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Research Article

Accelerated Polymer Biodegradation of Risperidone Poly(D, L-Lactide-Co-Glycolide) Microspheres

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Abstract. The influence of a tertiary amine, namely risperidone (pKa=7.9) on the degradation of poly(D, L lactide-co-glycolide) (PLGA) microspheres was elucidated. Risperidone and blank microspheres were fabricated at two lactide/glycolide ratios, 65:35 and 85:15. The microspheres were characterized for drug loading by high-performance liquid chromatography, particle size by laser diffractometry, and surface morphology by scanning electron microscopy. Polymer degradation studies were carried out with drug-loaded microspheres and blank microspheres in presence of free risperidone in 0.02 M PBS containing 0.02% Tween®80 at 37°C. Molecular weight was monitored by gel permeation chromatography. Risperidone and blank microspheres had similar size distribution and were spherical with a relatively nonporous smooth surface. The presence of risperidone within the microspheres enhanced the hydrolytic degradation in both polymeric matrices with faster degradation occurring in 65:35 PLGA. The molecular weight decreased according to pseudo-first-order kinetics for all the formulations. During the degradation study, the surface morphology of drug-loaded microspheres was affected by the presence of risperidone and resulted in shriveled microspheres in which there appeared to be an intrabatch variation with the larger microspheres being less shriveled than the smaller ones. When blank microspheres were incubated in free risperidone solutions, a concentration-dependent effect on the development of surface porosity could be observed. Risperidone accelerates the hydrolytic degradation of PLGA, presumably within the microenvironment of the drug-loaded particles, and this phenomenon must be taken into consideration in designing PLGA dosage forms of tertiary amine drugs.

KEY WORDS: mass loss; microencapsulation; PLGA microspheres; polymer degradation; risperidone; tertiary amine drug.

INTRODUCTION

To manage the chronic treatment of schizophrenia and bipolar disorders, quick-disintegrating oral tablets (1) and long-acting injections (2) have been approved for clinical use. In particular, Risperidal® CONSTA®, which provides risperidone encapsulated in poly(D, L lactide-co-glycolide) (PLGA) microspheres, has been shown to improve patients' compliance by eliminating the need for frequent administration (3), and reduce the risk of overdose in suicidal situations (2). Risperidone is a tertiary amine belonging to the benzisoxazole class.

Basic drugs have been reported to affect the degradation rate of PLGA and, as a consequence, the drug release. In particular, when uncapped PLGA is used to microencapsulate a basic drug, two opposite mechanisms of interaction with opposite outcomes have been reported, namely,

- basic drugs shield the polymer terminal carboxylic residues, thereby decelerating the catalytic effect of the acidic chain ends on polymer degradation (4–6)
- basic drugs behave as catalysts in the hydrolytic cleavage of the polymer chain ester bonds, thereby accelerating polymer degradation (7–9)

In a previous work, 7- and 15-day acting risperidone PLGA microspheres were formulated by a dispersion method and characterized *in vitro* and *in vivo* (10). These results suggested that the presence of risperidone accelerates the degradation rate of PLGA polymers. In a recent work, Risperidal® CONSTA® was used as reference formulation to validate USP apparatus 4 method for microsphere *in vitro* release testing. Early stages polymer degradation has been observed and ascribed to risperidone. Nevertheless, degradation studies were performed in non physiological temperature conditions (40°C and 45°C) and simply for the first 4 days acquiring an imperfect picture of the phenomenon (11).

The purpose of this study was to investigate the degradation process and changes of molecular weight distribution of PLGA microspheres in the presence of risperidone over a 30-day period of time. The effect of drug properties was evaluated on two PLGA polymers having different molecular weights (Mw) and lactide/glycolide ratios. A further attempt was made

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to elucidate the influence of a tertiary amine drug on the hydrolytic cleavage of polyester chains.

MATERIALS AND METHODS

Materials

Risperidone was supplied by Cipla (Bombay, India). Capped PLGA at two lactide/glycolide ratios, namely 65:35 (molecular weight (Mw), 78,000 Da) and 85:15 (Mw, 88,000 Da), were supplied by Medisorb (Cincinnati, Ohio) and used to formulate blank and drug-loaded microspheres. All the solvents were of high-performance liquid chromatography (HPLC) grade, unless specified.

Microsphere Preparation

Blank and risperidone-loaded PLGA microspheres were fabricated by a solvent extraction/evaporation method (10). Drug-loaded microspheres were prepared by dispersing a homogeneous solution of polymer and drug into an aqueous solution containing 0.35% polyvinyl alcohol, followed by solvent/diffusion evaporation at 40°C for 2 h. The theoretical drug loading was fixed at 30% (*w*/*w*). The solidified microspheres were recovered by filtration and dried under vacuum for 48 h. The characteristics of the formulations used in this study are reported in Table I.

