

# Porous Polystyrene Beads as Carriers for Self-Emulsifying System Containing Loratadine

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## ABSTRACT

The aim of this study was to formulate a self-emulsifying system (SES) containing a lipophilic drug, loratadine, and to explore the potential of preformed porous polystyrene beads (PPB) to act as carriers for such SES. Isotropic SES was formulated, which comprised Captex 200 (63% wt/wt), Cremophore EL (16% wt/wt), Capmul MCM (16% wt/wt), and loratadine (5% wt/wt). SES was evaluated for droplet size, drug content, and in vitro drug release. SES was loaded into preformed and characterized PPB using solvent evaporation method. SES-loaded PPB were evaluated using scanning electron microscopy (SEM) for density, specific surface area ( $S_{BET}$ ), loading efficiency, drug content, and in vitro drug release. After SES loading, specific surface area reduced drastically, indicating filling of PPB micropores with SES. Loading efficiency was least for small size (SS) and comparable for medium size (MS) and large size (LS) PPB fractions. In vitro drug release was rapid in case of SS beads due to the presence of SES near to surface. LS fraction showed inadequate drug release owing to presence of deeper micropores that resisted outward diffusion of entrapped SES. Leaching of SES from micropores was the rate-limiting step for drug release. Geometrical features such as bead size and pore architecture of PPB were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.

**KEYWORDS:** self-emulsifying system, loratadine, porous polystyrene beads, drug carrier.

## INTRODUCTION

In recent years, much attention has been focused on lipid-based formulations for delivering Biopharmaceutic Classification System (BCS) class II (low solubility, high permeability) drugs, which suffer limited oral bioavailability, high intra- and intersubject variability and lack of dose proportionality.<sup>1</sup> Self-emulsifying system (SES) is one of

the most popular and commercially viable approaches for the delivery of such “solubility problem” drugs that exhibit dissolution-rate-limited absorption. SES is ideally an isotropic mixture of oils and surfactants and sometimes cosolvents, which emulsifies spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under gentle agitation. Upon peroral administration, these systems form fine (micro) emulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility.<sup>2-4</sup> Conventionally, SES is contained in hard or soft gelatin capsules for ease of administration. However, certain problems such as leaking, leaching of components from the capsule shell, and interaction of SES with capsule shell components are often observed for such liquid-filled capsules.

Solidification of liquid systems has been a challenge that has attracted wide attention due to handling difficulties and machinability and stability problems that are often encountered with liquids. Various attempts have been reported in literature to transform liquids into solids. Many reports on producing “liquisolds” based on the concept of blending liquid systems with selected powder excipients to produce free-flowing, readily compressible powders have been documented in the literature.<sup>5-8</sup> However, this process required very high amounts of solidifying aids such as cellulose, lactose, and silicates. Nazzal et al<sup>9</sup> formulated eutectic-based solid self-nanoemulsifying drug delivery systems (SNEDDS) using interaction between ubiquinone and oils that formed wax-like paste, which was further mixed with copolyvidone, maltodextrin, and microcrystalline cellulose to obtain tablets. Solid SES comprising goat fat and Tween 65 were formulated for delivery of diclofenac.<sup>10</sup> But the goat fat, used as an oil phase, has very limited solvent capacity, and the tablets were produced using plastic molds without application of compression force. Booth et al<sup>11</sup> formulated solid SES using an extrusion spheronization technique, wherein lactose and microcrystalline cellulose were used as solidifying aids. Schwarz<sup>12</sup> reported transformation of SES in solid dosage forms by addition of large amounts of solidifying excipients (adsorbents and polymers). But in all these studies, to obtain solids with suitable processing properties, the required ratio of solidifying excipients to SEDDS was very high, and it seems to be practically infeasible for drugs having limited solubility in oil phase. Recently, gelled SES containing ketoprofen has been formulated with the view

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that such a gelled system may serve as an intermediate for further transformation into semisolid or solid dosage forms.<sup>13</sup>

