Development of pH sensitive polycaprolactone based microspheres for in-vitro release studies of Triprolidine Hydrochloride
CHAPTER IV

DEVELOPMENT OF pH SENSITIVE POLYCAPROLACTONE BASED MICROSPHERES FOR IN-VITRO RELEASE STUDIES OF TRIPROLIDINE HYDROCHLORIDE

ABSTRACT

A series of different blend ratios of polycaprolactone (PCL) and cellulose acetate phthalate (CAP) microspheres were prepared by double emulsion solvent evaporation method. Triprolidine Hydrochloride (TPH), is a propylamine antihistamine drug, was successfully loaded in to these microspheres via in-situ method. The maximum loading of TPH was found to be about 66%. The resulting microspheres were characterized by Differential Scanning Calorimetry (DSC), X-ray diffraction (X-RD), particle size analysis, and Scanning electron microscopic (SEM) studies. The DSC study revealed the blend compatibility of polymers. X-RD studies showed that the TPH drug particles are molecularly dispersed in the microspheres. Particle size and SEM studies indicated the formation of spherical microspheres with distinct size. The in-vitro release studies revolved that the release of TPH depends upon the pH condition, blend composition, and drug content. The release of TPH from microspheres achieved for more than 10 h.

Communicated:


IV.1. INTRODUCTION
Biodegradable polymers have been the major focus of attempts to develop improved delivery systems for pharmaceutical research [1, 2]. A variety of biodegradable polymers and their modified polymers with biocompatibility, biodegradability and absorbability have been used for drug delivery studies [3, 4]. The design and development of these polymeric materials can act as drug carriers by controlling the release of the bioactive drugs. The focus of current research on the blends of biodegradable polymers is due to their good biocompatibility, low cost, high performance and light weight materials [2].

Generally polyesters such as poly(lactide), poly(glycolide), polycaprolactone (PCL) and their copolymers have been used for drug delivery applications [5-9]. Among these, polycaprolactone is a biocompatible semi-crystalline polymer with a very low glass transition temperature [10]. The usage of PCL has been recently highlighted as platform for oral delivery of antigen and low molecular weight drugs [11]. Since the degradation of PCL is very slow, the release of small drugs has been supposed to be dilution controlled. Nevertheless, the release of drugs has been demonstrated to be often incomplete, the phenomenon being attributed to the high PCL crystallinity and hydrophobicity [12]. The design and development of drug delivery carriers based on blending of PCL with other polymers to improve the control release of drugs because high permeability of PCL [13-15].

Cellulose acetate phthalate (CAP) is commonly used as a polymer phthalate in the formulation of pharmaceuticals such as the enteric coating of tablets or capsules and for controlled release formulations [16-18]. CAP has been used for several decades as a pharmaceutical excipient due to its solubility dependent on the pH of the aqueous media. Enteric coatings based on CAP are resistant to acidic gastric fluids, but easily soluble in mildly basic medium of the intestine [19]. The pH sensitive solubility of CAP is mainly determined (as other properties of this mixed ester) by the degree of substitution (DS), namely the average number of substituent groups bound to an anhydroglucose unit (AGU), as well as by the molar ratio (acetyl and phthaloyl groups). These two structural characteristics of the polymer are dependent on the method employed for its synthesis.

Triprolidine \([1-(p\text{-tolyl})-1-(2\text{-pyridyl})-3-(1\text{-pyrrolidine}) \text{ prop-1-ene}]\) is a propylamine antihistamine drug. The drug works by blocking the action of histamine
at special sites in the skin, nose and blood vessels and also it is an important part of body’s defence mechanism. But sometimes the body releases too much histamine and this produces the allergic reaction. Triprolidine hydrochloride is used to relieve symptoms of allergies like high fever, seasonal rhinitis and perennial rhinitis [20, 21]. In a previous report Subha et. al. have developed TPH loaded pH sensitive microspheres composed with poly (acrylamide-co-acrylamidoglycolic acid) [22]. Sodium alginate based graft copolymer beads also developed by Chowdoji Rao et.al [23] for controlled release studies of TPH. In the present investigation for drug release study the author developed new biodegradable non toxic microspheres with the blend composition of PCL and CAP. The blends are good compatible and loaded with Triprolidine Hydrochloride drug via in-situ method for drug release studies. Hence, this system is new one because, dissolution of CAP in alkaline conditions, this exhibits pH responsive drug release property. Now, the author has taken TPH as a model drug for encapsulating in to these pH sensitive polymer microspheres. The drug loaded microspheres were characterized by various techniques to study the physicochemical properties. Based on in-vitro release studies the microspheres are potential to be used for oral drug formulations in pharmaceutical applications and the results are presented here.

**IV.2. MATERIALS AND EXPERIMENTAL METHODS**

The details of materials and the experimental procedures adopted in the present study have been explained in chapter II. Scheme IV.I. Represents formation of microspheres.
**IV.3. RESULTS AND DISCUSSIONS**

**IV.3.1. Differential scanning calorimetric studies**

DSC analysis of pure PCL, pure CAP and different blend compositions of PCL and CAP are presented in Fig.IV.1. Pure CAP (e) did not show any peak but PCL (a) showed a melting peak at 62°C. As the % of CAP increases in the blend composition the melting temperature also increases. This result may indicate that as the amount of CAP increases in the blend microspheres a significant crystallinity change was observed, this further indicate the miscibility between CAP and PCL.