Drug Loading

Risperidone loading was assessed using reverse-phase HPLC equipped with 2 LC-6A pumps, a SIL-6B autoinjector, a SPD-6AV detector, and a SCL-6B system controller (all from Shimadzu Scientific Instruments, Inc, Columbia, Maryland) after polymer solubilization and drug extraction. Established HPLC conditions were as follows: column, Phenomenex Nucleosil, C18, 250×4.6 mm, 100A, 5 μm; mobile phase, 70/30 water/acetonitrile containing 0.1% TFA; flow rate, 1 mL/min; wavelength, 275 nm; injection volume, 30 uL. The calibration standard curve ranged from 10 to 200 μg/mL of risperidone dissolved in a mixture 0.1 M pH4.0 acetate buffer/acetonitrile (80/20, %*v*/*v*).

Particle Size Distribution

Particles were sized by laser diffractometry using a Malvern 2600 laser sizer (Malvern 2600 particle sizer, Malvern, UK). The average particle size was expressed as the volume mean diameter in microns.

Surface Morphology

The surface morphology was examined by scanning electron microscopy (SEM; Hitachi Model S800, J) after palladium/gold coating of the microsphere sample on an aluminum stub.

In Vitro Degradation Studies

Blank and loaded microspheres were incubated in 10 mL round bottom vials containing 0.02 M PBS added with 0.02% Tween® 80 and 0.5% sodium azide at 37±1°C in static conditions (12). The amount of microspheres (10 mg for the time points 0–20 days; 20 mg for the time points 25–40 days) and the volume of buffer were calculated to maintain sink condition during the degradation study.

At specified time points microspheres were collected by filtration, rinsed with distilled water, and dried for 24 h under vacuum. The pH of the supernatant was monitored during the degradation study.

In order to simulate the microsphere internal microenvironments, blank microspheres were incubated in 0.02 M PBS containing 0.02% Tween® 80 and different concentration of free risperidone, namely 15%, 30%, or 45% *w*/*v*.

Determination of Molecular Weight

The average Mw and polydispersity index (PI) of blank and loaded microspheres were determined by gel permeation chromatography (GPC). A Waters M-45 solvent delivery system with a Shimadzu SPD 6-AV UV–vis Spectophotometric Detector was used (λ=220 nm). Two Ultrastyragel® columns connected in series (7.8×300 mm each, one 10^4Å pores and one with 10^3Å pores) were used. Samples, 5 mg/ml, were eluted with tetrahydrofuran at 0.4 mL/min. The Mw of each sample was calculated using monodisperse polystyrene standards, Mw ranging from 1,000 to 90,000 Da.

Specific interpretation of the polymer degradation behavior involves plotting the logarithm of the normalized Mw *versus* time. A linear fit of the resulting data gives a degradation rate constant as the slope of the line. This degradation rate constant, k_{obs}, allows comparison of the degradation of different formulations and different polymers. A more

Table I. Characteristics of Risperidone and Blank Microspheres

Formulation code	Actual drug loading (%)	Glycolic/lactic acid ratio	PLGA MW (Da)	PI	Size distribution (μm)		
					D10[a]	D50[b]	D90[c]
Risperidone A	29.48±3.62	D, L 65/35	62,079	1.68	11.9	40.6	83.8
Blank A	–	D, L 65/35	74,847	1.66	8.9	32.2	78.7
Risperidone B	23.53±0.95	D, L 85/15	79,237	1.54	11.0	38.0	82.4
Blank B	–	D, L 85/15	83,859	1.62	17.1	52.5	89.1

[a] Ten percent of particles were smaller than that number
[b] Fifty percent of particles were smaller than that number
[c] Ninety percent of particles were smaller than that number

negative degradation rate constant reflects faster degradation. The degradation half time ($t_{1/2}$) can be further calculated according to the following equation:

$$t_{1/2} = \log 2 / k_{obs} \quad (1)$$

RESULTS AND DISCUSSION

Risperidone and blank microspheres were spherical with a relatively nonporous smooth surface (Fig. 1). The risperidone microspheres as well as blank 65:35 microspheres had a similar size distribution with the mean volume diameter in the range of 40–60 μm, while the mean volume diameter of blank 85:15 microspheres was around 96 μm. Manufacturing of risperidone microspheres caused an initial drop in weight-average Mw for both types of PLGA, while the PI had almost constant values (Table I). It can be assumed that during the preparation of risperidone A and B microspheres, an early degradation of polymer took place because of the presence of drug in solution. Indeed, the mild conditions used in the present work did not induce polymer degradation in the absence of risperidone (Table I). Even if the time required for preparing microspheres was limited to a few hours, the presence of free risperidone in solution, instead of solid state, would enhance the degradation process and water-soluble oligomers and monomers could easily move from the inner organic phase to the outer aqueous phase without affecting the PI.

Figure 2 shows the changes in Mw of PLGA of the four formulations over a 30-day period. The data were normalized with respect to the maximum peak height for comparison. Due to an adequate buffer capacity of the release medium, there were no major changes in pH due to the release of the slightly basic drug or the acidic degradation products during the course of the study (13).

