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# Formulation and Control of Biodegradable Injectable in Situ Gelling System of Levonorgestrel

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*Abstract -* The aim of this study was to develop a new polymeric gel that used as a contraceptive system.Polymeric gel has been studied extensively for drug delivery systems. In this article, thermal-sensitive poly (DL-lactic acid)-poly (ethylene glycol) - poly (DL-lactic acid) (PLA-PEG-PLA) hydrogel was used as an implantable contraceptive system. Aqueous solution of this copolymer fromed a free flowing sol at room temperature and became a gel at body temperature. In this study, the biodegradable copolymer with molecular structure of PLA-PEG-PLA was synthesized and was investigated the sol-gel transition, hydrolytic degradation and In-vitro drug delivery from the system. In the current study Levonorgestrel was selected as a model contraceptive drug.

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## I. Introduction

Now a days, controlled release of contraceptive drugs using biodegradable polymers as drug carrier has been a very important approach for the contraception. Extensive research has been reported on inject able drug delivery systems, which are mostly based on micro spheres or specially designed shapes such as rods and films ( Ruiz JM et al. 1940, Suzuki k and price JC 1985, Tsakala M 1988, Cha Y and pitt C ,1988 , koosha F et al. 1989).

A typical fabrication process of micro spheres usually uses organic solvents because biodegradable polymers such as poly (DL-or L- lactic acid), poly (glycolic acid-co-lactic acid) and poly caprolactone are not soluble in water. The organic solvents (e.g. ethylene chloride and chloroform) are known to be difficult to remove completely and the residual solvent may cause harmful side effects such as suspected animal carcinogenesis, neurotoxicity and teratogenicity (International conference on Harmonization of Technical Requirements for the Registration of pharmaceuticals for Human Use 1995). In addition, a surgical procedure is needed to implant the drug delivery matrix with a special shape and mechanical tissue irritation may be induced around the implant site (U. S. pharmacopoeia 1995).

Recently, drug delivery using an In Situ gel-forming system upon injection of formulation has been reported for its advantages, which included no surgical procedure to implant the drug release matrix and patient compliance when clinically applied (Hill – west JL et al. 1994).

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However, in the current work an aqueous solution of PLA-PEG-PLA triblock copolymer was fabricated as a new biodegradable injectable depot system (Bernatchez SF et al. 1993). The temperature induced sol-gel transition of aqueous solution gives the advantage of easy formulation at the sol state. The drug loading can be achieved by simply mixing the aqueous polymer solution with a drug. The solubility of the drug, even for a hydrophobic drug, can be enhanced by the surfactant nature of the block copolymer in water. The actual formulation can be a homogeneous solution or a suspension (A. Hatefi and B. Amsden 2002, .N.A. Kshirsagar 2000,Deepak Chitkara, et al. 2006).

The formation of gel starts from the surface of the system by thermal conduction from the body environment, resulting in preventing an initial burst release. The final degradation products of PLA-PEG-PLA triblock copolymers were of PEG, glycolic acid and lactic acid and all of them approved as nontoxic (Dinarvand R and D Emmanuelle 1993, 1994,1995)

## II. Materials And Methods

### a) Materials

The PLA-PEG-PLA triblock copolymer was synthesized by the method of Afshar and co-workers in Alborz Daru Pharmaceutical Co.(Iran), poly ethylene glycol (PEG) with molecular weight of 400 and 1500 was purchased from Merck Pharmaceutical Co.(Germany), lactide (Dimer lactic acid, MW=144) was obtained from Sigma(USA), the sample of Levonorgestrel (LNG) used in this study was purchased from Iran Hormone Pharmaceutical Co.(Iran), ethanol 96° was used as a gift sample from Bidestan Co.(Iran).

### a) Methods

i. *Synthesis of triblock PLA-PEG-PLA copolymer*

The synthesis of this copolymer has been described in brief as follows. A ring opening polymerization of lactide (Lactic acid dimmer, MW=144) and PEG (MW=1500) followed by a coupling reaction was used to produce a triblock poly (lactic acid)-poly (ethylene glycol)-poly (lactic acid).

