



# INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAP /Vol.6 / Issue 1 / Jan - Mar -2017

Journal Home page: [www.ijpar.com](http://www.ijpar.com)

Research article

Open Access

## Comparative pharmacokinetics of PLGA & PCL based long acting injectable (LAI) risperidone microsphere formulations

Harish Kaushik Kotakonda<sup>1,4</sup>, Nagulu Malothu<sup>2</sup>, Yellu Narsimha Reddy<sup>3\*</sup>

<sup>1</sup> Department of Pharmacy, IST, Jawaharlal Nehru Technological University, Hyderabad, India;

<sup>2</sup> Department of Pharmacology, Swami Ramanandha Tirtha Institute of Pharmaceutical Sciences, Nalgonda, India;

<sup>3</sup> Department of Pharmacology & DMPK, UCPS, Kakatiya University, Warangal, India

<sup>4</sup> Department of DMPK, JVR Biosciences, Hyderabad, India

\*Corresponding Author: Harish Kaushik Kotakonda

Email: [ynrucpsc@gmail.com](mailto:ynrucpsc@gmail.com)

### ABSTRACT

The objective of the study was to compare and evaluate the pharmacokinetics of biodegradable PLGA & PCL microspheres with Risperidal Consta<sup>TM</sup> for achieving the sustained delivery of Risperidone in the schizophrenia therapy. Five microsphere formulations of risperidone were prepared by using two PLGA copolymers (50:50 and 75:25) and PCL (PCL-45000 and PCL-80000) polymer. All the five novel microsphere formulations (PLGA1-4 & PCL) and Risperidal Consta<sup>TM</sup> was administered to male Sprague Dawley rats through subcutaneous route at different dose. PLGA & PCL formulations achieved higher exposure than Risperidal Consta<sup>TM</sup> ie among PLGA based formulations ranked in the following order (PLGA1(1.6x) > PLGA2 (1.5x) > PLGA3 (1.2x) > PLGA4 (0.9x)) whereas PCL formulation demonstrated 1.3x higher exposure than Risperidal Consta. Simulations of multiple dosing at weekly or 15-day regimen to predict the in vivo profile of risperidone following subcutaneous administration of PLGA1-4 and PCL microspheres formulations and compared with marketed Risperidal Consta<sup>TM</sup> revealed pulsatile behavior for all formulations with steady state being achieved by the second dose. Based on simulations it was observed that PLGA & PCL based formulations can be utilised to provide weekly and once in 15 day dosing regimen which could be an effective approach for sustained delivery of this molecule and a possible alternative to the currently available combination therapy. Therefore based on our study we conclude that development of novel microsphere based formulation by combining the PLGA & PCL systems to prepare long acting dosage forms with atypical antipsychotics will ensure patient compliance, reduce side effects, and improve the quality of life for patients who suffer from schizophrenia.

**Keywords:** PLGA, PCL, Microspheres, Risperidone, Sustained delivery, Schizophrenia

## INTRODUCTION

Schizophrenia is a lifelong mental illness which is often associated with issues that are significant such as long lasting health, social, and financial burdens due to expenditures for hospitalization, treatment and rehabilitation [1-6]. Oral atypical antipsychotic drugs has generally resulted in improved clinical response, improved tolerability, and/or reduced side effects. However their benefit has been reduced due to the nature of the illness ie absent mindedness, recoil from ingestion, patient non-compliance and non-adherence rates of (24–74%) [7-11].

To overcome the issue of patient non-compliance and simplifying the medication process, a long-acting injectable depot (LAI) antipsychotic drug formulations were being developed. They have a number of advantages over oral medication which includes a) decrease in the frequency of dose administration ie IM/SC injection once in 3 or 4 weeks compared to oral tablets/capsules several times daily b) improvement in the patient adherence rates and predictable absorption c) reduced adverse effects as a result of small amounts of targeted and localized drug delivery and d) improved therapeutic response due to consistent drug blood levels. In this regard the marketed long-acting parenteral (IM) microsphere dosage form of Risperidone (Risperidal Consta<sup>®</sup>, Johnson and Johnson Corp. USA) has proven to be useful for maintenance (once every two weeks) therapy of psychotic behaviour especially when compared to conventional tablet therapy [12-16].

