The Preparation of Solid Core Drug Delivery Systems (SCDDS) For The Biomolecular Delivery

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ABSTRACT

In this study a solid core drug delivery system (SCDDS) is prepared with silica as a model core, fatty acid as a shell material and supercritical fluid technology as the process. SCDDS can be developed as targeted delivery systems or as sustained/controlled release platforms. SCDDS are coated with fatty acids using supercritical fluid technology (SCFT), allowing the creation of nano-particulate and micro-particulate delivery systems. The operating conditions of low temperature and pressure used to formulate these systems make it attractive for pharmaceutical research, especially for thermo-labile or sensitive bio-materials.

INTRODUCTION

Recent developments in drugs based on proteins and peptides have led to an increase in the search of novel drug delivery systems [1]. Advancement in biotechnology allows production of protein and peptide based drugs easily and economically however, delivery of these molecules is still a challenge. There are a number of physiochemical and biological barriers which hamper proteins and/or peptides to be used as drug molecules which can be summarised in four main points as follows [2, 3];

I. Poor intrinsic permeability across biological membrane due to their hydrophilic nature and large molecular size.
II. Short residence time of dosage form at the absorption sites.
III. Susceptibility to enzymatic attack by intestinal proteases and peptidases.
IV. Chemical instability, including tendencies to aggregate and/or non-specifically adsorbed to a variety of physical and biological surfaces.

Most conventional drug delivery systems for proteins and peptides are based on the polymers or lipid vesicles [4]. Although it is possible to synthesise biocompatible chemicals for drug delivery, systems prepared with them possess numerous drawbacks. Polymeric drug delivery systems are prone to premature release of the drug leading to release in non-targeted tissues which remain a matter of concern. To overcome these problems research has focused on the development of structurally stable drug delivery systems to deliver a relatively large amount of drug molecules to targeted tissues or even intracellular organelles.

A solid core drug delivery system involves adsorption of drug onto a solid surface and addition of a coating to achieve sustained release. In this approach a protein or peptide is immobilised onto the solid surface to provide greater stability and a polymer or lipid coating/encapsulation to ensure sustained release [5-7]. In SCDDS, depending on the choice of shell material/coating, site specific release can also be achieved [7, 8]. Fatty acids as shell material in SCDDS have been studied for colon-specific delivery of vancomycin, where

thermally cross-linked BSA was used as a core and vancomycin adsorbed particles were coated by spray drying [6-7]. A schematic of SCDDS is shown in figure 1.

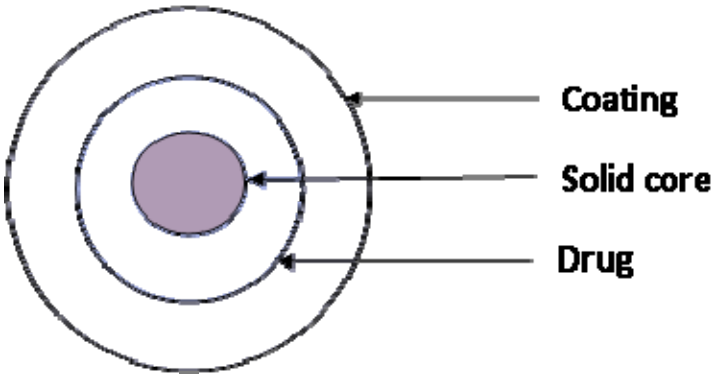


Figure 1: Schematic presentation of the solid core drug delivery system.

This paper discusses the preparation of SCDDS using silica as a solid core and bovine serum albumin (BSA) as model drug. Stearic, palmitic, myristic and lauric acid were used as coating materials and the coating was performed in liquid (lq) or supercritical carbon dioxide ($SCCO_2$).

MATERIALS AND METHOD

Fatty acids with the purity of more than 98% were purchased from Acros scientific (stearic and palmitic acid) or Sigma-Aldrich (Myristic and Lauric acid). Silica (≥99.0%) and Bovine serum albumin (≥96.0%) were obtained from Alfa Aesar and Fluka respectively. All chemicals were used as provided and without any further purification.