For synthesis of this copolymer, a small metallic reactor whit capacity of 50ml was used and a simethicone bath with stable temperature of 160 °C was applied. Stannous 2-ethyl hexanoate was used as

a catalyst. After complete synthesis, the triblock copolymer was purified by filteration method.

ii. *Characterization of Triblock Copolymer by $^1$H-NMR Spectroscopy and gel permeation chromatography (GPC)*

A$^1$H-NMR spectrometer was employed to record $^1$H-NMR spectrum of synthesized PLA-PEG-PLA and molecular weight was calculated on basis of known molecular weight of PEG (550 g/mol). A GPC (column: plGel, 300×7.8mm, refractive index detector, standard: polystyrene) was used to measure elution times using tetrahydrofuran (THF) as eluent. A calibration curve was constructed for determination of molecular weight distribution of the samples.

Molecular structure and molecular weight of this triblock copolymer respective ly have shown in scheme 1 and *Table 1.*

CH3 CH3

H (OC H CO) $_n$ – (OCH2 CH2)$_n$ – (OCCHO)$_n$ –H

Scheme 1: Molecular structure of triblock PLA-PEG-PLA copolymer

III. Determination of sol-gel transition temperature of PLA-PEG-PLA

PLA- PEG-PLA gel with concentration of 30 %( w/w) was dissolved in 15-ml vials containing distilled water. After equilibration at 4 °C for overnight, gel were applied in rheometer (Physica Apparatus) at given temperatures, ranging from 20 °C to 60 °C. Then the rheogram was recorded and Glass-Rubber Transition Temperature (Tg) of this copolymer was determined.

*Fig.1* : Rheogram of triblock copolymer PLA-PEG-PLA 30 %( w/w)

IV. *Formulation*

Aqueous solutions of PLA-PEG-PLA triblock copolymer with initial polymer concentrations of 15,20,22.5,25 and 30%(w/w) were prepared at 4 °C /24h in two different vials(15 and 25ml) containing 2ml distilled water.

All solutions were in sol form at room temperature. Vials were placed them in a thermostatic shaker water bath (37 °C). Then 12 ml of 40 %( v/v) hydroalcoholic solution was added to the each vial as dissolution medium. 12ml of medium was sampled every day and it was replaced by a fresh medium. The samples were diluted and assayed spectrophotometrically at λmax =250 nm.

Different formulations were shown in Tables 2, 3 and 4.

*Table 2:* prepared formulation with different rates of polymer and constant amount of drug in the vials with small surface area.

*Table 3:* prepared formulation with different rates of polymer and constant amount of drug in the vials with big surface area.

*Table 4:* prepared formulation with different amounts of drug and constant rates of polymer in the vials with small surface area.

## III. Results And Discussion

*a) Levonorgestrel release of PLA-PEG-PLA gels*

*Fig. 2 :* shows the drug release profile of drug loaded gel in 2 weeks from the formulations of A1-A5. Drug release patterns differ among different polymer concontractions.

*Fig 3:* Shows the effect of drug content in formulations with 22.5% of PLA-PEG- PLA.

*Fig .4:* and Fig .5 show the effect of PEG 400 as co- solvent and surface area of the vials, for formulations with 22.5% PLA-PEG-PLA, respectively.

Drug is speculated to release by a combined mechanism including drug diffusion and polymer erosion (degradation). At the early stage, drug release from the gel in a way mainly depending on the diffusion process. An increase in the daily release rate (the slope of release profile) within the second week occurred.

*Fig.2 :* Effect of polymeric concentration on drug release profile

*Fig.3:* Effect of drug content on release profile, formulatins with 22.5% PLA_PEG_PLA

*Fig.4:* Effect of PEG 400 as co solvent on drug release profile, formulation with 22.5% PLA_PEG_PLA

*Fig.5:* Effect of surface area of the vials on drug release profile, formulation with 22.5% PLA_PEG_PLA

*b) Kinetics of release profile*

*Table 5:* shows the drug release profile of drug – loaded gels, followed by higuchi kinetics.