Risperidal Consta<sup>™</sup> once injected can result in therapeutic levels only after 2-3 weeks. During this lag phase, oral supplementation is given. The therapeutic action then lasts for next 2-3 weeks. Co-administration of oral Risperidone, while necessary in an inpatient or outpatient setting, is inconvenient and poses major compliance issues in patients with psychotic disorders. Thus, the latency in drug release is a major shortcoming of the long acting Risperidone depot preparation. Therefore, there is a strong need for a non-oral controlled delivery dosage form for this drug.

Over the years, several polymers have been evaluated for development of controlled release injectable formulations. Of these polymers, one class of polymers which has achieved significant commercial success in the pharmaceutical

formulation world are biodegradable and biocompatible polymers such as poly (D, L-lactide-co-glycolide) (PLGA) and polylactide (PLA) polymers. Number of studies have demonstrated PLGA and PLA's biodegradable microsphere systems effectiveness in providing sustained drug delivery over an extended duration making them the most commercially successful and preferred delivery systems via the intramuscular or subcutaneous route [17,18].

However, PCL is another biodegradable polymer approved by FDA which is a hydrophobic polymer with degradation rates slower than commonly used PLGA and forms more porous sustained release parenteral depots which would result in a more prolonged drug release with no lag time and zero-order drug release. From the literature survey, it is found that polycaprolactones (PCL) has been in focus in the search for appropriate matrices for drug delivery microspheres, due to its ease of preparation, commercial availability at reasonable cost, versatility, biocompatibility and hydrolytic degradation into resorbable, harm-less products and also it is a promising candidate for controlled release applications. Further, it is compatible with numerous other polymers. Therefore PCL has been reported to be used for preparing microspheres and nano formulations for drug delivery [19-22].

In this study we chose to compare the drug release invivo from two widely used polymers ie PLGA & PCL and evaluate the clinical benefit in utilising these microsphere in developing LAI microsphere. The objectives of the study were is to prepare and compare the pharmacokinetics of

- Four different sustained release microspheres of Risperidone utilizing two PLGA copolymers with varying lactide : glycolide ratios (50 : 50 and 75 : 25) as well as molecular weights with the marketed Risperidal Consta<sup>®</sup> LAI formulation
- PCL (poly caprolactone) based Risperidone controlled release microsphere formulation performance with the marketed Risperidal Consta<sup>®</sup> LAI formulation
- Simulate the dosage regimen of PLGA & PCL based microsphere formulations

## MATERIALS & METHODS

Risperidone and PLGA 50:50 (45 and 70 kDa) and 75:25 (55 and 65 kDa) were gift samples from KJD Pharma Pvt Ltd., Hyderabad, India. PCL (M.Wts 45000 and 80000) were purchased from Sigma-Aldrich Ltd., Germany. Dichloromethane, polyvinyl alcohol, were purchased from SD Fine Chemicals Ltd.

### Preparation of Risperidone Microspheres Formulation's

#### PCL Risperidone Microspheres

PCL risperidone microspheres were prepared by solvent evaporation method. A 50 mg of drug was dissolved in 5ml of organic solvent (DCM) and then 45 mg each of PCL (45000 & 80000) polymer was added to this solution, stirred well. 50 mL of 4% w/v of polyvinyl alcohol was used as an aqueous phase. Microspheres were prepared by slowly injecting the organic phase into the aqueous solution, while stirring on a magnetic stirrer. This results in o/w emulsion. The magnetic stirrer was maintained at the required speed for 3-4 h to evaporate the organic solvent. Finally, the particles

formed were filtered and then kept in desiccator overnight for the absorption of moisture.

#### PLGA Risperidone Microspheres

The risperidone-encapsulated PLGA microspheres were prepared by o/w emulsion solvent evaporation method. The preparation of microspheres formulations is shown in Table 1. Briefly, 3 g of PLGA or their blends were dissolved with 1.5 g of risperidone in 15 mL of dichloromethane (DCM), the external phase was 0.5% (w/v) aqueous polyvinyl alcohol solution. First, the organic phase was emulsified with 1500 mL of 0.5% aqueous PVA solution (2000 rpm for 4 min) in a homogenizer at room temperature. Second, the dispersion was stirred with a Silverson L4R mixer (Silverson machines, MA, USA) at 5000 rpm for 4 h at room temperature to harden the microspheres. The microspheres were collected by filtration, washed extensively three times with deionized water. 0.5 mL of 15% mannitol aqueous solution was added to prevent the microspheres from aggregation. After freeze drying, the microspheres were weighed and stored at 4°C. Briefly, the four formulations prepared were given in Table-1

