Controlled Release Ammonio Methacrylate Copolymer-Based Microspheres of Oxypentifylline

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A b s t r a c t

The objective of this work was to formulate and evaluate a controlled-release Oxypentifylline microspheres that fulfill the requirements for extended release medications using Ammonio Methacrylate Copolymer RS100 as polymeric material. The microsphere were prepared by quasi-emulsion solvent diffusion technique. The effect of process variables such as drug to polymer ratio, stirring rate, and concentration of emulsifier on mean particle size, yield, entrapment efficiency and in vitro release characteristics of microspheres were studied. The prepared microspheres were spherical in shape. The size range varied from 325.45 to 518.54 µm. The microspheres showed high entrapment efficiency (94.22%) and the release was extended up to 24 hrs. The best microsphere formulation was selected and subjected for in vivo studies which reveal that the bioavailability of the drug increased by more than 3.4 times by formulating it into microspheres. This study indicated that Ammonio Methacrylate Copolymer RS 100 can use successfully to sustain the release of Oxypentifylline.

Keywords: Oxypentifylline; Ammonio Methacrylate Copolymer RS100; Microspheres; Sustained release; Entrapment efficiency

Introduction

Oxypentifylline [OXP] was the first drug approved for the treatment of intermittent secondary to chronic occlusive vascular disease and Reynaud’s syndromes [1]. In addition, it significantly increases red cells deformability in patients with chronic occlusive arterial disease, diabetic arteriopathies, cerebrovascular disorders and retinal vascular disorders [2,3]. [OXP] is a white, crystalline or microcrystalline powder, which has a bitter taste and only a slight characteristic odor [4,5], it is readily absorbed [at levels exceeding 95%] from the gastrointestinal tract, but undergoes extensive first-pass hepatic metabolism [60–70%] [6], with t1/2 of 1.63 ± 0.8 hours. [7]. About 89% of orally administered [OXP] was excreted in the urine after six hours [8]. Due to short half-life it require frequent dosing which lead to fluctuation in blood levels, and decrease patient compliance. These attributes make [OXP] a good candidate for controlled release dosage form.

Microspheres are one of the multiparticulate drug delivery systems [9], play a vital role in the development of controlled/sustained release drug delivery systems [10]. Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000 µm, containing dispersed drug in either solution [or] microcrystalline form [11].

Several methods, including Emulsion solvent evaporation technique [12], phase-separation or coacervation method [13], emulsification diffusion method [14], and spray drying method [15] are commonly used for the preparation of microspheres. Several publications have described drug-containing microspheres using the Ammonio Methacrylate Copolymer as the encapsulating materials. They are a family of polymers based on acrylic and methacrylic acids suitable for use in orally administered drug delivery systems. They have been used in the microencapsulation of drugs [16]. Some dissolve rapidly at clearly defined pH values, whereas two grades; RL and RS, are insoluble in aqueous media water and digestive juices, but swell and are permeable, which means that the drugs can be released by diffusion [17]. Therefore, the permeability of drug through Ammonio Methacrylate Copolymer RS and/or RL is independent of the pH of the digestive tract [18]. Ammonio Methacrylate Copolymer RS100 [AMRS-Polymer] is a water-insoluble polymer that is widely used as a wall material for sustained release microspheres due to its biocompatibility, good stability, easy fabrication and low cost. The main objective of this work was to investigate the possibility of obtaining a sustained release formulation of [OXP] microspheres by quasi-emulsion solvent diffusion technique using
[AMRS-Polymer] in various drug: polymer ratios. Investigation of the effect of various processing and formulation factors such as drug to polymer ratio, stirring speed, surfactant concentration and others on the shape, mean particle size, yield of production, particle size distribution, encapsulation efficiency, and in-vitro release rate of drug from the microspheres were performed.

Material and Methods

Materials

[OXP] [kindly supplied by ALKAN pharma company, 6th October City, Cairo, Egypt], Ammonio Methacrylate Copolymer RS100 [Rhom Pharma, GMBH, Dermstadt, Germany], Dichloromethane, ethanol, and sodium lauryl sulphate [Sigma, St.Louis, MO, U.S.A], polyvinyl alcohol [Merck, Germany]. All other chemicals were of analytical grade and distilled water was used for all experiments.

