Fabrication and Evaluation of Novel Risperidone Implants as a Long Term Antipsychotic Therapy

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ABSTRACT SUMMARY

A series of novel prolonged release risperidone implants were fabricated for treatment of psychotic disorders. Poly (DL-lactide-co-glycolide) (PLGA) polymer with either cholesterol (chol) or polyethylene glycol 400 (PEG) were selected as hydrophobic and hydrophilic excipients respectively. Implants were fabricated by injection molding method with cylindrical stainless steel molding device. Each implant with dimension of 10 mm in length and 2 mm in diameter evaluated for its physicochemical properties such as mechanical strength, water uptake and matrix erosion and physical state of risperidone in implant by differential scanning calorimetry (DSC) and X-ray diffraction analysis (XRD). The surface morphology of implants was assessed by scanning electron microscopy (SEM). Also drug loading and in vitro release analysis was performed for each formulation. Data showed higher mechanical strength for formulations with chol. Matrix erosion was calculated 0.8% and 1.6% for implants with chol and PEG as an excipient respectively. Also XRD analysis showed crystalline state of risperidone in implant matrix in all formulations. In vitro drug release studies showed 50 days slow and continuous release of about 95% of risperidone without significant initial burst for optimized respridone implants with chol as an excipient. Based on present study the prolonged released formulation of risperidone implant was obtained by using cholesterol as hydrophobic excipient in PLGA matrix.

INTRODUCTION

Among different drug delivery systems, implant is the most attractive system which is used both for hydrophobic and hydrophilic drugs with acceptable clinical outcomes. Basically implants composed of polymer(s), drug(s) and with or without excipients. Implant drug delivery has several advantages including, decreasing the frequency of administration with incorporating the total amount of needed drug in the defined period of time, excluding of missed dose especially in geriatrics, by passing first pass metabolism and also reduction of hospitalization and medical care[1]. There are lots of research in different field of therapies by implant drug delivery like contraception[2], ophthalmology[3], bone disease and fractions, dental implants and diabetes but it is less concentration on psychotic disorder and specially schizophrenia which is a chronic medical condition that needs long term of medical therapy.

Risperidone, a dopamine antagonist, is the most prescribed drug in the treatment guide line of schizophrenia. The chronic administration of this drug during the therapy makes it an attractive candidate for controlled release system. In this research different formulations of risperidone implants with PLGA and hydrophobic and hydrophilic excipients were fabricated and physicochemical characteristic and also in vitro release profile were studied.

EXPERIMENTAL METHODS

Risperidone implants were fabricated via injection molding method with cylindrical shaped stainless steel (AISI 316L) molding device. Different formulation with various amounts of PLGA and 100 mg risperidone either with PEG (F_1 and F_3) or Chol (F_2 and F_4) as an excipient were fabricated. For each formulation PLGA and risperidone were dissolved in 5 ml dichloromethane with either Chol or PEG. The resultant solution was heated to 50 ° C to evaporate dichloromethane and formed viscous paste. The paste was injected into the die of molding device. After 30 min the cylindrical rod with the length of 40 mm and 2 mm in diameter casted and cut into four equal implants of 10 mm. Each implant was evaluated for physicochemical properties including water uptake and matrix erosion, mechanical strength, physical state of risperidone in implant matrix by differential scanning calorimerty (DSC) and X-ray diffraction (XRD) method. The surface morphology of implants was assessed by scanning electron microscopy. Also each implant analyzed for risperidone content via RP-HPLC (Agilent Technologies®). The mobile phase was methanol with flow rate of 1 mL/min through C18 column (150 × 4.6 mm, ODS 35 µm) and peak detection wave length of 275 nm. For release profile evaluation of risperidone, different formulations were placed at 500 mL PBS (pH=7.4, T= 37° C) on a shaker bath (40 rpm). At the defined period of time 1 mL aliquot of each formulation was withdrawn for

analysis by RP-HPLC as mentioned above. After each sample removal a 1 mL of fresh buffer was replaced for maintaining of sink condition.

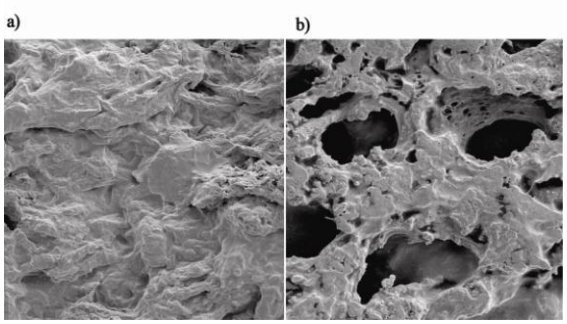

Fig 1. a) SEM image of risperidone implant (F_2) right after fabrication and b) after 30 days of release study

Table 1. Different formulation of Risperidone implants

Formulation	Risperidone (mg)	PLGA (mg)	Chol (mg)	PEG (mg)
F_1	25	25	-	15
F_2	25	25	15	-
F_3	25	50	-	15
F_4	25	50	15	-

RESULT AND DISCUSSION

Cylindrical risperidone implants were fabricated with drug content of 25mg ± 1.2 mg. Water uptakes and matrix erosion for implants with chol (F_2 and F_4) was 28.5% and 0.8% and for implant with PEG (F_1 and F_3) was 71% and 1.6% respectively, which indicates less erosion of implants with chol as an excipient in matrix forming material. Mechanical strength analysis showed higher forces needed to 10 mm displacement of implant with chol versus PEG (1.84 N relative to 0.16 N). DSC and XRD analysis demonstrate crystalline state of risperidone implants in both matrices either with chol or PEG. SEM images represented smooth surface area for both implants right after fabrication and hollows in matrix after 10 days of release experiment. In vitro release analysis showed 30 and 46 days slow and continuous release for PEG and chol implants respectively without significant burst effect. Release rate for both formulations followed zero order kinetics.

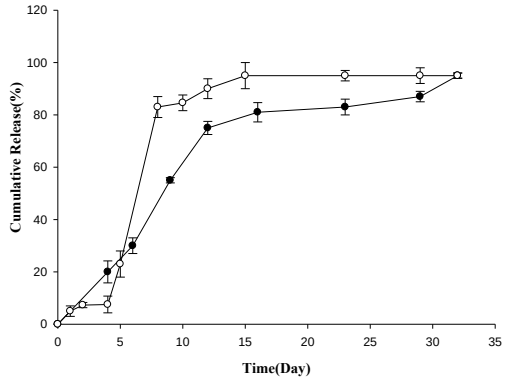

Fig 2. Release profile of risperidone implants (F_1: ○ and F_2: ●)

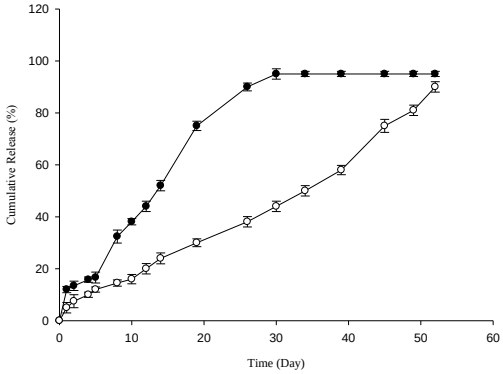

Fig 3. Release profile of risperidone implants (F_3● and F_4 :○)

CONCLUSIONS

Based on present study it can be concluded that PLGA risperidone implant with chol as an excipient, showed acceptable mechanical strength along with prolonged release profile without significant burst effect. Due to biocompatibility and safety of chol, it can be used in implant formulations in order to improve not only the mechanical properties but also sustain profile release of drugs.

REFERENCES

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