In an attempt to transform SES into a solid form with minimum amounts of solidifying aids, so as to avoid leaking and leaching problems of conventional liquid SES formulations, alternatively it was hypothesized that using capillary forces SES can be loaded into the microchannels of preformed porous polystyrene beads (PPB) typically produced by copolymerizing styrene and divinyl benzene. Porous materials with complex internal void structures have many uses in science and industry (eg, as supports for heterogeneous catalysts, absorbents of contaminants, as chromatographic support media).<sup>14</sup> PPB are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. PPB essentially consist of hydrocarbon backbone with benzene rings and are devoid of any functional groups.<sup>15</sup> Won<sup>16</sup> demonstrated entrapment of active ingredient in the network of noncollapsible pores of styrene-divinyl benzene beads for sustained release. Porous polymer structures such as macroporous high internal phase emulsion (HIPE) polymers were used as high-capacity reservoirs for included liquids<sup>17</sup> and as carriers for active pharmaceuticals for sustained delivery.<sup>18</sup> PPB have also been used as controlled release carriers for liquid biocides, added before copolymerization.<sup>19</sup>

Thus, the objective of the present study was to formulate SES containing a lipophilic model drug (ie, loratadine) and to explore the potential of preformed PPB to act as carriers for solidification of such SES. Loratadine, a class II drug and known P-glycoprotein (P-gp) substrate, is a widely used nonsedating antihistamine, which suffers high intra- and intersubject variability.<sup>20</sup> SES containing loratadine was formulated and evaluated for mean droplet size, drug content, and in vitro drug dissolution. Since the bead size distribution of the preformed and characterized PPB sample was quite wide, PPB were fractionated into 3 parts (ie, small size [SS], medium size [MS], and large size [LS]). SES containing loratadine was loaded into 3 PPB fractions separately using ethanol as a solvent aid and dried SES-loaded PPB were further evaluated.

## MATERIALS AND METHODS

### Materials

Diesters of caprylic/capric acids (Captex 200, Captex 355) and C<sub>8</sub>/C<sub>10</sub> mono-/diglycerides (Capmul MCM) were generous gifts by Abitec Corp (Columbus, OH). Medium chain triglyceride (Miglyol 812) and medium chain diesters of propylene glycols (Miglyol 840) were a generous gift from Sasol Corp (Frankfurt, Germany). Medium chain triglyceride (Labrafac CC, HLB 1) was a gift sample pro-

vided by Gattefosse (Gennevilliers, France). Cremophore EL was a gift sample from BASF Corp (Mount Olive, NJ). Loratadine (B No. LR0031547) was a generous gift by Wockhardt Ltd (Mumbai, India). Preformed and characterized styrene-divinyl benzene PPB (ADS 600, B No. 7003) was obtained as a gift sample from Thermax Ltd (Pune, India). Polyoxyethelene 20 sorbitan monooleate (Tween 80) was purchased from Merck (Darmstadt, Germany). All other chemicals and reagents were analytical grade and used as received.

### Methods

#### Formulation of Self-Emulsifying System

Different oils were screened for solubilization of loratadine. Captex 200 and Miglyol 812 showed better solubility. Ternary phase diagrams were constructed using titration method. Various SES comprising either of these oils and other surfactant and/or cosurfactant, in different proportions, were formulated by admixing the components and heating to 45°C for 10 minutes. SES were kept at ambient conditions for ~3 hours and then evaluated for visual isotropicity, turbidity, and quality of emulsion formed after dilution with water. A few promising SES, containing loratadine, were further evaluated for particle size and drug content. Based on the results of this evaluation, SES containing Captex 200 (63% wt/wt), Cremophore EL (16% wt/wt), Capmul MCM (16% wt/wt), and loratadine (5% wt/wt) was used for further studies.

#### Evaluation of Self-Emulsifying System

##### Droplet Size Analysis

Droplet size distribution of suitably diluted SES with water was determined using photon correlation spectrometer (Zetasizer 3000 HAS, Malvern Ltd, Malvern, UK) based on laser light scattering. Samples were directly placed into the module and measurements were done in triplicate after 2 minutes stirring. Particle size was calculated from the volume size distribution.