**Table-1: PLGA 1-4 formulation details**

Formulation	PLGA1	PLGA2	PLGA3	PLGA4
MW	45kDa	70kDa	55kDa	65kDa
PLGA type	50:50	50:50	75:25	75:25
Dose (mg/kg)	20	20	40	40

## IN VITRO RELEASE

The in vitro study was performed in 0.1 M phosphate buffered saline, pH 7.4, containing 0.05 % Tween-80 and 0.1 % sodium azide using a 'modified dialysis' method. Risperidone consta, PLGA1-4 and PCL microspheres were accurately weighed and placed in a 7-mL dialysis tube (Tube-O-Dialyzer®, MWCO 300,000 Da) filled with 5.0 mL of release media, which in turn was placed in a 50-mL tube containing 40 mL of the same release medium (outer bulk). The contents of the larger tube were continuously stirred with a magnetic stirrer. All tubes were incubated at 37°C. At each time point 1.0 mL was removed from the 50-mL tube (outer bulk) and 1.0 mL of fresh buffer was

added. Risperidone content was determined by HPLC.

## DRUG CONTENT

Risperidone content in the microspheres was analyzed by a reverse phase HPLC method using a Nucleosil C-18 column (Phenomenex, Torrance, CA) at a flow rate of 1 mL/min. The mobile phase consisted of 30% v/v acetonitrile and 0.1% (v/v) trifluoroacetic acid in water. The analysis was performed by injecting 50 µL samples in a HPLC (Agilent 1200, USA).

## BIOAVAILABILITY STUDY

### Animal handling and drug administration.

All animal procedures were performed according to “Principles of laboratory animal care” and approved by the Institutional Animal Ethics Committee (IAEC) all protocols and the study was conducted after following the CPCSEA guidelines at JVR Bio Life Sciences Pvt Ltd (Hyderabad, India).

Male Sprague-Dawley rats (8 - 10 weeks & 250–300 g) were divided into six groups (n = 6 per group): Risperidal Consta®, PLGA1, PLGA2, PLGA3, PLGA4 and PCL groups respectively.

The rats in the Group A received Risperidal Consta® 50 mg dose, in the PLGA1 and PLGA2 received a dose of 20mg/kg risperidone

microspheres injection in the PLGA3 and PLGA 4 groups received a dose of 40 mg/kg risperidone microspheres injection and the PCL group received a dose of 50mg/rat of risperidone microspheres. All groups received the dose through subcutaneous (SC) route at base of the neck.

All the microspheres formulations were sterilized under UV light for 24 h prior to administration. Briefly, vials containing freeze dried PLGA microspheres along with diluent were reconstituted with WFI (water for injection) before SC dose administration

After administration of the different formulations, blood samples were collected at different time intervals as mentioned in the Table-2 from the retro orbital plexus

**Table-2: Sampling schedule of Risperidone following administration of Risperidal Consta, PLGA1-4 & PCL microspheres through subcutaneous route in Male Sprague Dawley rats**

Treatment	Sampling schedule (days)
Risperidal Consta	0,1,5,3,5,5,10,20,30,40,50,60,70
PLGA 1 & 2	0,0.5,1,4,8,15
PLGA 3 & 4	0,0.5,1,4,8,15,20,30,45
PCL	0,0.25,1,25,2.5,4,10,20,30,40,50,60,70,80,90,100,110

Plasma was obtained by centrifuging blood samples at 3500 rpm for 10 min. under refrigeration (2-4 °C) within 30 minutes of sampling. The obtained plasma samples was separated in pre-labeled tubes and stored at -70±10 °C until analysis.

### SAMPLE EXTRACTION & LC-MS/MS BIOANALYSIS:

Previously published method (21) was modified to suit our analysis. Briefly, 300 µl plasma were added with 0.9 ml of 60 ng/mL of IS. Then the samples were vortex-mixed up vigorously for 5 min and centrifuged at 15000×g (2 °C) for 15 min. Its supernatants (2 µl) were injected into the LC-MS/MS system.

