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## Chapter 1 : Depot Based Drug Delivery System for the Management of Depression | BenthamScience

*for long-term delivery formulations, many factors Another significant and unique advantage of should be considered such as safety profile, ease parenteral injection is a long-term drug delivery of administration, patient's limited mobility, area by the formation of a depot or reservoir at the for target injection sites, quality of life and cost.*

Syringeability, which is the force required to push the prepared polymeric drug solution through the syringe needle, was also evaluated using universal syringe rig Stable Micro Systems, Surrey, UK. Each formulation was injected separately into PBS of pH 7. In vivo and pharmacokinetic study Male New Zealand White rabbits with an average weight of 2. During the experiment, animals were given full access to normal standard diet and tap water ad libitum. Rabbits were divided into three groups of six animals per group and kept fasted for at least 24 hours prior to the experiments. The first group received the marketed ATR tablet reference ; the second group was injected intramuscularly with the optimized ATR-ISG formulation into the right gluteus maximus muscle; while the third group was injected intramuscularly with PEG-free ISG formulation into the same muscle. The collected samples were deproteinized with acetonitrile. Quantification of the drug in the plasma was according to the method depicted by Gajula et al 26 with slight modifications. The mobile phase used was a mixture of 0. The ion spray voltage was set at 3, V. The common parameters were nebulizer N2 gas temperature: Maximum plasma concentration, time to reach the maximum plasma concentration tmax , and mean residence time were determined. The measured drug plasma concentrations were also used to calculate the area under the plasma concentrationâ€”time curve from time zero to the last concentration time point AUClast and the area under the plasma concentrationâ€”time curve from time zero to infinity AUCtotal. Each test animal was compared with the reference individually at the respective time point. The in vitro release of these formulations was studied for 72 hours and the release profile displayed a high initial burst release phase followed by an approximately steady state release phase Figure 2A â€” C. The initial burst release stage is mainly due to the lag time between administration of the drug polymeric liquid state formulation and solidification to form the ISG system. Ahmed et al 6 studied the effect of polymer concentration on haloperidol release from PLGA in situ implant and reported a similar finding. PLGA is available in different lactide to glycolide ratios,  Polymer rich in lactide results in a highly hydrophobic polymer which degrades slowly and absorbs less water. They reported a reduction in the initial burst release probably due to its plasticizing action. The solubilizing effect of PEG could be another possible mechanism for this effect. PEG permits homogeneous distribution of the administered drug in the prepared PLGA matrix, the effect that decreases adsorption of the drug particles at the polymeric matrix. Biocompatible surfactant such as pluronics, tweens, spans, and chromophores have also been proven to influence the initial burst release from a PLGA-based ISG system. Different researchers evaluated the drug initial burst by estimating the amount released at the first 24â€”48 hours. Mixing the drug with PEG in the form of physical mixture showed no considerable change in the spectrum of the pure drug while some changes in the characteristic peaks of the drug were noticed in the optimized formulation due to possible interaction of PEG with PLGA. These effects could explain the decrease in the drug burst effect after incorporation of PEG in the formulation. Response surface methodology for optimization of ATR-ISG formulation A central composite design with three factors in three levels was implemented to study the influence of three different formulation parameters on ATR initial burst release after 2 Y1 and after 24 hours Y2 , and evaluate the main effects, interaction effects, and quadratic effects of these factors on the dependent variables. The in vitro release profiles for the prepared formulations in comparison with PEG-free formulations are depicted in Figure 2. Estimation of quantitative effects of the selected factors To estimate the quantitative effects of the selected factors, statistical analysis of central composite statistical design batches was carried out by multiple regression analysis and two-way analysis of variance using Statgraphics software. Table 3 shows the estimated effects of the selected factors, F-ratios, and associated P-values for the two responses resulting from analysis of variance. Table 3 Estimated

effects of factors, F-ratio, and associated P-values for the initial drug release after 2 hours Y1 and 24 hours Y2 Note: On the other hand, X3 had no significant effect on both Y1 and Y2. Finally, it was found that the interaction terms of X1X2, X1X3, and X2X3 and the quadratic term of X2 and X3 had no significant effect on the studied responses. Figure 3 Standardized Pareto charts for the effect of the studied variables on Y1 and Y2. On the analysis of the obtained values for the responses regarding initial burst after 2 hours Y1 and initial burst after 24 hours Y2 , the mathematical model for each response was generated and is shown in Equations 1 and 2. By increasing the concentration of PLGA and using PEG with high molecular weight, the initial burst after 2 hours Y1 and after 24 hours Y2 was decreased as illustrated in the response surface plot in Figure 4. Figure 4 Estimated response surfaces with contour plots three-dimensional showing the effect of the studied variables on Y1 and Y2.