The solubility or phase change of lauric, myristic, palmitic and stearic fatty acids were determined in lq and $SCCO_2$. The method and results of the phase behaviour of fatty acids is published elsewhere [9].

1.5 mg/ml BSA solution was prepared in pH 5.0 phosphate/citrate buffer. The absorbance of the BSA solution was measured using UV spectroscopy at 280 nm and the exact concentration was calculated. 10 ml of the 1.5 mg/ml BSA solution was transferred to a 15 ml centrifuge tube containing 500 mg of silica. The sample was transferred to a tube rotator at 25 rpm and left for 8-10 hours at room temperature to ensure maximum adsorption. The sample was centrifuged for 20 minutes at 6000 rpm after the incubation period. The resultant precipitate after centrifuged was freeze dried for 48 hours to remove solvent and to obtain dry BSA-Si.

Coating of BSA-Si was performed simply by the deposition of fatty acid melt onto these particles. For coating experiments; a mixture of BSA-Si and fatty acid was introduced into the reaction vessel. Liquid CO_2 was pumped inside the cell by a high pressure pump until the desired pressure value (72 – 110 bar) was achieved. The cell was electrically heated to 30 – 55 ^{o}C depending on the fatty acid and the mixture was left stirring once the required pressure and temperature was achieved. The system was depressurised after 15 minutes at a rate of 6-8

bar/minute. The coating was performed with different ratios of fatty acids (FA:BSA-Si - 0.1:1, 0.25:1, 0.5:1). Table 5.1 summarises the processing parameters used to coat BSA-Si particles with different fatty acids.

Fatty acid	Temperature (^{o}C)	Pressure (bar)	Time (min)
Lauric acid (LA)	30	72-75	15
Myristic acid (MA)	38	72-75	15
Palmitic acid (PA)	50	75-80	15
Stearic acid (SA)	55	105-110	15

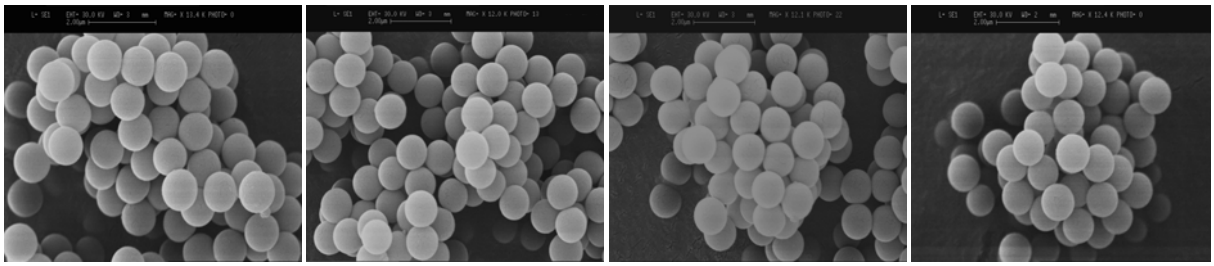
Table 1: Processing parameters for BSA-Si coating with fatty acid

Release of BSA from solid core drug delivery systems (SCDDS) was determined in pH 7.4 phosphate buffer saline (PBS) at room temperature.

RESULTS

Characterisation

SCDDS prepared with different fatty acids were characterised by XRD, DSC and solid state NMR (results not presented). XRD and DSC analysis indicated that no changes to the crystal structure of fatty acids took place due to the $SCCO_2$ processing. Solid state NMR analysis peaks confirmed the presence of fatty acids on the surface. It also suggested that BSA-Si particles were fully coated with fatty acids as peaks for BSA were not observed in any of the samples. Figure 2 presents micrographs of SCDDS prepared with different fatty acid.