![Scheme IV.I.](image-url)  

Scheme IV.I. Represents formation of microspheres.
**Figure IV.1.** DSC thermo grams of (a)Pure PCL (b) PC1(80:20) (c) PC2(70:30) (d) PC3 (60:40)(e) Pure CAP

**Fig. IV.2.** shows the DSC thermo grams of pure TPH [**Fig. IV. 2(a)**], and drug loaded microspheres (PC2) [**Fig. IV. 2(b)**] are shown in [**Fig. IV. 2.**] The drug, TPH, exhibit a sharp peak at 122.97 °C (**Fig. IV.2. a**) due to polymorphism and melting. However, no characteristic peak of TPH was observed in DSC curves of the drug loaded microspheres which indicates that the drug was molecularly dispersed in the polymeric matrix.
Figure IV.2. DSC thermo grams of (a) Pure TPH (b) Drug loaded microspheres (PC2) (70:30)

IV.3.2. X-ray diffraction studies

X-RD study is an important characterization technique in case of drug delivery applications, to study the crystallinity of drug present in the polymer matrix. XRD patterns of (a) pure TPH, (b) drug loaded microspheres, and (c) pure blend microspheres are shown in Fig.IV.3. XRD pattern of pure TPH provides the clues about the crystallinity of drug in the microspheres. Here, the TPH drug peaks are observed at 20 of 25.2° and 34.3° which are due to crystalline nature of TPH, while in the case of drug loaded microspheres the drug peaks are not observed which indicate that the drug particles are dispersed at molecular level in the polymer matrix.
IV.3.3. Morphology Studies

The SEM micrographs of TPH loaded microspheres before dissolution Fig.IV.4.(a) and after dissolution (b) are shown in Fig.IV.4. As seen in Fig.IV.4(a), they were spherical in shape and exhibited rough surfaces due to higher concentration of drug in the microspheres. Surface study of the microspheres after release study showed bigger pores (Fig.IV.4(b)) suggesting that the dissolution of CAP present in the blend in alkaline medium leading to release of TPH drug from the blend microspheres. The mean particle size of PC2 formulation is around 10 µm. The mean particle sizes of all formulations are shown in Table IV.I. The results of mean particle size with standard errors are presented in Table IV.I, while a size distribution curve (formulation) is presented in Fig.IV.5. The size distribution is normal distribution showing ~12µm. The particle size analysis also supports the formation of microspheres.
**Figure IV.4.** SEM micrographs of TPH loaded microspheres (a) before dissolution and (b) after dissolution.

**Figure IV.5.** Particle size distribution of microspheres
IV.3.4. Effect of CAP and pH

The release study of TPH from microspheres, in vitro release experiments were carried out in gastric and intestinal pH conditions. Releases of TPH from microspheres with variation of CAP content for formulations PC1, PC2, PC3 at pH 7.4 & pH 1.2 are displayed in Fig IV.6 & IV.7 respectively. The % of cumulative release is higher in case of high amount of CAP. The release of CAP is higher at pH 7.4 than at pH 1.2. This can be explained on the basis of dissolution behavior of CAP in alkaline conditions. A dense polymer network formed when microspheres could intact with acidic medium, but in alkaline condition CAP is easily leaching out from the microspheres giving porous network structure. This is also supported on the basis of SEM pictures (Fig.IV.4) taken before dissolution and after dissolution. Porous microspheres are produced after the dissolution, suggesting that the incorporation of CAP in to PCL indicates drug release is influenced by pH conditions. Based on these results we can conclude that the release of TPH restricts from microspheres at acidic pH, but maximum release at pH 7.4, due to the formation of porous network structure.

![Figure IV.6](image_url)

**Figure IV.6.** % Cumulative release of TPH through microspheres for different ratios of polymer composition (PCL: CAP) PC1 (80:20), PC2 (70:30), and PC3 (60:40) containing 20% TPH at pH 7.4.
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**IV.3.5. Effect of Drug content**

*Fig. IV.8 & IV.9* shows the release profiles of TPH loaded PCL:CAP blend microspheres at different amounts of drug loading at pH 7.4 and pH 1.2 media respectively. For both pH conditions (pH 1.2 and pH 7.4) release data showed that formulations containing highest amount of TPH (30 wt %) displayed higher release rates than those containing lower of amount of TPH. Formulation containing highest amount of TPH released 86.5 % (pH 7.4) of the total encapsulated drug. On the other hand, formulations containing lower amount of TPH have released only 79 % of TPH. Thus, sustained release was observed for the formulation containing lower amount of TPH. Thus the release rates are slower for lower amount TPH in the matrix, probably due to the availability of more free void spaces through which a lesser number of drug molecule will transport. The release of TPH is higher at pH 7.4 than at pH 1.2. This is due to the presence of CAP in the blend microspheres as explained as in the previous section.

