

3.1. Factorial design experiments

To study the effect of different variables, a 2² factorial design experiment was used. Drug-polymer weight ratio (X1), triplyphosphate concentration (X2) and chitosan concentration (X3) were selected as independent variables (Table I). The drug encapsulation efficiency of the bead (Y) was, however, selected as the dependent variable (Table 1). Furthermore, release studies as well as saturation effect of external phase with triplyphosphate on drug loading were investigated.

3.2. Preparation of chitosan beads

Initially, 200 mg chitosan were dissolved in 10 ml of 1% acetic acid under stirring for 20 min at room temperature. Then, brilliant blue was dispersed in this solution and finally brilliant blue-chitosan mixture was added dropwise into triplyphosphate solution at room temperature using a syringe. The beads formed were allowed to stand in triplyphosphate solution for 15 min to be cured. The beads were then separated, washed with water and dried using freeze-drying process.

3.3. Particle size determination

The particle size of 100 beads was obtained with a micrometer for each formulation and the mean particle size was calculated.

Table I - Types of freeze-dried bead formulation based on 2² factorial design experiment. The independent variables are the chitosan concentration (X1), triplyphosphate solution percent (X2) and drug-polymer weight ratio (X3). Drug loading (in triplicate) was selected as dependent variable (Y).

<table>
<thead>
<tr>
<th>Code</th>
<th>X1</th>
<th>X2</th>
<th>X3</th>
<th>Y (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.5</td>
<td>5</td>
<td>1</td>
<td>19.87 ± 1.63</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>34.56 ± 1.56</td>
</tr>
<tr>
<td>F3</td>
<td>1.5</td>
<td>10</td>
<td>1</td>
<td>22.07 ± 1.62</td>
</tr>
<tr>
<td>F4</td>
<td>1.5</td>
<td>5</td>
<td>5</td>
<td>33.05 ± 2.32</td>
</tr>
<tr>
<td>F5</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>33.92 ± 0.76</td>
</tr>
<tr>
<td>F6</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>38.32 ± 0.52</td>
</tr>
<tr>
<td>F7</td>
<td>1.5</td>
<td>10</td>
<td>5</td>
<td>36.93 ± 1.14</td>
</tr>
<tr>
<td>F8</td>
<td>1.5</td>
<td>10</td>
<td>10</td>
<td>52.82 ± 1.23</td>
</tr>
<tr>
<td>F9</td>
<td>2</td>
<td>saturated</td>
<td>5</td>
<td>73.25 ± 1.73</td>
</tr>
<tr>
<td>F10</td>
<td>2</td>
<td>10</td>
<td>saturated</td>
<td>98.00 ± 1.00</td>
</tr>
<tr>
<td>F11</td>
<td>2</td>
<td>10</td>
<td>saturated</td>
<td>60.45 ± 1.00</td>
</tr>
</tbody>
</table>

*Related to triplyphosphate saturation in external phase.
**Related to brilliant blue saturation in external phase.
***Related to decreasing external phase temperature to 0-2°C.

3.4. Drug loading

Initially, the beads were broken using a mechanical device in buffer phosphate solution pH 7.2 and spectrophotometric assay at 630 nm of brilliant blue was then performed.

3.5. Drug release studies

The release of brilliant blue from freeze-dried beads filled in coated capsules was measured using the USP basket method (Apparatus I) at 50 rpm and 900 ml of dissolution fluid at 37 ± 0.5°C. Six coated capsules were tested in simulated gastric fluid (SGF), pH 1.2, for the first 2 hours, phosphate buffer pH 6.0 for another 1.5 hours, and phosphate buffer pH 7.0 for the remaining period of the experiment. At predetermined intervals, 5 ml samples were removed for analysis and replaced with fresh buffer solution. The amount of drug release was measured spectrophotometrically at λ = 629 nm. The release pattern of brilliant blue in different media was plotted according to time.

3.6. Coating process

Dried beads were filled in hard gelatin capsule (size 2) and coated using pan coating procedure. At first, 10% Eudragit S100 was dissolved in acetone, then 1% triethyl citrate as plasticizer was added and stirred to obtain a homogenous solution. The spray coater used was made of stainless steel and the atomizing nozzle had a diameter of 0.5 mm. Compressed air with a pressure of 2 bars was used to atomize the coating solution with a spray rate of 0.8 g/min. The inlet temperature was 50°C. The mean coating weight and thickness were determined to be 45 ± 3 mg and 0.32 ± 0.01 mm, respectively.

3.7. Administration of capsules and acquisition protocol

A hard gelatin capsule (size 2) was filled with chitosan beads containing 50 μCi of isotopically enriched 14C. Capsules were coated with Eudragit S100 solution. The volunteers were in good physical health on the basis of physical examination, and well informed about the written informed consent before taking part in the study. After an overnight fasting period, volunteers ingested radiolabelled dosage form at 9:00 a.m. along with 150 ml of water containing 1 mCi of 99mTc-DTPA. Volunteers remained in an upright position quietly (sitting/standing) throughout the experiment and received a standard sandwich for lunch at 1:00 p.m. (19). Scintigraphic images were recorded at 30 min intervals with 50 s duration for 10 h to consider transit time of drug delivery process using a γ-camera with a 40 cm field of view and fitted with a high energy general purpose collimator. Further to the recording, the images were saved on optical disk for subsequent analysis.