As expected, in blank microspheres, the polymer Mw and lactide/glycolide ratio determined the extent of variation in Mw (*i.e.*, degradation rate). The presence of a higher fraction of lactide in the polymer backbone reduced both the onset and rate of the degradation process (Fig. 2). As the glycolide ratio is increased, the hydration and diffusion of water, and thus the hydrolysis, are facilitated (14,15). Also the difference in Mw at zero time between drug-loaded and blank microspheres suggested that PLGA 65:35 degraded to a greater extent during the preparation (Table I; 11).

Apparently, risperidone within the microspheres catalyzed polymer hydrolysis with faster degradation occurring in

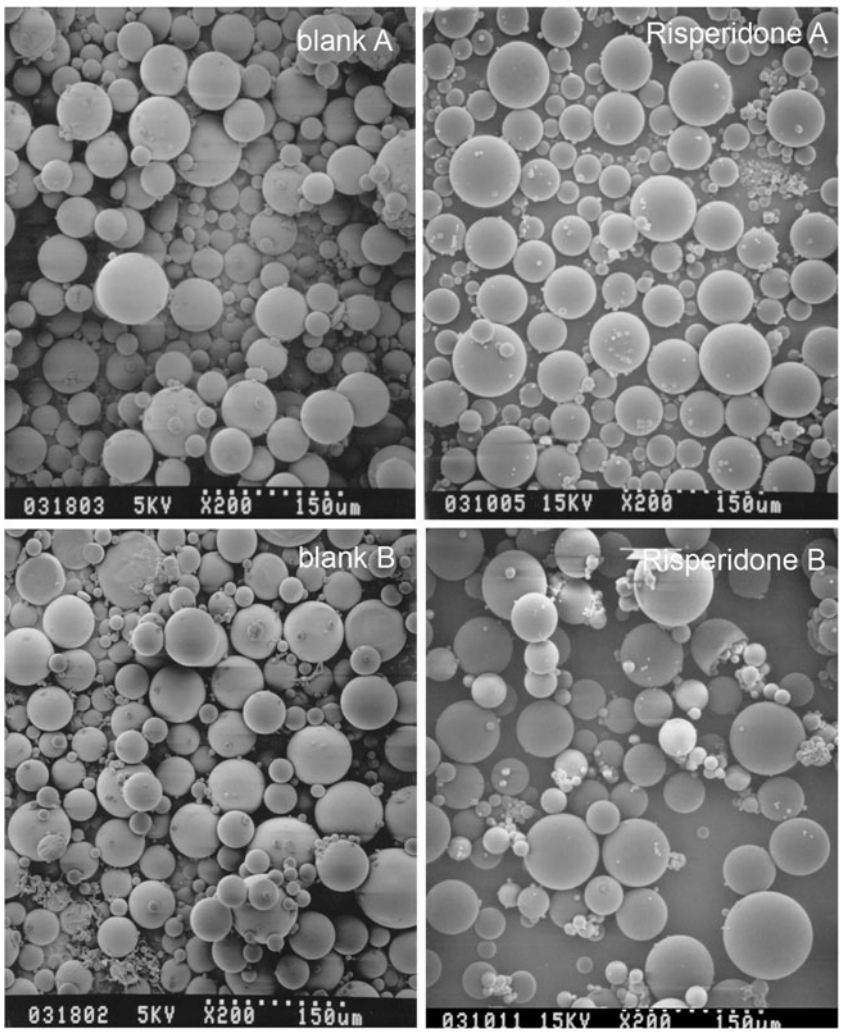

Fig. 1. SEM photomicrographs of drug-loaded and placebo microsphere after preparation

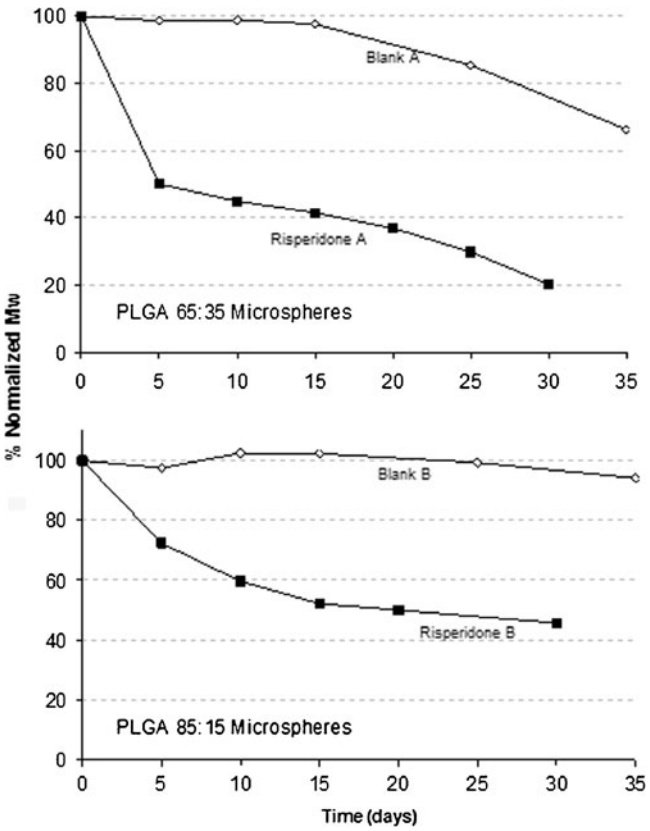

Fig. 2. A plot of percentage of the normalized weight average Mw as a function of time for risperidone and blank microspheres incubated in 0.02 M PBS containing 0.02% Tween® 80 at 37°C