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## Chapter 2 : [Full text] Depot injectable biodegradable nanoparticles loaded with recombinant h | DDDT

*The scope of drug-delivery systems has expanded significantly in recent years providing new ways to deliver life saving therapeutics to patients. The development of new injectable drug-delivery.*

The system comprises an injectable biodegradable block copolymeric drug delivery liquid having thermal gelation properties. The drug is released at a controlled rate from the copolymer which biodegrades into non-toxic products. Your petitioners, Byeongmoon Jeong, a citizen of the United States and resident of Utah, whose post office address is S. The present invention relates to the preparation of thermosensitive biodegradable block copolymers and their use for parenteral or subcutaneous administration of bioactive molecules such as peptide and protein drugs. This invention is made possible by the use of thermosensitive biodegradable polymers based on poly ether-ester block copolymers, which are described in detail hereinafter. The system is based the discovery that poly ether-ester block copolymers having certain molecular weight and composition ranges exist as aqueous solutions at elevated temperatures, e. Langer, Science, , ; Ishihara, et al. Sci , 29, , ; Thomas, et al. Chem Soc , , , and Kwon et al. Thermosensitive polymers have widely been investigated as drug carriers. Another type is triblock copolymers consisting of hydrophobic poly ropylene oxide as the center block and hydrophilic poly ethylene oxide as the side blocks, e. Poloxamer brand, as disclosed by Malston, et al. These polymers are generally nonbiodegradable and their toxicities are of concern. For example, following intraperitoneal injections, Poloxamer type copolymers have been shown to enhance plasma cholesterol and triglycerol in rats. Much work on polymeric drug delivery systems has focused on injectable microspheres or biodegradable implant systems that require organic solvents during fabrication. Controlled Release, 27,  Because the implant systems possess distinct solid form, they require surgical insertion. Patents 4,, and 4,, Surgical implants can result in tissue irritation and damage. The hydrophilicity of the material was increased by copolymerization with a polyether surfactant prepolymer Pluronic F It is known that Pluronic type of polymeric surfactants, particularly the poly propylene oxide block portions, are not biodegradable. Other implantable delivery systems, such as shown in Dunn et al, U. Patents 4,, and 5,,, have also been known for some time. These polymers are either thermoplastic or thermosetting. The thermoplastic solution requires the use of an organic solvent such as N-methylpyrrolidone, methyl ethyl ketone, dimethylformamide, propylene glycol, THF, DMSO, dodecylazacycloheptanone Azone and the like. The thermosetting system comprises the synthesis of crosslinkable polymers which can be formed and cured in-situ through the use of a curing agent. However, the major drawback of the thermoplastic formulations is the use of organic solvents which can be toxic or irritating to the body tissues. The thermosetting system requires that the drug be admixed with the prepolymer solution prior to additions of the catalysts because the curing reaction is quite rapid and injection must take place almost immediately following the addition of the curing agent. Using non-toxic photoinitiators, the macromers can be rapidly polymerized with visible light. Due to the multifunctionality of the macromers, polymerization results in the formation of crosslinked gels. However, in this system, a photoinitiator, an additional component, is employed as well as an additional process such as photocrosslinking. This concept is further exemplified in U. These copolymers possess thermal reverse gelation properties in that they form aqueous solutions below the body temperature of the animal to which they are to be administered and gel when the temperature is raised to body temperature. An optimum material for use as an injectable or implantable polymeric drug delivery device should be biodegradable, be compatible with hydrophilic or hydrophobic drugs, and allow fabrication with simple, safe solvents, such as water, and not require additional polymerization or reaction following administration. It is also an object of this invention to provide methods to fabricate copolymeric biodegradable thermosensitive drug delivery devices wherein the polymeric matrix can be stored at or below room temperature as a dry, solid dosage form prior to being formed as a solution for administration. A still further object of this invention is to provide a drug delivery system for the parenteral administration of bioactive agents where there is no