##### Emulsification Time

SES (0.5 mL) was added to 0.1 N hydrochloric acid (150 mL) under continuous stirring (50 rpm) on a magnetic plate (Ika-Werke, Staufen, Germany) at ambient temperature, and the increase in turbidity was measured using a turbidimeter (type 131, Systronics, Ahmedabad, India). Time required to disperse the system completely and uniformly was determined by observing change in turbidity as a function of time. Time point beyond which there was no increase in the turbidity was recorded as emulsification time.

### *Drug Content*

Loratadine from preweighed SES was dissolved in excess methanol, and loratadine content in the extract was analyzed spectrophotometrically (Jasco V-530, Hachioji, Japan) at 246.5 nm.

### *In Vitro Drug Dissolution*

SES containing ~10 mg loratadine was added to dissolution vessels of *United States Pharmacopeia (USP)*-24 type 2 dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The dissolution medium was 0.1 N hydrochloric acid (900 mL) maintained at  $37.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  and stirred at 100 rpm. A blank SES (placebo) was tested for dissolution, simultaneously, under identical conditions to check for interference, if any. Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through Whatman filter paper (No. 41, Mumbai, India), were analyzed by spectrophotometer at 279.6 nm for loratadine content. The data were analyzed using PCP Disso Version 3.0 software (Pune, India).

### *Characterization of PPB Fractions*

#### *Sieving of Porous Polystyrene Beads and Bead Size Analysis*

PPB were fractionated into 3 parts by sieving through No. 40 ASTM International mesh (425  $\mu\text{m}$ ) and No. 20 ASTM mesh (850  $\mu\text{m}$ ). Three PPB fractions (SS, MS, and LS), obtained after sieving, were evaluated for bead size analysis using a stereomicroscope (Stemi 2000-C, Carl Zeiss, Oberkochen, Germany), and average bead size was calculated.

#### *Bulk Density, Porosity, and Specific Surface Area of Porous Polystyrene Beads*

Bulk density of samples was determined using density tester *USP* (model ETD 1020, Electrolab). The pore distribution of PPB fractions was determined by mercury intrusion porosimetry using Carlo Erba porosimeter 2000 (Milan, Italy). Specific surface area ( $S_{\text{BET}}$ ) of fractionated PPB samples was determined from  $\text{N}_2$  adsorption-desorption isotherms. Prior to measurement, all samples were outgassed for 2 hours, and surface areas were calculated by the Brunauer-Emmett-Teller (BET) method using a surface area analyzer (FlowSorb II 2300, Micromeritics, Norcross, GA).

#### *Scanning Electron Microscopy*

Samples were mounted on double-faced adhesive tape and sputtered with thin gold-palladium layer by sputter coater unit (VG-Microtech, Sussex, UK), and surface topography

was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM) (Cambridge, UK).

### *Loading of Self-Emulsifying System into Porous Polystyrene Bead Fractions*

SES (1.0 mL) was diluted with ethanol (2.0 mL) in a stoppered test tube and one of the PPB fractions (600 mg) was added to it. The diluted SES surrounded the PPB from all sides. This mixture was shaken by vortexing for 10 minutes at ambient temperature and pressure. Ethanol was evaporated by heating at  $60^{\circ}\text{C}$  using a hot-water bath with intermittent stirring. SES-loaded PPB fractions were further dried to constant weight at  $70^{\circ}\text{C}$  in an oven (Kumar Industries, Mumbai, India) to ensure complete removal of ethanol. The dried PPB fractions were further used for subsequent evaluation.

### *Evaluation of Self-Emulsifying System-Loaded Porous Polystyrene Bead Fractions*

SES-loaded PPB fractions were evaluated for density, specific surface area ( $S_{\text{BET}}$ ) and surface topography, as described earlier.