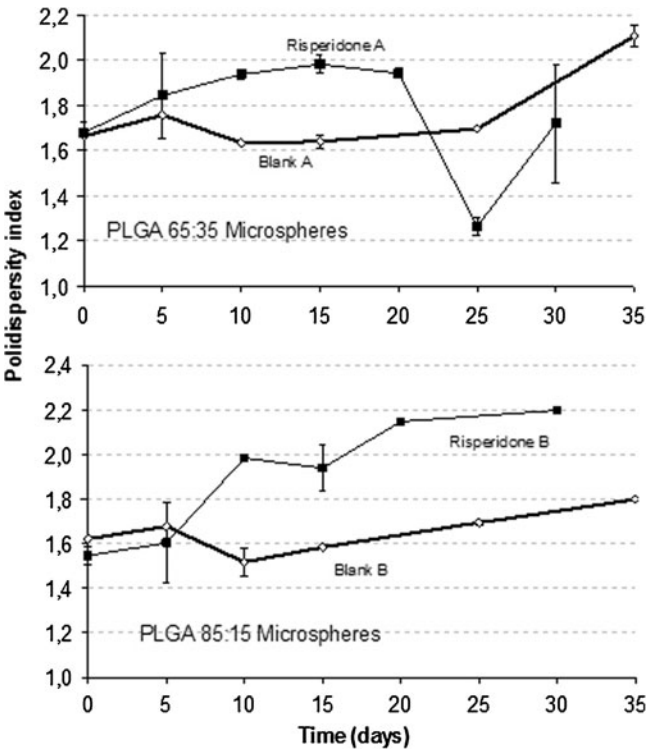

Fig. 3. A plot of PI as a function of time for risperidone and blank microspheres incubated in 0.02 M PBS containing 0.02% Tween®80 at 37°C

the case of PLGA 65:35 (Fig. 1). Indeed, in risperidone 65:35 microspheres, the degradation behavior of PLGA proceeded with an initial rapid decrease in Mw ($\Delta Mw \approx 50\%$ during the first 5 days), probably occurring at very early stages (*e.g.*, 24 h), followed by a more gradual loss in molecular weight (11). In risperidone 85:15 microspheres, the same Mw reduction was not observed until 15 days of incubation.

The Mw distribution of polymers in microspheres also became substantially broad compared to those of the blank microspheres. Asymmetrical and skewed peaks representing a mixture of high and low Mw fractions were observed "on" or "starting from" day15 (data not shown).

The PI offers an interesting representation of the molecular weight distribution progression. As shown in Fig. 3, the PI of risperdone 65:35 microspheres increased after 5 days and retained constant levels until 25 days when it sharply decreased. In contrast, PI of blank microspheres remained almost constant until a significant decrease of Mw took place. This is similar to the Mw behavior seen in Fig. 2 and suggests risperidone is enhancing the polymer degradation. The PI of risperidone 85:15 microspheres increased from 1.54 to 2.20 within 30 days (Fig. 3), while the PI of correspondent blank microspheres slightly increased from 1.62 to 1.80. This more closely correlates with the Mw changes seen in Fig. 2.

The values of polymer degradation half time, calculated using Eq. 1 and listed in Table II are consistent with those reported in literature (16). Assuming a constant concentration of water within the matrix, the PLGA degradation reaction is generally very well modeled assuming "pseudo-first order" kinetic (11,17). In the current scenario, due to the presence of a tertiary amine drug substance, the reaction kinetics should be of a higher degree and, therefore, the modeling can be very tedious. For instance, the degradation of blank microspheres 65:35 occurred according to pseudo-first-order kinetic ($r^2 > 0.87$) (16). Considering that the massive Mw reduction was observed in the first 5–10 days and then reverted to a slower degradation rate, it can be consistent to exclude from the regression the first point. In fact, the linear regression starting from day 5 can be satisfactory modeled as a pseudo-first-order reaction ($r^2 = 0.91$).

