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Research Paper

Controlled release formulations of risperidone antipsychotic drug in novel aliphatic polyester carriers: Data analysis and modelling

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ABSTRACT

In the present study a series of biodegradable and biocompatible poly(ε-caprolactone)/poly(propylene glutarate) (PCL/PPGlu) polymer blends were investigated as controlled release carriers of Risperidone drug (RISP), appropriate for transdermal drug delivery. The PCL/PPGlu carriers were prepared in different weight ratios. Miscibility studies of blends were evaluated through differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). Hydrolysis studies were performed at 37 °C using a phosphate buffered saline solution. The prepared blends have been used for the preparation of RISP patches via solvent evaporation method, containing 5, 10 and 15 wt% RISP. These formulations were characterized using FT-IR spectroscopy, DSC and WAXD in order to evaluate interactions taking place between polymer matrix and drug, as well as the dispersion and the physical state of the drug inside the polymer matrix. In vitro drug release studies were performed using as dissolution medium phosphate buffered saline simulating body fluids. It was found that in all cases controlled release formulations were obtained, while the RISP release varies due to the properties of the used polymer blend and the different levels of drug loading. Artificial Neural Networks (ANNs) were used for dissolution behaviour modelling showing increased correlation efficacy compared to Multi-Linear-Regression (MLR).

1. Introduction

Schizophrenia is a very common chronic mental disease often characterized by abnormal social behaviour and failure to recognize what is real. The disease is known over 100 years and was firstly identified by Dr. Bleuler [1]. A recent research showed that over 25 million of schizophrenic cases are expressed every year [2]. For the treatment of mental disorders, such as schizophrenia, antipsychotics are mainly used, including olanzapine and butyrophenones (phenothiazines chlorpromazine and levomepromazine were classified as first generation antipsychotic drugs). Risperidone drug belongs to the second generation of antipsychotics (SGA) and is an antagonist of the serotonin 5-HT and dopamine D receptors located in the brain. Specifically, risperidone is used for the treatment of schizophrenia and other related bipolar mania [3–6] and the most appropriate therapeutic treatment is the controlled release administration covering long therapeutic periods.

Controlled release (CR) formulations have become an increasingly important strategy in such therapeutic treatments because of their ability to release a drug at a controlled rate for an appropriate extended time. CR systems offer several advantages, such as reducing high total dose, reducing dosing frequency and gastrointestinal side effects, and improving patient acceptance and compliance [7]. Despite RISP high therapeutic action against mental disorders, its low solubility in water and low bioavailability, researchers classified Risperidone drug as a BCS class II compound [8,9]. To overcome these problems, pharmaceutical industry is focused on producing novel drug delivery systems, able to release sustainably poorly-water soluble drugs. These delivery systems can be either nano- or micro-particles vesicles [10,11], inclusion complexes using cyclodextrins [12] or solvent cast films, generally known as solid dispersion systems (SDs). The improved dissolution is based on the fact that drugs in nanoscale range or in amorphous phase are dissolved faster and to a greater extent than micronized drug particles. So, the target in the case of risperidone is to prepare formulations with enhanced drug dissolution behaviour and also to administrate it with controlled release manner.

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Injectable systems consisted of aliphatic polyester microparticles such as poly(lactic acid) or poly(lactide-co-glycolide) copolymers are such formulations. Another technique and more friendly to the patients, is the transdermal drug delivery system (TDDS). TDDS can deliver the drug through the skin portal to systemic circulation at a predetermined rate over a specific period of time. Transdermal patches are produced using biocompatible polymers which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects [13]. A variety of pharmaceutical products are approved for transdermal delivery today while numerous studies have been proposed to evaluate the potential of patches via transdermal route. Some of the significant advantages of transdermal systems are controlled absorption, avoidance of first-pass metabolism, improved bioavailability, reduced side effects, elimination of gastrointestinal irritation resulting from some drugs which reduced dosing frequency, and rapid termination of drug action flexibility of terminating drug administration by simply removing the patch from the skin.

There are several types of transdermal patches such as multi-layer drug in adhesive, reservoir system, matrix systems and matrix dispersion system which are the most used [14–17]. In the literature only one transdermal patch of risperidone was just recently proposed using Eudragit RS 100 as polymeric carrier [18]. *In vivo* pharmacodynamics on rodents used for the assessment of neuroleptic effect indicated that risperidone transdermal patches gave satisfactory results regarding its therapeutic efficacy. The particular formulations contain different types and amounts of olive oil, groundnut oil and jojoba oil, which could cause stability problems of the particular formulations during storage. To overcome this problem in the recent study transdermal patches consisted of aliphatic polyesters will be prepared.

