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RESEARCH ARTICLE

# Formulation parameters and release mechanism of theophylline loaded ethyl cellulose microspheres: effect of different dual surfactant ratios

Mohan Thakare<sup>1</sup>, Bridgette Israel<sup>2</sup>, Solomon T. Garner<sup>3</sup>, Hisham Ahmed<sup>4</sup>, Pamela Garner<sup>4</sup>, Deborah Elder<sup>4</sup>, James C. Price<sup>4</sup>, and Anthony C. Capomacchia<sup>4</sup>

<sup>1</sup>Renu Laboratories, Formulation Development, Greenville, USA, <sup>2</sup>Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, USA, <sup>3</sup>Jackson State University, Eagle-I Consortium, Jackson, USA, and <sup>4</sup>University of Georgia, Pharmaceutical Biomedical Sciences, Athens, Georgia, USA

## Abstract

Altering the combined hydrophilic-lipophilic balance (CHLB), by varying the ratio of dual surfactants, on formulation parameters and *in vitro* drug release of ethyl cellulose microspheres was examined.

Theophylline, a xanthine bronchodilator was used to model controlled release owing to its narrow therapeutic index. Microspheres were prepared using different ratios of dual surfactant in an emulsion-solvent evaporation process. Drug loading, encapsulation efficiency, particle size distribution, and geometric mean diameters were evaluated. Drug release was evaluated using several kinetic models including zero and first order, Higuchi square root, and Hixson-Crowell.

Microspheres presented as mostly spherical particles and diffusional drug release was affected by microsphere construction. For this novel, dual surfactant system the microsphere matrix is a hydrophobic polymer and the release rate may be modulated with variation in ratio of dual surfactants. Dissolution data followed the Higuchi model and supports the formation of a monolithic microsphere matrix that releases theophylline by Fickian diffusion.

Dual surfactants for preparation of microspheres are an inadequately studied research area that offers another means to modulate particle size and drug release. For the current study microspheres prepared with surfactant ratios of Span 65: Tween 40 between 3:1 and 2:1 provided the best control of size and drug release.

**Keywords:** Dual surfactants, CHLB, ethyl cellulose microspheres, emulsion solvent evaporation, dissolution, drug release mechanism

## Introduction

Controlled release drug delivery systems are constructed to release a drug at a controlled rate for a predetermined time period ranging from hours to months.<sup>[1]</sup> Controlled drug delivery can be achieved by polymeric microspheres due to their ability to encapsulate a variety of drugs, biocompatibility, high bioavailability and sustained drug release characteristics.<sup>[2-4]</sup> Various formulation and processing parameters affect microsphere characteristics and thus drug release. The design of microspheres by the emulsion-solvent evaporation method is affected by

solvent evaporation temperature, emulsion mixing speed, surfactant chemical structure (s) and HLB, polymer type (s) and specifications, drug/polymer ratio, core drug particle size, and solvent (s) specifications. Judicious selection of these to control particle size is crucial in designing a controlled drug delivery system.<sup>[5]</sup>

Theophylline, a xanthine bronchodilator is employed to treat both chronic and acute asthma, but possesses a narrow therapeutic index; judicious control of its release from formulations must be assured. Owing to its narrow therapeutic index controlled release dosage forms must

Address for Correspondence: Anthony C. Capomacchia Ph.D., University of Georgia, Pharmaceutical Biomedical Sciences, 250, Green Street, Athens, Georgia, USA. E-mail:tcapomac@rx.uga.edu, cell: 706.340.6400

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be carefully constructed to assure optimum but not toxic release.<sup>[6-9]</sup> This makes it an excellent drug candidate to model controlled release since faulty formulation could cause the uncontrolled release of large amounts of theophylline known as dose dumping and produce unwanted toxic effects.<sup>[10]</sup>

Theophylline cannot be loaded efficiently in microspheres prepared with o/w emulsion systems, because a significant amount of drug is lost in the external phase.<sup>[11]</sup> Many factors affect the characteristics of microspheres such as type and molecular weight of the polymer, the core drug particle size, the drug to polymer ratio, drug solubility in the polymer, mixing intensity, and polymer phase viscosity.<sup>[3,12-14]</sup> There are reports that the emulsifying agent (surfactant) also affects the characteristics of polymeric microspheres.<sup>[15,16]</sup>

