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In vitro evaluation of sol–gel processed spray dried silica gel microspheres as carrier in controlled drug delivery

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Abstract

The objective of this study was to evaluate sol–gel-derived spray dried silica gel microspheres as carrier material for dexmedetomidine HCl and toremifene citrate. The drug was dissolved in sol–gel processed silica sol before spray drying with Büchi laboratory scale equipment. Microspheres with a low specific surface area were spherical by shape with a smooth surface without pores on the external surface. The particle size distribution was quite narrow. The in vitro release of toremifene citrate and dexmedetomidine HCl showed a dose-dependent burst followed by a slower release phase, that was proportional to the drug concentration in the concentration range between 3.9 and 15.4 wt.%. The release period for toremifene citrate was approximately 10 days and for dexmedetomidine HCl between 7 and 50 days depending on drug concentration. Spray drying is a promising way to produce spherical silica gel particles with a narrow particle size range for controlled delivery of toremifene citrate and dexmedetomidine HCl.

Keywords: Spray drying; Drug release; Silica gel microspheres; Dexmedetomidine HCl; Toremifene citrate

1. Introduction

Microparticulate polymeric delivery systems have been widely investigated for sustained and targeted delivery of biologically active substances (Jain et al., 1998). The production technology mainly employs the solvent evaporation/solvent extraction process (Okada et al., 1994). Spray drying has been used in pharmaceutical technology since the early 1940s. It is a useful method because it offers a means to predetermine properties such as particle size, flowability, porosity and retention of activity of heat sensitive pharmaceuticals (Broadhead et al., 1992). The particles formed are in the micrometer size range. From a manufacturing viewpoint, spray drying offers the advantage of being a single-step process which can readily be scaled up. It is already widely used for preparation of microparticles from biodegradable

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polyester polymers (Wagenaar and Müller, 1994; Clarke et al., 1998). One example of a commercial parenteral product utilising these polymers as drug carrier, is Parlodel® (Sandoz) with bromocryptine.

Silica xerogels have been studied as carrier materials for controlled drug delivery. Unger with co-workers (Unger et al., 1983) has shown that basic drugs release in a sustained manner whereas neutral drugs are released very quickly from silica xerogel. In earlier studies silica xerogel was used as monoliths or crushed particles (Nicoll et al., 1997; Böttcher et al., 1998; Kortesuo et al., 1999; Ahola et al., 2000). Production of monoliths is time consuming and drying in particular, may cause cracking. Crushed silica xerogel particles are irregular in shape and release the active agent quite quickly (Nicoll et al., 1997). These facts led us to evaluate spray drying as a production method for silica gel microspheres with a narrow particle size range and to evaluate these microspheres as a carrier for controlled parenteral administration of drugs.

This paper describes the preparation sol–gel derived, injectable silica gel microspheres containing toremifene citrate or dexmedetomidine HCl. Furthermore, the purpose of this work is to study, how physicochemical properties of drugs affect the release profiles. Triphenylenethylene antiestrogen, toremifene citrate, and an imidazole derivative, dexmedetomidine HCl are both lipophilic drugs, but with different physicochemical properties (pK_a value, water solubility, log P, molecular weight).

2. Materials and methods

2.1. Preparation of silica gel microspheres

2.1.1. Microspheres containing toremifene citrate

Silica sol was prepared by the hydrolysis and polycondensation of tetraethoxysilane (TEOS, Aldrich) with distilled water and acetic acid in a mole ratio of 1.0:14.2:0.5 at room temperature. The pH of the sol at time of spray drying was 2.4. Toremifene citrate (Orion, Turku, Finland) was added to the clear hydrolysed silica sol at a concentration of 5, 10, 20, 25 and 30 mg/g. The mole ratio of the TEOS:drug varied between 1:0.0038 and 1:0.023.

2.1.2. Microspheres containing dexmedetomidine hydrochloride

Silica sol was prepared with a mole ratio of TEOS: H_2O: HCl, 1.0:14.2:0.003. The pH of the sol was 2.3. Dexmedetomidine hydrochloride (Orion) concentrations in silica sol were 5, 7.5, 10, 12.5, 15 and 20 mg/g. The mole ratio of the TEOS:drug varied between 1:0.0098 and 1:0.039.

