Multiple Vesicular Morphologies from Block Copolymers in Solution

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SUMMARY: It has been found that asymmetric, amphiphilic diblock copolymers can form a wide range of vesicle architectures in solution. These include small uniform vesicles, large polydisperse vesicles, entrapped vesicles, hollow concentric vesicles, onions, and vesicles with hollow tubes in the walls. The experimental conditions required for preparation and the proposed mechanisms for the formation of each type of structure are discussed.

1. Introduction

Over the past few years the ability of asymmetric, amphiphilic diblock copolymers to self-assemble into aggregates of multiple morphologies in solution has been the focus of several investigations in this group[1]. For these particular aggregates, the longer block forms the core of the aggregate while the corona is composed of the short segment. The manipulation of the relative block lengths, the solvent composition, the presence of additives, and the temperature has resulted in the formation of a wide range of morphologies, including spheres, rods, vesicles, lamellae, tubules, large compound micelles (LCMs), hexagonally packed hollow hoops etc. A number of other block copolymers have also been found to produce aggregates in solution[2]. Some representative examples of studies in this area from several groups are provided in reference 2, while others will be mentioned later in the text.

Several of the block copolymer morphologies are classified as vesicles because they all have hollow-spherical structures containing walls composed of bilayers of polymer molecules. Structurally, many of these different types of vesicular aggregates are not novel in that vesicles were first observed in small molecule surfactant systems[3]. This area was extensively explored in order to determine both the conditions for the formation of vesicles as well as the mechanistic details of the self-assembly processes involved in their formation. Closed,

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hollow, spherical aggregates formed from phospholipids are termed liposomes, while those prepared from synthetic molecules are called vesicles.

It has been only recently that research into block copolymer vesicle morphologies has been aggressively pursued. The earliest reports focused on vesicles prepared from bulk copolymer systems[4]. Much of the work completed by other groups on copolymers in solution has involved examining the ability to form vesicles using a variety of different polymers and techniques[5-29]. Discher *et al* have put together a review of the recent literature on this topic[5]. The simplest systems are those in which polymers self-assemble in a single solvent. This was accomplished, for example, by Holder *et al* in 1998 with pentablocks of poly (ethylene oxide)-b-poly (methylphenylsilane)[6]. Other studies have been carried out by Cornelissen *et al*[7] using charged polystyrene-b-poly (isocyanodipeptide) and by Discher et al with poly (ethylene oxide)-b-polyethylethylene[8]. Schillen *et al* have shown that vesicles can be prepared in water from a pluronic polymer (EO_5-PO_{68}-EO_5)[9]. The self-assembly of a variety of other polymers, including modified biopolymers, has also yielded vesicles in a single solvent[2b,10-14].

Mixed solvent systems are another medium from which copolymer vesicles can be obtained. Extensive studies have been completed in this group with diblock copolymers in blends of water with N, N-dimethylformamide (DMF), tetrahydrofuran (THF), or 1,4-dioxane, as well as mixtures of THF and DMF[1a, 30-47]. A series of studies have also been completed by Liu *et al* using such polymers as polyisoprene-b-poly (2-cinnamoylethyl methacrylate) and polystyrene-b-poly (2-cinnamoylethyl methacrylate)[15-19]. A number of other examples of on going research in this area have also appeared in the literature[20-23].

Vesicles can be prepared using techniques including the addition of salts, acids, and bases to the copolymer solutions[25, 45-47]. More complex structures, such as onions and hollow concentric vesicles have also been observed in copolymer solutions[26-29, 42].

In this paper, we review the families of vesicular structures that have been extensively examined by this group. This review focuses on the work completed by our group because it not only includes multiple studies on families of diblock copolymers in solution, with several investigations devoted to exploring the effects of various parameters on the wide range of vesicles observed with our systems, but also because it represents the first attempt to systematically categorize the multiple vesicles architectures obtained from the asymmetric,

amphiphilic block copolymers. Although some of the vesicles obtained are equilibrium structures, many of them, that have been quenched using a variety of methods, exist under non or near equilibrium conditions. This aspect of the behavior of asymmetric, amphiphilic diblock copolymers in solution is currently being investigated. Six different types of polymers have been utilized in these studies, including polystyrene-b-poly(acrylic acid) (PS-b-PAA), polystyrene-b-poly(ethylene oxide) (PS-b-PEO), poly(1,4-butadiene)-b-poly (acrylic acid) (PBD-b-PAA), polystyrene-b-poly(4-vinylpyrinium methyl iodide) (PS-b-P4VPMeI), polystyrene-b-poly(4-vinylpyrininium decyl iodide) (PS-b-P4VPDecI), and polystyrene-b-poly(methyl methacrylate)-b-poly(acrylic acid) (PS-b-PMMA-b-PAA).

