Formulation and Evaluation of Colon Targeted Drug Delivery of an Anti-Amoebic Drug

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Abstract:
A multiparticulate system combining pH sensitive property and specific biodegradability has been investigated to prepare and evaluate ES-100 coated sodium alginate microspheres for colon targeting of Tinidazole. Sodium alginate microspheres were prepared by inotroplc gelation method using different ratios of Tinidazole and sodium alginate (1:1, 1:2, 1:3, 1:4). Eudragit-coating of Tinidazole sodium alginate microspheres was performed by coacervation phase separation technique with different core: coat ratio (1:4, 1:5, 1:6, and 1:7). Sodium alginate microspheres and Eudragit-coated sodium alginate microspheres were evaluated for surface morphology, particle size and size distribution, micromeritic properties, percentage drug entrapment, and in-vitro drug release in simulated gastrointestinal fluids (SGF). The size of the core microspheres ranges from 370.44 ± 2.52 to 400.03 ± 3.25 µm and coated microspheres range from 435.88 ± 2.27 to 469.58 ± 2.43 µm. The core microspheres sustained the release for 8 hrs in a pH progression medium mimicking the condition of GIT. The release studies of coated microspheres were performed in a similar dissolution medium as mentioned above. In acidic medium the release rate was much slower, however the drug was released quickly at pH 7.4 and their release was sustained up to 24 hrs. It is concluded from the present investigation that Eudragit-coated sodium alginate microspheres are promising controlled release carriers for colon-targeted delivery of Tinidazole.

Key words: Tinidazole, sodium alginate, Eudragit–S-100, multiparticulate system,

Introduction [1–4]:
During the last decade there has been interest in developing site-specific formulations for targeting drug delivery to the colon. Colon, as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced enzymatic activity and a much greater responsiveness to absorption enhancers. This enables the visualization of colon as a site for local and systemic delivery of various drug molecules including proteins and peptides. For local pathologies of the colon, colon specific drug delivery increases the bioavailability of the drug at
the target site, reduces the dose to be administered and the side effects. A local means of drug delivery could allow topical treatment of amoebiasis, inflammatory bowel diseases, e.g. ulcerative colitis or Crohn’s disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine. Treatment might be more effective if the drug substances were targeted directly to the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Site-specific means of drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract. Vaccines, insulin and growth hormone are examples of such candidates. In addition, systemic absorption from the colon can also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms such as asthma, angina and arthritis. Since dosage forms remain longer in the large intestine than in the small intestine, colon-specific formulations could be used to prolong drug delivery.

Colonic drug delivery is governed by a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. For example, regardless of whether a local or systemic effect is required, the administered drug must first dissolve in the luminal fluids of the colon. Apart from drug solubility, the stability of the drug in the colonic environment is also considered. The drug could bind in a non-specific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug.

The most commonly used colon targeting mechanisms are: pH, time, pressure and bacteria dependent delivery.

The pH in the terminal ileum and colon (except ascending colon) is higher than in any other region of the GI tract. Thus a dosage form that disintegrates preferentially at high pH levels has good potential for site-specific delivery into this region. A simplest approach for designing pH dependent multiparticulate colon specific delivery system is to formulate enteric coated granules which prevent drug release in upper GIT. The incorporation of organic acids as enteric polymers in granule matrices retarded the in-vitro and in-vivo absorption of drug because of prolongation in disintegration time of the core system.

Tinidazole \([1-[2-(ethyalsulphonyl)ethyl]-2-methyl-5-Nitroimidazole]\) is a potent Antiamoebic, Antiprotozoal, Antibacterial mainly used for amoebiasis.

The main objective of the present study is to formulate and evaluate a colon targeted drug delivery of an anti-amoebic drug (Tinidazole).