Aliphatic polyesters belong to the biodegradable and biocompatible polymers and are favourable as carriers for controlled release devices of hydrophobic drugs and for biomedical applications. In the present research, polymer blends of poly(ε-caprolactone) (PCL) and poly(propylene glutarate) (PPGlu) are used to prepare the transdermal patches. This is because from a recent study in aliphatic polyesters it was found that the modulation of drug release was better achievable by altering the ratio of PCL to poly(DL-lactic acid) (PDLLA) or poly(L-lactide-co-glycolide) (PLGA) in the thin film blends, than in neat polyesters [19]. PCL is aliphatic polyester which is used extensively for drug release [20,21] but presents high crystallinity, which could affect the drug loading and its release. In contrast, PPGlu is a novel aliphatic polyester with low degree of crystallinity and low melting point [22], attributes that lead to enhancement of drug release.

The main target of the study is to prepare appropriate patches used in schizophrenics for long-term management of disease.

2. Materials and methods

2.1. Materials

Glutaric acid, 1,3-propanediol, tetrabutyl titanate catalyst of analytical grade, polyphosphoric acid (PPA) and ε-caprolactone (ε-CL) (purum 99%) were purchased from Aldrich Chemical Co (Steinheim, Germany). Risperidone drug was kindly donated by Jubilant Life Sciences Ltd. All other reagents and solvents used for the analytical methods were of analytical grade.

2.2. Synthesis of aliphatic polyesters

PPGlu polyester was synthesized according to the method described in our previous paper [22]. The molecular weight (Mn) of the prepared polyester, as was measured by gel permeation chromatography (GPC), is 14,000 g/mol and the degree of crystallinity is 29.3%.

For the synthesis of PCL, ε-CL was dried over CaH_2 and purified by distillation under reduced pressure prior to use. The bulk polymerization of ε-CL was carried out in 250 cm^3 round-bottomed flask equipped with a mechanical stirrer and a vacuum apparatus. The initiator was added as a solution in toluene at a final concentration of 1×10^{-4} mole per mole of monomer. The polymerization mixture was de-aired and purged with dry argon three times. The reaction was carried out for 2 h at 180 °C. Unreacted monomer was removed by distillation using a high vacuum (≈5 Pa) slowly, to avoid excessive foaming, over a time period of 15 min. Polymerization was stopped by rapid cooling to room temperature. The Mn of the prepared PCL, is 120,000 g/mol and the degree of crystallinity is 48.5%.

2.3. Blend preparation

The preparation of PCL/PPGlu blends was carried out via solvent evaporation method using dichloromethane (DCM) as solvent. Specifically, appropriate amounts of the above polymers were dissolved in 8 ml of DCM using a sonicator apparatus and the solvent was allowed to evaporate under magnetic stirring of the solutions at 25 °C. According to this procedure several PCL/PPGlu blends with weights ratios 100/0, 90/10, 80/20, 70/30, 60/40, 50/50 and 0/100 w/w have been prepared. The prepared blends were collected in the form of thin films (100–130 μm) for further characterization.

2.4. In vitro cytotoxicity study

The cytotoxicity of aliphatic polyester blends, in comparison with biocompatible poly(lactic acid) (PLA), was evaluated by measuring the viability of HUVE cells in the presence of different concentrations of the polymers. Cell viability was determined by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (MTT) assay. HUVEC cells were seeded in 24-well plates at a density of 30,000 cells per well in 500 μl cell culture medium. Twenty-four hours after plating, different amounts of aliphatic polyesters in the form of thin films (suspended in culture medium) were added in the wells. After 24 h of incubation at 37 °C, 50 μl of MTT solution (5 mg/ml in PBS pH 7.4) was added into each well and plates were incubated at 37 °C for 2 h. The medium was withdrawn and 200 μl acidified isopropanol (0.33 ml HCl in 100 ml isopropanol) was added in each well and agitated thoroughly to dissolve the formed crystals. The solution was transferred to 96-well plates and immediately read on a microplate reader (Biorad, Hercules, CA, USA), at a wavelength of 490 nm. The experiments were performed in triplicate. Biocompatibility of polymers was expressed as % cell viability, which was calculated from the ratio between the number of cells treated with the nanoparticles and that of non-treated cells (control).

2.5. Experimental design and preparation of risperidone transdermal patches

The transdermal patches of risperidone were prepared using the solvent evaporation method. For this reason solutions of PCL/PPGlu blends in DCM have been prepared in which risperidone was added. The solutions were ultrasonicated for 5 min and the solvent was evaporated under stirring. After 24 h patches in the form of thin films (50 ± 5 μm) were collected for further characterization and in vitro drug release studies.

A user defined experimental design (Table 1) was used to examine the effect of PCL/PPGlu ratio (X_1) and loading of the API (X_2) on dissolution behaviour. Three levels of PCL/PPGlu ratio (50:50,

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