Tableting Lipid-Based Formulations for Oral Drug Delivery: A Case Study with Silica Nanoparticle–Lipid–Mannitol Hybrid Microparticles

KRISTEN E BREMMELL,[1] ANGEL TAN,[2] AMANDA MARTIN,[2] CLIVE A PRESTIDGE[2]

[1]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia 5000, Australia

[2]The Ian Wark Research Institute, University of South Australia, Mawson Lakes, South Australia 5095, Australia

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ABSTRACT: Silica–lipid–mannitol hybrid (SLMH) microparticles have been developed that were compressible into high quality tablets suitable for oral dosing and delivery of poorly soluble drugs. SLMH tablets enable high lipid-loading levels (>40%) and retain the immediate release, enhanced lipase digestion and drug solubilisation performance. Specifically, we report formulation optimisation of SLMH microparticles and tablets using coumarin 102 ($\log P = 4.09$) as a model Biopharmaceutics Classification System class II drug. SLMH tablets were acceptable according to standard British Pharmacopoeia friability, hardness and disintegration tests; this is not the case for conventional dry emulsions. Furthermore, *in vitro* dissolution and pancreatic-lipase-induced lipolysis studies under simulated intestinal conditions have demonstrated enzymatic-digestion-mediated drug solubilisation. SLMH microparticles and tablets are suitable as liquid lipid containing solid dosage forms for enhancing and controlling oral absorption of poorly soluble drugs. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:684–693, 2013

Keywords: lipid-based formulations; poorly soluble drug; dry emulsion; tablet; lipolysis; oral drug delivery; solid dosage form; drug delivery systems; spray drying

INTRODUCTION

Oral delivery of drugs with poor aqueous solubility and dissolution profiles often results in incomplete and variable drug absorption and an unpredictable therapeutic response. This poses limitations on the potential application and delivery of a growing number of poorly soluble new chemical entities that are currently in the development pipeline. Lipid-based formulations have been demonstrated to enhance oral absorption of poorly soluble drugs[1–3] through a number of mechanisms, including prolongation of gastric residence time and enhanced drug solubilisation by incorporation into structures such as micelles formed upon secretion of bile salts and phospholipids in the intestinal lumen providing an advantageous environment for transport to the unstirred water layer of the intestinal membrane.[4–7] A number of different approaches to lipid-based formulation have been investigated including lipid emulsions, microemulsions and self-emulsifying drug delivery systems.[8,9] However, the large volume and physical and microbial instability of oil-in-water (o/w) emulsions are generally unsuitable for commercial formulations, leading to interest in dry emulsions. A number of different techniques, including spray drying[10] and lyophilisation,[11–13] have successfully removed the water phase resulting in a dry emulsion. In addition, the ability to produce a solid dosage form has the advantages of superior drug preservation and stability.

Only a few studies have successfully demonstrated the formulation of lipid emulsions into a tablet form. Of these, a number of formulations were lyophilised directly into the tablet form with the use of a mould,[11,12] and others were first dried and compacted using a conventional tablet press.[14,15] These emulsions were typically stabilised with polymer,[15] maltodextrin[11] or sugars[14] and achieved a maximum oil content of 24%[15] and 40%.[14] However, such approaches rarely produce tablets of high quality and

Correspondence to: Clive Prestidge (Telephone: +61-8-8302-3569; Fax: +61-8302-3683; E-mail: clive.prestidge@unisa.edu.au)

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the majority of commercial lipid-based delivery systems are formulated as hard gelatin capsules. There are limited studies of drug dissolution and lipid digestion for characterising the state of drug solubilisation and delivery from such dry lipid systems.

Silica–lipid hybrid (SLH) microparticles first reported by Tan et al.[16] and have been shown to be effective for encapsulation of poorly soluble drugs. They display an internal porous matrix structure of silica nanoparticles and lipid, with pore sizes 20–100 nm, and have the ability to be re-suspended after drying. Two model poorly soluble drugs, celecoxib[16,17] and indomethacin,[18] have been shown to be in a non-crystalline form when incorporated into SLH microparticles, with no solid-state changes over 1 year of storage. Because of the internal porous matrix structure of the microparticles, drug-loading levels were increased above the solubility in the pure oil. Dissolution of celecoxib was significantly increased and the time taken to achieve 50% of drug dissolution reduced approximately 50-fold in comparison with the pure drug. A novel characteristic of the SLH microparticles compared with other emulsion systems is the high surface area created by the porous silica matrix, which has been demonstrated to be beneficial for drug release and to provide some catalytic effect for the hydrolysis of adsorbed triglycerides and phospholipids. Importantly, orally dosed *in vivo* rat studies have confirmed superior pharmacokinetics in terms of higher fasted state bioavailability, maximum plasma concentration and linear dose dependence.[16]