#### *Loading Efficiency*

Efficiency of SES loading into SS, MS, and LS fractions of PPB was determined using following formula:

$$\% \text{ Loading Efficiency} = \frac{100(W_L - W_I)}{W_I}, \quad (1)$$

where  $W_L$  is the weight of SES-loaded PPB, and  $W_I$  is the initial weight of PPB.

#### *Drug Content*

Loratadine from the preweighed SES-loaded PPB fraction was extracted using excess methanol, and loratadine content in the extract was analyzed using spectrophotometer at 246.5 nm.

#### *In Vitro Drug Release*

In vitro drug release studies were performed using *USP*-24 type 2 dissolution test apparatus (TDT-06P, Electrolab). Samples of SES-loaded PPB (equivalent to 10 mg loratadine) and placebo SES-loaded PPB were placed in the dissolution vessel containing 0.1 N hydrochloric acid (900 mL) maintained at  $37.0^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  and stirred at 100 rpm. Aliquots were collected periodically and replaced with fresh and prewarmed dissolution medium. Aliquots, after

**Table 1.** Properties of SES Containing Loratadine\*

Mean Droplet Size (nm)	209 ± 7.0†
Emulsification time (minutes)	1.75 ± 0.42‡
Drug content (% wt/wt)	4.98 ± 0.14‡

\*SES indicates self-emulsifying system.

†Polydispersity index 0.324.

‡Mean ± SD (n = 6).

filtration through Whatman filter paper (No. 41), were analyzed using a spectrophotometer at 279.6 nm for loratadine content. The data were analyzed using PCP Disso Version 3.0 software.

## RESULTS AND DISCUSSION

Isotropic systems obtained in preliminary studies and yielding good quality emulsions showed varying ability to accommodate loratadine. SES formulated using Captex 200 and 1:1 wt/wt ratio of Cremophore EL (surfactant) to Capmul MCM (cosurfactant) could accommodate up to 5% wt/wt loratadine. It was a visually isotropic system, which after 200 times dilution with water yielded a slightly blue-colored, clear, and transparent emulsion (mean droplet size, 209 nm; polydispersity index, 0.324). There was neither haziness nor separation of components of SES after storage for 15 days at ambient conditions. Properties of this SES used for loading into PPB are shown in Table 1. The assay of loratadine in SES was 99.60% wt/wt and immediate in vitro drug release (96.25%, within 5 minutes) was observed in 0.1 N hydrochloric acid from such SES.

Physical properties of PPB fractions are summarized in Table 2. Since mercury intrusion porosimetry characterizes only macroporous structures, a nitrogen adsorption technique (BET method) was used to characterize microporous PPB. Specific surface area determined using BET method ( $S_{BET}$ ) was very high (4- to 6-fold) as compared with that determined using mercury intrusion porosimetry owing to better penetrability of nitrogen in the microporous structures of PPB. Preliminary studies employing composite

PPB sample for SES loading showed high variability in loading efficiency, drug content, and in vitro drug dissolution. This finding was attributed to wide bead size distribution of the PPB sample. Hence PPB were divided into 3 parts by sieving. Around 68.25%, beads ranged between 425  $\mu\text{m}$  to 850  $\mu\text{m}$  (MS fraction), while LS (>850  $\mu\text{m}$ ) and SS (<425  $\mu\text{m}$ ) fractions were ~12.55% and ~19.2%, respectively. The bulk density increased with decreasing bead size of PPB due to the better packing arrangement of SS beads. It was interesting to note that despite the bead size difference, the  $S_{BET}$  of all 3 fractions of PPB was comparable (Table 2). This finding indicated that very high surface area had been provided by the micropores as compared with the peripheral surface area, which had little contribution in surface adsorption.