#### LC-MS/MS Analysis

Chromatographic separation was achieved with a Surveyor HPLC with an Alltima-C18 column (2.1 mm×100 mm, 3.0 µm). A mobile phase consisting of 0.1% formic acid-acetonitrile (40:60, v/v) was

used with a flow rate of 0.2 ml/min. The mobile phase was filtered by passing through a 0.22 µm membrane filter. Measurements were made at 30 °C, and sample volume was 2 µl. The mass spectrometer operated in positive Turbo Ion Spray mode and selected reaction monitoring (SRM) was used for data acquisition of analyte and IS. The peak area of transition from m/z 411.3, [M+H]<sup>+</sup> ion, to m/z 191.1, a product ion, with collision energy of 30 eV was measured for RIS. Paroxetine was monitored using the transitions from m/z 330.1 to m/z 192.1 with collision energy of 27 eV. The underlined transitions were used for quantification. The MS parameters for the analysis were as follows: ion source temperature 350 °C; ion-spray voltage 3500 V; nebulizer gas 55 psi; auxiliary gas 50 psi; curtain gas 35 psi and medium collision gas. Conditions of mass spectrometric detection were optimized by direct infusion of standard solutions into the MS.

## PHARMACOKINETIC DATA ANALYSIS

Based on the individual plasma concentration, pharmacokinetic (PK) parameters were calculated (BLOQ was considered as zero for calculating PK parameters) by non-compartmental analysis by using Phoenix™ WinNonlin® Version 6.4 (Pharsight Corporation, USA). Pharmacokinetic parameters including (but not limited to) peak plasma concentration ( $C_{max}$ ), time to reach the peak plasma concentration ( $T_{max}$ ), half-life ( $T_{1/2}$ ),  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $V_d$ , CL, and MRT. The elimination rate constant (K) was assessed by the linear regression analysis of the terminal linear part of the log plasma concentration vs. time curve. The areas under the concentration–time curves (AUC) were calculated by the linear trapezoidal rule.

## RESULTS & DISCUSSION

The invitro release profile of PLGA1, PLGA2, PLGA3, PLGA4, PCL and Risperidal Consta is provided in figure-1. It is clear from the figure that PLGA1 and 2 formulations, prepared using the 50:50 copolymer, release drug much faster than PLGA 3 and 4 formulations that were manufactured using a copolymer with a 75:25 lactide:glycolide ratio. A moderate initial burst was observed (day 1)

with all four formulations after which drug release increased to reach between 15 and 20 % by day 3. After this, PLGA1 and 2 maintained their release rate such that nearly 50 % of the drug was depleted from the microspheres within a week. In contrast, the release rate for PLGA 3 and 4 formulations increase in a more sustained fashion to realize 50 % drug release in about 2 weeks, i.e., approximately twice the time observed with formulations containing the 50:50 copolymer. When approximately 85 % drug was released from PLGA 1 and 2 formulations (i.e., 2 weeks), the drug release rate slowed considerably till complete release was achieved. On the other hand, drug release from the 75:25 copolymer formulations remained consistently steady till 100 % of the drug was released from the microspheres. The polycaprolactone based formulations PCL showed complete release (100%) of the entrapped drug in 90 days and it showed complete drug release and achieved 3 month depot with zero-order release profile and without the lag phase and initial burst release. The drug release was further compared with marketed Risperidal consta. There was a significant lag time with Risperidal consta while with F5 formulation there was no lag time. While Risperidal consta released the drug for 60 days, the PCL formulation released the drug for 90 days.