In this study, addition of mannitol to the SLH microparticles for improving the flow behaviour and cohesive properties of the dried powder for effective tablet compression was explored. Direct compression of the unmodified SLH microparticles was challenging because of the high cohesiveness and poor flowing property of the powder. Mannitol is a widely used pharmaceutical polyol in tablet compression technology, being attractive for its high water solubility and low hygroscopic property, thus is compatible with moisture-sensitive compounds.[19] Drug dissolution and lipid hydrolysis have been documented for the SLH microparticles[16,20] ; however, the influence of mannitol addition on the microparticles formation and physical pharmaceutical properties remains to be determined. Dry emulsions were prepared with medium-chain triglycerides, lecithin (as an emulsifier) and Aerosil® silica nanoparticles. Coumarin 102 (representative of drugs of higher lipophilicity, log $P \geq 4$) was used as a model hydrophobic compound to explore dissolution from the SLH microparticles. Lipase-mediated digestion of the microparticles was also investigated. Formulation of the mannitol-modified microparticles into a tablet form suitable for oral delivery was described, including characterisation using standard tablet hardness, friability and disintegration tests. The current investigation also quantifies drug dissolution and *in vitro* lipolysis from the SLH tablet form.

MATERIALS AND METHODS

Materials

Caprylic/capric triglyceride (Miglyol® 812, Croda, Sydney Australia) was obtained from Hamilton Laboratories, Adelaide Australia, and soybean lecithin (containing >94% phosphatidylcholine and <2% triglycerides) from BDH Merck, Sydney Australia. Fumed hydrophilic silica nanoparticles (average primary diameter of 7 nm) (Aerosil® 380) were supplied by Degussa, Essen Germany. Coumarin 102 (dye content 99%), mannitol, sorbitol, polyvinylpyrrolidone (PVPP), PVP-K30 and magnesium stearate were purchased from Sigma–Aldrich, Sydney Australia and used as supplied. Sodium carboxymethyl starch (CMS-Na) was purchased form JRS Pharma, Rosenberg Germany.

In Vitro Dissolution

Phosphate buffered saline (PBS) tablets and sodium dodecyl sulphate (SDS) (for molecular biology, ~99%) were obtained from Sigma–Aldrich.

In Vitro Digestion

Sodium taurodeoxycholate (NaTDC), trizma maleate, type X-E L-α-lecithin (~60% pure phosphatidylcholine, from dried egg yolk), porcine pancreatin extract (activity equivalent to 8× United States Pharmacopeia (USP) specification), calcium chloride dihydrate and sodium hydroxide pellets were purchased from Sigma Chemical Company (St. Louis, Missouri). 4-Bromophenylboronic acid (4-BPB) was obtained from Sigma–Aldrich. The titration solution of 0.6 M NaOH was diluted from the 1 M NaOH stock solution (Titrisol; Merck, Germany). Polyallomer centrifuge tubes (13.5 mL; 16 × 76 mm^2) from Beckman Instrument Inc. (Palo Alto, California) were used. All chemicals were of analytical grade, and high purity (Milli-Q, Millipore Corp, Melbourne Australia) water was used throughout the study.

Preparation of SLH Microparticles

A two-step method was used for SLH microcapsule preparation: homogenisation followed by spray drying (see schematic in Fig. 1), based on Tan et al.[16] Briefly, o/w emulsions were prepared as follows: 0.6% (w/w) lecithin was dissolved in 10% (w/w) oil (Miglyol® 812), followed by the addition of coumarin 102 (1%, w/w, weight relative to the oil), Milli-Q water was added as the continuous phase and the system stirred for 2 h. The course o/w emulsions were homogenised (Avestin® Emulsiflex-C5 Homogenizer, Ottawa, ON

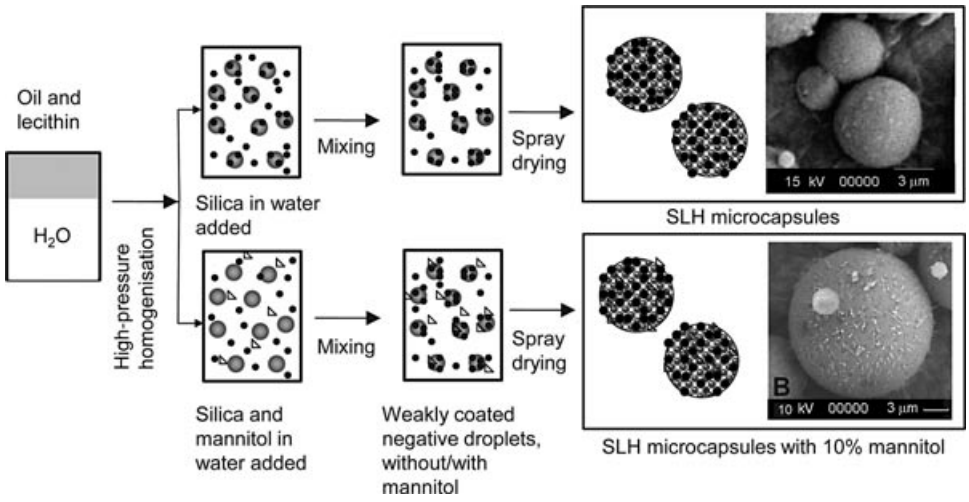

Figure 1. A schematic to illustrate the preparation of silica–lipid hybrid microparticles, including electron micrographs of silica–lipid microparticles containing (a) 50% (w/w) silica and (b) 10% (w/w) mannitol, 50% (w/w) silica. Lecithin was incorporated as an emulsifier in both preparations. For the microparticles including mannitol, mannitol was added to the oil-in-water emulsions with the silica particles.