Preparation of [OXP]-loaded microspheres

In order to prepare the microspheres, modified quasi-emulsion solvent diffusion method which was adapted from the process described by [19-22]. Briefly, weighed amount of [OXP] and [AMRS-Polymer] polymer were dissolved in ethanol at 45°C. The formed ethanolic solution was poured into water containing polyvinyl alcohol and was stirring continuously for 3-4 hrs until all solvent was evaporated. The system was thermally controlled at 20°C, the microspheres were separated by filtration, washed twice with 50 mL of water and then dried in oven at 37°C for 24 h. Dried microspheres were stored in a desiccators containing CaCl2.

The preparation of microsphere involves various process variables, include

- Effect of polymer concentration ([AMRS-Polymer] were used in ratios 1:1, 1:2, 1:3, 1:4 and 1:5 to obtain significant different characteristics)
- Effect of stirring rate [400, 800, and 1200 rpm]
- Effect of surfactant concentration [0.1%, 0.3%, and 0.6%]

Formulations with different variables were prepared as shown in table [1].

Fourier Transformed Infrared [FT-IR] Spectroscopy

The sample powder was dispersed in KBr powder and analyzed after converting into pallet. FT-IR spectra were obtained by powder diffused reflectance on a FT-Infrared spectrophotometer.

Differential Scanning Calorimetry [DSC]

DSC curves were recorded on a scanning calorimeter equipped with a thermal analysis data system [Shimadzu, Differential Scanning Calorimeter [Tokyo, Japan]. Pure drug, microspheres, [AMRS-Polymer], and compared for possible drug-polymer interactions.

Percentage Yield

The relative yield was calculated based on the amount of microspheres of each formulation obtained relative to the amount of solid materials used in the dispersed phase [23]. Using the following equation.

\[
\% \text{Yield} = \frac{\text{Weight of microspheres}}{\text{Weight of drug} + \text{Weight of polymer}} \times 100
\]

Particle size analysis

Simple optical microscope was used for particle size measurement of individual microsphere. Optical micrometer was calibrated using standard stage micrometer. According to microscopic method of particle size analysis, slides of various batches of microspheres were prepared using dilute suspension of microspheres in liquid paraffin. Particle size of 100 numbers of microspheres from each batch was measured for calculating size distribution and average particle size. Results were reported as means ± S.D. The mean particle size of microspheres was calculated using the following formula [24,25].

\[
\text{Mean Particle size} = \frac{\sum \text{[Mean particle size of the fraction X weight fraction]}}{\text{Weight fraction}}
\]

Entrapment efficiency

To evaluate the amount of the drug inside the microspheres, an indirect method was used [26]. Aliquots from the filtered solutions remaining after removal of the microspheres were assayed spectrophotometrically at 274 nm. The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. About 100 mg of microspheres were completely dissolved in 500 ml of phosphate buffer solutions [pH 7.4], and stirred for 1h. Then, 2 ml of solution was filtered and the concentration of drug was determined spectrophotometrically by UV at 274 nm. Efficiency of drug entrapment was calculated in terms of percentage drug entrapment [%EE] as per the following formula:

\[
\% \text{EE} = \frac{[\text{Practical drug loading}/\text{Theoretical drug loading}] \times 100}{100}
\]

In-vitro dissolution studies of OXP-loaded microspheres

Drug dissolution test of microspheres was performed by USP II paddle type apparatus. Microspheres equivalent to 400 mg of
drug were added to 400ml dissolution media. The content was rotated at 100 rpm at 37°C ± 0.5°C. The pH of dissolution media was kept 1.2 for 2 hr using 0.1N HCl, then 480ml of phosphate buffer and 20ml of 2M NaOH added to adjust the pH to 7.2 and maintained up to 24 hr. 5ml of each samples were withdrawn from the dissolution medium at various time intervals and replaced by an equal volume of dissolution medium [27]. After filtration and suitable dilution, the samples were analyzed spectrophotometrically at 274 nm. The concentration of [OXP] in sample was calculated based on calibration curves taken in both the acidic 0.1NHCl media \( [n=3, R^2 = 0.999] \), and basic media \( [n=3, R^2 = 0.999] \).[27]

**Morphology of microspheres**

The shape and surface characteristics of microspheres were analyzed by scanning electron microscopy [SEM]. Sample was dusted on a double sided adhesive tape applied previously to an aluminium stub. Excess sample was removed and stub coated [Polaron Sputter 7040] with 30 nm layer of gold palladium observed with a scanning electron microscope [27].

