Development and Characterization of Muco-Adhesive Microcapsules Containing Hypoglycemic Drug

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ABSTRACT
Pioglitazone is a poorly water soluble drug, having short biological half life (3-5 hour) so the present study was aimed to increase the biological half life by develop a sustained release microcapsule. The microcapsules of pioglitazone hydrochloride were prepared by employing sodium alginate as a cell forming polymer and by using a different bio-adhesive polymers as carbopol, HPMC and sodium CMC in a various ratios of 1:1, 3:1, 6:1 & 9:1, by orifice ion gelation method. Scanning electron microscope photographs of samples revealed that all prepared microcapsules were almost spherical in shape and have a slightly smooth surface. The in vitro release profile of Pioglitazone hydrochloride indicates that all the batches of microcapsules showed controlled and prolonged drug release over an extended period of 10 h. FT-IR spectra revealed no chemical incompatibility between drug and the polymers.

Keywords: Hypoglycemic Drug, Mucoadhesion, Microcapsule, Orifice Ionic Gelation Method.

1. INTRODUCTION
Pioglitazone is a Thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action (1,2). Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ) (3). Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patience compliance; there are few reports on the formulation of pioglitazone employing coated granules and matrix tablets. Microencapsulation has been accepted as a process to achieve controlled release and drug targeting. The choice of the methods for the preparation of microcapsules depends on many factors such as the drug solubility and its short half life 3-5 hour (2) and is eliminated rapidly. In the present study, an attempt was made to develop sustained release microcapsules to increase half-life of drug concentration in serum by using orifice ionic gelation method. The prepared microcapsules were evaluated for drug content, particle size, surface morphology, muco-adhesive testing and in vitro drug release studies. Mucoadhesion has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form at the site of application or the
absorption and to facilitate intimate contact dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs.  

2. MATERIALS AND METHODS:  
2.1 Materials:  
Pioglitazone HCl sample from Ontop Pharmaceuticals LTD (Bangalore, India), Sodium carboxymethylcellulose (sodium CMC), Methyl cellulose (Mc) and Hydroxypropylmethylcellulose (HPMC) was purchase in the market; all the chemicals were A.R. Grade.  

2.2 Estimation of Drug  
2.2.1 Linear regression equation method  
Accurately weighed about 100 mg of pioglitazone hydrochloride was dissolved in 100 ml Phosphate buffer (pH 7.4) to obtain 1000 µg/ml concentration of drug (stock A). Stock A (10 ml) was diluted up to 1000 ml with solvent system to obtain 10 µg/ml concentration (stock B). Aliquots of Stock B were diluted to obtain concentrations of 1, 2, 3, 4, 5 to 10 µg/ml of pioglitazone hydrochloride. All dilutions were scanned from 400 to 200 nm against solvent system as blank (figure 1) and their absorbance were observed at 269 nm (Figure 2). The LRE was developed as Y = 0.0202x + 0.0019, where Y = absorbance and C = concentration of solutions at 269 nm (Figure 2). The standard absorptivity method was used where five dilutions were prepared in triplicate and the absorbance was observed at 269 nm. The standard absorptivity e was calculated from the above observations (Table 1). 

2.2.2 Fourier transforms infrared spectroscopy:  
FT-IR spectra (500-4000 cm\(^{-1}\)) were obtained on a Nicolet Avatar 370 FT-IR spectrophotometer (Nicolet) with a resolution of 4 cm\(^{-1}\). KBr pellets were prepared by gently mixing 1 mg sample with 200 mg potassium bromide (Figure 3).  