Canada) under a pressure of 1000 bar for five cycles, and then tumbled for 12 h after addition of the silica nanoparticles to produce a final silica concentration of 50% weight relative to the oil content (for microparticles B, C and D, the silica particles were added to produce a final concentration as listed in Table 1). The silica nanoparticle-stabilised emulsion was then spray dried (Mini spray dryer B-290; Büchi Labortechnik AG, Flawil Switzerland) with a flow/pump rate of 5 mL/min, aspirator air flow rate 0.6 m^3/min, inlet and outlet temperatures of 170°C and 80°C, respectively, to form the microparticle powder. SLH microparticles developed by Tan et al.[16] did not contain mannitol. In the current study, for the microparticles containing mannitol, the required amount of mannitol (as listed in Table 1) was added with silica nanoparticles in the water phase.

Physicochemical Characterisation of SLH Microparticles

The oil content of the microparticles was determined using thermal gravimetric analysis (TGA; TA Instruments, Sydney Australia). Samples of 15 mg were heated at a rate of 10°C/min from 20°C to 600°C under nitrogen purging. After correction for the water content of spray-dried silica, the subtracted mass loss corresponds to the oil content of each microcapsule sample. Surface morphology of the SLH microparticles was examined by high-resolution scanning electron microscopy (CamScan CS44FE, Cranberry Twp, PA). Samples were mounted on double-sided adhesive tape and sputter-coated with gold–palladium (60%:40%) prior to imaging at an accelerating voltage of 10 kV. Crystallinity test (i.e. differential scanning calorimetry) was not performed as coumarin 102 (1%, w/w) was dissolved in the lipid phase at half of its equilibrium solubility in the selected lipid; hence, coumarin 102 is completely solubilised in the lipid phase before and after the formation of microparticles.

In Vitro Dissolution

The *in vitro* dissolution study was performed in 900 mL phosphate buffer (0.05 M and pH 7.2) containing 0% and 0.5% (w/v) SDS, using USP 23 type II apparatus (paddle method) operating at 0.2 g. Each

Table 1. Components Used to Prepare a Range of SLH Microparticles and Their Powder Properties

Microparticle	Mannitol (%)[a]	Aerosil® Silica (%)[a]	Yield (%)[b]	Lipid (%)[b]	Powder Properties (Angle and Repose, $n = 4$)[c]
A	0	50	62	64 ± 1	Cohesive powder
B	5	45	63	64 ± 0.2	Similar to microcapsule A control
C	10	40	64	64 ± 0.1	Slightly more fine than microcapsule A control, improved flowability
D	25	25	52	60 ± 0.3	More coarse (larger grain) than microcapsule A control, cohesive powder
E	10	50	65	61 ± 1	Soft, very fine, well flowing powder (47.3 ± 2.1)

[a] Present in wet emulsion, i.e. feed to spray dryer.
[b] Present after spray drying (dry emulsion).
[c] With the exception of microparticles E, angle of repose measurement was inconsistent because of the coherent nature of powder.

sample, containing approximately 1.5 mg of coumarin 102, was added to the dissolution medium, maintained at 37 ± 0.5°C. Samples of 3 mL were withdrawn at fixed time points and replaced with fresh dissolution medium. The samples were centrifuged at 9400*g* for 15 min to remove undissolved materials, and the supernatant subjected to another cycle of centrifugation under the same conditions. The supernatant was analysed using fluorescence spectroscopy (Cary Eclipse Fluorescence Spectrophotometer; Varian Inc., Melbourne Australia) at an excitation wavelength of 395 nm and emission wavelength of 488 nm. A linear calibration curve of fluorescence intensity of coumarin 102 against concentration was obtained with an r^2 value of greater than 0.9999. Coumarin 102 loading efficiency of the microparticles was also determined using fluorescence spectroscopy.[21] The microparticles (10 mg) were first dissolved in 1 mL of ethanol, vortex mixed and centrifuged at 9400 g for 15 min. Each sample was then diluted 1:1000 in Milli-Q water prior to fluorescence spectroscopy.

In Vitro Lipolysis

The digestion medium was prepared using a method adapted from Sek et al.[22] Fasted state phospholipid—bile salt (1.25 mM phosphatidylcholine (PC)–5 mM NaTDC) mixed micelles were prepared according to the following procedure: egg lecithin was dissolved in chloroform in a 50-mL round-bottom flask. The chloroform was then evaporated under vacuum (Rotavapor RE; Büchi, Switzerland) to form a thin film of lecithin; digestion buffer (50 mM Trizma maleate, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2{\cdot}2H_2O$) and NaTDC were then added and the mixture continuously stirred for approximately 12 h to produce a transparent micellar solution. Pancreatin extracts (containing pancreatic lipase and colipase) were freshly prepared each day by stirring 1 g of porcine pancreatin powder in 5 mL of digestion buffer for 15 min, followed by centrifugation at approximately 2200 g at 5°C for 15 min. The supernatant was collected and stored on ice until required.