II. RESULTS AND DISCUSSION

After freeze-drying, all of formed beads were spherical. The mean particle size of eight different formulations was between 1.17 ± 0.48 and 1.73 ± 0.49 mm. The mean particle size distributions of different formulations are exhibited in Figure 1 Scanning electron microscopy (SEM) was used to study the morphology of chitosan beads. The surface of dried beads seemed smooth and did not shrink during the freeze-drying process (Figure 2a).

Chitosan with polycationic characteristic forms gel beads with negatively charged counterion triplyphosphate. These studies have shown that the shape and preparation of the beads were critically dependent on the viscosity of the chitosan as well as the concentration of triplyphosphate solution. When 1% chitosan solution was used, no beads were formed. However, 2% chitosan solution was evaluated for bead formation and smooth beads were obtained upon dropping into different concentrations of triplyphosphate solutions. Bodmeier et al. [10] examined the pH effect on drug loading of some model drugs. Their studies showed that pH changes may alter the drug encapsulation efficiency due to an increased solubility of drug in external phase. However, brilliant blue did not show any significant changes by
changing the pH of external phase between 4.1-6 (p < 0.05). To study the swelling ratio of the formulations prepared, beads were dissolved in pH 1.2, 4.5 and 7.2. The highest swelling ratio was obtained in pH 4.5. Although the swelling ratio in pH 7.2 was slow (Figure 2b), the beads were broken after 2-3 h.

Various formulations (1-8) were prepared using 2 factorial design procedures. An optimum drug loading (52.82 ± 1.23) was obtained in formulation 8 (Table I). Three additional formulations (9-11) were prepared to increase drug entrapment efficiency (Table I). In formulation 9, the external phase was saturated with tripsolphosphate and the loading of the drug was increased to 73.25 ± 1.73. Surprisingly, saturation of brilliant blue in external phase caused a tremendous shift in loading of the drug up to 98.0 ± 1.0 in formulation 10. Furthermore, decreasing temperature of the external phase in formulation 11 caused a considerable increase in drug entrapment (90.45 ± 1.0) compared to formulation 8. Table II shows the results of ANOVA for 2 factorial experiments. All factors and interactions have significant effects on drug loading (p < 0.005). Increasing chitosan concentration enhanced drug loading due to the higher strength of gel formation. Triphospho-

**Figure 2** - Scanning electron micrographs (SEM) of (a) chitosan beads after freeze drying process. (b) chitosan beads in phosphate buffer solution pH 7.2.

**Figure 3** - The release of brilliant blue from coated capsules containing chitosan beads (formulations 8, 9, 10 and 11).

**Table II** - Results of analysis of variance for 2 factorial experiments (run in triplicate). Chitosan concentration, TPP concentration and drug:polymer weight ratio were chosen as the independent variables and drug loading as dependent variable, respectively.

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Exp 1</th>
<th>Exp 2</th>
<th>Exp 3</th>
<th>d.f.</th>
<th>Mean square</th>
<th>F ratio</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>18.03</td>
<td>20.45</td>
<td>21.13</td>
<td>1</td>
<td>1031.324</td>
<td>465.472</td>
<td>0.000</td>
</tr>
<tr>
<td>F2</td>
<td>34.31</td>
<td>33.14</td>
<td>36.21</td>
<td>1</td>
<td>124.347</td>
<td>56.122</td>
<td>0.000</td>
</tr>
<tr>
<td>F3</td>
<td>20.47</td>
<td>22.03</td>
<td>23.72</td>
<td>1</td>
<td>791.690</td>
<td>357.319</td>
<td>0.000</td>
</tr>
<tr>
<td>F4</td>
<td>35.05</td>
<td>33.89</td>
<td>30.21</td>
<td>1</td>
<td>106.021</td>
<td>47.851</td>
<td>0.000</td>
</tr>
<tr>
<td>F5</td>
<td>34.60</td>
<td>33.10</td>
<td>34.06</td>
<td>1</td>
<td>10.058</td>
<td>4.901</td>
<td>0.042</td>
</tr>
<tr>
<td>F6</td>
<td>38.90</td>
<td>38.16</td>
<td>37.90</td>
<td>1</td>
<td>22.668</td>
<td>10.240</td>
<td>0.006</td>
</tr>
<tr>
<td>F7</td>
<td>38.13</td>
<td>35.86</td>
<td>36.81</td>
<td>1</td>
<td>96.598</td>
<td>39.085</td>
<td>0.000</td>
</tr>
<tr>
<td>F8</td>
<td>54.05</td>
<td>51.59</td>
<td>52.82</td>
<td>16</td>
<td>1.276</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table III** - Concentration of the formulations of chitosan, TPP and drug used in the study.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Chitosan (g)</th>
<th>TPP (g)</th>
<th>Drug (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>F2</td>
<td>1.2</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>F3</td>
<td>1.5</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>F4</td>
<td>2.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>F5</td>
<td>2.5</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>F6</td>
<td>3.0</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>F7</td>
<td>3.5</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>F8</td>
<td>4.0</td>
<td>3.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Moreover, increment of bead hardness in formulation No. 11 resulted in a decreased dissolution rate due to a slower medium penetration in this formulation. As shown in Figure 3, approximately 60% of drug was released within 30 min after a lag time of 270 min and the remaining of the drug was released in between 1 to 3 h. As the system shows a constant rate, the decrease rate is not due to decreased thermodynamic activity or concentration gradient after swelling. Our data analysis for this part demonstrated that the n value was nearly 1.0 (data not shown), this suggests that the majority of the release is being controlled by swelling, as expected with a polymer. Fickian equation and non-Fickian (anomalous) behaviors were used in many studies, including the mechanism of drug diffusion from the polymeric systems. The following equation or its logarithmic form can be used in these systems [20]:

$$\frac{M}{M_w} = kt^n$$

where $M_t$ is the amount of drug released in a given time, $M_w$ the total amount of brilliant blue in the beads, $k$ and $n$ are equation constants and $t$ is the time. The initial section of the release curves ($M/M_w < 0.6$) was analyzed by this equation and the results including $n$ and $k$ were determined in Table III. For all formulations, the values of the exponent not obtained between 0.5 and 1 that indicate a non-Fickian transport. It seemed that transport was controlled by both diffusion and/or relaxation of the polymer chains.

The γ-scintigraphic results showed that all the capsules coated with Eudragit S100 were intact in the physiological environment of stomach and small intestine in all three volunteers. Transit data for colon-targeted delivery capsules following fasted administration are given in Table IV. The major factor for the gastric emptying of oral drug delivery was whether they were administered with or without food. In fasting conditions, capsules were retained in the stomach until they were removed by the phase III contractions of the migrating myoelectric complex (MMC) [21]. The mean gastric emptying time in this study was found to be 37 ± 10 min in volunteer groups. However, an average of 266 ± 41 min was obtained for small intestine transit time. Furthermore, arrival in the colon occurred on average at 266 ± 41 min post-administration in fasting conditions. Figure 4 shows the γ-scintigraphy of gastrointestinal transit of 99mTc-labelled capsules and water containing 99mTc-DTPA following administration in fasting conditions. As shown in this figure, coated capsules were disintegrated in the transverse colon.

Chitosan is a natural, biocompatible and biodegradable polymer that has been used as a vehicle for colon drug delivery systems. This investigation has demonstrated that controlled-release chitosan beads containing brilliant blue were successfully prepared by complexation of the cationic polysaccharide with the anionic coformer. The drug: polymer weight ratio and the concentration of chitosan and triply-phosphate have influenced drug entrapment efficiency. Furthermore, decreasing drug solubility in the external phase resulted in maximum drug loading. Moreover, the release of brilliant blue was sustained by decreasing the temperature. The values of a indicated that drug release from chitosan beads was non-Fickian and it was concluded that the release of brilliant blue from chitosan beads was due to the diffusion and relaxation mechanisms. The results of the transit time in this study have indicated that Eudragit S100, with suitable thickness, was appropriate for application in colon drug delivery. Moreover, scintigraphy studies have shown that the colon-targeted delivery was a suitable delivery system for targeting to the large bowel.

### Table III - Kinetic constants (k), diffusion exponents (n) and determination coefficient (r²) by linear regression of ln (M/M_w).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>n ± SD</th>
<th>k ± SD</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>0.22 ± 0.008</td>
<td>0.0085 ± 0.0055</td>
<td>0.930</td>
</tr>
<tr>
<td>F9</td>
<td>0.24 ± 0.006</td>
<td>0.0136 ± 0.0023</td>
<td>0.910</td>
</tr>
<tr>
<td>F11</td>
<td>0.19 ± 0.006</td>
<td>0.0107 ± 0.0036</td>
<td>0.950</td>
</tr>
<tr>
<td>F12</td>
<td>0.12 ± 0.007</td>
<td>0.0111 ± 0.0033</td>
<td>0.841</td>
</tr>
</tbody>
</table>

### Table IV - Transit profile for the colon drug delivery following fasted administration of coated capsules.

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>Gastric emptying (min)</th>
<th>Small intestine transit time (min)</th>
<th>Colon arrival time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>228</td>
<td>256</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>263</td>
<td>311</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
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<tr>
<td>Mean</td>
<td>37</td>
<td>228</td>
<td>266</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>35</td>
<td>41</td>
</tr>
</tbody>
</table>

### Figure 4 - γ-scintigraphy of gastro-intestinal transit of radolabelled capsules.

**REFERENCES**


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