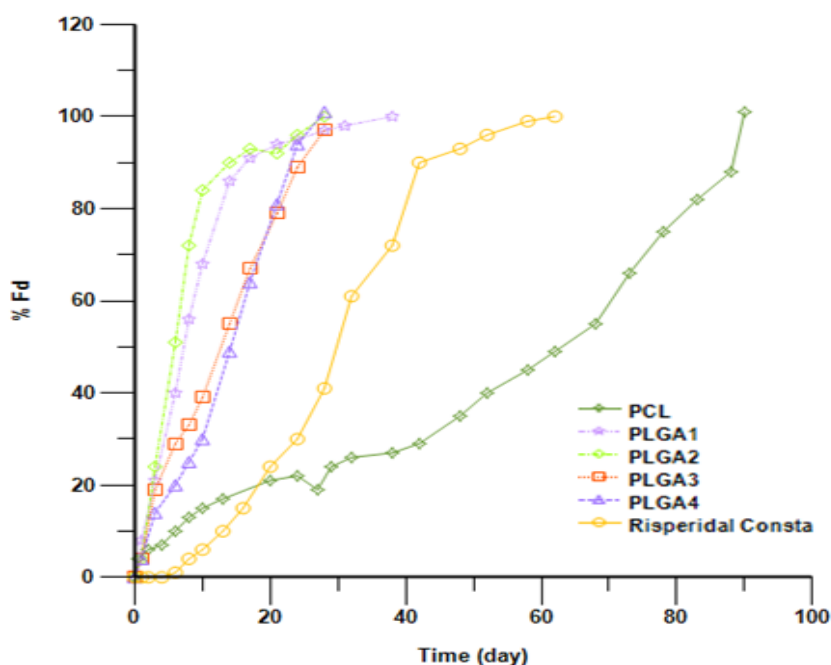
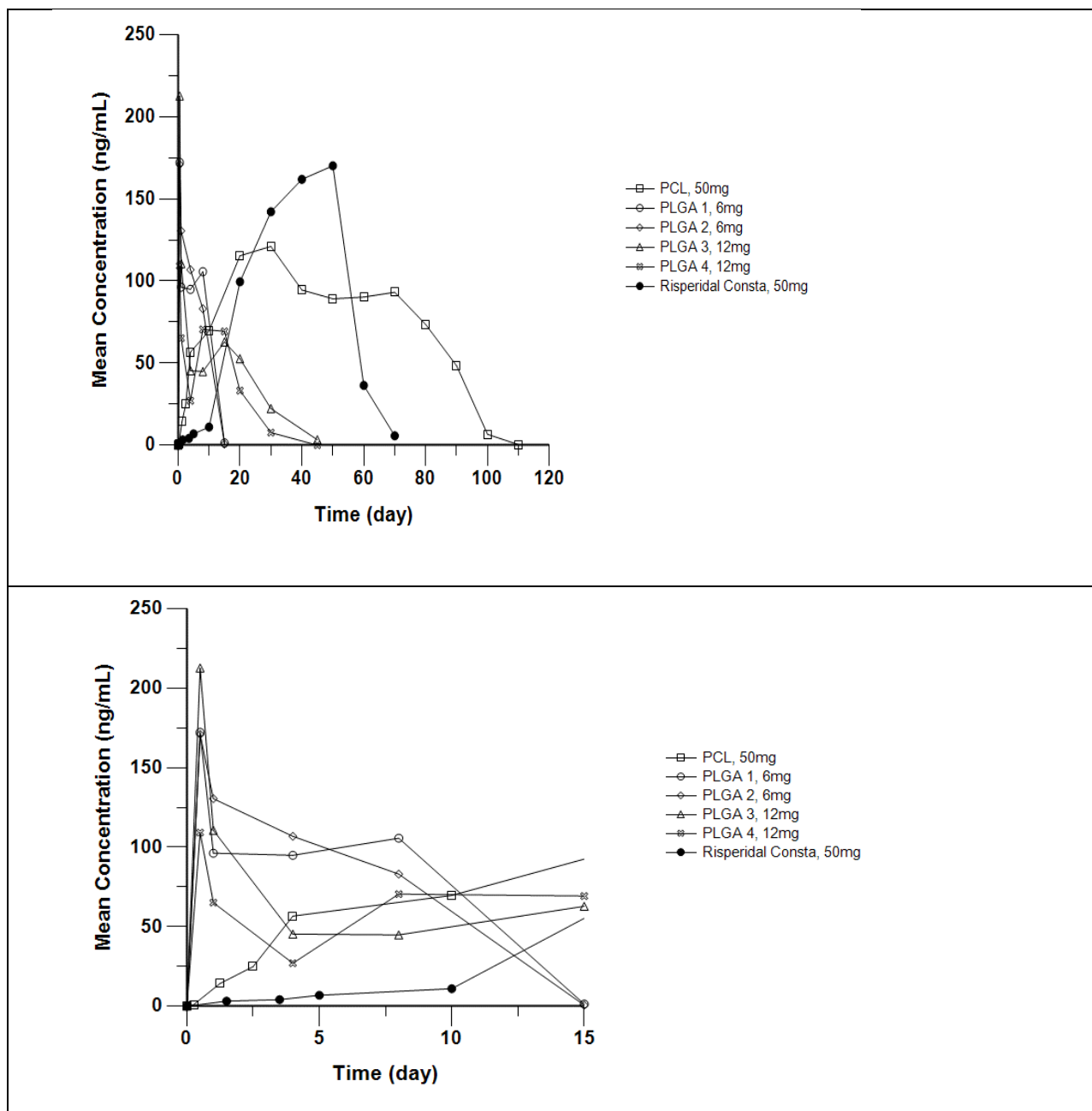


Figure-1: In vitro dissolution profile of PLGA1-4, PCL and Risperidal Consta formulations

The mean plasma concentration time profile of risperidone following Risperidal Consta, PLGA1-4

& PCL microspheres through subcutaneous route of administration are indicated in Figure 2.