**MATERIALS AND METHODS:**
The Tinidazole was gifted sample by M/s KAPL Ltd. (Bangalore, India); Sodium alginate was supplied by BASF, Germany; Eudragit S-100 was supplied by SD Fine Chemicals. (Mumbai, India); Calcium
chloride and Hydrocholoric Acid was supplied by Merck Pvt. Ltd.; n-hexane, Disodium hydrogen phosphate, Potassium di-hydrogen phosphate, Ethyl acetate was supplied by Rankem; Span 80 was supplied by Thomas Baker; Sodium Chloride was supplied by Reachem Lab Chemicals; Sodium Hydroxide Pellets was supplied by Karnataka Fine Chemicals.

**Standard calibration curve for Tinidazole in pH 1.2 and pH 7.4 Buffer:**
Weighed quantity of Tinidazole (100mg) was dissolved in pH 1.2 buffer and pH 7.4 buffer and the volume was made up to 100ml with the same medium. => 1000 mcg/ml (SS I). 5ml of SS I was then made up to 100ml with the same medium => 50 mcg/ml (SS II). Aliquots of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 ml of SS II was pipetted into 50ml volumetric flasks and the volume was made up to 50ml with same medium. The absorbance was measured at 278 and 320 nm against reagent blank. The absorbance values were recorded in triplicate and the results are tabulated as shown in the Table 1 and 2. The calibration curve was plotted using the recorded values and linear regression analysis was done on the absorbance points, shown in the Graph 1 and 2.

**Design and formulation of multiparticulate system of tinidazole:**
**Preparation of Drug Loaded Sodium Alginate Microspheres:** [5]
In the present study microspheres were prepared using sodium alginate as polymer by ionotropic gelation technique.

The microspheres were prepared by the method reported by Rana Mazumder et al with some modifications. The Tinidazole was dispersed in an aqueous solution of 40% w/v sodium alginate with stirring to produce a viscous form. Then polymer drug solution was added drop wise by using syringe of 22 G in diameter from a height of about 5 cms into a beaker containing 4% w/v solution of calcium chloride with continuous stirring by magnetic stirrer. Then the solution containing the gel formed microspheres was filtered by using Whatman filter paper no-1. The microspheres were allowed to dry at about 30 to 40°C and stored in well-closed container for further use.

**Process variables** [5]
The process variables were investigated (Bore diameter of the needle, concentration of sodium alginate, concentration of calcium chloride, height of dropping, stirring speed, and stirring time) and the different batches thus produced were analyzed for size, shape, easy of preparation, drug content and drug release. The microspheres were prepared using above discussed procedure. The process variables are Drug: Polymer ratio (1:1, 1:2, 1:3, 1:4).

Formula for the formulations of uncoated Tinidazole microspheres was given in the Table 3.

**Preparation of eudragit s-100 coated sodium alginate microspheres** [6]
Drug loaded sodium alginate microspheres were used as a core material for the preparation of double coated system. A coacervation phase separation method was applied for this step. A known amount of the microspheres (50 mg) was dispersed in an in Ethyl Acetate (25ml) solution containing ES-100 (200, 250, 300
and 350 mg) and containing 0.2% W/V span 80. This mixture was agitated for 5 min at 600 rpm. Subsequently 50 ml n-hexane (as the non-solvent) was poured into the polymeric solution containing the core material with the rate of 1 ml/min. The medium was stirred for 60 min to complete the process of microparticles coating. Coated microparticles were then washed with an excess of n-hexane, filtered and dried at room temperature.

Formula for the formulations of ES-100 coated Tinidazole microspheres was shown in the Table 4.

Evaluation of sodium alginate microspheres containing tinidazole:
Drug encapsulation efficiency of uncoated sodium alginate microspheres:

To determine drug entrapment within the microspheres, microspheres containing 50 mg of drug was dissolved in 50 ml of HCl (0.1 N). After complete dissolution of sodium alginate, solution was filtered using Whatman # 1 filter paper. 1 ml of the above solution was diluted to 50 ml with 0.1N HCl. The resulting solution was analyzed using a UV spectrophotometric method at 278 nm in the presence of a blank prepared from microspheres containing all materials except the drug.