Lipolysis was carried out according to the procedure of Sek et al.,[22] with the digestion progress monitored for 60 min by pH-stat titration unit (TIM854 Titration Manager; Radiometer, Copenhagen Denmark). The sample (equivalent to ~200 mg lipid) was dispersed in 18 mL of buffered micellar solution (pH adjusted with 0.1 M NaOH or HCl to 7.5 ± 0.01) with continuous stirring for 10 min at 37°C. Lipolysis was initiated through addition of pancreatin extract (2 mL) (containing ~20,000 tributyrin units (TBU) of pancreatic lipase activity). Production of the free fatty acids (FFAs) was titrated with NaOH (0.6 M) via an auto burette to obtain constant pH. NaOH consumption was used to quantify the amount of FFA liberated based on a 1:1 stoichiometric ratio. Aliquots of 1 mL were removed at time points of 1, 5, 15, 30, and 60 min, and 4-BPB was added to the samples to cease digestion. The samples were held at 37°C for at least 15 min before centrifugation (143 000 g for 1 h). Each formulation was tested in triplicate or quadruplicate. Micelles alone were used as a background measurement ($n = 2$). Analysis of coumarin 102 content in both the aqueous and pellet phases was undertaken as described above. The aqueous phase was simply removed and analysed for fluorescence, whereas for the pellet phase, 50 μL of 1 M HCl and 1 mL of EtOH were added to extract the coumarin 102, which was mixed and further diluted with 9 mL of EtOH. This mixture was then sonicated and centrifuged at 143 000 g for 40 min at 37°C, for fluorescence analysis of the different phases.

Preparation of Tablets

Tablets (300 and 400 mg) were prepared from the SLH microparticles E (60%, w/w), sorbitol (25%, w/w), PVPP (5%, w/w), CMS-Na (6%, w/w), PVP-K30 (2%, w/w) and magnesium stearate (2%, w/w). A batch was first directly compressed using a Korsch XP1 tablet press (Korsch, Berlin Germany) into 300 mg tablets. Half of these were granulated and then compressed into 300 mg tablets (dry granulated tablets).

A series of tablets were prepared with microparticles containing coumarin 102 for dissolution studies with the same formulation as above.

Tablet Characterisation

Uniformity of mass, disintegration (Electrolab disintegration tester, Electrolab, Cupertino CA), friability (Electrolab EF-2 Friabilator) and tablet hardness (Electrolab EH-01P) were determined according to the methods described in the British Pharmacopoeia (BP). A disintegration time of less than 15 min and friability less than 1% are considered acceptable.

Dissolution and digestion of the tablets was undertaken as for the SLH microparticles, with the following procedure. For the lipase-mediated digestion, the tablet was added to the micellar solution (18 mL) and the solution stirred for 10 min at 37°C to allow for equilibration of temperature. The pH was then adjusted to 7.5 with 0.6 M NaOH and the experiment started with the addition of digestive enzymes (2 mL). Aliquots (1 mL) were removed at time points of 1, 5, 15, 30 and 60 min for analysis of coumarin 102 in a solubilised state.

Statistical Analysis

All values are an average of a number of repeats (n) and expressed as the mean ± standard error of the mean.

RESULTS AND DISCUSSION

SLH Microparticles Containing Mannitol

Physicochemical Properties

Given that equivalent SLH microparticles have previously been shown to exhibit superior encapsulation and release profiles of poorly soluble drugs compared with other emulsions and commercial formulations,[18,20] it is desirable to formulate the microparticles into an oral tablet form. Thus, the focus here was to achieve improvements in the powder properties of the microparticles without unfavourably impacting on the drug encapsulation, lipid loading and delivery properties. In order to achieve this, a range of SLH microparticles (five formulations designated from A to E) were prepared incorporating varying ratios of silica, lipid and mannitol according to the scheme given in Table 1. SLH microparticles containing only lipid, lecithin and silica (microparticles A) were cohesive powders with poor flow qualities and produced inferior tablets. To improve the flowablity of these dried emulsions, addition of mannitol prior to spray drying was selected as it has previously been demonstrated to improve the flowability and density of dried emulsions.[14]

