



BIODEGRADABLE INJECTABLE IMPLANT SYSTEMS FOR SUSTAINED DELIVERY USING POLY (LACTIDE-CO-GLYCOLIDE) COPOLYMERS

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ABSTRACT

Poly (lactide-co-glycolide) (PLG) is one of the most widely used biodegradable synthetic polymer for sustained release formulations. In the present work, *in situ* gel formulation has been developed using poly (lactide-co-glycolide) to deliver an antidiabetic drug- rosiglitazone, that can be given by subcutaneous route. The effect of different vehicles (N-methyl-2-pyrrolidone, triacetin), polymer concentration and comonomer ratios such as (65:35, 75:25, 85:15) in the polymer on the release of drug from the formulation were studied. The initial burst effect was substantially reduced when the PLG concentration was increased. Out of different comonomer ratios of PLG, the ratio 85:15 showed more sustained release with comparatively less burst effect. The formulations containing triacetin as the solvent showed controlled release of the drug with least burst effect. Good sustained and prolonged release of the drug coupled with biocompatibility characteristics make injectable *in situ* gel forming implant systems of PLG, a prospective implantable controlled release dosage form to deliver the drug in the therapy of diabetes.

Keywords: *In Situ* Forming Polymer, Solvent Precipitation, Sustained Release, Rosiglitazone, Subcutaneous Delivery, Poly (Lactide-Co-Glycolide).

INTRODUCTION

The development of *in situ* gel systems has received considerable attention over the past few years. This interest has been sparked by the advantage shown by these delivery systems such as ease of administration, reduced frequency of administration improved patient compliance and comfort^{1,2}. This unique formulation approach incorporates the advantages of an implant while circumventing the need of surgery prior to administration or after the release is complete.

Significant research interest in the development of subcutaneously implantable polymeric devices for long term maintenance of therapeutic drug levels coincides with the increased medical and public acceptance of such systems³. *In situ* polymer precipitation is a strategy that has been utilized to produce an injectable drug delivery depot⁴. This

injectable implant system is comprised of a water insoluble biodegradable polymer such as poly (DL-lactide), poly (DL-lactide-co-glycolide) and poly (DL-lactide-co-ε-caprolactone) dissolved in a water miscible, physiologically compatible solvent such as N-methyl-2-pyrrolidone (NMP) or dimethyl sulphoxide (DMSO), propylene glycol, 2-pyrrolidone and triacetin. Upon injection into an aqueous environment, the solvent diffuses into the surrounding aqueous environment while water diffuses into the polymer matrix leading to the formation of solid polymer implant⁵.

An attempt has been made to envisage the potential advantages of injectable PLG implants for long term delivery of rosiglitazone, commonly used in the therapy of diabetes. The commercial formulation of rosiglitazone is an immediate-release dosage form containing rosiglitazone maleate known

as AVANDIA®. The available dosages are 2, 4, and 8 mg⁶. A recommended starting dose is 4 mg administered as a single dose or twice a day, with an increase to 8 mg administered as a single dose or twice a day if no response is observed in twelve weeks of treatment⁷. While the current immediate-release dosage form is suitable for its intended purpose, there remains a need for additional dosage forms of rosiglitazone, particularly dosage forms having controlled-release profiles.

MATERIALS AND METHODS

Rosiglitazone was obtained as a gift sample from Aristo Pharmaceutical Ltd., India. PLGA polymers were obtained from Birmingham Inc, UK. N-methyl-2-pyrrolidone, Triacetin from Sigma Chemicals Co., USA. Equipments used were UV-240 spectrophotometer (Shimadzu Corporation, Tokyo, Japan).

The method employed to prepare these formulations was similar to that adopted by Shah et al⁸. PLG solutions were prepared by stirring the polymer in the biocompatible solvent (such as NMP/Triacetin) at about 50⁰ using a water bath and cooled to room temperature (25⁰). Required quantity of rosiglitazone to give a final drug concentration of 1.0% w/w was added to the polymeric solutions and stirred until dissolved. Different formulations were prepared with different polymer ratios, solvents and polymer with different comonomer ratios. The formulations were filled in 10 ml glass vials, capped with rubber closures and were stored in the refrigerator until further use. The composition of the prepared *in situ* gel formulations are shown in table 1.