The presence of risperidone accelerated PLGA degradation, reducing the differences between the two polymers, namely the average molecular weight and the chemical structure. The degradation half time and constant rate for PLGA 85:15 were about tenfold higher than that of PLGA 65:35 when both were formulated as blank microspheres (Table II). The presence of similar amounts of risperidone within polymer matrices reduces this difference in degradation half-life and the degradation rate of risperidone 65:35 microspheres that resulted only about twofold faster than risperidone 85:15 microsphere (Table II). Obviously, these could

Table II. PLGA Degradation Rate Constants (k_{obs}) and Degradation Half-Time ($t_{1/2}$) for Risperidone and Blank Microspheres

Formulation code	$k_{obs} \times 10^{-3}$ (days^{-1})	$t_{1/2}$ (days)
Risperidone A	14.6	20.6
Blank A	5.8	51.8
Risperidone B	7.5	39.9
Blank B	0.6	487.5

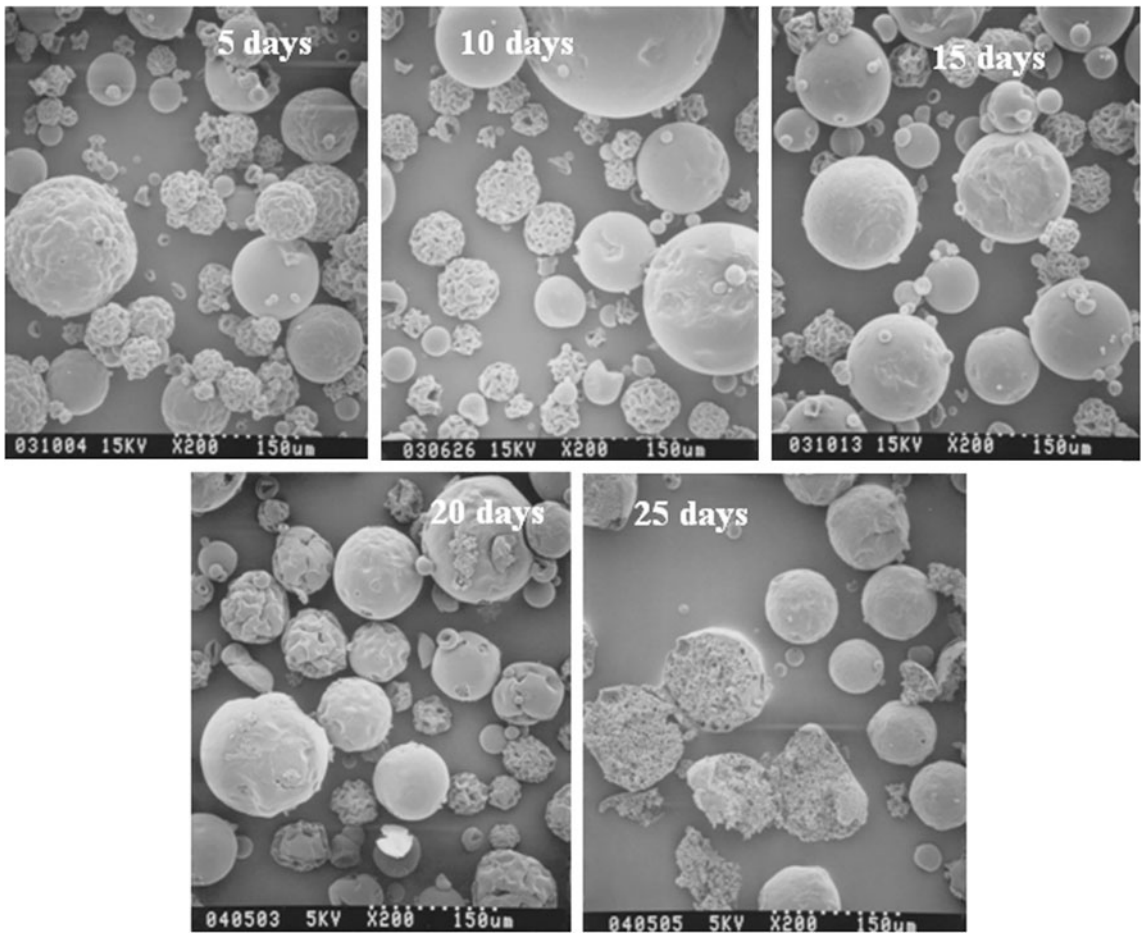

Fig. 4. SEM photomicrographs of risperidone A microspheres after 5, 10, 15, 20 and 25 days incubation in 0.02 M PBS containing 0.02% Tween® 80 at 37°C

happen if the risperidone release is minimal during early stages of incubation. Literature data are consistent with this hypothesis (11,18). For instance, Risperidal® CONSTA® showed the classical triphasic release pattern with a low burst effect (≤3.5%), a latent period of 4 weeks with no release, and the preponderant drug release between weeks 4–6. Counter intuitively, massive polymer degradation occurred (*i.e.*, Mw drop of about 80%) during the latent phase with no risperidone release (18).

It is possible to identify two effects of a tertiary amine drug substance on polymer degradation. Risperidone could react with carboxyl chain ends and reduce acid autocatalysis and degradation rate as demonstrated by Ara *et al.* (19) for PLGA matrices filled with inorganic basic compounds. Calcium carbonate and other inorganic salts, exerting a buffer role into the matrix, shifted the inner-particle pH toward neutral value, neutralizing the acidic microenvironment created by degradation byproducts concentrated within microparticles. As a function of their solubility and pK_a, these inorganic salts effectively delayed any appreciable degradation as compared with the unloaded PLGA (19).

