

Nanoparticles and Nanocapsules Created Using the Ouzo Effect: Spontaneous Emulsification as an Alternative to Ultrasonic and High-Shear Devices

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The preparation of polymeric particles and capsules by means of spontaneous droplet formation and subsequent polymer precipitation or synthesis is well-known. However, spontaneous emulsification is a phenomenon that has often been erroneously interpreted. This Minireview provides new insights into the preparation of metastable liquid dispersions by homogeneous liquid-liquid nucleation, and is based primarily on a recent study by Vitale and Katz (Langmuir, 2003, 19, 4105–4110). This spontaneous emulsification, which they named the Ouzo effect, occurs upon pouring, into water, a mixture of a totally water-miscible

solvent and a hydrophobic oil—and optionally some water—thus generating long-lived small droplets, which are formed even though no surfactant is present. Herein, we review and reinterpret the most relevant publications on the synthesis of a variety of dispersions (pseudolatexes, silicone emulsions, biodegradable polymeric nanocapsules, etc.), which we believe have actually been synthesized using the Ouzo effect. The Ouzo effect may also become a substitute for high-shear techniques, which, to date, have only been of limited utility on industrial scales.

1. Introduction

Well-known aperitifs (Ouzo in Greece, Pastis in France, etc.) are ethanol extracts of anis seeds. Upon dilution with water, such extracts, whose major components are water, ethanol, and the water-insoluble substance anethol, become cloudy instantaneously and remain so for a long period of time. This phenomenon is quite general; it can occur upon mixing large amounts of water with almost any solution consisting of a small concentration of an oil in a hydrophilic solvent [though only over a narrow range of concentrations (Figure 1)].^[1] The converse,

in the phase diagram of these mixtures there is a region, between the spinodal and the binodal curves, where a metastable dispersion can be generated (Figure 2). The Ouzo effect arises because, on mixing with water, the oil becomes greatly supersaturated, which results in the nucleation of oil droplets. Oil immediately begins diffusing to the nearest droplet, so that the supersaturation decreases and no further nucleation occurs (Figure 1).

This Minireview is not intended to exhaustively cover the published literature. Instead, it proposes new interpretations on polymer aqueous suspension preparation processes that we think have made use of the Ouzo emulsification technique. Most of these reported studies aimed at preparing either nanospheres or nanocapsules, depending on whether the samples contained or not, respectively, a liquid lipophilic oil in the solvent phase (during the emulsification, oil repels the polymer at the oil/water interface to form the capsule walls). Their typical intended use was in drug vectorization^[3–6] or cosmetic applications^[7] (details on the encapsulation efficiency or release will not be reviewed here). This Minireview also discusses the advantages of the spontaneous emulsification technique compared to high-shear and ultrasonification processes, particularly for systems where rapid “interfacial” polymerization occurs (for

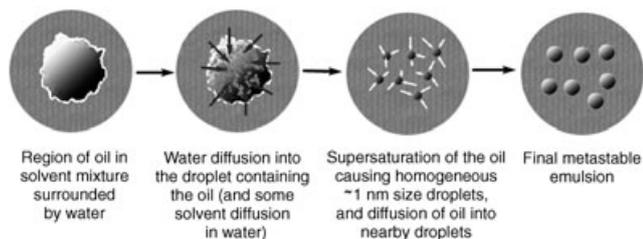


Figure 1. Schematics of the liquid-liquid nucleation process or Ouzo effect. The solvent phase, which contains the water-immiscible oil, is poured into the aqueous phase, to which a surfactant might be added. The diffusion of water into the oil-containing solvent droplet causes the supersaturation of oil and droplet nucleation. Droplet growth ceases when the aqueous phase is no longer supersaturated with the oil.

that is, the addition of small amounts of water to an oil-rich solution, can also produce an emulsion.^[1,2] A recent detailed study^[1] presented both an explanation for this phenomenon and a description of the conditions needed to cause these spontaneous emulsifications to occur. This study explains that

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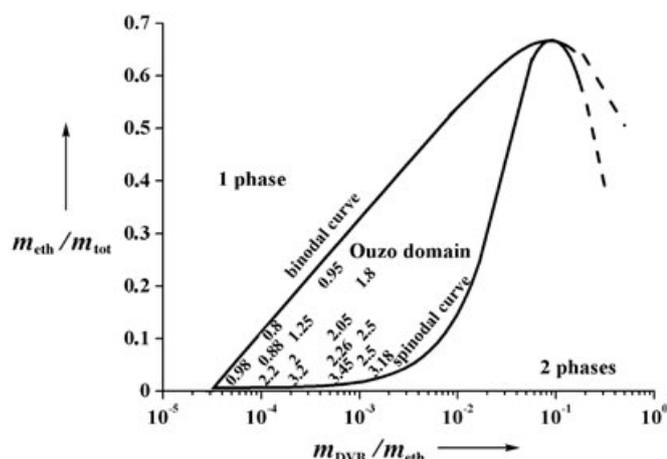


Figure 2. Phase diagram of divinylbenzene (DVB) dispersions (prepared according to the Ouzo procedure) plotted as the weight fraction of DVB (m_{DVB} in g) introduced originally in ethanol (m_{eth} in g) versus the weight fraction of ethanol in the final ethanol/water mixture (m_{tot} in g). The labels at different ethanol/water/DVB concentrations represent the average diameters, in microns, measured by PCS (adapted from Figures 2 and 3 of ref. [1]).

instance, the anionic polymerization of cyanoacrylates and methylidene malonates, or the polycondensation using monomers with water-sensitive groups, such as isocyanate or acid chloride).