Selecting a suitable surfactant as an emulsifier for a particular system often involves a great deal of experimentation. The hydrophile-lipophile balance (HLB) system introduced by<sup>[17-19]</sup> can be used to select a single surfactant for optimum efficiency<sup>[20]</sup> or alternatively a low and high HLB surfactant can be blended together in order to stabilize emulsions at a particular HLB; this is known as the required or combined HLB (CHLB). For example, many investigators have reported on the application of a single surfactant like Span 80, Span 85, aluminum stearate, or magnesium stearate for emulsion stabilization in the preparation of microspheres.<sup>[21-29]</sup> However, there is little literature on the subject of how dual surfactants affect a controlled release formulation physical properties and drug release mechanism.

Previous unreported data in this laboratory and literature reports demonstrated comparative changes in microsphere formulation properties upon using dual surfactants.<sup>[30,31]</sup> This could mean that formation of aggregated microsphere structures in solutions utilizing mixed surfactants could be substantially different from those using a single surfactant. Moreover, drug release may follow a number of kinetic or empirical models, including zero and first order, Higuchi square root, Korsmeyer-Peppas, and Hixson-Crowell that may be altered through the use of mixed surfactants. The aim of this research was to study the comparative effects of dual surfactants (one high HLB and one low HLB) at different ratios and therefore different CHLBs versus single surfactants, on some physical parameters and drug release characteristics of ethyl cellulose microspheres prepared with the emulsion-solvent evaporation method.

## Methods

### Materials

The following chemicals were used as obtained: ethyl cellulose (Scientific Polymer Products, Ontario, New York; CAT# 460, cps 300); micronized ( $\leq 10 \mu\text{m}$ ) theophylline, a gift from BASF; light mineral oil (Fisher Scientific, New Jersey); Span 65 (sorbitan tristearate), and Tween 40 (polyethylene monopalmitate), from Ruger Chemical

Company Inc., Irvington, NJ; methylene chloride (Fisher Scientific, NJ); acetone, monobasic potassium phosphate and sodium hydroxide (J.T. Baker, Phillipsburg, NJ).

### Instruments

Stirrer (Lab Stirrer LR 400D, Yamato Scientific Company Ltd., Tokyo, Japan); Dissolution Apparatus II USP (Dissolution Test system 5100, Distek Inc., North Brunswick, NJ), Aquamate UV Spectrophotometer, Thermo Electron Corporation, Mercer's Row, Cambridge, UK; Accumet 5 pH meter (Fisher Scientific, NJ); and, Precision Sieve Series, ATM Corp., Milwaukee Wis.; USP Standard sieve series for PSD (particle size distribution) studies.

### Preparation of microspheres

Preparation of ethyl cellulose microspheres containing theophylline was accomplished by the emulsion-solvent evaporation method in a 1 L tall glass beaker, in triplicate.<sup>[3,6,12-14]</sup> Acetone was selected as the hydrophilic solvent (internal phase) and mineral oil as the hydrophobic solvent (external phase) respectively, owing to reports stating that they facilitate microsphere formation;<sup>[32]</sup> and offer an advantage when scaling-up at the industrial level. Dual surfactants used in this process are presented in Table 1 with their respective HLBs and the ratios used to obtain the CHLBs. For preparation of all batches of microspheres, experimental conditions were kept identical. Light mineral oil (300 ml) containing the low HLB surfactant was used as the external or continuous phase (phase A). In a separate glass vessel the internal phase, 100 ml of a 5 % (w/v) solution of ethyl cellulose in acetone was prepared (phase B). Micronized anhydrous theophylline was dispersed in phase B to give a 33.3% theoretical drug loading—1 part theophylline (2.5 g) to 2 parts ethyl cellulose (5.0 g). The entire contents of this vessel (phase B) were added into the glass beaker containing the solution of light mineral oil and low HLB surfactant (phase A) under vigorous agitation at 1200 rpm using three stacked 2.5 cm diameter propeller type blades. The total amount of surfactant used was 16 g: either 16 g of high HLB, Tween 40; or 16 g of low HLB, Span 65; or 16 g of their mixture = (xg of Tween 40 + yg of Span 65) for CHLB values between those of Tween 40 (HLB 15.6) and Span

Table 1. The CHLB values for mixtures of Span 65 (S) and Tween 40 (T) and HLB values for S and T, column 1; the ratio of S:T that produced the CHLB values, column 2; % theophylline loaded in the microsphere formulations, column 3; % encapsulation efficiency, column 4; and the Geometric Mean Diameter of microspheres formulated, column 5.