*Figure IV.7.* % Cumulative release of TPH through microspheres for different ratios of polymer composition (PCL: CAP) PC1 (80:20), PC2 (70:30), and PC3 (60:40) containing 20% TPH at pH 1.2.
Figure IV.8. % Cumulative release of TPH through microspheres containing different amounts of drug PC2 (20%), PC4 (10%), and PC5 (30%) at pH 7.4

Figure IV.9. % Cumulative release of TPH through microspheres containing different amounts of drug PC2 (20%), PC4 (10%), and PC5 (30%) at pH 1.2
IV.3.6. In-vitro release studies

Results of encapsulation efficiencies are given in Table IV.1. The % of encapsulation efficiency varied depending upon the initial loading of the drug. In general, the formulations of PC4, PC2, & PC5, the % encapsulation efficiencies increased systematically with increasing drug content of the matrices. In the present study, the highest % encapsulation of 56.92 was observed for PC5 containing 30% of drug. These are in accordance with the results reported in literature by Rao et al. [24].

IV.3.7. Kinetics of In-vitro release studies

Drug-release kinetics was analyzed by plotting the cumulative release data versus time by fitting the data to a simple exponential equation [25].

\[(\frac{M_t}{M_\infty}) = k t^n\] ........................(1)

Where \(M_t\) and \(M_\infty\) represent the fractional drug release at time \(t\), \(k\) is a constant characteristic of the drug-polymer system and \(n\) is an empirical parameter characterizing the release mechanism. Using the least square procedure, the values of \(n\) and \(k\) for all the formulations are calculated and are given in Table IV.2. If \(n=0.5\), the drug diffuses and release from the polymer matrix following a Fickian diffusion. If \(n > 0.5\), anomalous or non-Fickian drug diffusion occurs. If \(n = 1\), a completely non-Fickian or case-II release kinetics is operative. From Table IV.2, the intermediary values of \(n\) ranging between 0.5 and 1.0 are attributed to an anomalous type diffusive transport [26] in the present study.

From the results of this study, the values of \(k\) and \(n\) showed a dependence on the blend composition, pH, and % of drug loading. The values of \(n\), for microspheres prepared by using various amounts of CAP (10, 20, 30 wt%) while keeping TPH (20%) constant ranged from 0.209 to 1.007 for pH 1.2 and 0.581 to 1.038 for pH 7.4 shows a shift of transport from Fickian to the anomalous type. Correlation coefficients, \(r\) obtained while fitting the release data are in the range from of 0.896 to 0.995. (Table IV.2.)
IV.4. Conclusions

Biodegradable blend microspheres of polycaprolactone (PCL) and Cellulose acetate phthalate (CAP) were developed by double emulsion solvent evaporation method to study the controlled release of TPH drug. SEM, particle size analysis gave surface morphology and particle size of microspheres. DSC and XRD analysis of TPH loaded microspheres have shown molecularly dispersed drug in the microspheres. Based on in-vitro release studies the TPH was released in a controlled manner by influencing the variation of blend composition, pH, and drug for more than 10 h.

Table IV.1. Results pertaining to percentage of encapsulation efficiency and mean particle size of different formulations

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<thead>
<tr>
<th>Formulation code</th>
<th>PCL:CAP (Wt/Wt)</th>
<th>% of drug</th>
<th>% of PVA</th>
<th>% EE</th>
<th>Mean particle size(µm)</th>
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<tr>
<td>PC1</td>
<td>80:20</td>
<td>20</td>
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<td>48.76±1.8</td>
<td>15±6</td>
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<tr>
<td>PC2</td>
<td>70:30</td>
<td>20</td>
<td>1</td>
<td>51.23±3.6</td>
<td>12±16</td>
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<tr>
<td>PC3</td>
<td>60:40</td>
<td>20</td>
<td>1</td>
<td>56.81±2.8</td>
<td>11±9</td>
</tr>
<tr>
<td>PC4</td>
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<td>10</td>
<td>1</td>
<td>53.21±3.2</td>
<td>14±4</td>
</tr>
<tr>
<td>PC5</td>
<td>70:30</td>
<td>30</td>
<td>1</td>
<td>55.92±2.7</td>
<td>19±11</td>
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Table IV.2. The release kinetic parameters $k$, $n$ and correlation coefficient ($r$) of different formulations at pH=1.2 & pH=7.4.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>pH=1.2</th>
<th></th>
<th>pH=7.4</th>
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</thead>
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<tr>
<td></td>
<td>$n$</td>
<td>$r$</td>
<td>$k$</td>
<td>$n$</td>
</tr>
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<td>0.991</td>
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<td>0.581</td>
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<tr>
<td>PC2</td>
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<td>0.899</td>
<td>2.7669</td>
<td>0.613</td>
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<tr>
<td>PC3</td>
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<td>0.995</td>
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<td>PC4</td>
<td>0.686</td>
<td>0.870</td>
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<td>0.99</td>
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<td>PC5</td>
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<td>0.944</td>
<td>0.3451</td>
<td>1.038</td>
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IV.5. References