After loading of SES into PPB fractions, the order of bulk density completely reversed (ie, LS fraction showed the highest, while SS fraction had the lowest density values). This reversal could be attributed to their varying SES accommodation abilities. SEMs of PPB are shown in Figure 1. Dried PPB showed rough surfaces with small pits on it. Upon SES loading, these pits filled up, accommodating SES within the micropores. The number of such filled pits was significantly reduced after adding SES-loaded PPB into aqueous phase and stirring for 45 minutes. The leaching of entrapped SES resulted in subsequent formation of a very fine oil-in-water microemulsion (mean droplet size, 170 nm; polydispersity index, 0.381).

Loading efficiency indicates the ability of PPB to hold SES within its micropores. SES to PPB ratio was found to be  $\geq 1$  for all fractions, indicating that a very low amount of PPB was required to solidify liquid SES (Table 3). Loading efficiency of SS fraction was quite low as compared with MS and LS fractions of PPB. When  $S_{BET}$  was almost similar for SS, MS, and LS, different loading efficiencies could be attributed to varying micropore architecture within PPB that could accommodate SES. The term "pore architecture" encompasses surface area, pore length (ie, bead size), average pore radius, and total porosity. Pore radius was found to decrease with decreasing bead size. During

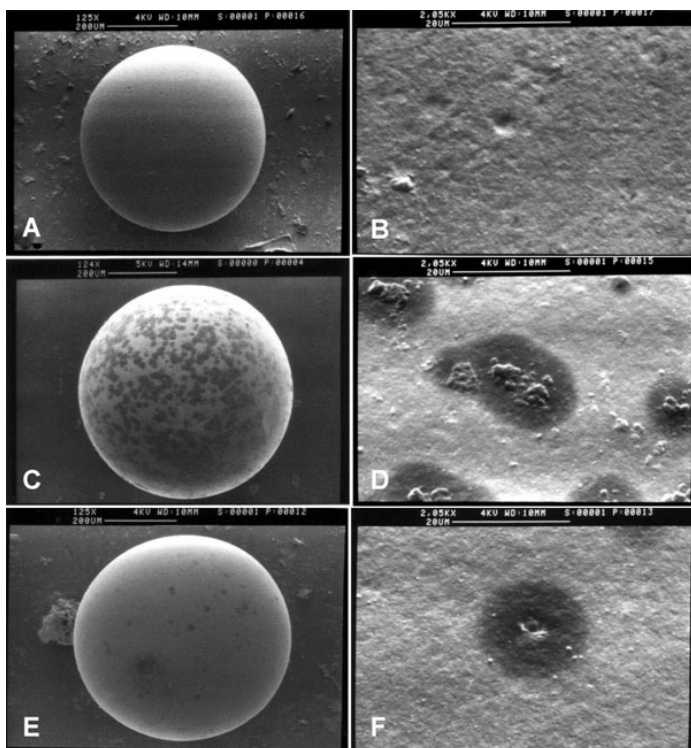
**Table 2.** Physical Properties of PPB Fractions\*

PPB	Bead Size $\pm$ SD ( $\mu\text{m}$ )†	Specific Surface Area ( $\text{m}^2/\text{g}$ )	Pore Radius ( $\text{\AA}$ )	Total (%) Porosity	Bulk Density ( $\text{g}/\text{cm}^3$ )‡		$S_{BET}$ ( $\text{m}^2/\text{g}$ )	
					As Such	SES-loaded	As such	SES-loaded
SS	403.12 ± 56.23	153.12	503	44.25	0.30 ± 0.011	0.59 ± 0.019	668.71	36.08
MS	715.5 ± 76.66	110.68	525	50.38	0.28 ± 0.015	0.66 ± 0.021	662.16	22.66
LS	1035.55 ± 89.86	86.58	554	44.17	0.27 ± 0.009	0.65 ± 0.021	677.73	7.01

\*PPB indicates porous polystyrene beads; SES, self-emulsifying system;  $S_{BET}$ , specific surface area; SS, small size; MS, medium size; and LS, large size.

†n = 60.

‡Mean ± SD (n = 6).