requirement for any surgical procedure for implantation. Yet another object of this invention is to provide a method for the parenteral administration of drugs in a biodegradable polymeric matrix resulting in the formation of a gel depot within the body from which the drugs are released at a controlled rate with the corresponding biodegradation of the polymeric matrix. The hydrogel contains an appropriate balance of hydrophilicity B block and hydrophobicity A block enabling the hydrogel to have thermoreversibility. Furthermore, organic solvents are not used to load such polymer systems with bioactive agents. Therefore, the need to remove any organic solvent is eliminated. The drug will be homogeneously contained in the solution or gel. Basic to the present invention is the utilization of a block copolymer having hydrophobic or "A" block segments and hydrophilic or "B" block segments. Generally the block copolymer will be a triblock BAB type block copolymer. However, the block copolymer could also be a diblock BA type copolymer. Generally, any water insoluble biodegradable copolymers can be utilized as the hydrophobic A block including semicrystalline polymers and amorphous polymers. When formed into diblock copolymers the average molecular weight of the A block is between about and 15, and is more preferably between about and 10, When formed into triblock copolymers the average molecular weight of the A block is between about and 20, and is more preferably between about and 15, The hydrophilic B block segment is poly ethylene oxide PEO which is also referred to as polyoxyethylene or poly ethylene glycol PEG having an average molecular weight of between about to 25, and is more preferably between about 1, and 10, The same average molecular weight range is applicable to both diblock and triblock type copolymers. The diblock copolymers are synthesized by various methods. The diblock copolymers may be synthesized by the ring opening polymerization of a cyclic monomer for the biodegradable hydrophobic A block, e. L-lactide from one end of a PEO block with or without the use of a catalyst. When catalyzed, typical catalysts include stannous octoate, antimony oxide, tin chloride, aluminum isopropoxide, yttrium isopropoxide, sodium, potassium, potassium t-butoxide, sodium t-butoxide and the like. Typically stannous octoate will be used as the catalyst. A monomer such as L-lactic acid, D,L-lactic acid, glycolic acid and the like is used. Direct coupling of monofunctional PEO with monofunctional biodegradable hydrophobic blocks in the presence of coupling agents is another method in which the coupling agent may be present as a linkage in the copolymer. Coupling agents such as a diisocyanate, e. Also, coupling after activation of the functional group with activating agents such as carbonyl diimidazole, succinic anhydride, N-hydroxy succinimide, and p-nitrophenyl chloro formate may be utilized. The triblock copolymers may be prepared by various means. A difunctional biodegradable hydrophobic A block may be coupled with monofunctional PEO to form a BAB copolymer utilizing the coupling techniques mentioned above for the coupling of B and A blocks to form a diblock, e. In the alternative, diblock copolymers can be coupled using the end functional group of biodegradable hydrophobic B i. Triblock copolymers can also be prepared by ring opening polymerization of ethylene oxide at both ends of a biodegradable hydrophobic A block, e. L-lactide, followed by ethylene oxide another cyclic monomer for PEO. As noted, the B block is formed from appropriate molecular weights of hydrophilic poly ethylene oxide PEO. PEO was chosen as the hydrophilic water-soluble block domain because of its unique biocompatibility, nontoxicity, micelle forming properties, and rapid clearance from the body. The hydrophobic A blocks are synthesized and utilized because of their biodegradable and biocompatible properties. The in vitro and in vivo degradation of these hydrophobic polymer blocks is well understood and the degradation products are natural metabolites that are readily eliminated by the body. Also, the proportionate weight ratios of hydrophilic B block to the hydrophobic A block must also be sufficient to enable the block copolymer to possess good water solubility at the required concentrations at temperatures above body temperature. All resulting diblock and triblock copolymers should be soluble in aqueous solutions at functional concentrations. There is a minimum concentration for each copolymer for gelation, i. Also, if concentrations are too high, aqueous solutions will be too viscous to inject parenterally. The only concentration parameter that is critical is that under which the polymer is functional. Therefore, the concentration at which the block copolymers are soluble at temperatures to be utilized for parenteral administration may be considered as the functional concentration. In order to