Particle size distribution of microspheres:

Many methods are available for determining particle size, such as optical microscopy, sieving sedimentation and particle volume measurement. Optical microscopy is most commonly used for the particle size determination.

The particles were observed and measured along an arbitrarily chosen fixed line. Totally 100 microspheres were observed and their particle size was recorded.

The mean diameter of the microspheres was calculated by using the formula derived by Edmundson.

\[ D_{mean} = \frac{\sum nd}{\sum n} \]

Where, \( n \) – Number of microspheres observed, 
\( d \) – Mean size range

In Vitro Drug Release Studies in Simulated Gastrointestinal Fluids:

Eudragit-coated sodium alginate microspheres and uncoated sodium alginate microspheres were evaluated for the in-vitro drug release in simulated GI fluids (SGF). The drug dissolution test of microspheres was performed by the paddle method specified in USP XXIII. Microspheres (equivalent to 50 mg of
drug) were weighed accurately and gently spread over the surface of 900 ml of dissolution medium (SGF). The content was rotated at 100 rpm at 37°C ± 0.5°C. Perfect sink conditions prevailed during the drug dissolution study period. The simulation of GI transit condition was achieved by altering the pH of dissolution medium at different time intervals. The pH of the dissolution medium was kept 1.2 for 2 hours using 0.1 N HCl. Then KH₂PO₄ (1.7 g) and Na₂HPO₄.2H₂O (2.2 g) were added to the dissolution medium, adjusting the pH to 4.5 with 1.0 M NaOH, and the release rate study was continued for an additional 2 hours. After 4 hours, the pH of the dissolution medium was adjusted to 7.4 with 0.1 N NaOH and maintained up to 24 hours. The samples were withdrawn from the dissolution medium at various time intervals using a pipette fitted with a cellophane membrane. The samples pipetted out were suitably diluted with 1.2 pH buffer and 7.4 pH and rate of Tinidazole release was analyzed using UV spectrophotometric method at 278 nm and 320 nm. The receptor volume was maintained constant by replacing equivalent amount of suitable SGF. The concentration of Tinidazole in the samples was calculated based on average calibration curves. All dissolution studies were performed in triplicate.

**Scanning electron microscopy:**[8, 9]

Scanning electron microscopy (SEM) is an electron optical imaging technique that yields both photographic images and elemental information. SEM is useful for characterizing the size and the morphology of microscopic specimens.

**In vitro drug release kinetics:**

The release data obtained was fitted into various mathematical models 13, 14. The parameters ‘n’ and time component ‘k’, the release rate constant and ‘R’, the regression co-efficient were determined by Korsmeyer – Peppa equation to understand the release mechanism.

To examine the release mechanism of Tinidazole from the coated and uncoated Tinidazole sodium alginate microspheres the release data was fitted into Peppa’s equation, \( \frac{M_t}{M_\infty} = K t^n \)

Where, \( \frac{M_t}{M_\infty} \) is the fractional release of drug, ‘t’ denotes the release time, ‘K’ represents a constant incorporating structural and geometrical characteristics of the device, ‘n’ is the diffusional exponent and characterize the type of release mechanism during the release process.

Other Equations for to study drug release kinetics from dosage forms:

1. **Zero Order** \( \% R = kt \):
   
   This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets containing low soluble drugs.

2. **First Order** \( \log (\text{fraction unreleased}) = kt/2.303 \):
The model is applicable to hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

3. Matrix (Higuchi Matrix) \[ \% R = kt^{0.5} \]:
   This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drug.

4. Peppas Korsmeyer Equation:
   \[ \% R = kt^n \]
   \[ \log \% R = \log k + n \log t \]

Results:
The aim of this project was to design and develop an oral, controlled release multiparticulate drug delivery system of Tinidazole proposed for colonic targeting. In this regard formulation studies were carried out. The results for the experiment conducted are as follows,

Drug encapsulation efficiency of uncoated sodium alginate microspheres:
After performing the drug encapsulation efficiency test of uncoated sodium alginate microspheres, the result which was found was shown in the Graph 3.