**Figure 1.** Photomicrographs of PPB. As such, (A and B); SES-loaded, (C and D); after SES leaching (E and F).

formation of PPB, high-speed shearing yielded some smaller droplets, which might have undergone contraction due to solvent evaporation, thus forming rigid porous structures. As a result, in the case of SS PPB, pore radius and total porosity were found to be less (Table 2). Small pore radius and relatively shallow micropores might have limited the SES loading into SS PPB. On the other hand, LS fraction should have shown very high loading efficiency owing to higher pore radius and pore length (bead size). But SES-loading efficiency of LS PPB was found to be comparable with that of MS PPB. Also, total porosity of the LS fraction was lower than that of MS PPB. This result can be ascribed to the presence of “sealed voids” within LS beads, which are not exposed and hence could not contribute to SES entrapment. This observation was further confirmed using a dye indicator, which was similarly loaded into the PPB. The cross-section of such dye-loaded LS PPB

**Table 3.** Loading Efficiency and Drug Content of SS, MS, and LS Fractions of PPB\*

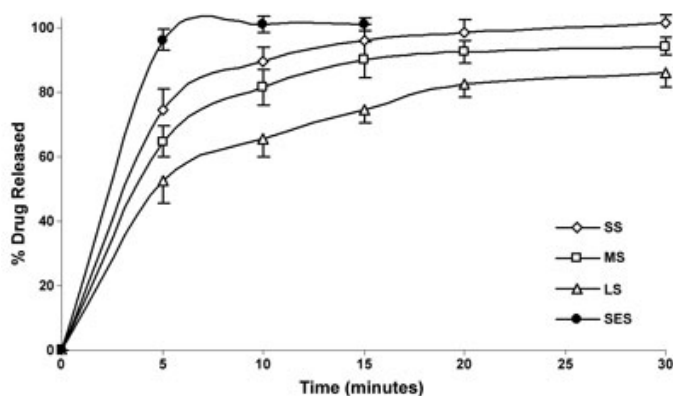
PPB	Loading Efficiency (%)†	Drug Content (% wt/wt)†
SS	96.56 ± 2.351	2.46 ± 0.021
MS	138.00 ± 2.154	2.90 ± 0.019
LS	143.33 ± 1.985	2.94 ± 0.022

\*PPB indicates porous polystyrene beads; SS, small size; MS, medium size; and LS, large size.

† Mean ± SD (n = 3).

showed many, small, uncolored areas when observed under microscope (data not shown). It was obvious that such sealed voids resulted in lesser porosity and poorer SES-loading efficiency for LS beads than expected. Thus, loading efficiency seemed to be a function of bead morphology and micropore architecture. This observation was in line with an earlier report by Salis et al<sup>21</sup> demonstrating the relationship between enzyme loading and geometrical features of mesoporous hydrophobic polypropylene substrate (Accurel MP1004).

Drug content in SES-loaded dried PPB (Table 3) was in accordance with their loading efficiencies, indicating selective loss of solvent used for SES loading without disturbing the contents and their equilibrium in SES. In vitro drug release profiles of SES-loaded PPB are shown in Figure 2. SES-loaded SS beads showed immediate drug release (~90% released in initial 10 minutes). The dissolution profile obtained from MS beads was in-between that for SS and LS beads. During in vitro drug release from SES-loaded PPB, first hydrated SES yielded oil-in-water microemulsion upon stirring. Loratadine from fine oil droplets readily partitioned into dissolution medium, which was not a rate-limiting step due to sink conditions. Thus, it appeared that when SES was withheld in the nonreactive micropores using capillary forces alone, drug dissolution was primarily governed by the rate of leaching SES entrapped from PPB micropores. Rate of outward diffusion of SES entrapped within micropores of PPB and its subsequent hydration to form oil-in-water microemulsion are the 2 essential rate-governing steps for drug dissolution in this case. Under identical and sink environments, varying drug-release profiles of SS, MS, and LS fractions indicated different micropore lengths present across these PPB. Also, in the case of LS beads, inadequate extent of drug release (~86% released in 30 minutes) was observed under sink conditions. This finding also may be due to both the high depth of micropores, probably interconnected, within LS beads



