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Biodegradable polymer and its biomedical application

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Abstract
In the last half-century, biodegradable polymers have been widely used in biomedical applications such as drug carrier, medical devices, tissue engineering and antibacterial biomaterials. Polymers that are biodegradable provide the significant advantage of being able to be broken down and removed after they have served their special function. Our interest is to synthesize novel biodegradable polymers to be used as carriers for sustained and controlled release of medicaments. In this respect, our efforts have been made to synthesize and characterize several biodegradable polymers using different catalyst, of them, malic acid-butane 1,4-diol copolyester exhibited drug release behavior corresponding to BP standard enteric coating profile. Sub-acute toxicity of this polymer was also investigated and was found to be non-toxic. The polymer is expected to be usable as enteric coating material.

Keywords: Biodegradable polymer, microbial degradation, dissolution studies, enteric coating

Introduction
The past decades have seen significant research effort in the field of polymers for a range of biomedical applications, driven by the promising prospect of these materials for realizing next generation therapeutics in the clinic [1] and now considerable interest is being focused on the development of biodegradable polymers for biomedical carriers [2-6]. Biodegradable polymeric materials are favored in the development of therapeutic devices, including temporary implants and three-dimensional scaffolds for tissue engineering. Further advancements have occurred in the utilization of biodegradable polymeric materials for pharmacological applications such as delivery vehicles for controlled/sustained drug release. These applications require particular physicochemical, biological, and degradation properties of the materials to deliver effective therapy. As a result, a wide range of natural or synthetic polymers able to undergo hydrolytic or enzymatic degradation is being studied for biomedical applications [7].

Many of the existing biodegradable carriers are linear polyesters [8] such as polylactic acid, polyglycolic acid and their copolymers [9-10] which are being used for specialized application such as controlled release drug formulation [11-13], insecticide and pesticide carriers as well as non-toxic surgical implant materials. A large number of polymers have a built-in self-destruct mechanism by which they undergo slow hydrolytic and microbial degradation releasing the impregnated material at controlled rates. Poly (L-lactic acid) is a biodegradable polyester having good biocompatibility, it has been utilized as an useful biodegradable material in the medical and pharmaceutical fields. But the application scope of Polyla is limited because it is highly crystalline polyester [3].

Apart from the high molecular weight polyesters produced by microorganisms and by ring-opening polymerization of lactones or lactides, aliphatic polyesters from the condensation of hydroxycarboxylic acid or the condensation of diols with dicarboxylic acids have also attracted the attention of many researchers [14].

Our objective is to devise novel, non-toxic, biodegradable polymers to be used as carriers for sustained and controlled release of drugs, as conventional dosage forms produce toxicity or inefficacy problems if they are taken regularly or omitted in between dose intake time respectively [15-18].

This paper is intended to provide a brief outline of work that is under way in the area of biodegradable polymer research and development. Now, I would like to present the in-vitro drug release profile and sub-acute toxicity study of Malic Acid-Butane 1,4-diol Copolyester when synthesized using $FeCl_3$ as catalyst.

Experimental

Synthesis: Malic acid- butane 1,4-diol co-polyester was synthesized using $FeCl_3$ (0.4% of the total weight) as catalyst in 250 mL R.B. flask connected by Dean-Stark apparatus at 110-120^{0}C under nitrogen atmosphere for about 7 hrs.

Characterization

The co-polymer was characterized by their IR spectrum, molecular weights, solubility in common organic solvents, elemental analysis, hydrolytic degradation and swelling behavior.

Coating of the core (uncoated) tablets

The malic acid-butane 1,4-diol co-polyester was used as a coating material. The co-polyester was dissolved in ethyl acetate to prepare its 40% coating solution, which was sprayed over the core tablets in a small coating pan with continuous hot air flow. The coating pan was allowed to rotate until the solvent evaporated and tablets dried.

Preparation of Diclofenac Sodium Standard Calibration Curve

0.05g. of pure diclofenac sodium (DS) was dissolved in buffer medium of pH 7.4 to make 1000 ml solution. These solutions were used for the preparation of the standard calibration curves of diclofenac sodium in experimental buffers spectrophotometrically.

Dissolution Studies

The dissolution studies for both the core tablets and the coated tablets were performed in order to evaluate the efficacy of the polymer as a coating material on the release of the drug. A USP type II dissolution apparatus (paddle stirrer), "Electrolab TDT-04" with a rotation speed of 50 rpm was used for dissolution experiments. A solution of pH 1.2 was prepared[19] by 2g of NaCl and 9.82 mL of conc. HCl dissolved in 1 liter distilled water and used as the simulated gastric fluid. A buffer solution of pH 7.4 was prepared by KH_2PO_4 & Na_2HPO_4, and was used as the simulated intestinal fluid[19]. The simulated gastric fluid (900 mL), heated at 37 ± 0.5℃, was used initially for the dissolution studies which was replaced after 2 hrs. by 900 mL of simulated intestinal fluid heated previously at 37 ℃.

Samples (5 mL) were withdrawn from the simulated gastric fluid at 30 minutes intervals for 2 hrs. and from simulated intestinal fluid at 15 minutes intervals for 45 minutes which were immediately compensated with the same amount of fresh medium preheated at 37 ± 0.5 ℃.

The amount of drug released was calculated by measuring the absorbance after suitable dilution if necessary using a Shimadzu UV – 1200 spectrophotometer at 274 nm. Concentration of the released drug were then obtained by comparing with standard calibration curve prepared from pure drug in phosphate buffer solution of pH 7.4 in the appropriate concentration region. The in-vitro release studies were performed on coated and core tablets.