CHLB or HLB	S:T ratio	% Drug loading	% Encapsulation efficiency	GMD
ST 4.5	82:18	21.62	64.9	370
ST 5.5	77:23	21.90	65.8	355
ST 6.5	67:33	25.47	76.5	345
ST 7.5	60:40	22.52	67.7	375
S 2.1	100 S	22.58	67.8	380
T 15.6	100 T	31.70	95.2	690

65 (HLB 2.1). Agitation was continued at 25°C until the acetone evaporated and the microspheres formed (12 hours). Mineral oil was decanted from the microspheres deposited on the bottom of the vessel prior to their placement on a vacuum filter and washed with mineral spirits (25 ml × 5 washes) to remove residual mineral oil. The clean microspheres were dried in an oven at 50°C overnight and were free flowing and readily pourable.

### Particle size distribution

The size distribution of theophylline microspheres was determined by passing the microspheres through a set of US standard sieves of range 90–710 μm. The aggregate sample was placed on the top sieve of largest size, covered, and then vibrated until no change in weight was observed for the microspheres collected in the sieves. Visual inspection assured that all particles retained on a sieve were larger than the sieve apertures. After sieving, the quantity of each fraction of particles was weighed. Particle size distribution and geometric mean diameters (GMD) were determined. GMD were obtained from log-probability plots of frequency versus log particle diameter.

### Drug loading and encapsulation efficiency

The 355 μm fraction of each batch of ethyl cellulose microspheres was analyzed for theophylline loading. Drug loading was determined spectrophotometrically at 276.5 nm by placing accurately weighed samples, 100 or 10 mg of microspheres (in triplicate) in 50 or 5.0 ml volumetric flasks, respectively and dissolving them in methylene chloride. Spectrophotometric interference from ethyl cellulose was not observed at this wavelength. An analytical curve of theophylline in methylene chloride prepared at concentrations 0.005–0.05% (w/v) was linear. Drug loading and encapsulation efficiency were calculated using the equations below:<sup>[20,33]</sup>

$$\% \text{ drug loading} = \left( \frac{\text{mg of drug in microspheres}}{\text{mg of microspheres}} \right) \times 100$$

$$\% \text{ encapsulation efficiency} = \frac{\% \text{ drug loading}}{\% \text{ theoretical drug loading}} \quad (33.3\%)$$

### In vitro dissolution studies and drug release

*In vitro* release studies of theophylline from ethyl cellulose microspheres prepared with both single and dual surfactants were performed using a USP dissolution apparatus II (Distek Inc., New Jersey). The 355 μm fraction of each batch of microspheres was selected for evaluation. Microsphere samples (100 mg) in triplicate for each batch were suspended in 900 ml of Simulated Intestinal Fluid, USP (Simulated Intestinal Fluid, pH 6.8 (SIF); USP 26; KH<sub>2</sub>PO<sub>4</sub> (6.805 g); NaOH (0.0896 g); deionized water to 1.0L) and no enzymes. The dissolution study was carried out at 37 ± 0.5°C at 100 r.p.m for 12–24 hours until no further drug was leached from the microsphere samples. Three ml of samples were withdrawn, using a syringe fitted with a filter at needle end to exclude particulate

material, at specific time intervals and replaced with fresh simulated intestinal fluid medium. Drug release was determined spectrophotometrically at 274 nm to obtain the dissolution profile and evaluate the mechanism of drug release.

Data obtained from the *in vitro* drug release studies were fitted to zero order, Eqn. 1;<sup>[34]</sup> first order, Eqn. 2;<sup>[34]</sup> Higuchi square root model, Eqn. 3;<sup>[34–38]</sup> Korsmeyer-Peppas, Eqn. 5;<sup>[34,39,40]</sup> and Hixson-Crowell, Eqn. 6<sup>[34,41]</sup> to evaluate the mechanism of drug release from ethyl cellulose microspheres prepared with both single and dual surfactants.