Table 1: Composition of the prepared in situ gelling formulations

Batch code	Drug (%w/w)	NMP (w/w)	Triacetin (w/w)	PLG (w/w)
N1 [#]	1	q.s	---	10
N2 [#]	1	q.s	---	12.5
N3 [#]	1	q.s	---	15
N4 [#]	1	q.s	---	18
N65*	1	q.s	---	12.5
N75*	1	q.s	---	12.5
N85*	1	q.s	---	12.5
T1 [#]	1	---	q.s	10
T2 [#]	1	---	q.s	12.5
T3 [#]	1	---	q.s	15
T4 [#]	1	---	q.s	18

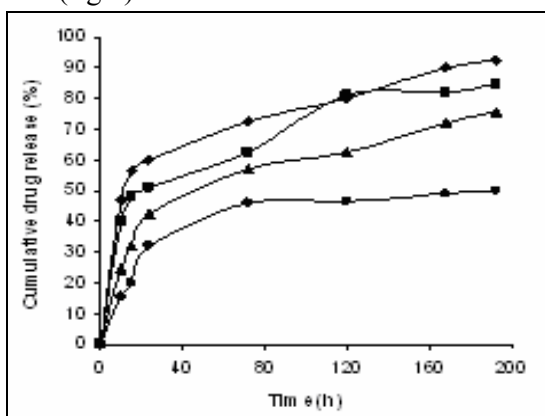
* The formulations prepared with PLG having comonomer ratios of 65:35, 75:25, 85:15 respectively.

[#] Formulations N1 to N4 and T1 to T4 contain PLG (75:25) comonomer ratio.

For the determination of drug content the vials containing the formulations were shaken for 1-2 min and then a specified volume of formulation was transferred to the volumetric flask with a micropipette. Methanol was added to completely precipitate the polymer and centrifuged at 5000 rpm for 15 min⁹. A sample of clear supernatant was suitably diluted with methanol. This solution was analyzed spectrophotometrically for the drug content against the appropriate blank at 314 nm. To study the *in vitro* drug release profile, 100 mg of each of the formulations were placed in the vials containing 15 ml of phosphate buffer saline (pH 7.4) and kept on a shaker water bath set at 37⁰ and 60 oscillations per minute. Clear 1 ml samples were withdrawn at predetermined intervals during 7 days. The drug released was determined spectrophotometrically at 314 nm against appropriate blank (placebo formulations treated in the same manner).

The drug content and the clarity of the formulations were found to be satisfactory

and the prepared formulations were liquid at both room temperature and refrigerated conditions. The drug content of the formulations ranged from 98.9 to 99.2 %. The release of the drug from the gel matrix was mainly dependent on the PLG concentration. It was noted that the burst effect was more in the case of N1, N2 and N3 formulations with 10%, 12.5% and 15% w/w of PLG respectively. On the other hand, the initial burst effect was substantially reduced when the PLG concentration was increased to 18% w/w (fig 1).



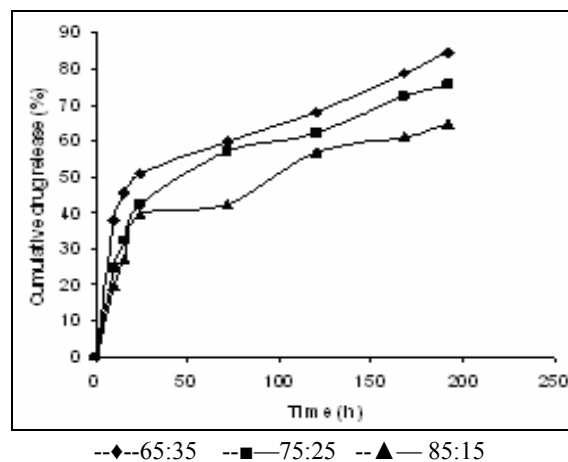
N1--◆-- 10% PLGA N2--■-- 12.5% PLGA N3--▲-- 15% PLGA N4--□-- 18% PLGA

Fig. 1: Effect of NMP as a vehicle on *in vitro* release of Rosiglitazone from the *in situ* gel formulations using different polymer concentrations