Impact of mannitol on the physical powder properties of SLH microparticles was dependent on the ratio of mannitol incorporation. Addition of 5% (w/w) mannitol did not influence the powder properties; however, incorporation of 10% (w/w) mannitol with 40% silica (microparticles C) improved flowability compared with that of preparations A, B and D. Microparticles E, with a preparation composition of 10% (w/w) mannitol and 50% (w/w) Aerosil® silica, were found to yield a non-cohesive, free-flowing powder and show excellent tablet characteristics upon compression. After spray drying, the percent yield was observed to increase as the powder properties improved from microparticles D to E (Table 1) and is related to the coherent powder properties of the microparticles; the least coherent powders adhered least to the spray dryer. Angle of repose analysis confirmed visual observation of the microparticles. Only microparticles E with 10% mannitol and 50% silica nanoparticles repeatedly resulted in an angle of repose measurement (47.3 ± 2.1). All other samples were sufficiently coherent to partly remain in the funnel used for analysis. Cohesiveness of the SLH microparticles is comparable between microparticles ranging from 1 to 15 μm; therefore, the compositional factor of mannitol incorporation is predominating the particle size effect in the resulting cohesive forces. In addition, the final percentage of lipid contained in microparticles E did not significantly decrease compared with microparticles A, suggesting that the potential for incorporation of high loading levels of lipophilic drugs would not be influenced. Thus, further microcapsule characterisation and tablet studies were performed on microcapsule preparations A and E. In order to test flowability, friability, disintegration and crushing strength, a large batch of microparticles E was prepared with an increased yield of 76% after spray drying compared with the small batch with a yield of 65%. This is indicative that the final yield could be optimised by increasing the size of each formulation batch. Oil content of the microparticles was determined to be 61% by TGA. In addition, a batch containing coumarin 102 was prepared for dissolution and lipolysis studies (78% yield).

Scanning electron microscopy (Fig. 1) revealed the SLH microparticles A prepared with lecithin and silica (50%, w/w) to be almost spherical and have a smooth texture. It has been previously demonstrated that the silica nanoparticles form a porous matrix that extends throughout the microcapsule[18] providing the improved drug loading and release characteristics. When 10% (w/w) mannitol was included in the formulation with 50% (w/w) silica (microparticles E), highly spherical microparticles approximately three to four times larger than microparticles A resulted, with needle-shaped mannitol crystals visible on the surface (Fig. 1). Mannitol has been observed in the crystalline form after spray drying in previous studies.[14,23] As mannitol crystals are visible on the microparticles exterior, this provides a low hygroscopic interface,[19] improving flow properties of the powder.

IN VITRO DISSOLUTION AND LIPOLYSIS

Dissolution of coumarin 102, a model lipophilic compound, from the SLH microparticles with and without mannitol was determined to investigate the influence of mannitol addition on drug release capabilities (Fig. 2). While coumarin is in a molecular form in the oil phase and would technically be considered to be dispersing, the term dissolution will be used in this manuscript as it is describing coumarin release from the solid SLH microparticles using standard pharmacopoeial dissolution tests. Coumarin 102 release from the microparticles produced low and variable dissolution behaviour in PBS at pH 7.2 and 37°C (i.e. non-sink conditions[21]). However, addition of 0.5% SDS, a wetting and solubilising agent for simulating the sink effect in the gastrointestinal tract, produced more reproducible and complete dissolution data, exhibiting approximately 94% release of coumarin 102 from the SLH microparticles. During these experiments, the optimal concentration of coumarin 102 for sink conditions was determined to be 600 μg/L of dissolution media for the SLH microparticles. Dissolution was rapid, with full dissolution obtained within 5 min from microparticles A under simulated intestinal

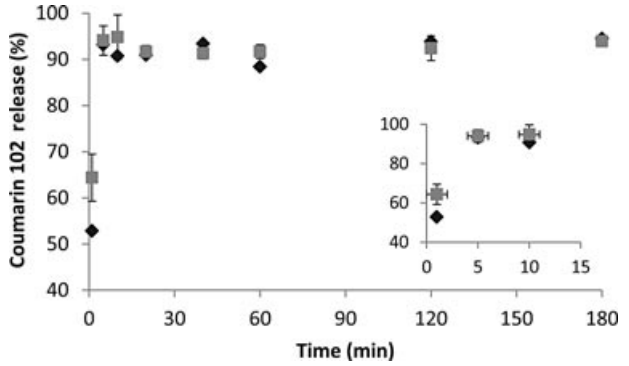

Figure 2. Dissolution profiles of coumarin 102 from SLH microparticles A (◆) (without mannitol) and E (■) (containing 10% mannitol) under sink conditions ($n = 3$). The inset represents the first 15 min of dissolution.