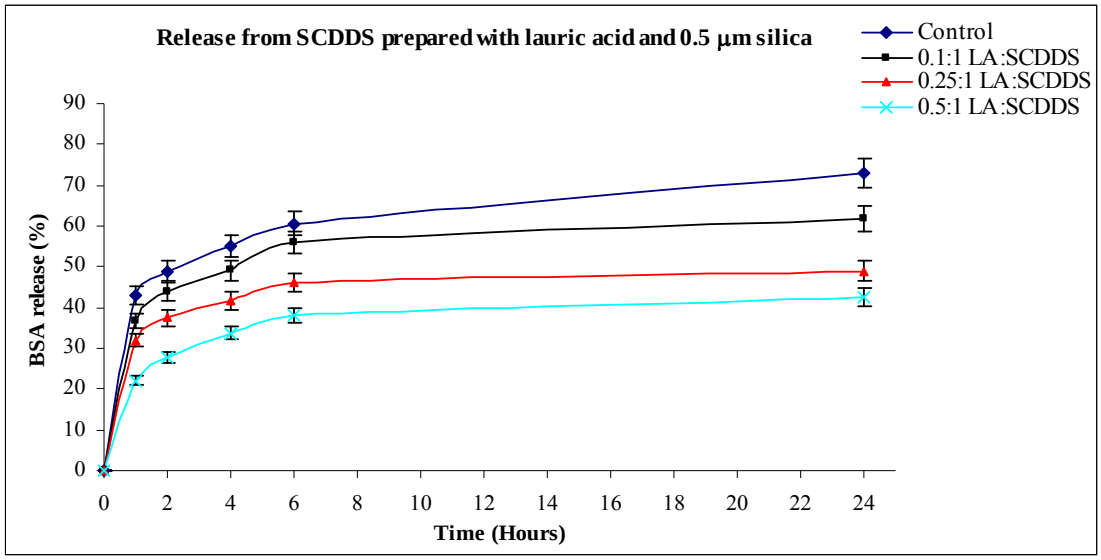
0.1:1 SA:SCDDS 0.1:1 PA:SCDDS 0.1:1 MA: SCDDS 0.1:1 LA:SCDDS

Figure 2: SEM micrographs of SCDDS prepared with different fatty acids [0.1:1 (FA:BSA-Si)]

Release studies

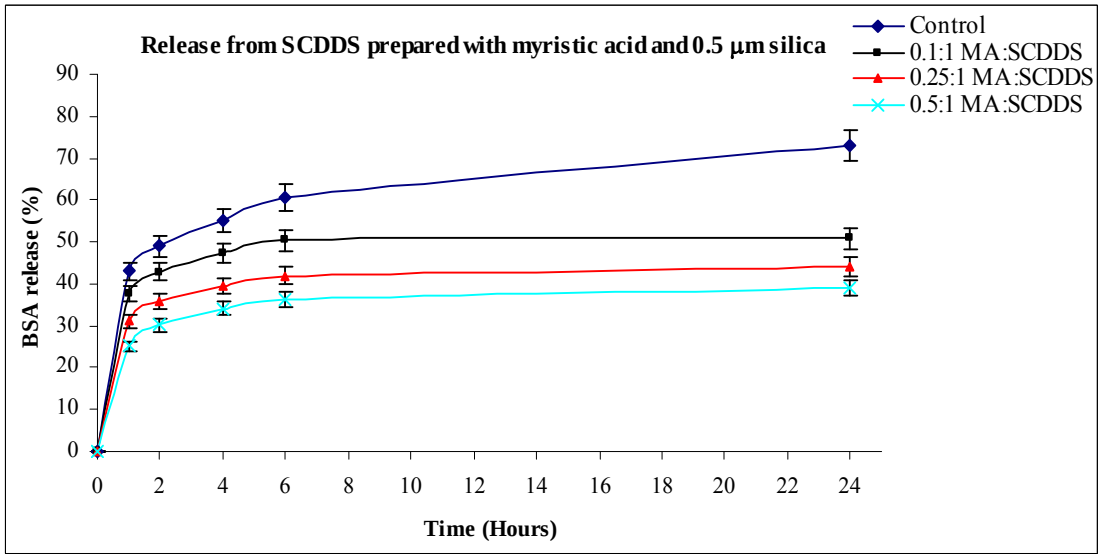
Release studies were performed at room temperature in PBS (pH 7.4). Figures 3-6 present release of BSA from SCDDS formulations.