However, in this specific case, results suggest the second interaction mechanism (*i.e.*, shift of the microenviroment pH toward basic values with faster hydrolysis) as the most reliable. In fact, polyester hydrolysis can be described by an autocatalytic degradative mechanism, the kinetics of which is a function of pH (20) and literature documented that faster hydrolysis of ester bonds occurs in a basic environment (7–9,21). At early stages, PLGA microspheres tend to be a closed system in which hydration proceeds very fast (*i.e.*, within minutes; 22), even if a small amount of water is absorbed due to the hydrophobic nature of the polymer (23). Since risperidone loaded in the microspheres was higher than 20% by weight and only small amounts of water might be present (24), it can be conjectured that the entrapped risperidone formed a saturated solution within the matrix. Moreover, at the early stage, only few carboxyl end groups were available because of the high Mw of PLGA. The aforementioned conditions could reasonably cause a shift toward basic values of inner-particles pH (25). This situation is supposed to last until a significant mass loss occurs increasing porosity of the matrix and permitting the exchange of buffering ions and risperidone molecules. On the other hand, the tertiary amine functional group in risperidone could cause basic catalysis and thus accelerate the degradation process.

The phenomena described above could occur over time; but in the case of risperidone-loaded microspheres, the drug content and matrix characteristics were favorable to create the aforementioned conditions probably during the first 5–10 days of degradation. Indeed, as shown in Fig. 2, polymer degradation proceeded according to a biphasic trend and the reduction of Mw was greatest within the first 5–10 days.

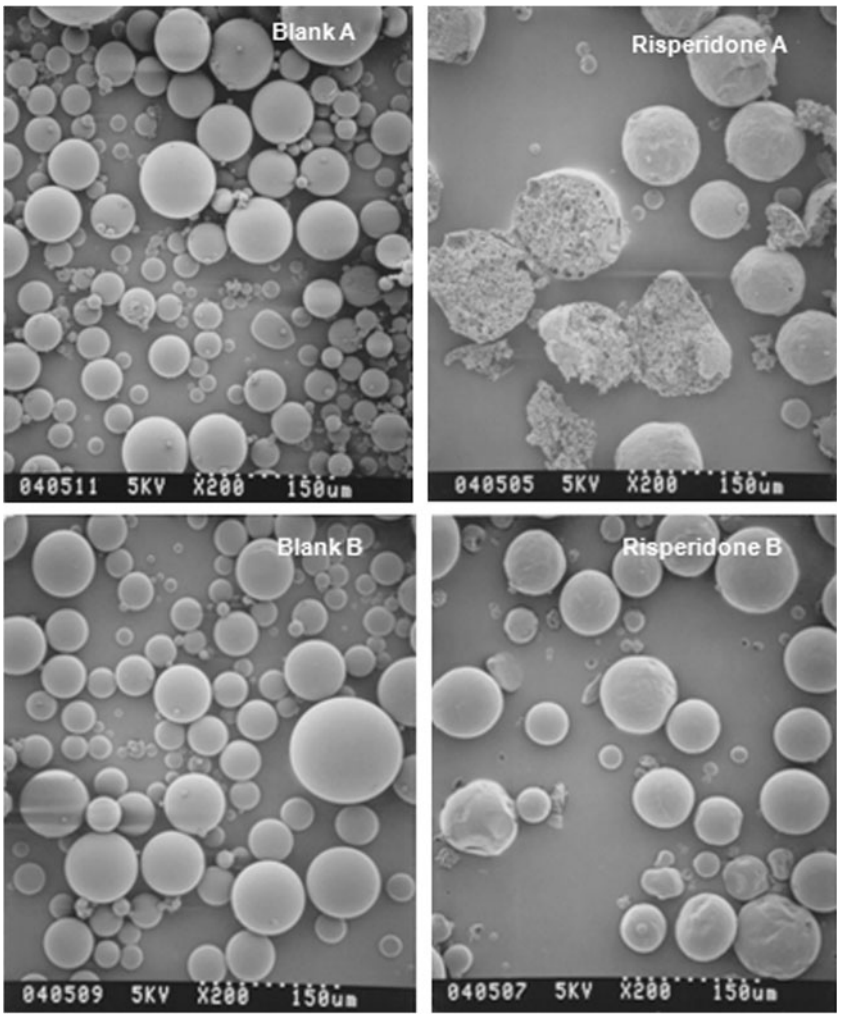

Fig. 5. SEM photomicrographs of all formulations after 25 days of incubation in 0.02 M PBS containing 0.02% Tween®80 at 37°C

In addition, it should be kept in mind that the massive Mw reduction recorded at early stages produced a substantial increase of carboxyl groups within the matrix (*i.e.*, oligomers and monomers) which could reverse the polymer internal microclimate.