**Figure-2: Mean Plasma Concentration vs Time profile of Risperidone following administration of Risperidal Consta, PLGA1-4 & PCL microspheres through subcutaneous route in Male Sprague Dawley rats**



The mean ( $\pm$ ) SD pharmacokinetic parameters of risperidone are provided in Table 3.

**Table-3: Mean ( $\pm$ SD) Pharmacokinetic Parameters of Risperidone following administration of Risperidal Consta, PLGA1-4 & PCL microspheres through subcutaneous route in Male Sprague Dawley rats**

Treatment	Dose (mg)	T <sub>max</sub> * (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (hr.ng/mL)	AUC <sub>0-inf</sub> (hr.ng/mL)	MRT <sub>last</sub> # (hr)	T <sub>1/2</sub> # (hr)
Risperidal Consta	50	1200	170.092 $\pm$ 20.079	149874.100 $\pm$ 17692.55	ND	911.2	ND
PLGA 1	6	12	172.202 $\pm$ 20.328	28126.81 $\pm$ 3320.353	28204.88 $\pm$ 3329.569	128.1	40.2
PLGA 2	6	12	170.851 $\pm$ 20.169	27517.14 $\pm$ 3248.381	27550.15 $\pm$ 3252.278	114.2	34.2
PLGA 3	12	12	212.623 $\pm$ 25.1	42701.53 $\pm$ 5040.89	43398.17 $\pm$ 5123.127	348.6	147.9
PLGA 4	12	12	109.144 $\pm$ 12.884	32482.42 $\pm$ 3834.53	33737.2 $\pm$ 3982.655	283.4	113.4
PCL	50	720	120.996 $\pm$ 14.284	195275.1 $\pm$ 23052.11	195303.7 $\pm$ 23055.49	1110.5	65.6

\*Median; #Mean; ND: Not determined due to insufficient points in the terminal phase