**In-vivo evaluation of microspheres**

**Chromatographic conditions:**

The mobile phase was a mixture of acetonitrile: water [40: 60], adjusted to pH 3 with glacial acetic acid. The mixture was filtered by passing it through a 0.45 um membrane filter and degassed by mean of vacuum pump. The mobile phase was delivered into the HPLC apparatus at a flow rate of 1 ml/min, the detection was conducted at 274 nm.

**Preparation of in-vitro Standard calibration curve**

1. **Stock and Working Standard Solutions:** The standard solution was prepared by dissolving 100 mg [OXP] in 100 ml mobile phase. The working standard solution was prepared by taking 10 ml of the above solution in 100 ml volumetric flask and completed to the volume with mobile phase [100 µg/ml].

2. **Stock and Working Internal Standard Solution:** The internal standard solution was prepared by dissolving 100 mg of ciprofloxacin HCl in 100 ml volumetric flask and completed to the volume with the mobile phase. The working internal standard was prepared by taking 10 ml of the above solution in 100 ml volumetric flask and completed to the volume with mobile phase [100 µg/ml].

**Calibration Curve:**

Standard samples were prepared to provide final concentrations of [OXP] ranging from 10 to 70 ug/ml, by transferring 0.5 ml of working internal standard solution and aliquots of [OXP] working standard.

**Bioavailability study of [OXP] in experimental animals:**

Male albino rabbits [weighing 1.5-2 kg] were used for the bioavailability study. Animals were divided into three groups of three rabbits in each group. Twelve hours before drug administration, food was withdrawn until 24 hrs post-dosing, and the rabbits had free access to water throughout the experiment. The study was designed as a single oral dose. All groups received an equivalent of 10 mg [OXP] / kg body weight of rabbits [28]. Group 1 received [OXP] alone, group 2 received [OXP] commercial preparation [Trental® SR 400 mg], group 3 received formula F8 [the best microspheres formulation that exhibited high EE% and the optimum release rate]. One hard gelatin capsule was administered to each rabbit through a stomach tube with the aid of distilled water. Blood samples [about 1ml] were withdrawn from the sinus orbital into heparinized tubes at 0, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after each administration. The blood samples were centrifuged immediately at 3000 rpm for 10 min to obtain the plasma samples and were stored at -20°C for subsequent assay. Robert et al [29], developed a HPLC method for determination of [OXP] and its metabolites in human serum, the method required extraction of the analytes with a mixture of 5% isopropanol in chloroform, after addition of 0.1 N HCl or NaOH. The detection was effected using the UV absorbance at 273 nm, and the detection limit was found to be 5 ng/ml.

Pharmacokinetics parameters were calculated from the plasma level data obtained for the individual rabbit per each group and presented as mean ± S.D. [\( C_{\text{max}} \), µg/ml], [\( T_{\text{max}} \), hr], [\( \text{AUC}_{0-24} \), µg ml\(^{-1}\) h], [\( \text{AUC}_{0-\infty} \), and relative bioavailability were calculated.

**Statistical analysis**

All results are represented as mean ± S.D. One way analysis of variance [ANOVA] was employed to assess the significance of the difference between the tested microsphere formulations and the control at a level [\( p \leq 0.05 \)] using SPSS program [30].

**Results and discussion**

**Particle size analysis of [OXP] loaded microspheres**

Results showed that particle size of prepared microspheres was in the range of 325.45±6.65 to 518.54±10.03 µm as shown in table [1]. The data obtained showed that, at a low concentration of polymer [1:1 ratio] no microsphere product was obtained [formula F1, F4, and F5], the mean diameter was increased significantly \( [P=0.001] \) as the drug: polymer ratio varied from 1:2 to 1:5. Low concentration of AMRS-Polymer resulted in a low viscosity of the polymer solution which in turn resulted in smaller emulsion droplets in the aqueous phase [31,32]. It was observed that as the stirring rate was 400 rpm [formulae F1, F2, F3], there was no formation of spherical microspheres and mass crops were obtained. This could be due inadequate agitation to disperse the inner phase in the total mass. Therefore, particles were found to settle at the bottom of vessel. At stirring speeds of 800, 1200 rpm, the resulting high turbulence caused frothing and adhesion to the container wall and paddle. Therefore, the mean particle size of microspheres decreased. Similar results were reported by [33].
Increasing the concentration of surfactant from 0.1 % to 0.6 % resulted in a significant decrease [P<0.05] in the mean diameter of microspheres. This can be attributed to the lower concentration of emulsifier may not be sufficient to cover the droplets of emulsion resulting in coalescence of emulsion droplets and lead to aggregation and fusion of the formed droplets resulting in increasing microspheres particle size [34].