Hydrolysed silica sol was spray dried with a mini spray dryer (B-191, Büchi Labortechnik AG, Switzerland). Process parameters were the following for all batches, inlet temperature 134°C, pump 16, aspirator setting 90, spray-flow 600 NL/h and pump setting 2–5 ml/min. A 0.77-mm nozzle was used throughout the experiments.

Some of the physicochemical properties of toremifene citrate and dexmedetomidine HCl are listed in Table 1.

Table 1
Physicochemical parameters of toremifene citrate and dexmedetomidine HCl

Drug	Molecular weight	Log P	pK_a	Solubility (mg/ml) in 0.5% SDS/SBF-buffer at pH7.4 at 40°C
Toremifene citrate	598.09	3.38	8.0	3.7
Dexmedetomidine HCl	236.7	2.8	6.9	>100

2.2. In vitro dissolution test

The dissolution profiles (each data point is the mean of three values) were studied using the USP XXIII dissolution apparatus II (paddle method, Sotax AT6, Basel, Switzerland) at constant temperature (37°C). Simulated body fluid (SBF, pH 7.4) containing 0.5 wt.% sodiumlaurylsulphate (SDS) was used as dissolution medium for toremifene citrate and dexmedetomidine HCl microspheres. SDS was used to increase the solubilisation of sparingly water-soluble toremifene citrate. SBF was prepared by dissolving reagent grade NaCl (136.8 mM), $NaHCO_3$ (4.2 mM), KCl (3.0 mM), $K_2HPO_4 \times 3H_2O$ (1.0 mM), $MgCl_2 \times 6H_2O$ (1.5 mM), $CaCl_2 \times 2H_2O$ (2.5 mM) and Na_2SO_4 (0.5 mM) in distilled water. The solution was buffered at pH 7.4 with tris(hydroxymethyl)aminomethane (50mM) and hydrochloric acid.

The volume of the dissolution medium was 250 ml and the amount of microspheres in the dissolution test was approximately 47.5 mg (S.D. 4.5). At each sample interval, a sample of one millilitre was withdrawn from each flask and replaced immediately with an identical volume of fresh medium. The rotation speed was 50 rpm and the temperature 37°C.

The absorbance values of the dissolution samples were measured on an UV-visible spectrophotometer (Hewlett Packard 845/A, USA) at the maximum absorbance of toremifene citrate (A_{278}) and dexmedetomidine HCl (A_{220}). The degradation of silica gel was determined by measuring dissolved $Si(OH)_4$ spectrophotometrically as a molybdenum blue complex at A_{820}(Koch and Koch-Dedic, 1974).

2.3. Characterisation of microspheres

Volumetric particle size and size distribution of the microspheres was obtained by laser diffractometry using Sympatec–Helos laser diffraction equipment (Sympatec GmbH, Germany). The samples were dispersed in water and treated with ultrasound equipment for 5 s to ensure a homogenous dispersion. The measurements were carried out using a 50 or 100-mm lens. The results are the average of five withdrawals.

The shape and surface morphology of the microspheres was determined from micrographs taken with scanning electron microscope (SEM-EDX Stereoscan 360, Cambridge Instruments, UK).

The specific surface area was measured using the BET technique based on nitrogen gas adsorption (Coulter SA3100, Coulter, Miami, FL). The samples were vacuum dried for 20 h in 25°C.

3. Results

3.1. Preparation of microspheres

Toremifene citrate and dexmedetomidine HCl were dissolved in the silica sol before spray drying. Theoretical concentration of toremifene citrate or dexmedetomidine HCl in spray dried microspheres is shown in Table 2. It was assumed that the amount of drug added to the solution was entirely incorporated into the microspheres. The microsphere yield of toremifene citrate batches was in the range of 42.8–77.7% as calculated from the theoretical amount of silica gel (SiO_2). Dexmedetomidine HCl microparticles were produced with quite a low yield (20.6–49.2%).

Examination by scanning electron microscope showed that the silica microspheres were, to some extent, in clusters or aggregated (Fig. 1). Microspheres with dexmedetomidine HCl formed more aggregates than microspheres with toremifene citrate. All microspheres were spherical and had a smooth surface without visible pores on the external surface (Fig. 1). The particle size distribution of microspheres was quite narrow (Table 2). The 10% fractile varied between 1.0 and 2.2 μm. The 90% fractile for toremifene citrate containing microspheres were lower (between 13.1 and 25.7 μm) than that of dexmedetomidine HCl containing microspheres (between 25.3 and 41.6 μm).