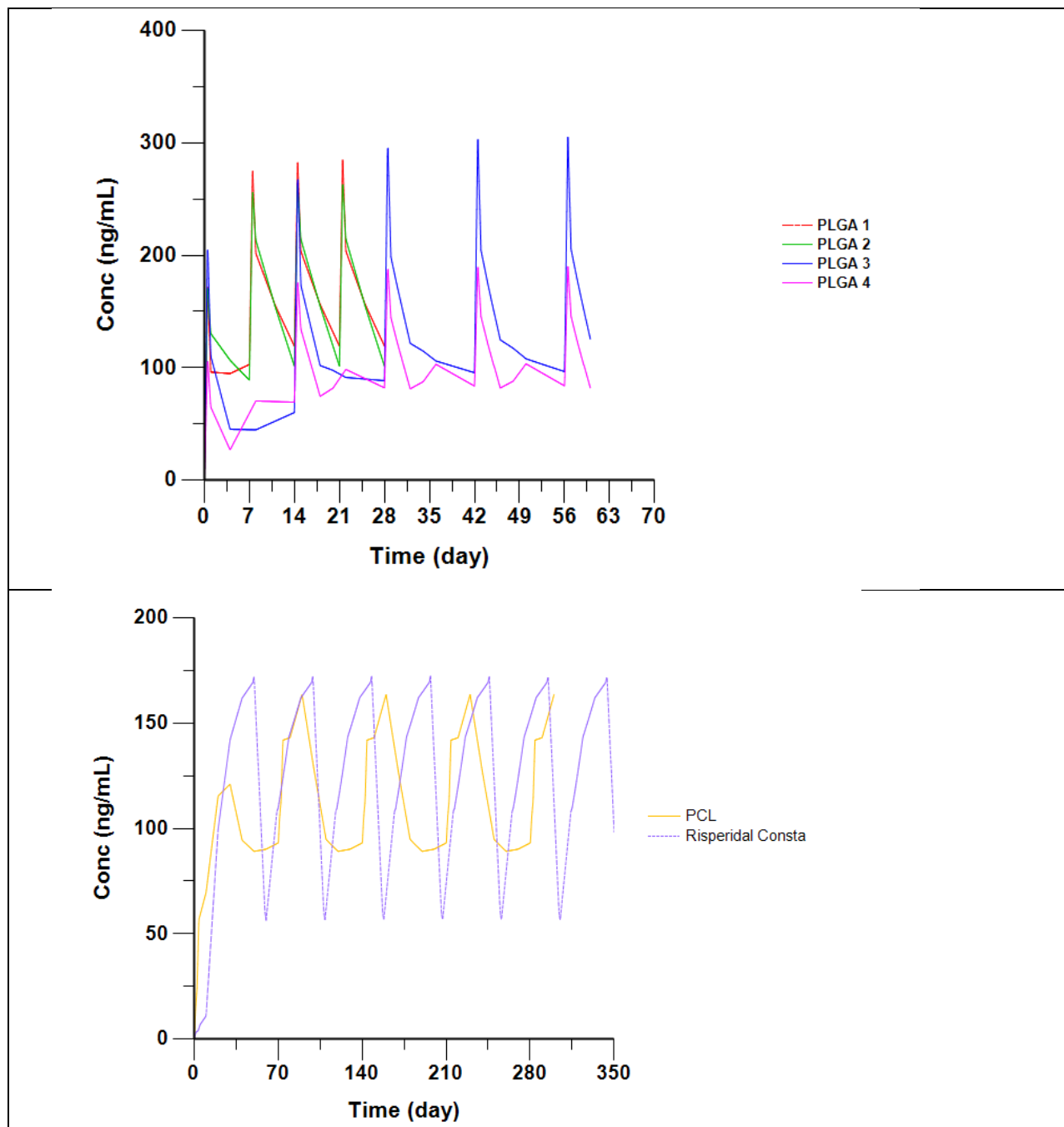
PLGA 1 & 2 formulations showed an initial burst around 170 ng/mL of Risperidone followed by a decrease in levels by day 1. Levels rose slightly by day 4 to release drug in a sustained manner through day 15 with levels being depleted slowly. With PLGA 3 & 4 an initial burst was also observed around 212.62 ng/mL & 109.14 ng/mL respectively. The highest initial burst was observed with PLGA-3 formulation. Apart from the initial burst, PLGA 3 & 4 demonstrated similar profiles. After an initial burst, a sharp drop occurred and the drug levels increase to show a second peak around 15<sup>th</sup> day with levels being around 62.80 & 69.25 ng/mL for PLGA-3 & 4 formulations respectively and from day-15 to 45 the drug levels progressed to a decline upto day 45 for both formulations. Therefore, PLGA 1,2 & 3 formulations demonstrated similar in vivo behavior ie a high initial burst followed by depletion of circulating levels of drug led to a trough that was followed by a slow sustained release of drug from the PLGA matrix until values diminished. Risperidal Consta and PCL formulations didn't demonstrate the pattern observed with PLGA based formulations mean C<sub>max</sub> of 170.092 ng/mL and 120.996 ng/mL was observed around 50<sup>th</sup> day and 30<sup>th</sup> day for Risperidal consta and PCL formulation respectively.

The exposure (AUC<sub>0-t</sub>) of PLGA 1-4 formulations were 28126.81, 27517.14, 42701.53 and 32482.42 hr.ng/mL respectively. In case of PLGA 1 & 2 formulations which exhibited a high initial burst, more than 98% of the AUC was contributed by drug encapsulated in the polymer matrix with initial burst amounting to a mere 1.4–1.8% of the total profile whereas for PLGA 3 formulation initial burst contributed nearly 2% to the cumulative AUC whereas, with PLGA 4 formulation, the value was smaller (1%) which suggests that suggest that most of the in vivo activity was due to drug incorporated in the polymer matrix that was available for release in a sustained fashion whereas both Risperidal Consta and PCL formulations do not exhibit any initial burst phenomenon due to which oral therapy supplementation is needed to achieve pharmacologically effective levels of the drug. PLGA & PCL formulations achieved higher exposure than Risperidal consta ie among PLGA based formulations ranked in the following order (PLGA1(1.6x) > PLGA2(1.5x) > PLGA3(1.2x) > PLGA4(0.9x)) whereas PCL formulation demonstrated 1.3x higher exposure than Risperidal Consta.

Simulations were done to predict the in vivo profile of risperidone following subcutaneous

administration of PLGA1-4 and PCL microspheres formulations and compared with marketed

Risperidal Consta using the superposition principle.



