Study of Paracetamol Release from a Castor Oil Based Copolyester Matrix

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ABSTRACT
The copolyester prepared from the monomers is mechanically stable and it undergoes slow hydrolytic degradation under physiological condition. Paracetamol is incorporated in the polymer during its synthesis and the release of the drug from the polymer is studied by UV spectrophotometer. After an initial burst release for the first day, the rate is gradually decreased.

Key Words: biodegradable, controlled release, castor oil, paracetamol, in vitro experiment

INTRODUCTION
The technique used for drug release from the polymer matrix can be used to deliver the drug controllably, by changing the mole ratios of the monomers till the greater crosslink density is obtained[1–3]. This can be studied by IR spectroscopy. The technique turns to be advantageous if the polymer so developed has self-destructive mechanism which facilitates its degradation in the physiological environment into non-toxic metabolized products during or after the release process. The application of the biodegradable polymer for ineffective chemotherapy has been a current field in the polymer research[4,5].

EXPERIMENTAL
Materials
Citric acid (BDH, India); Castor oil (Upjohn Chemicals, India); Anhydrous FeCl₃ (A.R. grade, E. Merck, India); Paracetamol (Sujani Organics Ltd., India) were used without further purification.

Polymer Synthesis
The monomers citric acid (2.11 g), castor oil (3.14 g) and catalyst, anhydrous FeCl₃ (13.6 mg) were taken in 50 mL beaker, thoroughly mixed with a glass rod and then heated about 4 hours at 170 °C in a vacuum oven until bubbling ceased followed by 2 hours post-curing. The polymer was then allowed to cool at the ambient temperature and purified by leaching several times with boiling ethanol dried under vacuum at 50 °C. The polymer sample was almost transparent, slightly brownish, rubbery and glassy to touch.

Drug Incorporation
Drug was incorporated in the polymer by the bulk method i.e., during the preparation of the polymer from the monomers. Paracetamol (25 mg) was suspended in warm monomer mixture containing the appropriate amount of catalyst and then stirred
with a glass rod over a hot plate till the mixture was prepolymerized to a transparent liquid and then polymerization was completed at elevated temperature under vacuum as described in the polymer synthesis. Thus a drug loaded matrix in which the drug was homogeneously and molecularly distributed was obtained.

**Preparation of Phosphate Buffer**
Phosphate buffer solution was prepared by taking 4.1825 g of dipotassium hydrogen phosphate and 0.1482 g of potassium dihydrogen phosphate in 250 mL of distilled water. The pH of this solution was adjusted to 7.4 by adding phosphoric acid.

**In vitro Drug Release**
Before performing an *in vivo* experiment, it is customary to carry out the same experiment in the laboratory producing a nearly identical environment in a glass apparatus as exists in a living body. Hence for the study of *in vitro* [6] drug release under physiological condition, a drug loaded polymer slab was placed in 250 mL phosphate buffer of pH 7.4 under unstirred condition. The release of the drug in the medium was determined by taking an aliquot portion (0.1 mL) at suitable time intervals and measuring its absorbance (after suitable dilution) at the $\lambda_{max}$ of the drug using a 160 A Hitachi UV spectrophotometer. Concentrations of the released drugs were then computed by comparing the absorbancies with standard curves prepared for the pure drugs in the buffer by the appropriate concentration region.

**Characterization**
The polymer was characterized by elemental analysis, IR and $^1$H NMR spectroscopy. Carbon and hydrogen were analyzed by a Heraeus Carlo Ebra 1108 elemental analyzer.

IR spectrum was recorded with KBr pellet using a Perkin-Elmer model 837 spectrophotometer.

Proton magnetic resonance spectrum was recorded with Varian EM 390, 90 MHz NMR spectrometer using CDCl$_3$ and DMSO-d$_6$ as solvent.

Equilibrium swelling of the polymer samples in phosphate buffer of pH 7.4, ethanol and ethylene carbonate at ambient temperature was measured gravimetrically [7]; carefully avoiding any loss during measurement.

**Hydrolytic Degradation of the Polymer**
The polymer is a crosslinked polyester of citric acid having three carboxyl and one hydroxyl functions and castor oil, potential triol, and is expected to undergo degradation by the hydrolysis of the ester links. Hence hydrolytic degradation [8,9] of the polymer sample under physiological condition was studied. A rectangular slab of the polymer sample weighing about 0.1 g was cut from the bulk polymer synthesized and was placed in 250 mL phosphate buffer of pH 7.4 at 37 °C under unstirred condition and the degradation was observed.

**RESULTS AND DISCUSSION**

**Synthesis**
For the synthesis of polymer, citric acid and castor oil were mixed with catalyst thoroughly. The polymerization temperature and time varied at the maximum attainable vacuum in the vacuum oven at 170 °C for 4 hours cure time followed by 2 hours post-curing (under the same condition) were found to be optimum. The mole ratio of citric acid to castor oil was approximately 1 (Figure 1). Polymer was insoluble in water and in common organic solvents and expected to be highly crosslinked [10].