We classify each vesicle morphology into various categories, and outline the conditions required for the existence of each structure. We then speculate on the mechanism leading to the formation of these vesicles with special attention paid to similar transitions in the small molecule surfactant literature. This aspect of the discussion is supported by evidence of the non-equilibrium structures that have been trapped in the transition regions between two types of stable morphologies. Changes in a number of factors lead to these transitions. These include the solvent composition, the temperature, and the addition of ions to the system. These factors can induce morphological changes by altering the parameters that control the architecture of these aggregates, i.e. core chain stretching, interfacial tension, and corona repulsion. It should be noted that block copolymers differing only in their relative block lengths may yield different morphologies under identical experimental conditions.

2. Classification of Vesicle Architectures

Vesicles are the most commonly observed class of aggregates of all of the bilayer structures in solution. There are a wide variety of structural sub-classes that are considered to be vesicular aggregates such as small uniform, polydisperse, entrapped, and hollow concentric vesicles, as well as solid onion structures and those with tubes in the walls. Small uniform and large polydisperse vesicles have been also prepared from copolymer solutions with the addition of salts, HCl, and NaOH.[45-47)]

2.1 Uniform bilayer vesicles

A number of the systems investigated were able to form small monodisperse vesicles under given conditions (Figure 1A)[1a, 32, 34-36, 39-41, 43]. The shared characteristic of all of the systems is that each polymer contains a block of polyacrylic acid (Table 1).

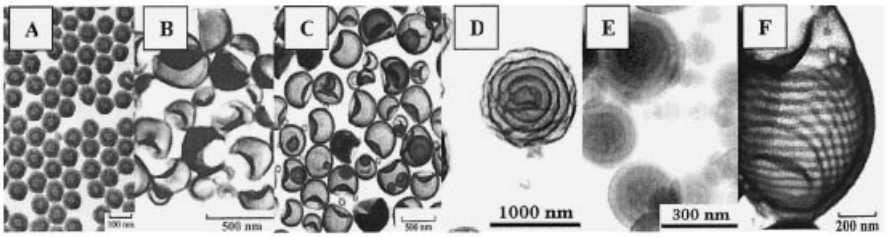

Fig. 1: Representative Micrographs of each family of vesicles. A: small uniform vesicles[1a)], B: large polydisperse vesicles[31)], C: entrapped vesicles[36)], D: hollow concentric vesicles[42)], E: onions[42)], F: vesicles with tubes in the wall[44)].

Table 1. Conditions for the formation of small uniform vesicles.

Polymer	Content of 2nd Block (mol %)	wt % polym.[a]	Solvent (wt %)	Diameter (nm)	Ref.
PS_{200}-b-PAA_8	3.8	2.0	<25 % H_2O in DMF	50	32
PS_{410}-b-PAA_{16}	3.8	2.0	<25 % H_2O in DMF	150	1a
PBD_{360}-PAA_{16}	4.3	0.25	<33 % H_2O in THF	70	34
PS_{410}-b-PAA_{20}	4.7	2.0	<25 % H_2O in DMF	80	32
PS_{500}-b-PAA_{58}	8.3	2.0	<50 % H_2O in THF	115	36
PS_{200}-b-PAA_{18}	8.3	0.5 & 2.0	<50% H_2O in 10-40 % THF in DMF	60	36
PS_{190}-b-PAA_{20}	9.5	2.5-3.5	6.5-9.5 % H_2O in DMF	----	43
PS_{500}-b-PAA_{58}	10.4	2.0	<50 % H_2O in dioxane	----	36
PS_{49}-b-$PAA_{7.2}$	12.8	0.1-10	31-50 % H_2O in dioxane	----	41
PS_{310}-b-PAA_{52}	14.4	0.1-10	14-50 % H_2O in dioxane	100	39-41
PS_{180}-b-$PMMA_{67}$-b-PAA_{37}	-----	3	<25 % H_2O in dioxane	60	35

[a] Initial copolymer concentration.

2.2 Large polydisperse bilayer vesicles

Large polydisperse vesicles are formed more frequently than other types of vesicles (Fig. 1B). They have been formed, in this laboratory, from three different copolymers, PS-b-PAA,

PS-b-PEO, and PS-b-P4PMEI as outlined in Table 2[30-33, 36, 38, 41]. The most notable feature of this subcategory of vesicles is that for some polymers, they can be prepared from a single solvent (alcohol) at high temperatures[30].

Table 2. Conditions for the formation of large polydisperse vesicles.