**Figure-2: Simulation of multiple dosing regimen of risperidone following subcutaneous administration of PLGA 1-4 ,PCL and Risperidal Consta formulations in Male Sprague Dawley rats**

Simulations of once a week dosing for PLGA1 &2 formulations (Figure 3) shows risperidone levels between 100 and 270 ng/mL with an initial spike in drug levels observed after the

administration of the first dose. As dosing continues, the peaks occur immediately after each administration but then fall quickly to 100ng/mL only to repeat the peak and trough profiles



throughout the 4 doses administered. In general, peak values of 270 ng/mL were obtained after dose 4 (steady state) with trough values of 100 ng/mL. Therefore PLGA 1 and 2 formulations exhibited a pulsatile profile after simulations of multiple dosing. For PLGA 3 & 4 formulations, a 15-day dosing regimen was attempted. Once again, a pulsatile release profile is observed primarily due to the initial burst observed with both formulations. From an initial peak active moiety value of ~200 ng/mL for PLGA3 formulation and nearly 110 ng/mL for PLGA-4 formulation, values reach 304 ng/mL for PLGA3 formulation and 190ng/mL for PLGA-4 formulation. The in vivo profiles of the two formulations are nearly similar, with the exception of the peak height of the initial spike. Throughout the course of dosing, risperidone levels ranged between 85 and 305 ng/mL and are similar to the range observed with PLGA 1 and 2 formulations. Hence the pulsed behavior of these formulations also confirms that co-administration of Risperidone oral tablets is not necessary with all four formulations evaluated in this study.

In case of Risperidone administration of the first dose shows minimal levels of risperidone through 3 weeks with drug release occurring from week 4 to 7. Therefore, even after administration of the first dose, risperidone levels in vivo will continue to be minimal. This suggests that when therapy is terminated, a longer washout period will be needed for patients dosed with the marketed preparation. Whereas for PCL microspheres formulation administration of the first dose achieves therapeutic levels from 4 days to within 3 weeks. After 2<sup>nd</sup> dose administration post 70 days maximum concentrations are achieved within 12 weeks. Overall due to the longer release pattern of PCL microspheres formulation the number of doses given are reduced.

To overcome the weaknesses mentioned above, several groups developed novel parenteral sustained release implants and microspheres for risperidone. Su et al., has developed a PLGA based risperidone microspheres without a lag period and tested it successfully in a rat model [23]. Further, the microspheres released the drug according to a zero-order release profile. D'Souza et al., have developed novel risperidone microspheres and successfully avoided co-administration of oral tablets [24]. Further, this study demonstrated that

microsphere dosage form for risperidone can be formulated with an optimum particle size and drug loading to provide initial bolus followed by maintenance levels, thereby eliminating combination therapy and improving the patient compliance. The microsphere formulations developed in the study by D'Souza et al., prolonged the release of the drug by only 45 days. On the other hand, all the implants that are reported so far are based on PLGAs and are able to release the drug for 1 or 2 months. Rabin et al., demonstrated in vitro and vivo proof of concept for risperidone implants using biodegradable PLGA copolymers [25, 26]. Jithan et al have developed PCL based microsphere formulations and demonstrated the extended release of risperidone both in vitro and in vivo [27, 28]. In our study we have evaluated the performance of PLGA & PCL based microsphere formulations in a single study and compared the performance of these novel drug delivery systems and evaluated the possibility of utilising these polymers to develop a novel formulation which can be developed for clinical purpose.

## CONCLUSIONS

The study demonstrated that sustained release microspheres of Risperidone utilizing PLGA copolymers with varying lactide : glycolide ratios (50 : 50 and 75 : 25) and PCL copolymers based microspheres with (PCL-45000 and PCL-80000) had a strong potential to be excellent for providing initial and maintenance levels of Risperidone. Based on simulations performed it was observed that PLGA based formulations can be utilised to provide weekly and once in 15 day dosing regimen which could be an effective approach for sustained delivery of this molecule and a possible alternative to the currently available combination therapy. In contrary PCL based microsphere formulations could provide extended release of risperidone longer than PLGA based microsphere formulations. Therefore based on our study we conclude that development of novel microsphere based formulation by combining the PLGA & PCL systems to prepare long acting dosage forms with atypical antipsychotics will ensure patient compliance, reduce side effects, and improve the quality of life for patients who suffer from schizophrenia.

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