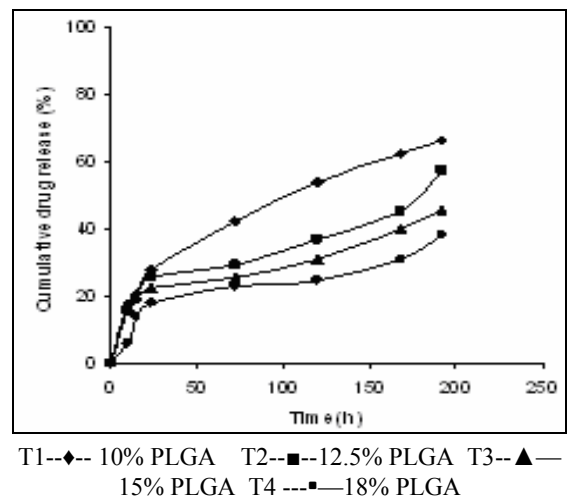
Formulations with the PLG having different comonomer ratios were prepared to evaluate its effect on the drug release. The release rates were in the following manner N65> N75> N85 and are shown in fig 2.

The PLG matrices with more hydrophilic comonomer (i.e. the matrices with lower lactide/glycolide ratio) have faster hydration and thus higher drug release rates were observed for matrices made with polymers having lower lactide/glycolide ratio. Matrix hydration may affect drug release rate via increasing drug diffusional path length and drug diffusion rate inside the hydrated

polymeric matrix as well as increasing matrix release surface area.



--◆--65:35 --■--75:25 --▲-- 85:15
Fig. 2: Effect of comonomer ratio of PLG on *in vitro* release of Rosiglitazone from the *in situ* gel formulations using NMP as a vehicle
Triacetin was also tried as a solvent for the *in situ* gel formulations. It was noted that burst effect of drug from these formulations (T1 to T4) was very less and more sustained release was obtained as compared to the formulations prepared using NMP as a vehicle (fig 3).



T1--◆-- 10% PLGA T2--■-- 12.5% PLGA T3--▲-- 15% PLGA T4--□-- 18% PLGA
Fig. 3: Effect of Triacetin as a vehicle on *in vitro* release of Rosiglitazone from the *in situ* gel formulations using different polymer concentrations

It was observed that the burst effect was dependent on the concentration of polymer in the formulation. The T4 formulation showed the less ease of injection. It was further

noticed that T3 formulation showed almost zero order release after the initial burst. *In vitro* drug release: Upon injection of PLGA in solvent, into aqueous environment, the solvent diffuses into water, while PLGA (polymer), insoluble in water precipitates out as solid matrix. In case of biodegradable polymers, pores are created upon erosion of the polymer matrix enabling release of drug from dosage form. All the formulations released the drug in a biphasic manner, with an initial burst release followed by sustained and controlled release of drug. The initial burst effect could be due to the drug at the surface of the matrix, while the second phase of slow and sustained release could be attributed to slow diffusion of the dissolution fluid in the polymeric matrix and elution of the drug. The release of the drug from the gel matrix was mainly dependent on the PLG concentration. The reason may be attributed to the fact that there is a lag between the injection and the formation of the solid implant⁴. Although N1 and N2 formulations facilitated the ease of injection due to their lower viscosities, their *in vitro* release rates were very high with high burst effect where almost 50-60% of the drug was leached out within 24h. N4 formulation was too viscous due to high (18% w/w) PLG content and hence had the disadvantage of less ease of injection. N3 formulation offered an optimum ease of injection and also the drug release was comparatively better. The burst effect can be monitored by controlling the weight of the polymer and type of solvent^{11,12}. The slow release mechanism for higher polymer concentration can be explained by a reduction in permeability due to changes in the morphology of the polymer. Increased polymer concentration may have provided the matrix with lower tortuosity and poor

porosity for diffusion of drug. Moreover, higher polymer concentration would have resulted in viscous microenvironment of the system inhibiting the movement of water into the matrix for easy diffusion of drugs into the surroundings.

The *in situ* gel formulation is for a single administration and it was shown to release the drug *in vitro* for a period of seven days. Therefore, PLG-gel forming implant system may be said to be a better formulation as compared to the oral formulation of rosiglitazone in terms of therapeutic activity offered for an extended period of time, improved patient compliance, absence of first pass effect and reduced dosing frequency hence fewer side effects. This delivery system has still unique challenges associated with its development that are related to drug stability, sterilization and solvent compatibility with body tissues which if solved can make them more acceptable and excellent drug delivery systems.

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