**Percentage yield of microspheres**

The data revealed that, the % yield of different microspheres varied from [70.89±2.04 to 93.13±2.87], as shown in table [1]. The data obtained showed that, the percentage yield was decreased at a low concentration of polymer [1:2 ratio]; at higher stirring rate [1200 rpm]; and at high surfactant concentration [0.6%]. This reduction in the percentage yield in these cases may be due to; a- the small size of microsphere obtained in all these cases which may loss during filtration and washing processes, b- increasing surfactant concentration results in a brittle surface of microspheres, which lead to a drug loss during washing of microspheres[35,36].

The maximum percentage yield obtain in formulae F8, F9 which contain higher ratio of drug:polymer [1:4, 1:5] and prepared at intermediate stirring rate [800 rpm], with intermediate surfactant concentration [0.3%].

**Analysis of entrapment efficiency**

The results indicate that the EE% increased significantly [P<0.05] as the drug:polymer ratio varied from 1:1 to 1:5 as shown in table [1], which can be explained by increased viscosity of the organic phase and dense internal structure, therefore less drug loss during evaporation [37,38]. The results indicate that there was a significant decrease [P> 0.05] in the EE% with increasing the stirring rate for preparation of microspheres. The encapsulation increased with decreasing the stirring rate. A probably explanation is that, the surface area of large particles is lower which lead to less transport of the drug into the external aqueous phase [31], formulae F8, F9 also showed higher %EE.

**In-vitro release studies of OXP loaded microspheres**

The results indicate that the dissolution of the pure drug was faster in comparison to that released from any microsphere formulation. The release from microspheres was greatly extended and delayed by increase polymer concentration [figure 1, 2], this may be due to; a- increase in the wall thickness of the microspheres arising due to the increase in polymer conc. leading to increase the length of diffusional pathway through the polymer membrane [39], b- increase polymer conc. Lead to decrease amount of drug close to surface [27], c- as the conc. Of polymer increase, large amount of drug got bind in the polymer matrix as a result the rate of release decrease [26].

At low polymer conc,[drug:polymer ratio 1:2], more than 35% released during first hour [formulae F6,10,14,18] which was not satisfactory to the desired criteria for sustained release. By increase polymer conc. [ drug:polymer ratio 1:3, 1:4], 25% and 20% were released in first hour respectively, which fulfilled the desired criteria. At high polymer conc. [drug:polymer ratio 1:5] less than 9% released in first hour [formulae F9,13,17 and 21] which was not satisfactory to the desired criteria.

The results also indicate that, increasing the stirring rate resulted in increase in the rate of drug release. These may be due to; a- that smaller particle size microspheres are produced at higher stirring rates, which possess a large surface area leading to higher release rate. B- microsphere prepared at higher stirring rate are more porous, exhibit fast release of drug [27,40], formulae F19, F20 release more than 90% in 7 hours, which was not acceptable to the desired criteria for sustained release. The rate and amount of drug release is increased as the concentration of the surfactant is increased at constant drug:polymer ratio as shown in figure [3]. This is due to the increase in wettability and better solvent penetration as the surfactant is increased. [41].

Formulae F8 fulfilled all the desired criteria required in sustained release product [20% released in first hour, 150% dissolution was 7 hr, and 185% dissolution was 20hr].

The release mechanism of OXP from formulation was determined by comparing their respective correlation co-efficient. It would appear that the mechanism of release from microspheres was diffusion-controlled.

When the release rate constants of microspheres were compared, it was found to follow the Higuchi model. According to this model, the drug releases from these formulations may be controlled by diffusion through the micropores.