conditions (i.e. pH 7.2) (Fig. 2). This dissolution behaviour of coumarin 102 correlates with that measured for a poorly aqueous soluble drug celecoxib,[16] where 95% celecoxib dissolution was observed to occur in 15 min, which was a significant increase compared with 24% dissolution for the pure drug and 55% for the commercially available Celebrex formulation. Enhanced dissolution was attributed to the role of the hydrophilic carriers (silica particles) present in a porous matrix structure enhancing lipid dispersion, and also to the molecular state of celecoxib in the oil, which exhibited a higher intrinsic solubility in comparison with the crystalline form. Molecular dispersion of coumarin 102 throughout the microparticles has been confirmed with confocal microscopy, demonstrating coumarin 102 to be dispersed evenly throughout the lipid phase after encapsulation by nanoparticles and transformation into the dried state.[24] Fast dissolution may also be a result of low resistance to diffusion from the microparticles into the surrounding aqueous medium. Drug transfer may then be driven by the presence of SDS micelles capable of incorporating lipophilic compounds into their structure. Alternatively, SDS may be acting as a wetting agent in dispersing oil droplets incorporating the drug. In the present study, addition of mannitol to the SLH microparticles (microparticles E) prior to spray drying did not significantly change the dissolution behaviour of coumarin 102, with an average release of 94% (Fig. 2). Significantly, the release behaviour of coumarin 102 was also independent of the size of the microparticles, as microparticles E were three to four times the size of microparticles A, demonstrating the ease of lipophilic molecule dispersion from the carrier systems. Dissolution was also found to be independent of microcapsule size in the study by Lim et al.[21] when investigating the influence of different lipids on the *in vitro* performance of SLH microparticles. Therefore, in the current study, both SLH microparticles (A and E) achieved greater than 85% coumarin 102 release within 30 min under simulated sink conditions, which conforms to the US Food and Drug Administration criteria for classification as immediate-release dosage forms.[25]

Efforts to use standard pharmacopoeial dissolution models for *in vivo* correlation of Biopharmaceutics Classification System class II drug formulations have been challenging because of the complex nature of intra-luminal processes, and recent studies have established the importance of lipid digestion on the solubilisation ability of lipid-based formulations.[26–28] Upon oral dosing of lipid-based delivery systems, the presence of acid-stable lipases initiates hydrolysis of triglycerides. The resulting digestion products, combined with secreted bile salts, phospholipids and cholesterol, form a range of colloidal species including micelles, vesicles and emulsion droplets. These structures provide ideal environments for poorly soluble drugs to partition into, creating depots of drug at the gastrointestinal absorption site. Thus, lipid hydrolysis of emulsion drug delivery systems is an integral process that occurs prior to absorption of the drug from the lipid phase. *In vitro* lipolysis models have shown some success in ranking the *in vivo* performance of a number of lipid-based formulations of poorly soluble drugs.[22,27,29,30] More recently, it has been demonstrated that a lipid digestion model can be used for predicting the *in vivo* outcome of orally dosed SLH microparticles.[20] In the case of SLH microparticles, influence of mannitol inclusion on lipid digestion as a function of time is represented in Figure 3. During 1 hour of reaction time, the lipids were hydrolysed to 86% for the SLH microparticles, similar to that determined in a previous study.[20] When the microparticles included mannitol, lipolysis proceeded to 83%. Thus, the presence of mannitol has no significant impact on lipid digestibility of the SLH microparticles,

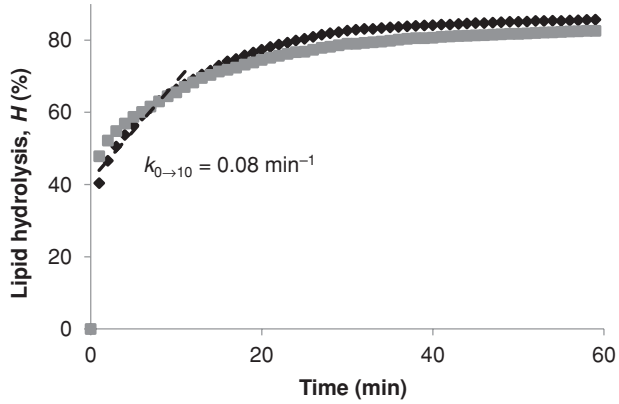

Figure 3. Time dependence of the lipase-mediated digestion of SLH microparticles A (®) (without mannitol) and E (■) (including mannitol) under simulated fasted intestinal conditions ($n = 3$).

although some polysaccharides have been reported to inhibit lipase activities in a dose-dependent manner[31] and produced relatively lower drug bioavailability.[16] Additionally, this study also demonstrates the lipid hydrolysis to be independent of microcapsule size, as SLH microparticles including mannitol were three to four times larger than SLH microparticles. A study by Li et al.[32] found emulsion droplet size to be influential in determining the rate and extent of lipid digestion, thus further highlighting significance of the porous nanoparticle silica matrix structure in drug release performance of the SLH microparticles. As the presence of mannitol was not found to interfere with lipophilic molecule release characteristics and lipid digestion kinetics, further exploration into the production of an oral dosage form of the microparticles was desirable and described below.

SLH Tablet Characterisation

Standard disintegration, friability and crushing strength characterisation tests were applied to tablets (300 mg) produced using (1) direct compression of the microparticles with excipient mixture and (2) after dry granulation (Table 2). The following test properties were observed for tablets prepared using microparticles E (including mannitol): complete disintegration occurred within 15 min; during friability testing, the mass loss was less than 1% and the crushing strength was low; therefore, the tablets produced are considered acceptable according to the BP. Disintegration was observed to occur within 9 min for the directly compressed tablets and within 14 min for granulated tablets. Granulation generally increases the interlocking strength of particles,[19] which has increased the disintegration time for these tablets. As listed in Table 2, these tablets have a lipid content of 36.6%, which is significantly greater than that has been achieved previously for tablets of dry emulsions prepared from spray-dried emulsions with hydroxypropylmethylcellulose as a solid carrier, where a maximum of 24% lipid content was achieved,[15] and similar to the maximum lipid content reported by Hansen et al.[14] when compressing spray-dried powders produced with medium-chain triglycerides, magnesium aluminosilicate and mannitol or trehalose. These two previous studies of dry emulsion tablets did not report drug release or lipid hydrolysis from the tablets.