**Figure 2.** In vitro drug release profiles of SS, MS, and LS fractions of PPB and SES.

and that the SES entrapped within such long-length micropores could not effectively migrate toward the surface because of inadequate stirring. This observation was concurrent with the loading efficiencies of PPB fractions, wherein higher loading efficiency of LS beads could be attributed to longer length of micropores within its core. The “tubular model” of micropores justified variable leaching rates at different depths across the fine tubules of PPB that resulted in slower and inadequate drug release from LS beads. The drug release from SES entrapped in micropores of PPB can be expressed using Poiseulli’s equation for capillary diffusion, as given below.

$$\text{Rate of Leaching, } Q = \frac{(\delta P \cdot d^4)}{(128 \eta L)}, \quad (2)$$

where  $\delta P$  is the pressure drop across capillary (here, “pull” due to sink condition);  $d$  is the diameter of capillary;  $\eta$  is the viscosity of entrapped liquid; and  $L$  is the capillary length.<sup>22</sup>

To further confirm this observation, one sample of MS PPB was loaded with neat loratadine and the other with loratadine and same amount of surfactant in a similar manner. It was observed that in the first case, approximately 30% of drug was released in vitro (with high variability) at 2 hours, after which there was no significant drug release up to 6 hours. In the second case, more than 82% drug release was observed at 2 hours, and almost 100% drug was released up to 6 hours (Figure 3). Presence of surfactant along with drug enhanced its in situ solubilization and also reduced the resistance to its outward diffusion. In this particular study, SES migrated to the surface of PPB to form a fine oil droplet that readily dispersed in the bulk to form oil-in-water microemulsion. Resistance to diffusion of drug containing SES, governed by micropore size and length, seems to be the decisive factor, as described by Poiseulli’s equation above. In the present study, although the pore

diameter of LS PPB was higher than that of SS and MS, its favorable effect on SES leaching was probably overweighed by deeper penetration of SES into longer micropores and the net effect was retardation of SES migration toward the surface. Similar observations were reported by Iconomopoulou et al,<sup>19</sup> who demonstrated that the morphology of the polystyrene-divinyl benzene polymer seemed to have a significant effect on the liberation of entrapped low molecular weight biocides by diffusion. Landgraf et al<sup>18</sup> also reported that porous polymeric substrates (Cavilink) released their contents by diffusion over a 24-hour period, following near zero-order kinetics. The drug release was independent of drug composition or form, but entirely dependent on morphology and geometrical features of such porous polymeric substrates. Similarly, Li et al,<sup>23</sup> who fabricated porous hollow silica nanoparticles (PHSN) for drug delivery, reported that the drug release was mainly governed by PHSN conformation and its structural properties such as  $S_{BET}$ .

## CONCLUSION

PPB are potential carriers for solidification of SES, with high SES to PPB ratios required to obtain solid form. Geometrical features such as bead size and pore architecture of PPB were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.

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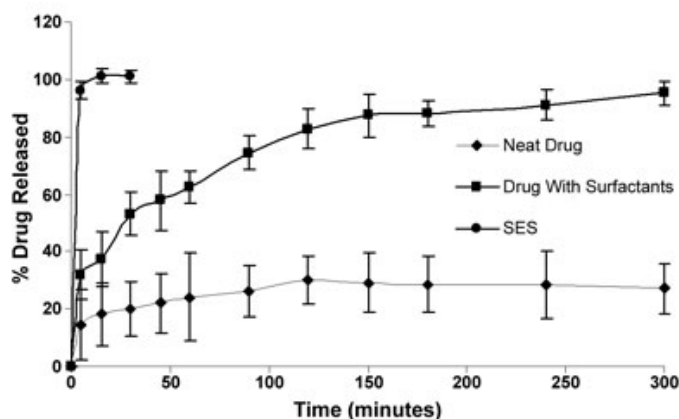


Figure 3. In vitro drug release profiles of MS PPB.

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