**In-vivo evaluation of microspheres**

**Bioavailability of [OXP] after oral administration**

The mean pharmacokinetic parameters of [OXP] from different formulations represented by the value of C_{max}, T_{max}, K_{el}, t_{1/2}, AUC_{0-24} and AUC_{0-∞} are represented in table [2]. And the mean plasma concentrations as a function of time for [OXP] were illustrated in figure [3]. From the obtained results, there was a noticeable difference in the T_{max} between the pure drug and the tested formulations, it was observed that, the absorption of plain [OXP] was rapid and reached its peak plasma concentration in [1.23±0.9 h], whereas, the mean T_{max} for the commercial trental SR tablet and the tested formulation [F8] were 5.32±0.51 and 7.79±0.24 h, respectively. [C_{max}] were 2543±5.4ng/ml for trental tablet, 22.54±1.43 ng/ml for formula [F8] compared to 37.43±2.97 ng/ml for plain [OXP]. The increase in the mean T_{max} and the decrease in the mean C_{max} compared to the plain drug indicated the controlled release effect of the microsphere formulations. The mean AUC_{0-24} was found to be 2340.65±10.43ng.h.ml^{-1} for formula [F8] compared to 660.87±8.64 ng.h.ml^{-1} for plain OXP, and 1420.54±8.85 ng.h.ml^{-1} for trental tablet. These results confirmed the prolonged release of the tested formulation.

From the obtained data, it was found that, the relative bioavailability of [OXP] from formula F8 was 340% compared to control [plain drug] and 164% compared to commercial available trental tablet. One of the main reasons for such a big difference...
between sustained-release [OXP] microspheres and [OXP] is that the absolute bioavailability of [OXP] was extremely low because of the poor solubility of the drug [42], and extensive first-pass hepatic metabolism [60–70%] [80], with t1/2 of 1.63 ± 0.8 hours. About 89% of orally administered [OXP] was excreted in the urine after six hours [8]. Also, the increase in the relative bioavailability may be due to the slow release of the drug from the microspheres which led to a longer absorption and distribution period for the drug loaded microspheres than that of the free form which increase the half life of drug from 1.6 hr to about 6.1hr.

References


[7]. Grigoleith,G., H. Leonhardt Rheology of blood and pentoxifylline, Pharmatherapeutica, 1, 10 (1997) 642 – 651


[22]. Devrim B, Canefe K. Preparation and evaluation of modified release ibuprofen microspheres with acrylic polymers (eudragit) by quasi emulsion Solvent diffusion method: effect of


Table (1): The composition, mean diameter, yield%, and entrapment efficiency of different microspheres formulations.