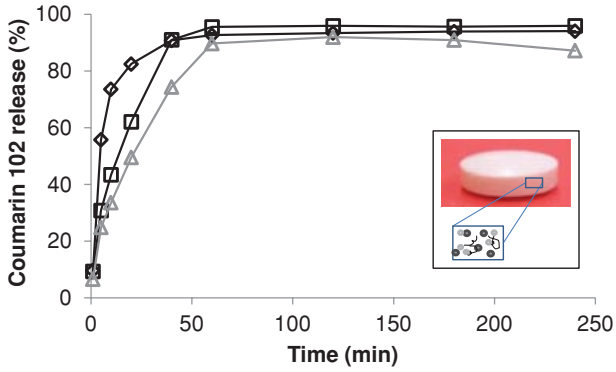

Figure 4. Dissolution profiles for coumarin 102 from the formulated tablets containing 60% (w/w) microparticles E [300 mg direct compression tablets (◇), 300 mg dry granulated tablets (□), 400 mg dry granulated tablets (△)]. Inset: 300 mg directly compressed tablet showing a schematic of the components (polymer components include sodium carboxymethyl starch, PVPP and PPVP-K30; • represents the SLH microparticles and • represents the solid excipients sorbitol and magnesium stearate).

A series of 300 and 400 mg tablets containing the same ratio of microparticles E to excipients (including sorbitol, PVPP, CMS-Na, PVP-K30 and magnesium stearate) was prepared by direct compression (see photograph in insert of Fig. 4) and after dry granulation. Coumarin 102 dissolution from these tablets prepared from the SLH microparticles was complete, although occurred at a relatively slower rate compared with the microparticles alone (Fig. 4). The time for 50% coumarin 102 dissolution increased from approximately 4 min for the 300 mg directly compressed tablets to 17 and 20 min, respectively for 300 and 400 mg dry granulated tablets. This compares with less than 2 min for dissolution from microparticles E. Full dissolution of coumarin 102 was observed after approximately 50 min for all tablets. The potential drug release mechanism is believed to be related to that of the microparticles, which is phase transfer or diffusion; silica matrix disintegration also occurs when subjected to constant agitation.[17,24] Longer dissolution times compared with SLH microparticles is thought to be related to the disintegration time of the compressed tablets. Tablet disintegration was observed to take 9 and 14 min for the directly compressed and dry granulated tablets, respectively. Therefore, disintegration of the tablet was required prior to complete coumarin 102 dissolution being

Table 2. Characterisation of Compressed Tablets Comprising 60% by Weight Microparticles E Prepared by Direct Compression and After Dry Granulation

	Average Mass (mg)	Disintegration	Friability (%)	Crushing Strength (N) ($n = 6$)	Lipid Content (%)
60% Direct compression	298 ± 9	✓	0.7	13.13 ± 1.21	36.6
60% Dry granulated	300	✓	0.5	7.45 ± 1.15	36.6

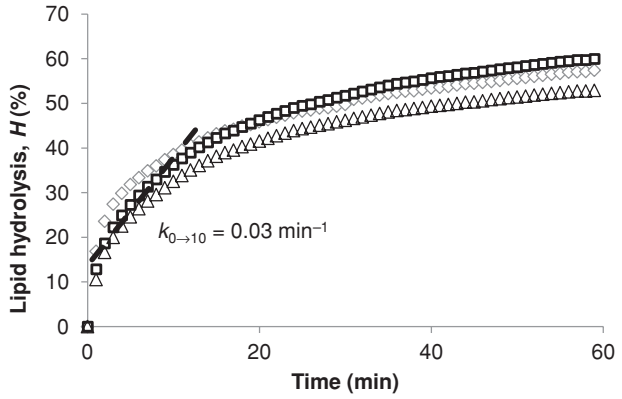

Figure 5. Lipase-mediated digestion of tablets formulated with SLH microparticles E. [300 mg direct compression (◇), 300 mg dry granulated (□), 400 mg dry granulated (△)] ($n = 3$).

observed; which delays the first step of drug dissolution. Dry granulated tablets were determined to take longer for disintegration and consequently the dissolution profile was also slower; however, it reached a similar plateau value to the directly compressed tablets at approximately 45–60 min (i.e. near to 100% drug dissolution). In addition, other excipients formulated in the tablet with the microparticles may interfere with the dissolution process of the lipophilic molecule. For example, magnesium stearate has been associated with retarded dissolution from tablets.[33,34]