Polymer	Content of 2nd Block (mol %)	wt % Polym.[a]	Solvent (wt %)	Diameter (nm)	Ref.
PS_{410}-b-PAA_{20}	4.7	3.0	<25 % H_2O in DMF	50-500	32
PS_{420}-b-PAA_{26}	5.8	2.0	<50 % H_2O in dioxane	580-1830	36
PS_{240}-b-PEO_{15}	5.9	2.0	<25 % H_2O in DMF	250-500	31,38
PS_{420}-b-PAA_{32}	7.1	2.0	<50 % H_2O in dioxane	----	36
PS_{200}-b-PAA_{18}	8.3	0.5 & 2.0	< 50% H_2O in 40-67 % THF in DMF	140-570	36
PS_{195}-b-$P4VPMEI_{18}$	8.5	1.0	<50% H_2O in 50% THF in dioxane	120-160	33
PS_{390}-b-PAA_{41}	9.5	2.0	<50 % H_2O in THF	----	36
PS_{132}-b-PAA_{16}	10.8	0.1-10	21-50 % H_2O in dioxane	75-380	41
PS_{390}-b-PAA_{41}	12.4	2.0	<50 % H_2O in dioxane	115-430	36
PS_{132}-b-PAA_{20}	13.3	0.1-10	22-50 % H_2O in dioxane	70-300	41
PS_{240}-b-PEO_{45}	15.8	1.5	4.0 % H_2O in DMF	----	38
PS_{132}-b-PAA_{26}	16.5	0.1-10	24-50 % H_2O in dioxane	75-250	41
PS_{386}-b-PAA_{79}	16.8	0.1	Methanol	----	30
PS_{386}-b-PAA_{79}	16.8	0.1	Propanol	----	30
PS_{386}-b-PAA_{79}	16.8	0.1	Ethanol	110-260	30
PS_{100}-b-PEO_{30}	23.1	1.0	<90 % H_2O in THF	200-400	44
PS_{125}-b-PEO_{30}	19.3	1.0	<90 % H_2O in THF	200-400	44
PS_{215}-b-PEO_{37}	14.7	1.0	<90 % H_2O in THF	200-400	44

[a] Initial copolymer concentration.

2.3 Entrapped vesicles

Entrapped vesicle structures are composed of a single or multiple vesicles encased within a larger vesicle as shown in Figure 1C. It is possible to obtain these structures from both PS_{200}-b-PAA_{18} and PS_{240}-b-PEO_{15} in mixtures of H_2O/THF/DMF and H_2O/DMF respectively (Table 3)[36, 38].

Table 3. Systems that form Non-Classical Vesicles

Morphology	Polymer	Content of 2nd Block (mol %)	wt % Polym.[a]	Solvent (wt%)	Diameter (nm)	Ref.
Entrapped Vesicles	PS_{240}-b-PEO_{15}	5.9	2.0	<25 % H_2O in DMF	300-600	38
	PS_{200}-b-PAA_{18}	8.3	3.0	<50% H20 in 50% THF in DMF	200-300	36
Solid Onions	PS_{260}-b-P4VPDecI$_{70}$	21.2	1.0	<50 % H_2O in DMF	100-500	42
Hollow Concentric Vesicles	PS_{132}-b-PAA_{20}	13.2	10	<25 % H_2O in dioxane	500-1200	42
Vesicles with Tubes in the Walls	PS_{100}-b-PEO_{30}	23.1	1.0	<90 % H_2O in THF	200-400	44
	PS_{125}-b-PEO_{30}	19.3	1.0	<90 % H_2O in THF	200-400	44
	PS_{215}-b-PEO_{37}	14.7	1.0	<90 % H_2O in THF	200-400	44

[a] Initial copolymer concentration.

2.4 Hollow concentric vesicles

Hollow concentric vesicles represent a new morphology, which has been observed only recently for the first time in these block copolymer systems (Fig. 1D). So far, they have been formed only from a solution of 10 wt % PS_{132}-b-PAA_{20} in 25wt% H_2O/dioxane (Table 3). The structure resembles an onion with spaces between the layers, where each layer is an individual vesicle and each concentric vesicle may contain as many as 6 layers with a spacing between the walls of 58 ± 11 nm (95 % confidence)[42].

2.5 Onions

Onions are another type of layered structure (Fig. 1E). In this case, the layers are lamellar aggregates attached to each other, with up to eight layers detectable. This particular structure has been observed in this group only with polystyrene-block-poly (4-vinyl pyridine decyl iodide) in a mixture of water and DMF as indicated in Table 3[42].

2.6 Vesicles with hollow tubes in the wall

Asymmetric polystyrene-b-poly(ethylene oxide) diblock copolymers have been found to produce vesicles with a bilayer wall composed of hollow tubes as an intermediate in the transition between small uniform vesicles and hexagonally packed hollow hoops (Fig. 1F). However, these large vesicles have thicker walls than classical vesicles. The tubes are

between 5 to 10 nm in diameter with 15 to 20 nm spacing between each tube. Table 3 summarizes the systems that form these structures. They can also be prepared from mixtures of PS-b-PEO copolymers with varying PEO block lengths[44].

