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 so 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 studyLevonorgestrel was selected as a model contraceptive drug.

Index terms— thermal-sensitive, biodegradable, in situ, injectable, sol-gel transition

Pegah Dadras ? , Rasoul Dinarvand ? , Seyed Mostafa Khezri ? A 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.

1 Keywords

: thermal-sensitive,biodegradable,in situ,injectable,sol-gel transition . 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).

Author ? : Dr. Seyed Mostafa Khezri Department of Environment & Energy , Science & Research Branch Recently, drug delivery using an In Situ gelforming 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).

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. 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 a) Materials 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 ^{o}C was applied. Stannous 2-ethyl hexanoate was used as 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. All solutions were in sol form at room temperature. Vials were placed them in a thermostatic shaker water bath (37 ^{o}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 ?max =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. Fig . 4: and Fig . **??** 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. **??** : 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. **??**: 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.

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

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

best, and release pattern from them is better than the other formulations.

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 cosolvent,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. [1] [2]

[1] (J) 2011 December

[2] December

Figure 1:

Figure 2:

Figure 3:

Figure 4: N

Figure 5: Scheme 1 :

Figure 6: Fig. 1 :

Figure 7: Table 4 :

3 III.

Figure 8: Fig 3 :

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Figure 9: Fig. 1 :Fig. 2 :Fig. 3 :

1

1 H-NMR		GPC
Mean±SD		

Figure 10: Table 1 :

2

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

Figure 11: Table 2 :

3

area.

Name	PLA-PEG-PLA%	Drug (mg)
B 1	20	2
B 2	22.5	2
B 3	25	2

Figure 12: Table 3 :

4

Figure 13: Table 4 :

5

	Formulation name		
PLA-PEG-PLA25%	PLA-PEG-PLA22.5%	PLA-PEG-PLA20%	Drug (mg)
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
	R 2 (RegressionCoefficient)		
Formulation			
	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

Figure 14: Table 5 :

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