The specific surface area of microspheres presented as 5-point surface area was measured for microspheres containing 15.4 wt.% toremifene citrate and 11.6 wt.% dexmedetomidine HCl (Table 2). The specific surface area of

Table 2
Particle size, yield and specific surface area of silica xerogel microspheres containing toremifene citrate or dexmedetomidine HCl[a]

Toremifene citrate			
	Particle size (μm) D10%–D90%	Yield %	Specific surface area, m^2/g
23.1 wt.%	1.5–18.6	75.7	n.d.
19.3 wt.%	1.5–21.0	42.8	n.d.
15.4 wt.%	1.4–13.1	77.7	1.19
7.7 wt.%	2.10–25.7	65.4	n.d.
3.9 wt.%	1.5–14.9	62.3	n.d
Dexmedetomidine HCl			
	Particle size (μm) D10%–D90%	Yield %	Specific surface area, m^2/g
15.4 wt.%	2.2–36.0	20.6	n.d.
11.6 wt.%	1.2–39	45.4	0.77
9.6 wt.%	1.0–25.3	28.5	n.d.
7.7 wt.%	1.31–41.6	49.2	n.d.
5.8 wt.%	1.1–40.6	21.5	n.d.
3.9 wt.%	1.43–29.6	30	n.d.

[a] n.d., not determined.

dexmedetomidine HCl microspheres was 0.77 m^2/g and of toremifene citrate microspheres 1.19 m^2/g.

3.2. Release of toremifene citrate and dexmedetomidine HCl and degradation of silica gel microspheres

The in vitro release of toremifene citrate and dexmedetomidine HCl showed an initial, dose-dependent burst followed by a slower release phase (Figs. 2 and 3). The slower release phase was also proportional to the drug concentration. The plot of slower release was linear with respect to the square root of time, when toremifene citrate concentration was between 3.9 and 15.4 wt.% (r between 0.989 and 0.998). Dexmedetomidine HCl release was linear with respect to the square root of time between drug concentration 5.8 and 15.4 wt.% (r between 0.99 and 0.97).

Silica gel microspheres degraded slower than toremifene citrate or dexmedetomidine HCl were released (Fig. 4). After 30 h the amount of silica gel left was about 90% for microspheres containing 7.7 wt.% toremifene citrate and 96% for microspheres containing 7.7 wt.% dexmedetomidine HCl.

4. Discussion

Sol–gel derived silica xerogel has a number of properties that make it a promising controlled release carrier of biologically active agents; it is non-toxic, biocompatible and biodegradable (Radin et al., 1998; Kortesuo et al., 1999). Furthermore the sol–gel-derived silica xerogels are processed at room temperature and the technology does not require complex equipment. Silica xerogel has earlier been studied in the form of monoliths or crushed particles (Nicoll et al., 1997). Since production of silica monoliths is time consuming, spray drying offers a promising technique for producing microspheres for parenteral delivery.

Microspheres had a narrow particle size distribution, but were to some extent aggregated. The aggregation tendency after atomisation may be due to attractive forces between hydrophilic, probably humid microspheres. Adhesion of microparticles to the inside wall of the spray-drier cylinder can also produce an aggregation of the microparticles (Takada et al., 1995). The specific surface area of the microspheres seems to be very low when compared with monoliths prepared using the high water content sols (Tan et al., 1996;

Ahola et al., 2000). Silica gel microspheres seem to have a condensed structure that probably leads to slow degradation of the matrix and release of the drug, although the surface area to volume ratio (SA/V) of the microspheres is higher than that of monoliths. In earlier studies increase in the surface to volume ratio (SA/V) by crushing monoliths to particles, enhanced the release rate of active agent (Nicoll et al., 1997; Böttcher et al., 1998).