3. Possible Mechanisms for the Formation of Vesicle Morphologies

The mechanistic aspects of vesicle formation involve a number of different processes. A detailed investigation has enabled us to map out the steps involved in the formation of small uniform vesicles from rods[39-40]. In so far as these aggregates originate from rod-shaped structures, they are converted into aggregates containing one or more paddle-like protrusions (Fig. 2A). The ribbon portion of the aggregate becomes incorporated into the circular lamellar regions; the aggregate curves into a bowl-shaped structure, which closes to form a vesicle in the final step[39]. This may well be the predominant means of forming small uniform vesicles from rods.

There is considerable evidence that indicates that large polydisperse vesicles can originate from lamellae. Figure 2B is a micrograph of a bent lamella[38]. It is believed that this is an intermediate structure, and that the lamella continues to bend until it closes to form a vesicle. Although bent lamellae have never been observed in small molecule surfactant systems, it is widely believed that large surfactant vesicles are formed from lamellae[48]. It is suggested that large disk-shaped bilayers can bend due to thermal fluctuations, which may lead to vesicle formation[49].

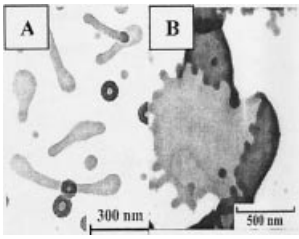

Fig. 2: Intermediate precursors to vesicle morphologies. A: paddle structures[39], B: bent lamella[38].

It has been speculated that the formation of an entrapped vesicle is initiated by the formation of a large vesicle from a solution of relatively high copolymer concentration in a water rich co-solvent mixture[42]. Such vesicles contain polymer molecules trapped within their cores,

which are able to self-assemble into a smaller vesicle as the organic solvent in the core of the large vesicle is gradually replaced with water through a diffusion process with the outside solvent. This solution process is also associated with the ability to form hollow concentric vesicles. The mechanistic details are the same in this case, but the large parent vesicle is bigger and the polymer concentration in its core is higher. Hence, smaller vesicles can form inside the larger sized parent vesicle[42]. It is also possible that this process may resemble that occurring in small molecule surfactant systms[50].

The formation of solid onions in solution appears to be similar to the preparation of the lamellar phase in bulk[42] At low water contents large micelles form. As the water content increases, the internal structure of the micelles undergoes rearrangement. This is accompanied by the diffusion of the solvent mixture out of the core of the micelles, which leads to the formation of dense concentric vesicles. Dense onions are formed when solvent diffuses out of the hydrophobic and hydrophilic layers at nearly the same rate. In contrast to the scenario in large samples, e.g. bulk, flat lamellae do not form because the small size of this structure leads to curvature in order to avoid the thermodynamic rim penalty[51].

Vesicles with hollow tubes in the walls are non-equilibrium intermediate structures formed during the transition from of small classical vesicles to hexagonally packed hollow hoops[44]. Although this transition has been observed in systems of both PS-b-PEO and PS-b-PAA, these intermediate vesicles are seen exclusively in the PS-b-PEO systems[2c, 44]. It is believed that they are formed in the first step of a three-step mechanism. Initially vesicles containing hollow regions in the walls are formed from small classical vesicles. This is associated with the thickening of the walls of the vesicles and the development of hollow rods running parallel to the wall surface. The overall size of the vesicles also decreases during this process[44].

4. Conclusion

It has been shown that a diversity of vesicle structures can be prepared from asymmetric, amphiphilic diblock copolymers in solution. The morphology can be controlled by altering the influence exerted by a given parameter on the interplay of three of the major components of the free energy of the aggregates. These components include the stretching of the core forming block, the interfacial free energy, and the inter-corona interactions.

The morphological capabilities of six different copolymers have been examined in this laboratory over the past few years. It is possible to group the vesicular aggregates formed from each copolymer into six general categories, small uniform, polydisperse, entrapped, and hollow concentric vesicles, as well as solid onion structures and those with tubes in the walls. The classification has been made in order to examine the specific experimental conditions required for the preparation of each structure. This work summaries the conditions leading to the formation of these aggregates. However, vesicles are only one of many bilayer morphologies that have been observed by this group[1e, 31, 37-38, 40-41, 45].

Although extensive investigations of the mechanisms for the preparation of most of these aggregates have yet to be completed, it is possible to hypothesize the steps involved in these processes from micrographs of the intermediate structures and from theories developed for similar processes in small molecule surfactant systems.

All of this knowledge contributes to the control that can be exerted over vesicular morphologies. Such influence may prove to be useful for several potential applications of such aggregates including their use as model vehicles for the delivery of various species, e.g. drugs.

Acknowledgements

The authors would like to thank the Natural Sciences and Engineering Research Council of Canada and the Petroleum Research Fund for supporting this research.

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