**Characterization**
**IR Spectra**
Comparison of the IR spectra of the monomers and copolyester shows that the broad band in the spectrum around 3400 cm$^{-1}$ due to -COOH and -OH in the spectrum of citric acid and the broad band in the region 3500-3350 cm$^{-1}$ due to -OH in the spectrum of castor oil have become quite smaller around 3400 cm$^{-1}$ in the spectrum of copolyester. Again the C=O stretching frequency of the acid monomer at 1700 cm$^{-1}$ has shifted to 1750 cm$^{-1}$ in the spectrum of the copolyester. All
these indicate the formation of ester bonds. The smaller broad band around 3400 cm\(^{-1}\) in the spectrum of the copolyester is in all probability due to an unreacted tertiary hydroxyl of citric acid.

**Elemental Analysis**

The results of the elemental analysis compared to the theoretical values are as follows:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>C (%)</th>
<th>H (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>66.16</td>
<td>9.00%</td>
</tr>
<tr>
<td>Calculated</td>
<td>68.45</td>
<td>9.16</td>
</tr>
</tbody>
</table>

The experimental results are in good agreement with calculated data.

**\(^1\)H NMR Spectrum**

The chemical shifting between 2 and 4 ppm is due to the presence of free OH group. A shift at 2.3 ppm is due to the presence of aliphatic ester linkage. A shift at 1.3 ppm is due to the presence of aliphatic linkage (Figure 2).

It is expected from polymer structure and proton magnetic resonance study that the release is to be controlled at a suitable rate due to the presence of two free OH groups bearing lone pair of electrons. This is due to the interaction between free OH groups and the drug molecule.

**Degradation of the Polymer**

A drug-free polymer in the form of a rectangular slab when placed in phosphate buffer of pH 7.4 at 37 °C was found to maintain its shape and physical integrity for about 3 days. It began to disintegrate very slowly from the 4th day, and by the 9th day only some few particles disintegrated from the body of the slab could be found. It took about 2 months for the complete disintegration of the slab into fine particles turning the entire buffer medium into colloidal suspension.

**Swelling Behaviour**

The swelling values of polymer in phosphate buffer of pH 7.4, ethanol and ethylene carbonate (\(-30°C\)) are 7.4, 39.2 and 9.9% respectively indicating the crosslink density. For each polymer sample the equilibrium swelling value in the three solvents is in the order:

ethanol > ethylene carbonate > phosphate buffer.

This is probably because of the presence of three large hydrocarbon chains (hydrophobic) of castor oil in the repeat unit.

In a given solvent at a fixed temperature, the extent of swelling for a series of chemically similar crosslinked polymers is inversely proportional to the crosslink density in the network [11].

**In vitro Drug Release**

*In vitro* release pattern of therapeutics from a polymer matrix gives an idea of its ability to function as a sustained and controlled drug release delivery system and its knowledge is a prerequisite for studying its *in vivo* performance.
Study of Paracetamol Release from a Castor Oil

The drug loaded polymer matrix weighed 220 mg and contained 1.05 mg of the drug. Curves in the Figure 3 show respectively the cumulative release (C') and release rate per day (C) with time. In the 1st day a slightly higher release of about 2μg was observed. On the 2nd day the release fell to about 1.8 μg per day and from 2nd to the 4th day release rate remained almost steady at this level. From the 5th day onwards the release rate continued to decrease [12].

Release Mechanism

It has been observed that after an initial boost release in the 1st day an almost zero release occurs for two days and then release rate decreases continuously with time. It has also been observed that a drug free or drug loaded matrix in the form of a rectangular slab in phosphate buffer of pH 7.4 retains its shape and physical integrity for 3 days. Then from the 4th day polymer particles begin to separate out from the matrix but in a very slow manner. By the time drug release is over only a few disintegrated particles from the slab can be found.

Thus matrix erodes while release is occurring, but erosion rate is quite slow. It appears that drug release occurs simultaneously by diffusion and erosion. In a purely diffusional release through an unchanging matrix the release rate decreases with time.

Simultaneous erosion of the matrix throughout its bulk by gradual cleavage of crosslinks should increase the permeability of the drug through matrix. It seems that at the beginning the two opposite effects counterbalance each other and a nearly uniform release rate is observed for the first few days. But erosion of the matrix being a very slow process in the present case, after the first few days the slowly increasing release rate due to matrix erosion cannot counterbalance the decreasing release rate due to diffusion through an unchanging matrix. The overall effect is a gradual decrease in the release rate with time after a uniform release for a short initial period.

CONCLUSION

In in vitro experiment our purpose was to examine the micro release of drug from the polymer matrix.
drug loaded polymer matrix weighed 220 mg and contained about 1.05 mg of drug. The release rate was very minute of about 2 µg for the 1st day and decreased gradually which was observed for about 15 days.

The release rate obtained by our in vitro experiment can be used effectively in curing normal fever.

ACKNOWLEDGEMENT

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REFERENCES