Toremifene citrate and dexmedetomidine HCl release showed a dose-dependent burst effect followed by a slower release, which was also proportional to the drug concentration. The increased initial burst at higher drug concentrations may be associated with a sufficiently high amount of drug close to the surface of the silica gel matrix. When the drug was depleted from the surface the silica gel degradation again becomes the limiting factor for the release of toremifene citrate or dexmedeto-

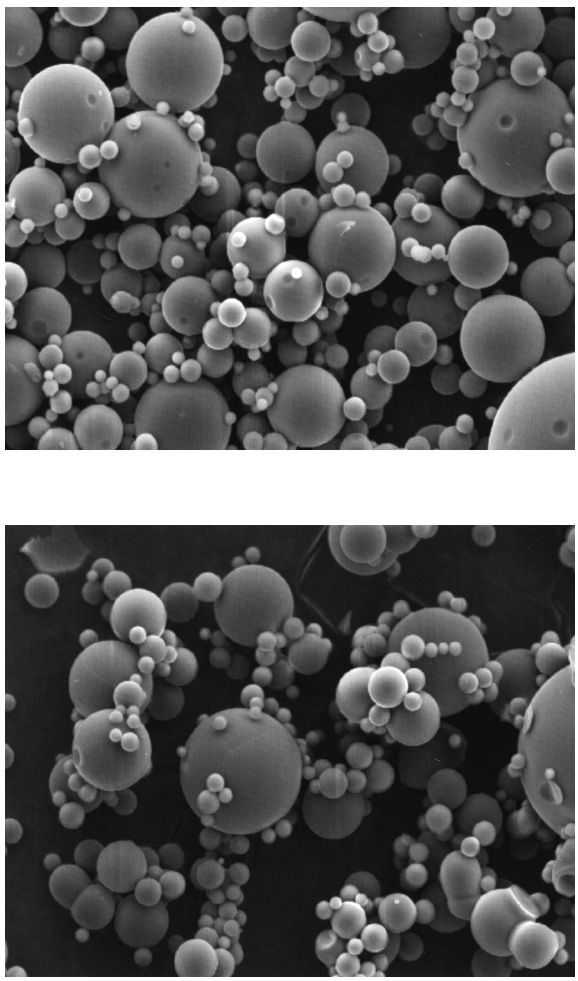

Fig. 1. Scanning electron microgpraphs of silica gel microspheres with 7.7 wt.% toremifene citrate (A) and 7.7 wt.% dexmedetomidine HCl (B). Original magnification × 2500.

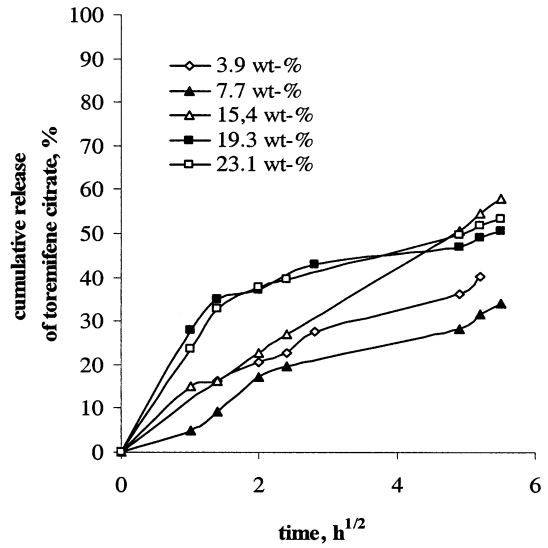

Fig. 2. The release profiles of toremifene citrate from silica gel microspheres with a drug concentration of 3.9, 7.7, 15.4, 19.3 and 23.1 wt.%.

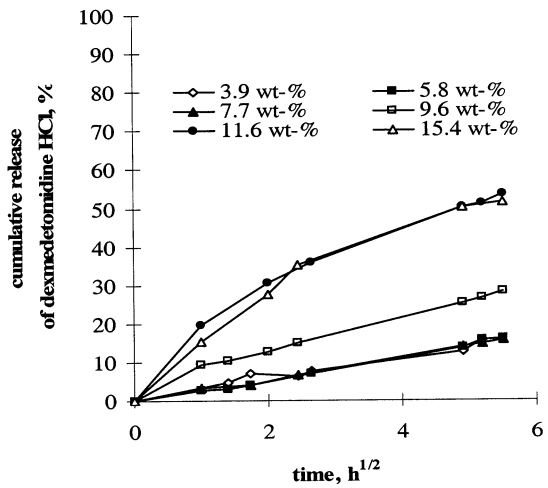

Fig. 3. The release profiles of dexmedetomidine HCl from silica gel microspheres with a drug concentration of 3.9, 5.8, 7.7, 9.6, 11. 6 and 15.4 wt.%.

midine HCl. However after the burst the release of toremifene citrate and dexmedetomidine HCl were linear with respect to the square root of time, when the drug concentration was15 wt.% or lower. In earlier study release of toremifene citrate from silica xerogel monoliths was proportional to the drug concentration between 11.5 and 34.4 wt.% (Ahola et al., 2000). The concentration of drug that can be incorporated into silica gel microspheres is considerably lower than in silica xerogel monoliths possibly due to the condensed, non-porous structure of spray dried silica gel.