Figures 3 presents the release of BSA in first 24 hours from SCDDS prepared with 0.5 μm silica and lauric acid. 0.1:1 LA:SCDDS formulation showed highest release in the group followed by 0.25:1 and then 0.5:1 LA:SCDDS. The percentage BSA release from 0.1:1 LA:SCDDS was found to be 37 % after first hours and 62 % after 24 hours. 0.5:1 LA:SCDDS provided a percentage BSA release of 32 % in first hour leading to 49 % after 24 hours period. The slowest release was obtained from 0.5:1 LA:SCDDS with only 22 % and 43 % after first and 24 hours respectively.



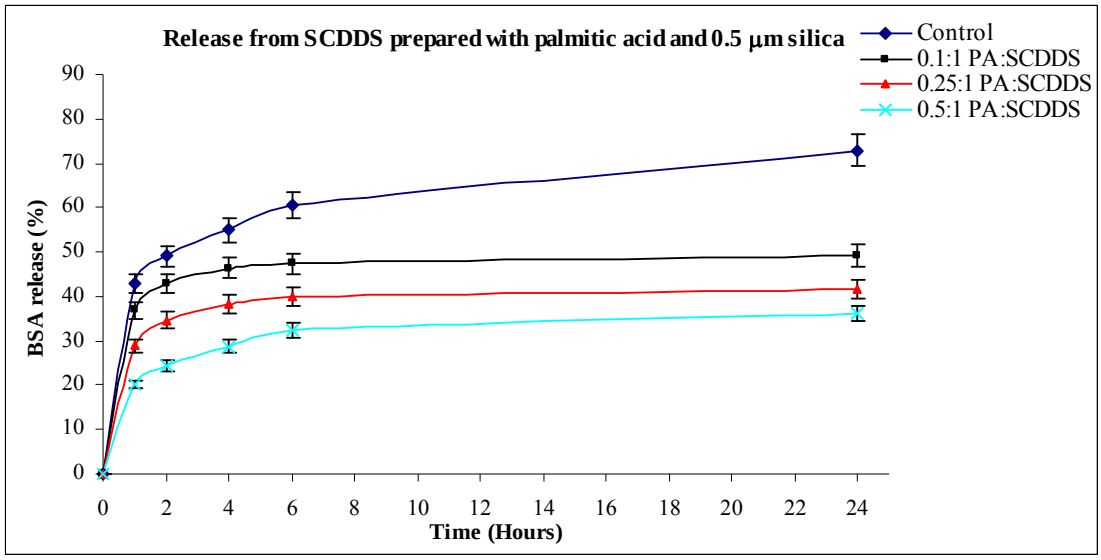
Figures 3: Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and lauric acid.

Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and myristic acid can be seen in figure 4. 0.1:1 MA:SCDDS gave a percent BSA release of 37 % after the first hour and 51 % after 24 hours. 0.25:1 MA:SCDDS provided a BSA release of 31 % after the first hour and 44 % after the 24 hours period. 0.5:1 myristic acid formulations provided BSA release of 25 % and 39 % after first and 24 hours respectively.