The compressed tablets (both granulated and non-granulated) containing microparticles E were tested for lipase-mediated digestion (Fig. 5). Lipid digestion at 60 min was determined to be only 60% for the tablets; it did not appear that equilibrium had been reached after 1 hour (the curves are still trending upward as described in Fig. 5). Similar to the dissolution findings, lipid hydrolysis for the compressed tablets was slower than for the microparticles and this can be related to the time for tablet disintegration (9 and 14 min for the directly compressed and dry granulated tablets, respectively), or the ease of enzyme penetration to the lipid substrate interface. With respect to the lipolysis kinetics, there is no significant difference between the three different tablets; however, the lipolysis kinetics was reduced more than twofold for SLH tablets [i.e. k (0–10 min) = 0.03 min^{-1}] in comparison with the SLH microcapsule powder [k (0–10 min) = 0.08 min^{-1}]. This indicates the possibility to further control lipid digestibility (and hence drug release and absorption) of the SLH formulations via tabletisation. The ability to control lipid digestibility is particularly important for drugs exhibiting high lipophilicity (i.e. log $P > 5$) which have been shown to undergo significant precipitation under lipolysis conditions resulting from rapid digestion and dissipation of the solubilising lipid phases which act as the drug reservoir.[35,36] In order to illustrate the ratio of coumarin 102 partitioned between the supernatant and pellet phases, the phase partition percentages have been reported (Fig. 6) based on the total amount of fluorescence detected in the samples withdrawn from the digesting medium. The total amount of drug recovered in the centrifuged samples was less than 50% of the initial added amount, possibly because of two reasons: (1) instability of coumarin 102 during digestion and (2) some drug remained in the undigested oil phase; however, there was no clear separation of an oil layer after centrifugation; therefore, analysis of the oil phase was not feasible. Importantly, there is a clear trend of increasing drug solubilisation (i.e. from approximately 60% to more than 80%) as lipid digestion progressed (from approximately 10% to 60%). At 50% lipolysis, less than 15% of coumarin 102 was detected in the pellet phase and this suggests adequate solubilising capacity resulting from digestion of the medium-chain lipid phases. Therefore, mannitol-containing SLH tablets retain drug solubilisation

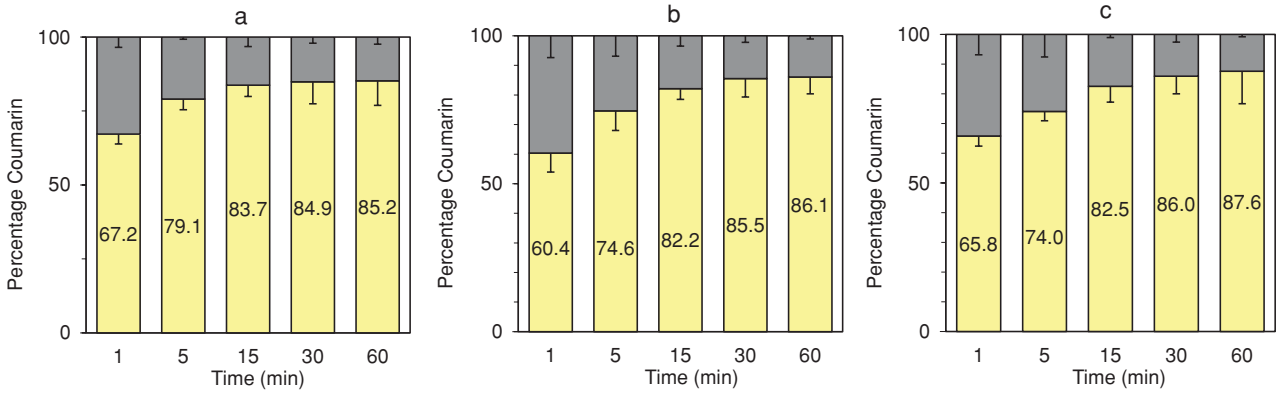

Figure 6. Distribution of coumarin 102 into the aqueous (yellow column) and pellet (grey) phase during digestion of tablets formulated with SLH microcapslues E: (a) 300 mg direct compression, (b) 300 mg dry granulated and (c) 400 mg dry granulated ($n = 3$).

performance of the SLH microparticles under simulated intestinal conditions, confirming preservation of the internal porous structure of the SLH microparticles after tableting.

CONCLUSIONS

Silica–lipid hybrid microparticles have been successfully compressed into tablets suitable as a solid-oral dosage form for poorly soluble drugs. The inclusion of mannitol in the microcapsule preparation enabled free-flowing non-cohesive powders to be produced and the yield after spray drying could be optimised by increasing the formulation batch sizes. Mannitol had negligible influence on *in vitro* dissolution of coumarin 102, which proceeded to 94% release or on the lipase-mediated digestion from the microparticles. Dissolution and enzyme-mediated lipid hydrolysis were found to be independent of the SLH microcapsule size. Once compressed into tablets by direct compression and also utilizing dry granulation, dissolution of coumarin 102 proceeded to approximately 84% and enzymatic-digestion-mediated drug solubilisation progressed to a similar extent. SLH microparticles have demonstrated to be a suitable form for lipid tablet formulation for the oral delivery of poorly soluble drugs.

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