Dexmedetomidine HCl released slower than toremifene citrate from the silica gel matrix at drug concentrations lower than 11.4 wt.% and at the same rate as toremifene citrate, when the drug concentration was 11.4 wt.% or more. The duration of release for toremifene citrate was about 10 days and varied between 7 and 50 days for dexmedetomidine HCl. In an earlier study toremifene citrate released approximately in 10 days from silica xerogel monoliths processed from sol with water:TEOS molar ratio 14.2:1 (Ahola et al., 2000). The difference in release characteristics is probably due to the different physicochemical properties of dexmedetomidine HCl and toremifene citrate. Being basic drugs, they are both adsorbed to the negatively charged SiO_2 and released in a sustained manner (Unger et al., 1983). Basic drugs also act as external catalysts, thus increasing the release rate of the drug and the degradation of the silica gel matrix in the concentration and pK_a dependent manner (Unger et al., 1983). In addition to ionic properties, molecular weight, water solubility and lipophilicity may also influence the release behaviour. Toremifene citrate, which is more lipophilic and a larger molecule than dexmedetomidine HCl, may be concentrated on the air/sol interface of hydrophilic silica sol during spray drying. More controlled release of lipophilic drugs may be achieved by using organomodified metal alkoxides, which increase the hydrophobicity of the silica gel matrix (Böttcher et al., 1998).

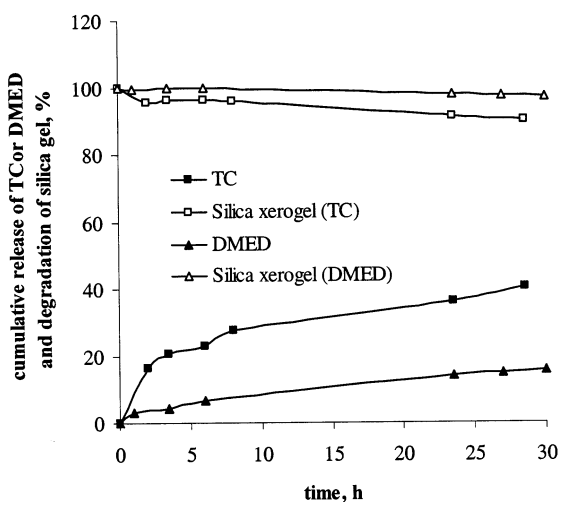

Fig. 4. In vitro release of toremifene citrate (TC) and dexmedetomidine HCl (DMED) and degradation of silica gel microspheres containing 7.7 wt.% of drug.

Toremifene citrate and dexmedetomidine HCl were released faster than silica gel microspheres degraded. Therefore the dissolution of toremifene citrate and dexmedetomidine HCl is deemed to occur due to both diffusion and erosion of the matrix. Compared with silica xerogel monoliths spray dried silica gel degrades more slowly (Ahola et al., 2000). During spray drying at an increased temperature (135°C) the hydrolysed silica sol is very quickly dried into small particles. This probably results in a more condensed structure comparable to the structure of sintered silica xerogels.

In conclusion, spray drying is a promising method for preparation of sol–gel derived silica gel microspheres for controlled drug release. Physicochemical properties (pK_a, lipophilicity, water solubility, molecular weight) of the drug affected the release rate. Toremifene citrate and dexmedetomidine HCl release were proportional to the drug concentration in the range of 3.9 to 15.4 wt.%. The duration of release for dexmedetomidine HCl was significantly longer than that for toremifene citrate at drug concentrations lower than 11.4 wt.%. This study shows that controlled release of toremifene citrate and dexmedetomidine HCl was achieved at drug concentrations lower than 15.4 wt.%.

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