1. zero order ( $M_t = M_o + k_o t$ )
2. first order ( $\ln M_t = \ln M_o - k_t t$ )
3. Higuchi square root ( $M_t = M_o - k_{H-sqrt} t^{1/2}$ )
4. Korsmeyer-Peppas ( $M_t/M_\infty = k_{KP} t^n$ )
5. Hixson-Crowell ( $M_o^{1/3} - M_t^{1/3} = k_{HC} t$ )

Where,  $M_t$  = cumulative percentage drug released at time  $t$ ;  $M_o$  = percentage drug dissolved at time 0;  $k$  = respective model rate constants.

### SEM analysis of microspheres

The surface morphology of the formulated theophylline microspheres was observed by scanning electron microscope (SEM) using a Zeiss model 1450 EP scanning electron microscope prior to dissolution. Microspheres were mounted onto metal multi-stubs using double-sided adhesive tape and SEM images were taken at specific magnifications after being gold coated.

## Results and discussion

### Geometric mean diameter (GMD) and particle size distribution (PSD)

Microspheres prepared with a single surfactant such as Span 65 (S2.1) or Tween 40 (T15.6) showed variation in the GMD, as shown in Table 1, with Span 65 showing a much lower GMD compared to those prepared with Tween 40. When the Span 65 and Tween 40 were employed as dual surfactants microsphere GMD was slightly smaller for CHLB 5.5 (ST5.5) and 6.5 (ST6.5), but almost equivalent for CHLB 4.5 (ST4.5) and 7.5 (ST7.5), to those prepared solely with Span 65 and much smaller than those prepared solely with Tween 40. This may be attributed to the apparent formation of a strong droplet interfacial film during the emulsification process.<sup>[31]</sup> Surfactants in many cases maintain an emulsion with short-range repulsion or disjoining pressure that prevents droplet coalescence aiding smaller microsphere formation. This effect apparently diminishes as CHLB values approach those of either Span 65 or Tween 40.

The particle size distribution (PSD) varied significantly for microspheres prepared using single or dual surfactant microspheres (Figures 1 and 2). Microspheres prepared using the single surfactant Tween 40 (T15.6) displayed a skewed PSD with the majority of the particles in 710 μm fraction; while Span 65 (S2.1) showed

a skewed distribution with most particles in both the 710  $\mu\text{m}$  and 355  $\mu\text{m}$  fractions (Figure 2). A bell-shaped PSD was observed when dual surfactants were used and the microspheres presented with most in the 355 range regardless of CHLB (Figure 1). The differences may be attributed to stabilization of the emulsion that must have occurred from using dual surfactants. Coalescence was most likely restricted at all CHLB values leading to a greater proportion of smaller microsphere particles relative to the PSD observed when single microspheres were used.<sup>[31]</sup>

### Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency studies of the 355  $\mu\text{m}$  fractions of the microsphere batches revealed that there was no significant difference between microspheres as surfactant CHLBs were changed with the exception of CHLB 6.5 (ST6.5 in Table 1). For microspheres prepared at CHLB 6.5 drug loading was 12–19 % greater than at all other CHLBs with a corresponding small decrease in GMD. The single surfactant Tween 40 (T15.6) showed greater drug loading compared to dual surfactants; and may be due to coalescence as reflected by the creation of larger size microspheres, as well as an

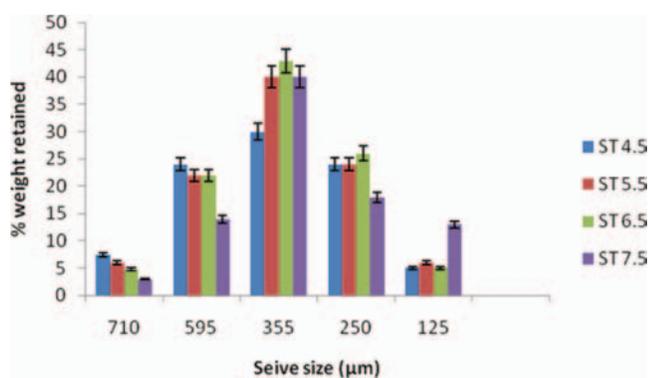


Figure 1. Effect of different CHLB values on the particle size distribution for microspheres prepared with dual surfactants (Span 65 and Tween 40).