*Table 5: Regression coefficient (R2) of the best formulations based on zero order, first order and higuchi kinetics.*

*c) Determination of best formulations*

After extensive assessment and study of drug release profile from the all of formulations, this result was obtained that A2, A3 and A4 formulations are the best, and release pattern from them is better than the other formulations.

## IV. Discussion

The PLA-PEG-PLA triblock copolymer was synthesized as a carrier of contraceptive drug, Levonorgestrel. Drug– loaded gel, which was a sol turned into gel state within minutes when it was heated at 37°c.

It was shown that drug release profile of the system is increased by increasing Different factors, such as polymer / drug ratio, using of PEG 400 as a co-solvent,Surface area of the vials and drug loading. This result, indicates this system could de used as drug carrier having controlled release capability.

For extensive studies in the future, we suggest that the "in vivo" release profile is assessed and increasing the length of the chain of PLA for the synthesis of triblock copolymer can be tested for long time period of drug release.

## V. Acknowledgements

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*Table 1:* Theoretical calculations of MW PLA-PEG-PLA Copolymer by $^1$H-NMR spectrum and results obtained by GPC analysis.

| | $^1$H-NMR | GPC |
|---|---|---|
| | Mean±SD | |
| MW of PLA-PEG-PLA | 6050±0.68 | 6150±0.22 |

(*n*=3)

*Table 2:* prepared formulation with different rates of polymer and constant amount of drug in the vials with small surface area.

| Name | PLA-PEG-PLA% | Drug (mg) |
|---|---|---|
| $A_1$ | 15 | 2 |
| $A_2$ | 20 | 2 |
| $A_3$ | 22.5 | 2 |
| $A_4$ | 25 | 2 |
| $A_5$ | 30 | 2 |

*Table 3:* prepared formulation with different rates of polymer and constant amount of drug in the vials with big surface area.

| Name | PLA-PEG-PLA% | Drug (mg) |
|---|---|---|
| $B_1$ | 20 | 2 |
| $B_2$ | 22.5 | 2 |
| $B_3$ | 25 | 2 |

*Table 4 :* prepared formulation with different amounts of drug and constant rates of polymer in the vials with small surface area.

| Formulation name | | | Drug (mg) |
|---|---|---|---|
| PLA-PEG- PLA25% | PLA-PEG-PLA22.5% | PLA-PEG-PLA20% | |
| $E_1$ | $D_1$ | $C_1$ | 1 |
| $E_2$ ($A_4$) | $D_2$ ($A_3$) | $C_2$ ($A_2$) | 2 |
| $E_3$ | $D_3$ | $C_3$ | 3 |
| $E_4$ | $D_4$ | $C_4$ | 4 |

*Table 5:* Regression coefficient ($R^2$) of the best formulations based on zero order, first order and higuchi kinetics.

| Formulation | $R^2$(RegressionCoefficient) | | |
|---|---|---|---|
| | Zero Order | First Order | Higuchi |
| $A_2$ | 0.9463 | 0.7824 | 0.9941 |
| $A_3$ | 0.9620 | 0.7998 | 0.9892 |
| $A_4$ | 0.9720 | 0.8133 | 0.9819 |