The morphology of drug-loaded microspheres was affected by the presence of risperidone and resulted in mostly shriveled particles (Fig. 4). The intrabatch variation could be due to the different particle diameters within the size distribution which is one of the main factors influencing the diffusion

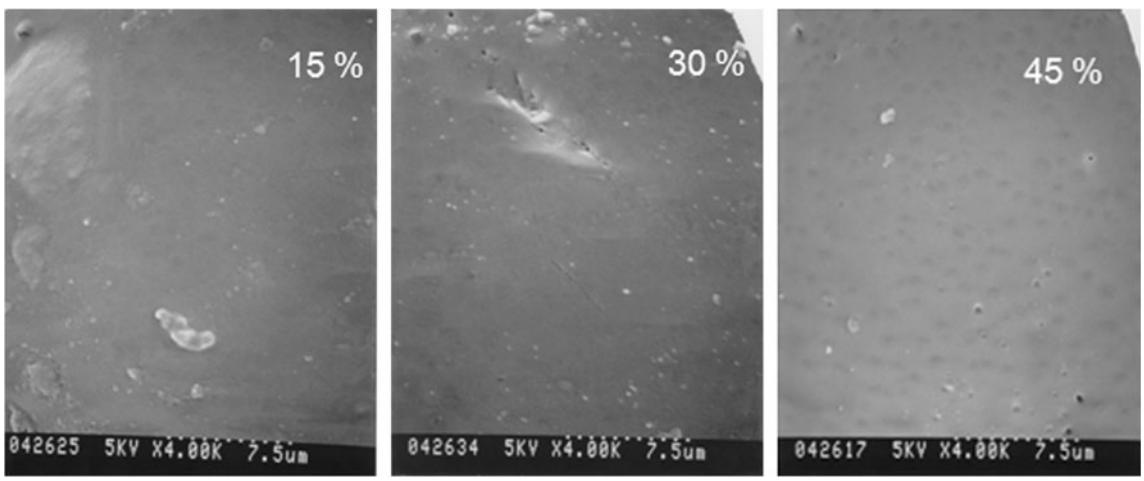

Fig. 6. Variation in surface morphology of blank A microspheres after 15 days of incubation in presence of 15%, 30%, and 45% of free risperidone solution

rate of drugs and acidic soluble oligomers and/or monomers, generated upon PLGA degradation, from the microparticles (24). With increasing microparticle size, the diffusion path lengths increase and, thus, the concentration gradients and mass transport rates decrease. For blank 85:15 microspheres, SEM examination reveals that the change in surface morphology was much slower; only after 15 days, the microspheres exhibited shriveled surface and small pores appeared on the surface of larger particles. The shriveled microspheres, which were the smaller microspheres, seem to dissolve or collapse in fragments after 20 days and are less evident at 25 days (data not shown).

These results on risperidone 65:35 microspheres seemed to correlate well with GPC data, in particular PI. In the very beginning, the microspheres looked shriveled, still maintaining their spherical shape, while after 25 days the matrices collapsed and released the drug as well as polymeric fragments.

Figure 5 provides an interesting comparison of the morphology of the particles for the four formulations. After 25 days, the blank microspheres still showed smooth surface and were relatively spherical. Porosity seemed to be more extensive at a lactide/glycolide ratio of 65:35.

When blank microspheres were incubated in free risperidone solutions, the formation of a shriveled surface was not evident as in the case of loaded microspheres, while the development of superficial porosity over time seemed to be concentration dependent (Fig. 6). This observation, even though questionable, was confirmed by GPC data. For instance, in the case of blank 65:35 microspheres only when incubated in 30% (*w*/*v*) and 45% free risperidone, the average molecular weight decreased from about 74,800 to 72,000 Da and to 67,000 Da in 15 days, respectively. No significant variations were observed at the lowest concentration. Obviously, the experimental setup did not reproduce the identical conditions present within the microsphere, as the free drug could not simulate the intimate contact between risperidone molecules and polymer chains, showing only a moderate catalysis of ester bond hydrolysis. Indeed, it can be reasonably assumed that the drug was not able to diffuse deep into the matrix to achieve the same concentration and the same molecular dispersion as in loaded microspheres.

CONCLUSION

The value of PLGA as a suitable polymer for several applications, namely drug delivery systems, medical devices, and tissue engineering, can be negated by the microenvironment effects of the active ingredient and excipients on polymer biodegradation and knowledge of instability issues should be a real asset to optimize the formulation on the basis of the desired performances. Analysis of PLGA molecular weight distribution shows that the presence of a tertiary amine, *i.e.*, risperidone, in the microspheres enhanced the hydrolytic degradation. The surface morphology of drug-loaded microspheres was affected by the presence of risperidone and resulted in shriveled microspheres in which there appeared to be an intrabatch variation with the larger microspheres being less shriveled than the smaller ones.

Since this phenomenon could lead to obvious consequences on drug release and affect microsphere performances, the physicochemical characteristic of the loaded drug should be considered as relevant as the features of the polymer in designing biodegradable dosage forms.