Drug encapsulation efficiency ES-100 coated sodium alginate microspheres:
After performing the drug encapsulation efficiency test of ES-100 coated sodium alginate microspheres, the result which was found was shown in the Graph 4.

Particle size distribution of microspheres:
Each microsphere sizes were classified under different size range, the frequency distribution was recorded and particle size distribution was shown in the Table 5 and Graph 5.

In Vitro Drug Release Studies in Simulated Gastrointestinal Fluids:
The result was shown in the Graph 6 and 7.

Scanning electron microscopy:
After performing the size and morphological test of microscopic specimens, photographic images were found was shown in the Figure 1-4.

In vitro drug release kinetics:
The release kinetic data is presented by Graphs, was given in the Graph 8-15.

Discussion:
Multiparticulate dosage forms exploit the enteric polymers and maintain their integrity and do not cause the release of the drug in the strongly acidic environment of the stomach. As they arrive in the alkaline pH of the small intestine they start to dissolve the drug. This multiparticulate system combines a pH sensitive property and biodegradability in the colon.

Discussion for uncoated Tinidazole Sodium Alginate microspheres
Sodium alginate microspheres of Tinidzole were successfully prepared by ionotropic gelatination method. Uniform and almost spherical microspheres were obtained. The mean diameter of sodium alginate microspheres varied with varying drug : polymer ratio (1:1, 1:2, 1:3, 1:4).
The % entrapment of formulation with varying drug: polymer ratio was found to be between 65.14±1.13% to 73.71±1.37%. The incorporation efficiency increased progressively with increase in polymer concentration.

The prepared microspheres were in the range of 370.44±2.54 to 400.03±3.25 µm. The higher ratio of drug and polymer was associated with increase in microsphere size. This could be due to higher viscosity at higher drug concentration and increased drug content.

The in-vitro release of Tinidazole from the prepared microspheres exhibited a biphasic mechanism. Initially the microspheres exhibited a burst effect, which was due to presence of drug particles on the surface of the microspheres. This was followed by a slow release phase, due to drug release occurring by matrix erosion and drug diffusion occurring from the inner core of the sodium alginate. The release rate of drug from all uncoated Tinidazole-load sodium alginate microspheres showed considerable drug release at pH 1.2, because sodium alginate is a non-enteric polymer. The release of drug increased with increase in drug: polymer ratio (1:1, 1:2, 1:3, 1:4). The higher polymer concentration appears to have enhanced drug diffusion and resulted in significantly higher release flux. The drug release mechanisms from the sodium alginate microspheres involve the following processes; i) water penetration into the microspheres, ii) sodium alginate swelling/gelling and dissolution of the drug and iii) diffusion of the active compound through the sodium alginate matrix.

**Discussion for ES-100 coated Tinidazole microspheres:**

The second part of this work was focused on the microencapsulation of the Tinidazole sodium alginate cores. These cores were microencapsulated by coacervation phase separation technique using ES-100, an enteric acrylic polymer which dissolves at pH values above 7. This polymer was selected to protect the Tinidazole cores through the gastrointestinal tract avoiding any significant drug release before they reached the colonic region. Once the enteric coat dissolves, it is expected that Tinidazole microspheres will control the drug release in the target area. Tinidazole cores needed to be suspended in the ES-100 organic solution in order to be encapsulated. Ethyl acetate was selected as the polymer solvent because it dissolves the ES-100 while maintaining the integrity of the Tinidazole microspheres. On addition of n-hexane, ethyl acetate diffuses in to the n-hexane, resulting in a rapid polymer precipitation and the entrapment of the Tinidazole microspheres.

Morphologically, ES-100 microencapsulated Tinidazole-cores were spherical, with a smooth surface and were free-flowing.