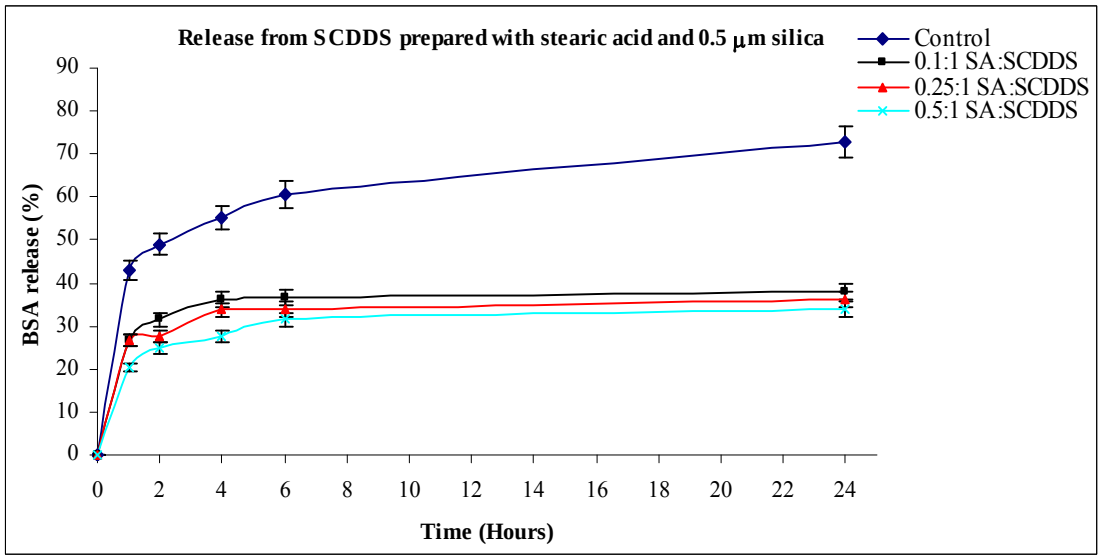
Figures 4: Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and myristic acid.

Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and palmitic acid is presented in figure 5.The BSA release from PA:SCDDS was found to be less than the lauric acid or myristic acid formulations. A release of 36 % was obtained in the first hour from 0.1:1 PA:SCDDS reaching 49 % after 24 hours. 0.25:1 and 0.5:1 PA:SCDDS provided a percentage BSA release of 29 % and 20 % in the first hour, 42 % and 36 % after 24 hours.



Figures 5: Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and palmitic acid.

SCDDS prepared with stearic acid (Figure 6) showed slowest release amongst all fatty acid formulations. Where, 0.1:1 SA:SCDDS provided a BSA release of 27 % in the first hour and 38 % after 24 hours. 0.25:1 SA:SCDDS provided similar release in the first hour but the percentage release of BSA in 24 hours was found to be 36 %. Only 20 % and 34 % of BSA was released from 0.5:1 stearic acid formulation after 1 and 24 hours respectively.



Figures 6: Release of BSA in first 24 hours from SCDDS prepared with 0.5 µm silica and stearic acid.

Figure 7 shows the release of BSA obtained in the extended 24 hours period after previously shown results (figures 3 to 6) in replenished PBS.