2.3 Preparation of muco-adhesive microcapsules  
Microcapsules are prepared by orifice- ionic gelation method\(^{(8, 9)}\) by employing the Sodium alginate as a cell forming polymer and Sodium CMC, HPMC and Carbopol as muco-adhesive\(^{(10)}\) polymers are dissolved in purified water in a corresponding ratio 1:1, 1:3 and 6:1 separately to form a homogenous polymer solution. Core material pioglitazone hydrochloride (1 gm) is added to polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion is then added manually drop wise into CaCl\(_2\) (10% w/v) solution through a syringe with a needle of size no. 18. The added drop lets are related in the CaCl\(_2\) solution for 15 min to complete the curing reactions and to produce spherical rigid microcapsule. The microcapsules are collected by decantation, and the product thus separated, washed repeatedly with water and dried at 45°C for 12 hrs. (Table 2).
Formulation code | Composition and ratio | Drug (mg) | Cell forming polymer (mg) | Mucoadhesive Polymer (mg)
---|---|---|---|---
MC1 | SA: SCMC (1:1) | 1000 | 500 | 500
MC2 | SA: HPMC (1:1) | 1000 | 500 | 500
MC3 | SA: Carbopol (1:1) | 1000 | 500 | 500
MC4 | SA: SCMC (3:1) | 1000 | 750 | 250
MC5 | SA: HPMC (3:1) | 1000 | 750 | 250
MC6 | SA: Carbopol (3:1) | 1000 | 750 | 250
MC7 | SA: SCMC (6:1) | 1000 | 857.14 | 142.86
MC8 | SA: HPMC (6:1) | 1000 | 857.14 | 142.86
MC9 | SA: Carbopol (6:1) | 1000 | 857.14 | 142.86

Table: 2. Composition of different muco-adhesive microcapsules
Note: Sodium alginate =SA, Sodium CMC = SCMC

2.4 Characterization of microcapsules:

2.4.1 Physical characterization
The surface and inner part of the microspheres was observed through the Scanning Electron microscopy (SEM). (SEM) was performed for surface and inner morphological characterization of microspheres using the scanning electron microscope (SEM- LEICA S430, London, UK). (Fig-4)

2.4.2 Particle Size Distribution
Different sizes of microcapsules in a batch were separated by sieving method using a range of standard sieves (#10, #22, #44, #52 and # 60). The amount retained on different sieves was weighed. From the obtained data, weight percent retained on different sieves and average size of microcapsules were calculated.

2.4.3 Practical yield:
The percentage yield of Pioglitazone in the microencapsulated product is determined by using the formula:

\[
\% \text{ Yield} = \frac{\text{Weight of Microcapsules}}{\text{Theoretical Weight of drug and polymer}} \times 100
\]
2.4.4 Encapsulation efficiency:
The encapsulation efficiency of microcapsules was calculated by using the formula:

\[
\% \text{ Encapsulation efficiency} = \left( \frac{\% \text{ Drug content}}{\% \text{ theoretical drug content}} \right) \times 100
\]

2.5 In-vitro drug release

2.5.1 Release in pH 7.4-phosphate buffer:
In vitro release rate of Pioglitazone HCl from microcapsules of different samples was determined using single station USP dissolution test apparatus. The dissolution medium consisted of phosphate buffer (pH 7.4) was used, 9gm of SLS mixed in the buffer to enhance the solubility of pioglitazone in the phosphate buffer. Samples of drug, microcapsules equivalent with 100 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium at 37°C. Aliquots of 5 ml were withdrawn at regular intervals of time i.e. (5, 1, 2, and 3 up to 18 hour) and the same is replaced with fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper no. 1. The filtrate was diluted up to 6 ml with phosphate buffer (pH 7.4). Then the absorbance was measured at 269 nm (Figure 5).

2.5.2 Drug release kinetics studies:
In order to understand the kinetics and mechanism of drug release, the results of the in vitro drug release study were fitted with various kinetic equations like zero order, first order, Weibull model, Korsmeyer -peppas model, Hill equation, Michaelis- Menten model. The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient (r) values obtained in various models.

3. RESULTS AND DISCUSSION:

3.1 Compatibility Studies:
FTIR studies were done to detect the possible interactions between the drug and the polymers in the microencapsulation process.
microcapsules. Fig. 3 shows the IR spectra of drug and the polymers. Comparing the spectra of individual drug and polymers with those of microcapsules prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state between cell forming polymer (Sodium alginate) and Mucoadhesive polymer (Sodium alginate, Carbopol, Sodium CMC, HPMC) with pioglitazone HCl under investigation. The absence of any significant change in the IR spectral pattern of drug-polymer mixture indicated the absence of any interaction between the drug and the polymer (Figure 3).