REFERENCES

1. Edwards NC, Locklear JC, Rupnow MFT, Diamond RJ. Cost effectiveness of long-acting risperidone injection *versus* alternative antipsychotic agents in patients with schizophrenia in the USA. PharmacoEconomics. 2005;23:75–89.
2. Altamura AC, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E. Intramuscolar preparations of antipsychotic: used and relevance in clinical practice. Drugs. 2003;63:493–512.
3. Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. CNS Drugs. 2004;18(2):113–32.
4. Miyajima M, Koshika A, Okada J, Kusai A, Ikeda M. Factors influencing the diffusion-controlled release of papaverine from poly (L-lactic acid) matrix. J Control Rel. 1998;56:85–94.
5. Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Ad Drug Del Rev. 1997;28:5–24.
6. Mauduit J, Bukh N, Vert M. Gentamycin/poly(lactic acid) blends aimed at sustained release local antibiotic therapy administered per-operatively. I. The case of gentamycin base and gentamycin sulfate in poly(D,L-lactic acid) oligomers. J Control Rel. 1993;23:209–20.
7. Maulding HV, Tice TR, Cowsar DR, Fong JW, Pearson JE, Nazareno JP. Biodegradable microcapsules: acceleration of polymeric excipient hydrolytic rate by incorporation of a basic medicament. J Control Rel. 1986;3:103–17.
8. Cha Y, Pitt CG. The acceleration of degradation controlled drug delivery from polyester microspheres. J Control Rel. 1989;8:259–65.
9. Kishida A, Yoshioka S, Takeda Y, Mitsuru M. Formulation-assisted biodegradable polymer matrices. Chem Pharm Bull. 1989; 37:1954–6.
10. D'Souza SS, Jabar AF, Giovagnoli S, Richey T, Thanoo C, DeLuca PP. Development and evaluation of long-acting microsphere dosage forms of risperidone. AAPS PharmSci. 2003; 5(S1)
11. Rawat A, Stippler E, Shah VP, Burgess DJ. Validation of USP apparatus 4 method for microsphere *in vitro* release testing using Risperdal® Consta®. Int J Pharm. 2011;420:198–215.
12. Schoubben A, Blasi P, DeLuca PP. Effect of agitation regimen on the *in vitro* release of leuprolide from poly(lactic-co-glycolic) acid microparticles. J Pharm Sci. 2012;101:1212–20.
13. Dorati R, Colonna C, Genta I, Modena T, Conti B. Effect of porogen on the physico-chemical properties and degradation performance of PLGA scaffolds. Polym Degrad Stab. 2010;95:694–701.
14. Park TG. Degradation of poly(lactic-co-glycolic acid) microspheres: effect of copolymer composition. Biomaterials. 1995;15:1123–30.
15. Ding AM, Schwendeman SP. Determination of water-soluble acid distribution in poly(lactide-co-glycolide). J Pharm Sci. 2004;93:322–31.
16. Farrar D. Modeling of the degradation process for bioresorbable polymers. In: Buchanan F, editor. Degradation rate of bioresorbable materials, prediction and evaluation. New York: Taylor & Francis; 2008. p. 183–203.
17. Cilurzo F, Selmin F, Minghetti P, Montanari L. Design of methylprednisolone biodegradable microspheres intended for intra-articular administration. AAPS PharmSciTech. 2008;9:1136–42.
18. Ramstack JM, Grandolfi GP, Mannaert E, D'Hoore P, Lasser RA. Risperdal CONSTA™: prolonged-release injectable delivery of risperidone using Medisorb® microsphere technology. AAPS PharmSci. 2002; 4(S1).
19. Ara M, Watanabe M, Imai Y. Effect of blending calcium compounds on hydrolytic degradation of poly(DL-lactic acid-co-glycolic acid). Biomaterials. 2002;23:2479–83.
20. Li SM, Garreau H, Vert M. Structure–property relationships in the case of the degradation of massive aliphatic poly-(α-hydroxy acids) in aqueous media, part 1. J Mater Sci: Mater Med. 1990;1:123–30.

21. Burnbaum DT, Brannon-Peppas L. Molecular weight distribution changes during degradation and release of PLGA nanoparticles containing epirubicin HCl. J Biomater Sci Polymer Edn. 2003;14:45–61.
22. Batycky RP, Hanes J, Langer R, Edwards DA. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J Pharm Sci. 1997;86:1464–77.
23. Blasi P, D'Souza SS, Selmin F, Deluca PP. Plasticizing effect of water on poly(lactide-co-glycolide). J Control Rel. 2005;108:1–9.
24. Fu K, Pack DW, Klibanov AM, Langer R. Visual evidence of acidic environment within degrading poly(lactic-co-glycolic acid) (PLGA) microspheres. Pharm Res. 2000;17:101–6.
25. Houcin ML, Neuenswander SA, Topp EM. Effect of excipients on PLGA film degradation and the stability of an incorporated peptide. J Control Rel. 2007;117:413–20.