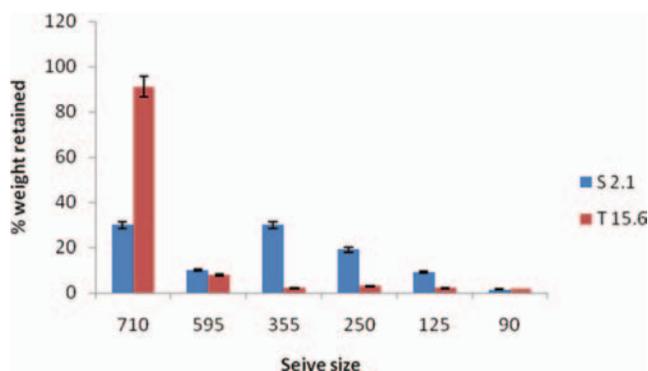


Figure 2. Effect of HLB on particle size distribution for microspheres prepared with single surfactants (Span 65 and Tween 40).

increased viscosity of the theophylline-ethyl cellulose dispersion comprising the emulsion internal phase. This view has been substantiated with reports that increased viscosity in the internal phase develops an emulsion with larger droplets.<sup>[13,14]</sup> Owing to this coarser emulsion larger microspheres are ultimately formed.

### In vitro drug release

Figures 2–4 depict drug release profiles of the 355  $\mu\text{m}$  fraction plotted according to zero order (Eqn. 1), and Higuchi square root (Eqn. 3); and Table 2 lists the rate constants, and correlation coefficients ( $R^2$ ) obtained from the respective plots. Plots generated from first order (Eqn. 2), and Hixson Crowell (Eqn. 5) equations were also constructed and data tabulated in Table 2, but are not shown here. Plots generated from the Korsmeyer-Peppas model were also constructed; and Korsmeyer rate constants and  $n$ -values obtained, but are not reported here (Table 2) as discussed later.

The solvent evaporation method has been described as developing non-porous or relatively less porous

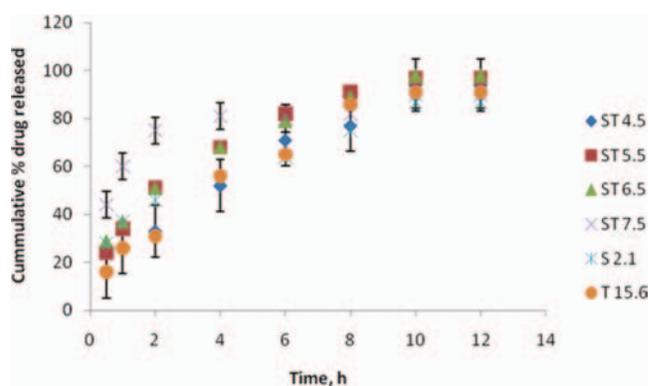


Figure 3. Drug release profile for dissolution according to the zero order kinetic model for microspheres prepared with varying ratios of dual surfactants Span 65 and Tween 40 (ST 4.5–7.5), or with either Span 65 (S 2.1) or Tween 40 (T15.6).

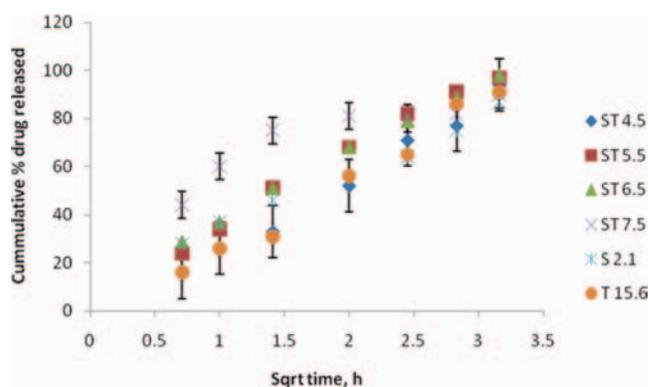


Figure 4. Drug release profile for dissolution according to the Higuchi square root kinetic model for microspheres prepared with varying ratios of dual surfactants Span 65 and Tween 40 (ST 4.5–7.5), or with either Span 65 (S2.1) or Tween 40 (T15.6).