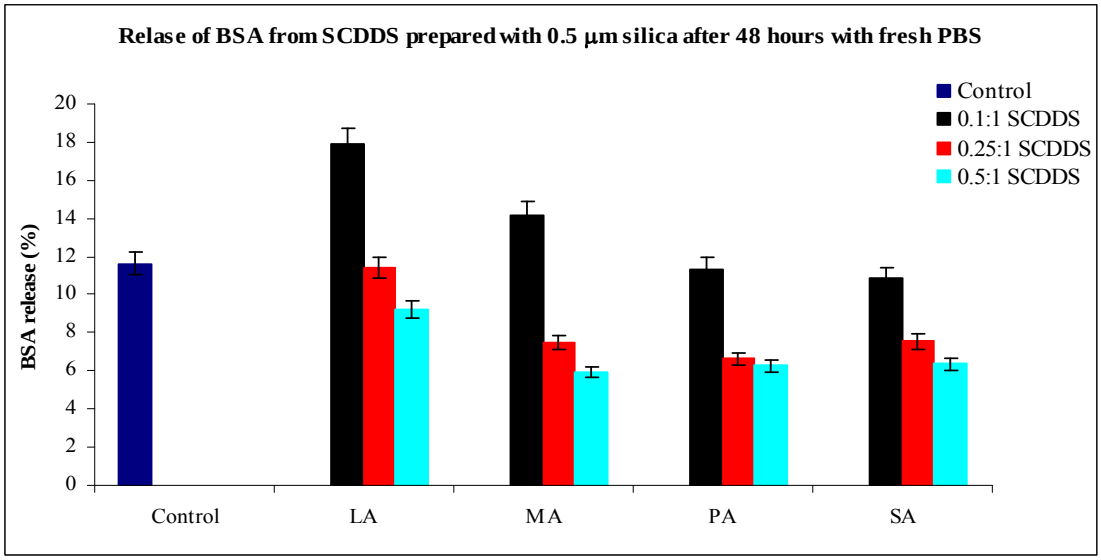


Figure 7: Release of BSA in 48 hours with fresh PBS from SCDDS prepared with 0.5 µm silica.

In this group, BSA release was in the range of 6 % to 18 % from SCDDS prepared with different fatty acids. As seen previously, lauric acid formulation showed the highest BSA release of 18 % (0.1:1), 11 % (0.25:1) and 9 % (0.5:1) in the fresh PBS after 24 hours. BSA release from myristic acid formulations was found to be 14 %, 8 %, and 6 % for 0.1:1, 0.25:1 and 0.5:1 formulations. Palmitic acid preparations provided a BSA release of 11 % for 0.1:1, 7 % for 0.25:1 and 6 % for 0.5:1 SCDDS. A subsequent BSA release of 11 %, 8 %, and 6 % for 0.1:1, 0.25:1 and 0.5:1 SA:SCDDS was obtained after initial 24 hours period in fresh PBS.

The release profiles of BSA from SCDDS suggest that release is dependent on the continuous erosion of fatty acid coating from the surface. It was also observed that release profiles obtained with different fatty acid formulations were significantly different. These variations in the release profiles can be explained by the differences in the solubility of fatty acids in water or PBS. Solubility of saturated fatty acids decreases in water as the carbon chain length increases [10]. The solubility of fatty acids has also been studied in pH 7.4 PBS and an increase in the solubility was observed specially for lauric and myristic acid in comparison to their solubility in water [11]. It was found that in pH 7.4 PBS solubility of lauric acid can be more than 200 mg/L and myristic acid solubility increases 3 folds to 6.9 mg/L. Authors were not able to quantify solubility of palmitic and stearic acid in PBS. However, they suggested that even though palmitic and stearic acid may not exist as a true solution in PBS, these can form liposomes up to the concentrations of more than 6 to 7 mg/L. This behaviour of liposome formation or aggregation can occur with all fatty acids which also means that a slow erosion of fatty acid coating can take place even above their solubility limits. Maximum release of BSA was obtained from lauric acid formulations in each group. The solubility behaviour of fatty acids supports the release pattern, where lauric acid formulations show the highest release followed by myristic, palmitic and stearic acid. It can also be clearly seen that release of BSA decreases substantially as the ratio of fatty acid increases in the formulation. This is because erosion or dissolution of the fatty acid from the surface of the coated particles becomes very slow once the solubility limit has been achieved in the given volume of PBS. The reason behind slow and less BSA release from SCDDS prepared with stearic acid is due to stearic acid having the lowest solubility amongst all fatty acids used in these experiments.

CONCLUSION

The strategy of protein immobilisation on solid surfaces and a coating by supercritical processing with fatty acids was successfully achieved. As a result sustained release of BSA from all SCDDS formulation prepared with different fatty acids was obtained at all ratios studied in the project. SCDDS prepared with lauric acid showed highest and quickest BSA release from the formulations followed by myristic, palmitic and stearic acid. BSA release was also found to be directly related to the ratio of fatty acid in the formulation. Formulations with higher ratios of fatty acid provided further decrease in release rate. It was also observed that although protein immobilisation and fatty acid coating resulted in retarded release of BSA from the formulation, the initial burst release from these systems could not be successfully prevented. The burst release of BSA seen from these systems can be due to the uneven or partial coating of fatty acids on protein immobilised silica particles. However after this burst release a continuous and slow release of BSA was obtained throughout the duration of experiments.

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