Subacute Toxicity Study

Grouping of Rats: Rats were weighed individually and divided into two groups; group A (average body weight 133.25 gm rat^{-1}) and group B (average body weight 140.05 gm rat^{-1}), each comprising of 4 rats. Group A received vehicle only to act as control, while group B received malic acid-butane 1,4-diol copolyester.

Administration of sample

Malic Acid-butane 1,4-diol co-polyester was dissolved separately in distilled water with the help of polyoxyethylene 20 sorbitan mono laurate (Tween-20) in such a way that 0.3 ml of final preparation contained 300 μg of the co-polyester. The polymer was administered to the rats of group B intraperitoneally at a dose 300 μg rat^{-1}day^{-1} respectively for 21 consecutive days.

Gross general observation after co-polymer administration

The rats were observed daily very keenly to note the following features: Behaviour, CNS excitation, CNS depression, Food intake, Salivation, Diarrhoea, Muscular weakness. Prior to sacrificing the animals, the body weights of each rat of group A and B were measured before the administration of the copolymer and after the completion of the investigation.

Results and Discussion

The polymer synthesized from Malic acid and butane 1,4-diol using $FeCl_3$ as catalyst was black in color, solid and slightly sticky at room temperature. It was purified by dissolving in acetone and then by precipitating using ethanol as non-solvent.

The polymer sample was insoluble in water and ethanol, but soluble in common organic solvents e.g., acetone, ethylacetate etc. The polymer was cryogenically powdered and its IR spectrum on KBr pellets was recorded by a Perkin-Elmer IR Spectrophotometer. In the IR spectrum of the polyester the >C=O stretching frequency shifted from1690 cm^{-1}to1715 cm^{-1}. The band representing –OH group in the region 3600-3640 cm^{-1} in the spectrum of the diol is almost absent in the spectrum of the polymer. A new band representing ester linkage appeared in 1050-1200 cm^{-1} in the spectrum of the polymer. All these indicate the formation of ester bonds. Hydrolytic degradation study was carried out in acid, base and buffer. Molecular weight determination was carried out by end group analysis and viscosity measurement. It can be seen from the result that the molecular weight obtained by viscosity method was slightly higher than the same obtained by end group analysis.

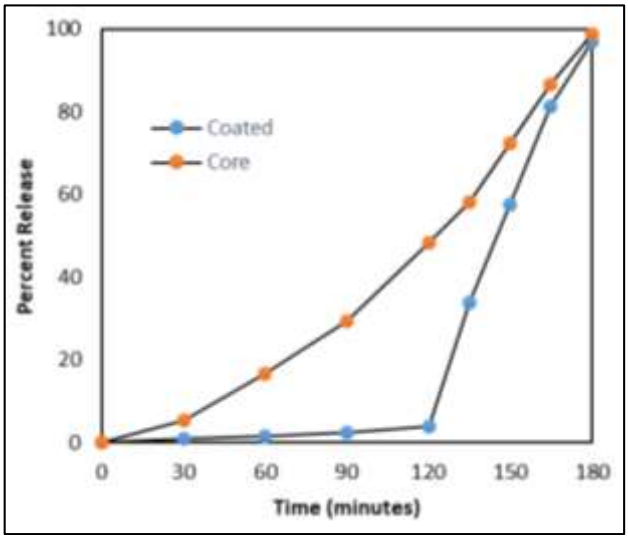

Fig 1: Mean (±SEM) percent release of diclofenac sodium core and malic acid- butane 1,4-diol co-polyester coated tablets in simulated gastric fluid (pH 1.2) and in simulated intestinal fluid (pH 7.4).

From the degradation study it was found that malic acid-butane 1,4-diol co-polyester slab remained intact in the gastric fluid (pH 1.2) but gradually degraded in intestinal fluid (pH 7.4). So, the co-polyester was chosen for enteric coating. Enteric coating material resists the release of the drug from the core tablet in the gastric environment but it helps drug release in the intestine.

In this study, it was found that the polymer did not degrade or swell in the gastric fluid when coated on a core tablet for two hours and drug release was observed not more than 4%, where as 48% of diclofenac sodium was released from the core tablets (uncoated tablets) in that time in the simulated gastric fluid (Fig 1). But in the intestinal fluid it gradually degraded and drug release was observed from the malic acid-butane 1,4-diol co-polyester coated tablets. Fig. 1 also shows that around 81% of diclofenac sodium was released in the simulated intestinal fluid within 45 min. The release pattern of the co-polyester coated diclofenac sodium corresponds to the BP drug release profile of enteric-coated tablets [20].

The sub-acute toxicity study of the co-polyester was carried out in albino rats. The gross general observations such as changes in body weight, hematological profiles, biochemical parameter of blood and histopathology of liver, kidney, heart, lungs and spleen were investigated both in control and experimental rats. The body weights of the rats, the changes of their hematological and biochemical parameters are statistically insignificant. No abnormalities were found in the histopathology of the liver, kidney, heart, lung and spleen in the experimental group of rats when compared with control group of rats. One of the advantage of this co-polyester is to use $FeCl_3$ as catalyst instead of *p*-toluene sulfonic acid which is less toxic.

So to conclude, polymer synthesized from Malic acid and butane 1,4-diol using $FeCl_3$ as catalyst would be usable as an enteric coating materials or other biomedical purposes where biodegradable polymers be needed to use safely.

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