microspheres in which the drug is distributed homogeneously throughout the polymeric matrix; and release from such a matrix is either by erosion or by diffusion.<sup>[42]</sup> Furthermore, release was described as occurring in three stages, i.e. initial diffusional release from the superficial region of microsphere, followed by slower release by polymer hydrolysis and then finally a rapid release resulting from polymer erosion. The data presented here indicates excellent correlation for the dissolution rate constants using Higuchi's square root model and implies diffusional drug release for all single and dual surfactant microspheres, except ST 7.5 (Table 2). Drug release is apparently not dependent on the chemical or physical erosion of the polymer as seen from the poor correspondence to the Hixson Crowell model (Table 2). However, this point indicates the reduced utility for the Higuchi model when used to describe drug release in hydrophobic matrix systems, since neither matrix erosion nor hydration and swelling are considered by the model.<sup>[43,44]</sup> For this reason, the dissolution data presented here was initially recast in the Korsmeyer-Peppas equation. However, upon close review of the work of Ritger and Peppas it became clear that this approach could only be used to describe drug release from non-swelling polymeric matrices from a monodisperse sample.<sup>[40]</sup> Since the microspheres prepared here were a polydisperse sample the model could not be utilized as explained below.

The  $n$  values for the Korsmeyer-Peppas model have been shown to be dependent on the range and shape of the particle size distribution.<sup>[40]</sup> For a monodisperse sample limiting values of  $n$  have been established for non-swelling spherical particles, where:  $n=0.43$  indicates Fickian diffusion;  $0.43 < n < 0.85$  indicates anomalous (non-Fickian diffusion); and  $n=1.0$  indicates zero order release.<sup>[40]</sup> Values of  $n$  falling within the above ranges shed light on the drug release mechanism, e.g. Fickian diffusion. In Figures 1 and 2, the 355  $\mu\text{m}$  fraction was employed for dissolution studies, and is a polydisperse microsphere sample with particle sizes ranging from 355  $\mu\text{m}$ –594  $\mu\text{m}$ ; therefore the limiting values for  $n$  theoretically calculated for a monodisperse sample cannot be reliably used as limits to identify the release mechanism for this sample of particles. The explanation for this is that for any collection of particles, those particles smaller than the mean size release drug faster than particles larger than the mean,

thus skewing the curve and evaluation of  $n$ .<sup>[40]</sup> For the current study, particle size distribution varies comparatively between formulations, for example ST4.5 versus ST5.5, and also between triplicate batches within each formulation selected, e.g. within batches of ST4.5. This makes their use impractical to identify a drug release mechanism using the Korsmeyer-Peppas model for the microspheres examined here, since the limiting  $n$  values for each mechanism in the polydisperse sample is unknown.

The comparatively poor fit for the first order model and the excellent fit with the Higuchi model, support the formation of a monolithic microsphere matrix system that releases drug by Fickian diffusion for all formulations except ST7.5. The relatively good fit for the zero order model seen in formulations ST4.5 and S2.1 may indicate the existence of multiple drug release mechanisms for these two formulations prepared at the lower end of the HLB scale.

### Scanning electron microscopy (SEM) analysis

The SEM micrographs of microspheres prepared from single and dual surfactants are shown in Figure 5. Use of single and dual surfactants at all CHLBs affected microsphere morphology and resulted in free flowing particles that were mostly spherical to slightly oblong. Formulations A, B, D, and E in Figure 5 presented with smooth to slightly rough surfaces depending on the surfactant system used. Microsphere formulations C and F presented with comparative increased roughness in surface morphology, which may be related to changes in drug release only for the latter, but not the former.

### Conclusions

The use of dual surfactants for the preparation of microspheres is an inadequately studied research area that offers another means to modulate particle size and drug release. For the current study microspheres prepared with surfactant ratios of Span 65: Tween 40 between 3:1 and 2:1 provided the best control of size and drug release.

Dissolution data reported here followed the Higuchi model for drug release and supports the formation of a monolithic microsphere matrix that releases drug by Fickian diffusion for most dual and single surfactant formulations examined.

Table 2. Dissolution rate constants,  $R^2$  and  $n$  values for the tested formulations obtained from the kinetic models.