The values of the entrapment efficiency were found to decrease with increase in the initial drug loading, which can be better drug entrapment within the cores with decrease in ES-100 levels. There was an increase in mean diameter of the ES-100 coated microspheres compared to uncoated microspheres. This increase in...
particle size of the microspheres can be attributed to an increase in viscosity with increasing polymer concentrations, which resulted in larger emulsion droplets and finally in greater microsphere size. Eudragit S-100 is an enteric polymer showing complete dissolution at pH greater than 7. The cumulative percentage drug release from Eudragit-coated Tinidazole microspheres showed the desired rate, as there was no measurable drug release observed up to 2 hours in SGF (pH 1.2), while at pH 4.5, the Tinidazole release was quite insignificant (>2%) up to 4 hours. Tinidazole release from Eudragit-coated sodium alginate microspheres in SGF followed the order $F_5 > F_6 > F_7 > F_8$. In pH progression medium mimicking GIT up to 24 h, the release of Tinidazole from ES-100 sodium alginate microspheres decreased as the ES-100 concentration increased, suggesting that drug release could be controlled by varying the ES-100 concentration. The results might also be explained by the fact that the higher ES-100 content resulted in larger particles with proportionately less drug, so that the drug–polymer ratio was changed and thus release was reduced.

The dissolution data was fitted to zero order, first order, Higuchi models and Korsmeyer-Peppas model to analyse the drug release mechanism. The correlation coefficient ($R^2$) for zero order ranges from 0.8623±0.006 to 0.9698±0.003 and that for Higuchi model ranges from 0.9406±0.005 to 0.9741±0.003. $R^2$ fits predominately to the square root of time model suggested by Higuchi for drug release from dosage forms. The coefficient values for equation $Q = Kt^{1/2}$ suggest diffusion as mechanism of drug release.

**Conclusion:**
The experimental results demonstrated that F5 batch of ES-100 coated sodium alginate microspheres have the potential to be used as a drug carrier for an effective colon-targeted delivery system.

**References:**


8. S.K.Senthilkumar, B. Jaykar, S. Kavimani; Formulation and characterization and in-vitro evaluation of floating microsphere of Rabeprazole Sodium; JITPS; 2010;vol.1(6);274-282.

Table 1: Calibration Curve Data for Tinidazole in pH 1.2 buffers

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance Mean±SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.062±0.004</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.124±0.003</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.188±0.005</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>0.232±0.004</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>0.302±0.004</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>0.379±0.003</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>0.424±0.003</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>0.471±0.006</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>0.542±0.004</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>0.603±0.006</td>
</tr>
</tbody>
</table>

*All values represented as mean ± standard deviation (n = 3)

Table 2: Calibration Curve Data for Tinidazole in phosphate buffer pH 7.4

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<th>Sl. No.</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance Mean±SD*</th>
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<td>2</td>
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<tr>
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<tr>
<td>4</td>
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<td>5</td>
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<td>0.303±0.008</td>
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<td>14</td>
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<td>9</td>
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<td>10</td>
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<td>0.721±0.005</td>
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<tr>
<td>11</td>
<td>20</td>
<td>0.807±0.006</td>
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Table 3: Formula for the formulations of uncoated Tinidazole microspheres

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug: Polymer ratio</th>
<th>CaCl₂ solution</th>
<th>Speed of rotation</th>
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<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>4% w/v</td>
<td>500</td>
</tr>
<tr>
<td>F2</td>
<td>1:2</td>
<td>4% w/v</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>1:3</td>
<td>4% w/v</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>1:4</td>
<td>4% w/v</td>
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</table>

Table 4: Formula for the formulations of ES-100 coated Tinidazole microspheres

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Tinidazole core: ES-100 Conc. of Span 80</th>
<th>Rotational Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>F5</td>
<td>1:4</td>
<td>0.2%</td>
</tr>
<tr>
<td>F6</td>
<td>1:5</td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>1:6</td>
<td></td>
</tr>
<tr>
<td>F8</td>
<td>1:7</td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Micromeritic property of microspheres of Tinidazole