obtain a viable phase transition of the polymer, a certain minimum concentration is required. The mixture of the biodegradable polymer and bioactive agents or drugs may be prepared as an aqueous solution at a higher temperature than the gelation temperature of the polymeric material. This system will cause minimal toxicity and mechanical irritation to the surrounding tissue due to the biocompatibility of the materials and will be completely biodegradable within a specific predetermined time interval. Once gelled, the drug release from the polymeric matrix can be controlled by proper formulation of the various copolymer blocks. The only limitation as to how much drug can be loaded onto the copolymer is one of functionality. This invention is applicable to the delivery of any drug that is stable in the solution as prepared and that will release from the hydrogel matrix following administration. It would serve no useful purpose to attempt to catalog drugs as it will be readily apparent to those skilled in the art the type of drugs that can be used and minimal experimentation will be required to prove the viability of the invention as to any particular drug or class of drugs. The invention may be particularly useful in the delivery of peptide or protein based drugs. Residual water was removed by azeotropic distillation to a final volume of 30 ml. Then, polymerization of L-lactide LLA 4. The solution was precipitated in diethyl ether and the residual solvent was eliminated by vacuum after filtering. Diblock BA copolymers were prepared wherein the A block had molecular weights of , , and Monomethoxy PEO 10 g was added in ml of dried toluene. Residual water was removed by azeotropic distillation and in this case, all of the toluene was removed by distillation. The reaction mixture was dissolved in methylene chloride, precipitated in diethyl ether, and the residual solvent was eliminated by vacuum after filtering. Residual water was removed by azeotropic distillation to a final volume of 70 ml. The resulting triblock copolymers were purified by fractional precipitation of the copolymers out of methylene chloride using diethyl ether. The coupling reaction was monitored by GPC. The copolymers were stored in a refrigerator under nitrogen gas. Other triblock copolymers were synthesized by the same method. The resulting triblock copolymers consisted of two B PEO blocks having a molecular weight of each and a central A PLLA block having molecular weights of , and respectively. Initially, the polymers were dissolved in distilled water at an elevated temperature at the stated concentrations and placed in a tightly sealed 4 ml vial. The gels were equilibrated for 20 minutes at a given temperature in a water bath.

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## Chapter 3 : [Full text] Depot injectable atorvastatin biodegradable in situ gel: development, | DDDT

*Injectable routes, types of long-acting injectables (i.e., oil-based injections, injectable drug suspensions, injectable microspheres, and injectable in situ systems), drugs and polymers for depot injections, commercially available depot injections, and future injectable sustained-release drug-delivery systems are also discussed.*

This work is published and licensed by Dove Medical Press Limited The full terms of this license are available at https: By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. This article has been cited by other articles in PMC. Abstract This study aimed to develop an optimized depot injectable atorvastatin ATR biodegradable in situ gel ISG system with minimum initial burst using a central composite design. The optimized formulation was investigated using scanning electron microscopy, Fourier transform infrared spectroscopy, and in vitro drug release in phosphate-buffered saline of pH 7. A double-blind, randomized, parallel design was used in comparison with those of the marketed ATR tablet. The optimized formulation was composed of  Incorporation of PEG in the formulation causes a slight decrease in the glass transition temperature value of PLGA, leading to a slight change in Fourier transform infrared spectroscopy spectrum due to possible interaction. Moreover, scanning electron microscopy photomicrograph showed smooth surface with disappearance of the cracks which characterize the surface of PEG-free formulation. The optimized ATR-ISG formulation has shown minimal initial drug burst which confirms the suitability of the ISG system in the prolongation of drug release in patients with chronic long-term therapy. Poly d, l-lactide-co-glycolide PLGA is one of the commonly used polymers utilized in this system. One of the major disadvantages associated with the ISG system is the initial drug burst. Among these are the use of hydrophobic solvents, 10 , 11 choice of PLGA of higher lactide rather than glycolide ratio, 12 use of higher polymer concentration and molecular weight, 13 , 14 and incorporation of plasticizer or surfactant. Its mechanism of action involves inhibition of the enzyme 3-hydroxymethyl-glutaryl-coenzyme A HMG-CoA reductase which catalyzes the conversion of HMG-CoA to mevalonate in the process of cholesterol biosynthesis. So, the aim of this study was to develop an optimized depot injectable long-term therapy of ATR formulation with a low initial drug burst using a biodegradable PLGA with different molecular weight polyethylene glycol PEG in different concentrations. Intramuscular administration of this formulation could be considered as an alternative for the commercially available drug oral daily tablets. This will avoid the drug peroral first pass effect, enhance the drug bio-availability, and is expected to achieve better patient comfort and compliance due to decreased drug dosing frequency. Jeddah, Kingdom of Saudi Arabia. All materials used were of analytical grade and were used without further modification. Briefly, the specified amount of polymer was dissolved in NMP in scintillation glass vials and kept shaking in a thermostatically controlled water bath shaker Model ; GLF Corp. The design was implemented to get polynomial equations that relate the independent variables to the dependent responses. The design was performed to minimize the dependent responses Y1 and Y2. Table 1 summarizes the independent variables with their levels and the dependent variables with their constraints to perform the central composite design. Table 1 Independent and dependent variables in a central composite experimental design Independent variables.