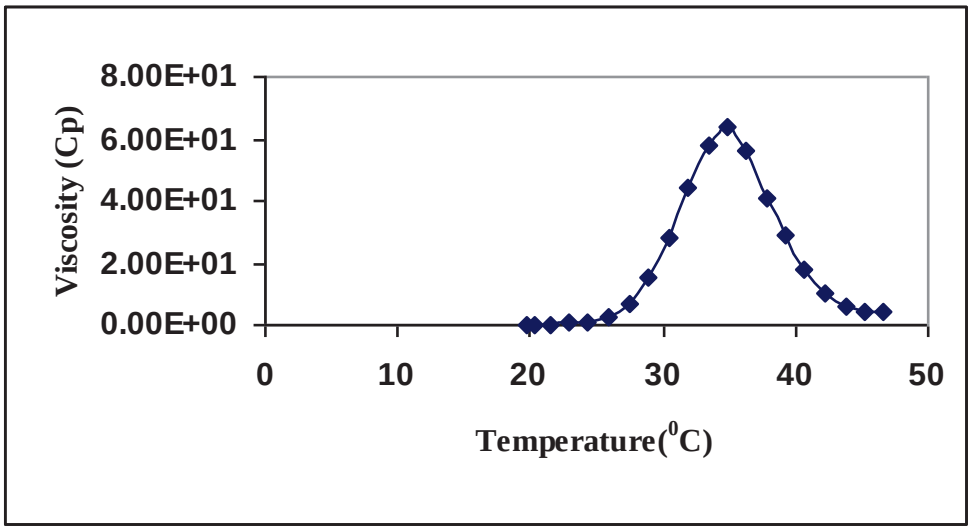


*Fig.1* : Rheogram of triblock copolymer PLA-PEG-PLA 30 %( w/w)

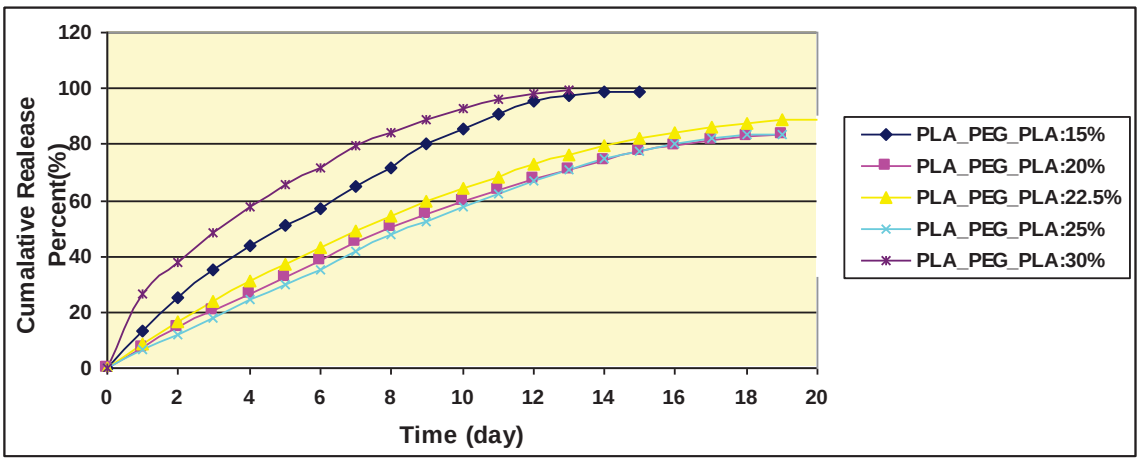


*Fig.2 :* Effect of polymeric concentration on drug release profile

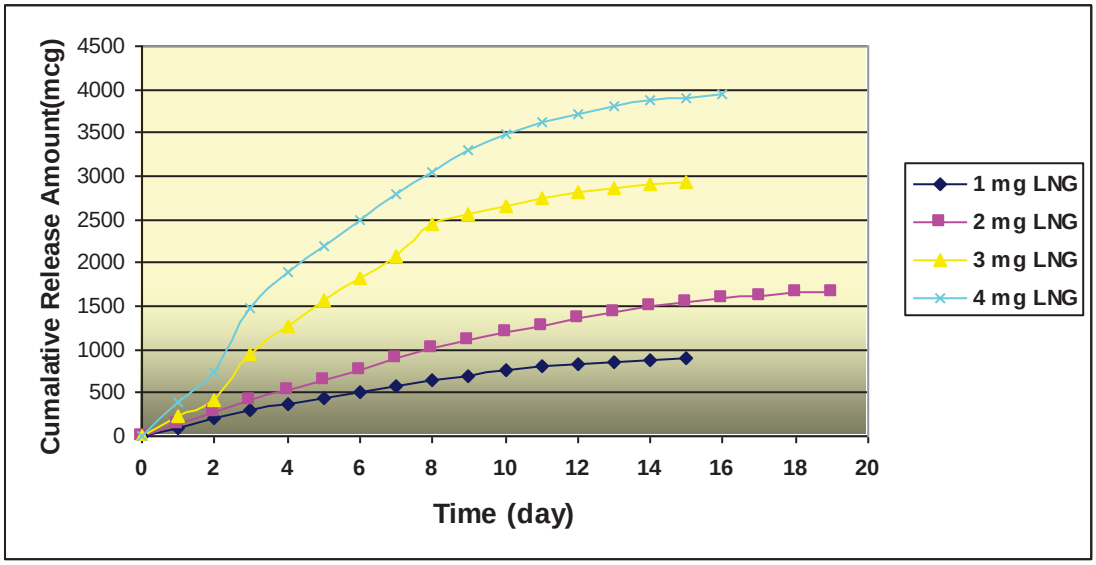


*Fig.3:* Effect of drug content on release profile, formulatins with 22.5% PLA_PEG_PLA