CHLB or HLB	Zero order rate constant, K0	Higuchi, sqrt rate constant, KH-sqrt	First order rate constant, K1	Hixson-Crowell rate constant, KHC
ST 4.5	7.92 R <sup>2</sup> 0.9813	31.02 R <sup>2</sup> 0.9893	0.2441 R <sup>2</sup> 0.9146	0.1984 R <sup>2</sup> 0.9322
ST 5.5	7.53 R <sup>2</sup> 0.9635	28.14 R <sup>2</sup> 0.998	0.3301 R <sup>2</sup> 0.9134	0.1678 R <sup>2</sup> 0.8697
ST 6.5	7.07 R <sup>2</sup> 0.9688	30.26 R <sup>2</sup> 0.9905	0.2804 R <sup>2</sup> 0.8628	0.1529 R <sup>2</sup> 0.9095
ST 7.5	3.62 R <sup>2</sup> 0.697	15.25 R <sup>2</sup> 0.8113	0.137 R <sup>2</sup> 0.7988	0.0728 R <sup>2</sup> 0.651
S 2.1	5.98 R <sup>2</sup> 0.9807	22.28 R <sup>2</sup> 0.985	0.2263 R <sup>2</sup> 0.9687	0.1316 R <sup>2</sup> 0.9461
T 15.6	8.03 R <sup>2</sup> 0.9734	30.77 R <sup>2</sup> 0.9847	0.165 R <sup>2</sup> 0.9555	0.1957 R <sup>2</sup> 0.9194

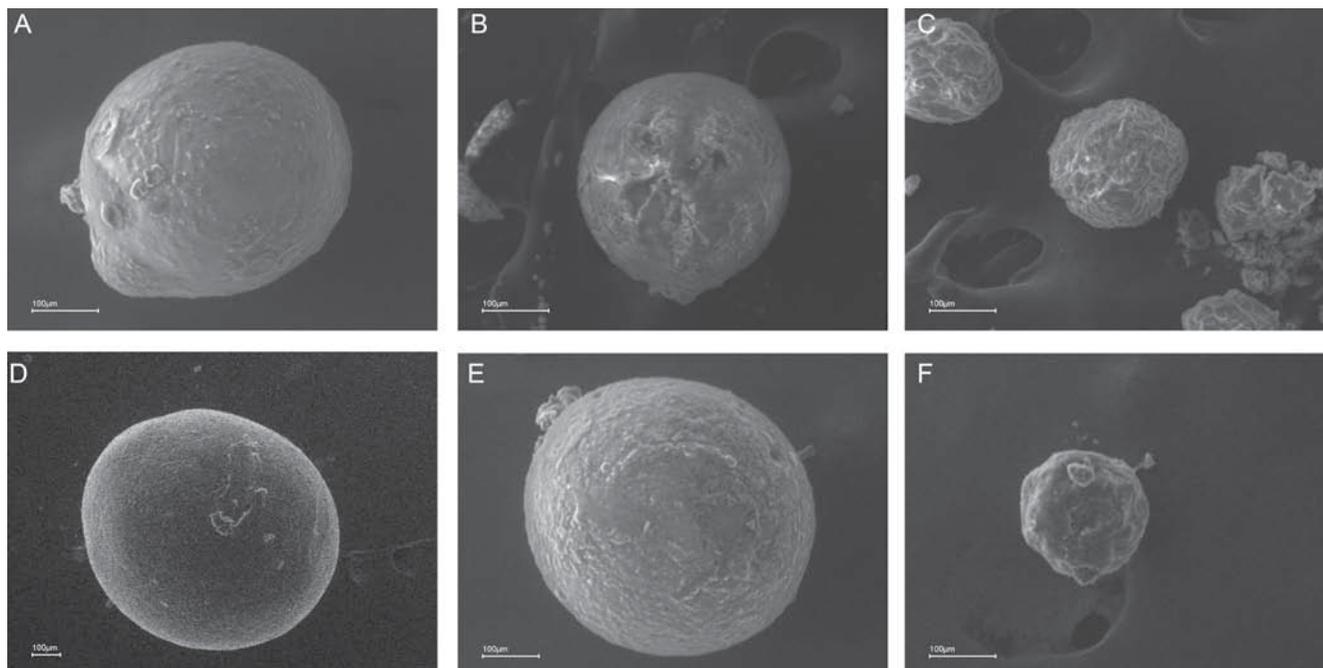


Figure 5. Scanning electron micrograph of microspheres prepared with A: Span 65 (HLB 2.1); B: Tween 40; C-F: Span 65 + Tween 40 (CHLB 4.5, 5.5, 6.5, & 7.5, respectively) Note: Figures are not to scale.

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## Declaration of interest

The authors report no conflicts of interest.

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