<table>
<thead>
<tr>
<th>Form. No.</th>
<th>Drug:polymer ratio</th>
<th>Stirring rate</th>
<th>Surfactant Conc.</th>
<th>Mean diameter (µm) ± S.D.</th>
<th>Yield (%) ± S.D.</th>
<th>Entrapment efficiency (%) ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>400</td>
<td>0.1%</td>
<td>No Microsphere</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>F2</td>
<td>1:3</td>
<td>400</td>
<td>0.3%</td>
<td>No Microsphere</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>F3</td>
<td>1:5</td>
<td>400</td>
<td>0.6%</td>
<td>No Microsphere</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>F4</td>
<td>1:1</td>
<td>800</td>
<td>0.1%</td>
<td>No Microsphere</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>F5</td>
<td>1:1</td>
<td>800</td>
<td>0.6%</td>
<td>No Microsphere</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>F6</td>
<td>1:2</td>
<td>800</td>
<td>0.3%</td>
<td>425±8.34</td>
<td>72.87±3.22</td>
<td>74.65±3.87</td>
</tr>
<tr>
<td>F7</td>
<td>1:3</td>
<td>800</td>
<td>0.3%</td>
<td>453±7.34</td>
<td>84.76±3.23</td>
<td>85.87±5.45</td>
</tr>
<tr>
<td>F8</td>
<td>1:4</td>
<td>800</td>
<td>0.3%</td>
<td>478±6.76</td>
<td>92.87±1.43</td>
<td>91.34±4.54</td>
</tr>
<tr>
<td>F9</td>
<td>1:5</td>
<td>800</td>
<td>0.3%</td>
<td>518±10.3</td>
<td>93.13±2.87</td>
<td>94.22±2.43</td>
</tr>
<tr>
<td>F10</td>
<td>1:2</td>
<td>800</td>
<td>0.6%</td>
<td>364±7.43</td>
<td>74.65±3.76</td>
<td>70.76±2.09</td>
</tr>
<tr>
<td>F11</td>
<td>1:3</td>
<td>800</td>
<td>0.6%</td>
<td>387±9.54</td>
<td>78.54±3.43</td>
<td>80.76±3.65</td>
</tr>
<tr>
<td>F12</td>
<td>1:4</td>
<td>800</td>
<td>0.6%</td>
<td>402±6.98</td>
<td>85.34±1.87</td>
<td>84.96±1.65</td>
</tr>
<tr>
<td>F13</td>
<td>1:5</td>
<td>800</td>
<td>0.6%</td>
<td>423±5.98</td>
<td>90.34±3.43</td>
<td>88.76±2.08</td>
</tr>
<tr>
<td>F14</td>
<td>1:2</td>
<td>1200</td>
<td>0.3%</td>
<td>385±8.45</td>
<td>70.89±2.04</td>
<td>72.34±3.65</td>
</tr>
<tr>
<td>F15</td>
<td>1:3</td>
<td>1200</td>
<td>0.3%</td>
<td>412±9.45</td>
<td>75.45±2.44</td>
<td>83.34±3.85</td>
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<tr>
<td>F16</td>
<td>1:4</td>
<td>1200</td>
<td>0.3%</td>
<td>432±7.54</td>
<td>85.23±3.09</td>
<td>87.56±3.27</td>
</tr>
<tr>
<td>F17</td>
<td>1:5</td>
<td>1200</td>
<td>0.3%</td>
<td>461±7.95</td>
<td>88.65±3.43</td>
<td>89.58±4.65</td>
</tr>
<tr>
<td>F18</td>
<td>1:2</td>
<td>1200</td>
<td>0.6%</td>
<td>325±6.65</td>
<td>71.34±3.53</td>
<td>68.54±3.86</td>
</tr>
<tr>
<td>F19</td>
<td>1:3</td>
<td>1200</td>
<td>0.6%</td>
<td>339±9.34</td>
<td>77.34±3.23</td>
<td>78.45±1.08</td>
</tr>
<tr>
<td>F20</td>
<td>1:4</td>
<td>1200</td>
<td>0.6%</td>
<td>354±7.56</td>
<td>80.65±4.11</td>
<td>82.65±1.87</td>
</tr>
<tr>
<td>F21</td>
<td>1:5</td>
<td>1200</td>
<td>0.6%</td>
<td>387±6.87</td>
<td>82.45±3.45</td>
<td>86.14±2.98</td>
</tr>
</tbody>
</table>

Table (2): Pharmacokinetics parameters of OXP after oral administration of plain OXP, Trental SR, and Formula F8.

<table>
<thead>
<tr>
<th>Pharmacokinetics parameters</th>
<th>Formula [OXP]</th>
<th>Trental SR</th>
<th>Formula [F8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>37.43±2.97</td>
<td>25.43±2.54</td>
<td>22.54±1.43</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.23±0.09</td>
<td>5.32±0.51</td>
<td>7.79±0.24</td>
</tr>
<tr>
<td>Kc (h⁻¹)</td>
<td>0.430±0.12</td>
<td>0.175±0.023</td>
<td>0.113±0.053</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.61±0.10</td>
<td>3.95±1.21</td>
<td>6.12±0.43</td>
</tr>
<tr>
<td>AUC0-24 (ng.ml⁻¹.h)</td>
<td>660.87±8.64</td>
<td>1420.54±8.65</td>
<td>2340.65±10.43</td>
</tr>
<tr>
<td>AUC0-24 (ng.ml⁻¹.h)</td>
<td>720.65±3.12</td>
<td>1580.43±4.65</td>
<td>2470.43±11.43</td>
</tr>
</tbody>
</table>
Figure 1: % OXP released from different formulae which was not satisfactory to the desired criteria for sustained release

Figure 2: % OXP released from different formulae which fulfilled all the desired criteria required in sustained release product
Figure 3: Mean plasma levels of [OXP] after oral administration of different [OXP] formulations [equivalent to 10 mg/ kg] in rabbits.