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mean particle size (µm) ±SD</th>
<th>Bulk density (gm. /cm$^3$) ±SD</th>
<th>Tapped density (gm. /cm$^3$) ±SD</th>
<th>Hausners ratio±SD</th>
<th>Carrr’s index±SD</th>
<th>Angle of repose±SD</th>
</tr>
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<tbody>
<tr>
<td>F1</td>
<td>394.25±2.54</td>
<td>0.357±0.010</td>
<td>0.401±0.018</td>
<td>0.890±0.04</td>
<td>11.13±0.11</td>
<td>32.49±1.71</td>
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<tr>
<td>F2</td>
<td>370.44±2.52</td>
<td>0.412±0.012</td>
<td>0.464±0.015</td>
<td>0.884±0.05</td>
<td>12.03±0.64</td>
<td>27.72±1.89</td>
</tr>
<tr>
<td>F3</td>
<td>392.04±3.88</td>
<td>0.430±0.007</td>
<td>0.495±0.014</td>
<td>0.868±0.03</td>
<td>13.46±0.24</td>
<td>31.88±2.78</td>
</tr>
<tr>
<td>F4</td>
<td>400.03±3.25</td>
<td>0.357±0.014</td>
<td>0.402±0.014</td>
<td>0.887±0.01</td>
<td>11.3±0.33</td>
<td>27.00±1.93</td>
</tr>
<tr>
<td>F5</td>
<td>435.88±2.27</td>
<td>0.415±0.015</td>
<td>0.467±0.015</td>
<td>0.887±0.02</td>
<td>11.4±0.26</td>
<td>26.02±1.80</td>
</tr>
<tr>
<td>F6</td>
<td>439.99±2.25</td>
<td>0.431±0.012</td>
<td>0.497±0.021</td>
<td>0.868±0.01</td>
<td>13.2±0.33</td>
<td>26.56±1.43</td>
</tr>
<tr>
<td>F7</td>
<td>438.48±2.36</td>
<td>0.388±0.018</td>
<td>0.437±0.022</td>
<td>0.888±0.03</td>
<td>12.7±1.5</td>
<td>26.80±1.68</td>
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<tr>
<td>F8</td>
<td>469.58±2.43</td>
<td>0.456±0.015</td>
<td>0.516±0.027</td>
<td>0.885±0.01</td>
<td>12.4±0.86</td>
<td>27.11±1.59</td>
</tr>
</tbody>
</table>

Graph 1: Standard Graph of Tinidazole in pH 1.2 buffers.

Graph 2: Standard Graph of Tinidazole in pH 7.4 buffer.
Graph 3: Drug encapsulation efficiency of uncoated sodium alginate microspheres

Graph 4: Drug encapsulation efficiency of ES-100 coated sodium alginate microspheres

Graph 5: Comparison of average particle size of coated and uncoated microspheres of Tinidazole

Graph 6: Comparative drug release profile of formulation F1, F2, F3, F4

Graph 7: Comparative drug release profile of formulation F5, F6, F7, F8
Graph 8: Zero order plots of Tinidazole from formulation F1 to F4

Graph 9: First order plots of Tinidazole from formulation F1 to F4

Graph 10: Higuchi order plots of Tinidazole from formulation F1 to F4

Graph 11: Peppas order plots of Tinidazole from formulation F1 to F4
Graph 12: Zero order plots of Tinidazole from formulation F5 to F8

Graph 13: First order plots of Tinidazole from formulation F5 to F8

Graph 14: Higuchi order plots of Tinidazole from formulation F5 to F8

Graph 15: Peppas order plots of Tinidazole from formulation F5 to F8
Figure 1 and 2: SEM of uncoated Tinidazole microspheres

Figure 3 and 4: SEM of ES-100 coated Tinidazole microspheres