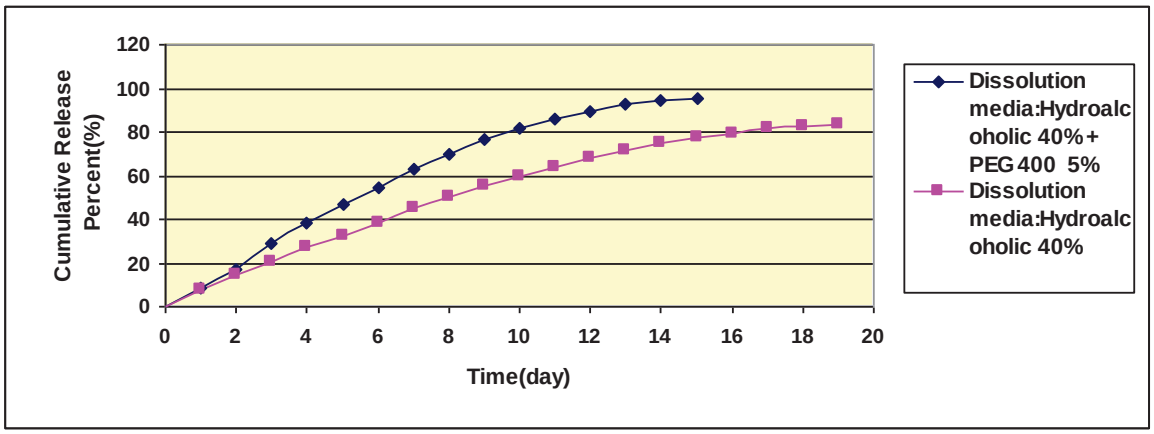


*Fig.4:* Effect of PEG 400 as co solvent on drug release profile, formulation with 22.5% PLA_PEG_PLA

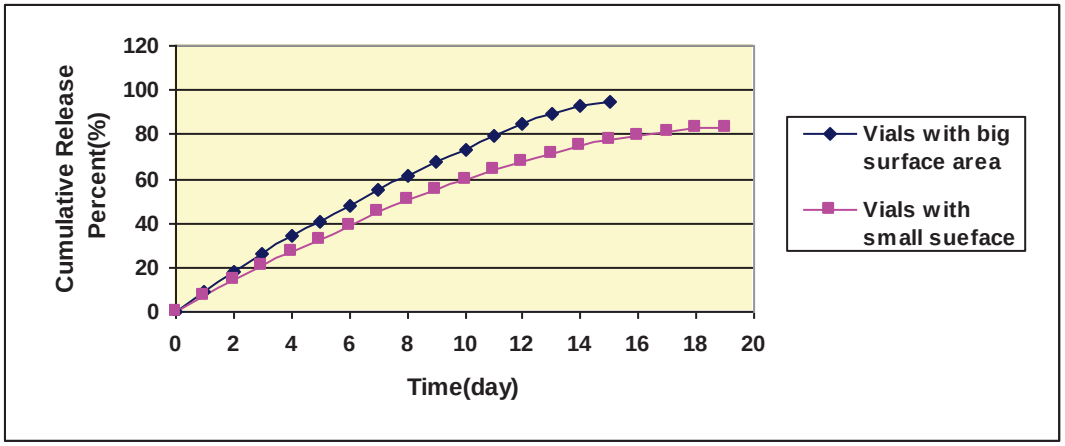


*Fig.5:* Effect of surface area of the vials on drug release profile, formulation with 22.5% PLA_PEG_PLA