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Regression Coefficient (r) value</th>
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<tbody>
<tr>
<td>MC1</td>
<td>0.98 751 88 9600 9859 0.9484</td>
</tr>
<tr>
<td>MC2</td>
<td>0.97 751 37 8988 0.9404 0.9289</td>
</tr>
<tr>
<td>MC3</td>
<td>0.98 752 71 9340 0.9522 0.9041</td>
</tr>
<tr>
<td>MC4</td>
<td>0.98 650 54 9645 9158 0.9735</td>
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<td>MC5</td>
<td>0.98 279 99 9310 9443 0.9406</td>
</tr>
<tr>
<td>MC6</td>
<td>0.97 311 86 9159 0.9571 0.9296</td>
</tr>
<tr>
<td>MC7</td>
<td>0.99 611 49 9732 0.9571 0.9888</td>
</tr>
<tr>
<td>MC8</td>
<td>0.99 503 40 9722 0.9538 0.9903</td>
</tr>
<tr>
<td>MC9</td>
<td>0.99 492 51 9691 0.9578 0.9889</td>
</tr>
</tbody>
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Table: 4. In vitro release kinetics studies of Pioglitazone microcapsules

3.2 Physical characterization:
The mucoadhesive microspheres of pioglitazone prepared by the orifice-ionic gelatin method were found to be discrete, spherical, free flowing, and the monolithic matrix type. The microcapsules were uniform in size, with size range of 300 μm. The SEM photographs indicated that microcapsules were spherical and completely covered the coat polymer (Figure 4).

3.3 Particle Size Distribution: The average size of microcapsules in various batches was found to be 350 μm, 347 μm, and 389 μm, 410 μm 387 μm, 341 μm, 354 μm, 372 μm and 345 μm for MC1, MC2, MC3, MC4, MC5, MC6, MC7, MC8 and MC9 respectively. (Table 3)

3.4 Practical yield: The percentage practical yield was found to be in the range of 79.87 to 89.77%. The maximum percentage practical yield was found to be 89.77% for MC-9. (Table 3)

3.5 Percentage drug content and encapsulation efficiency: The actual drug content and encapsulation efficiency of all nine formulations are given in Table 3. The encapsulation efficiency ranges from 66.91 to 81.04% for formulation MC1 to MC9. The maximum encapsulation efficiency was found to be 81.04% in MC7.

3.6 In-vitro drug release: The *in vitro* release profiles of nine formulations MC1 to MC9 are shown in Fig. 5. It shows the plot of cumulative percent drug released as a function of time for different formulations. The cumulative percentage drug released indicates a controlled and prolonged drug release over an extended period of time. From the *in vitro* drug release profiles, it was observed that the drug release from microcapsules was decreased with an increase in cell forming material in the microcapsules (MC7, MC8, and MC9). The regression coefficient (r) values for formulations MC1 to MC9 are tabulated in Table 4. The model that gave higher ‘r’ value was considered as best fit model. The regression coefficient ‘r’ values were found to be higher in the zero order models, Hill equation model, Michaelis menten model, Korsmeyer peppas modal and Weibull model respectively, indicating that the dissolution of pioglitazone from all formulations followed following above model. The order of release rate observed with all microcapsules was MC8>MC9>MC7>MC4>MC6>MC5>MC1>MC2>MC3. The drug release from the microcapsules was diffusion controlled.

4. CONCLUSION:
Sustained release pioglitazone muco-adhesive microcapsules could be formulated by using cell forming polymer sodium alginate and muco-adhesive polymers (Carbopol, Sodium CMC and HPMC) as a release retardant by orifice ion gelation method. The Muco-adhesive microcapsules of all the formulated batches were spherical, discrete and free flowing. The drug content was found to be almost uniform in a batch of muco-adhesive microcapsules. Increasing the concentration of cell forming polymer (sodium alginate) in microcapsule formulation decreases the rate of drug release, best result were found in alginate Carbopol formulations in both cases.

5. REFERENCES


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Conflict of Interest: None Declared