Note that there are several reviews^[8–10] on spontaneous emulsification, which discuss the “diffusion and stranding” process,^[11] but these articles neither explain the starting point of the emulsification nor do they quantify the effect. In few of the articles reviewed here,^[12,13] a Marangoni effect was invoked as the explanation for spontaneous emulsification; it was thought that emulsification occurred because severe fluctuations in surface tension caused the fingering of the organic phase into the aqueous phase and the subsequent formation of capsules or particles. However, spontaneous emulsification was observed to take place on mixing both *with* and *without* surfactant. Without surfactant, it would only be very near the critical point that strong surface-tension variations would occur, while the Ouzo domain includes regions far from the critical point. Some evidence that suggests that the Ouzo effect is the controlling cause of spontaneous emulsification is given below.

2. Spontaneous Emulsification

The key features of this homogenous liquid–liquid nucleation process come from the paper published by Vitale and Katz,^[1] and from some complementary information obtained in studies that did not make use of polymers or reactive monomers.^[12,14,15] A phase diagram for the divinylbenzene (DVB)/ethanol/water system, adapted from ref. [1], is given in Figure 2. Below the binodal curve, typically at high solvent concentration, the oil is completely soluble in the continuous medium. This homogeneous mixture of monomer/ethanol/water is, for example, the starting point for the so-called “dispersion polymerization process”, which is used to produce, after polymeri-

zation, large particles (on the order of 10 to 1000 μm). Inside the spinodal region, emulsification occurs by means of the process known as “spinodal decomposition”, which produces coarse emulsions that, therefore, rapidly separate.

The size range of the metastable emulsions described in the Vitale and Katz paper varied typically between 1 and 4 μm (Figure 2), the particle size increasing with increasing proximity to the spinodal curve, as well as with increasing oil concentration in the initial solution (i.e. before mixing into water). Diameters as small as 200 nm have also been obtained using larger ethanol-to-oil ratios^[14] than those used by Vitale. In the Ouzo domain, the droplet diameter was shown to be a function only of the ratio of excess oil to ethanol (i.e. subtracting the oil which remains dissolved in the final ethanol/water solution from the initial amount of oil).^[1,15] It did not depend on stirring rate, pH, or ionic strength.^[12]

The emulsions thus produced are kinetically stable, *without* the presence of any surfactant. The Ouzo effect produces droplets, which are homogeneously sized and are large enough so that the Ostwald ripening is greatly retarded, but are small enough so that creaming is slow, especially when the density of the oil is close to that of water. Emulsions were made, via the Ouzo effect, using an oil whose density was close to that of water; these emulsions were almost monodisperse and were stable for months.^[1] Nonetheless, in most of the studies reported below, surfactants (mostly PEO–PPO block copolymers or Dextran) were added to the aqueous phase prior to emulsification to obtain stable emulsions, which lasted for very long times (typically more than 6 months).^[12]

The droplet size distribution is strongly affected by the temperature or the nature of the solvent used during the process.^[1] Increasing the temperature raises the content of oil in the final solution (i.e. water plus a little solvent), thus producing droplets with smaller sizes. As the emulsion temperature is decreased to room temperature, the oil becomes increasingly insoluble, causing the excess to diffuse into preexisting droplets. This diffusion narrows the size distribution, since diffusing a fixed amount of oil into a larger droplet causes its diameter to increase less than the diameter increase of a smaller droplet. Solvents which partition much more into water than into the oil do not swell the emulsion droplets, as demonstrated by the constant diameters of the oil droplet prior to and after solvent evaporation.^[14,15] However, for solvents which partition more evenly, for example, acetonitrile,^[1] large droplets with a large size distribution are produced.

There are, of course, some limitations to the use of the *Ouzo* emulsification process. One of the main problems is that the content of oil in the emulsion is rather small (typically 1% initially and less than 5% after solvent evaporation, see Figure 2). Another requirement for the *Ouzo effect* is that the solvent should be soluble in water in all proportions.^[1,15] Solvent recovery is less of a problem than one might think. It is true that many of the most appropriate solvents, for example, ethanol, acetonitrile, and THF, form azeotropes with water; however, azeotropes represent no difficulty, since their composition is more than rich enough in solvent to be directly usable (e.g., the water–ethanol azeotrope is 95% vol. ethanol). After all, the

concentration of ethanol in French Pastis is only 45% ethanol by volume prior to emulsification.

3. Spontaneous Polymer Precipitation

Polymer dispersions in water can be prepared by well-known emulsification techniques,^[4] which include solvent evaporation, mechanical means (sonication, microfluidization), and coacervation. The Ouzo effect, which has also been called “coacervation with addition of a nonsolvent”, “solvent displacement process”,^[16] “spontaneous emulsification”,^[6] “nanoprecipitation”,^[17–21] or “microprecipitation”,^[22] is clearly a simpler method that could be used to prepare drug-loaded particles or oil-filled capsules of various commercial polymers.

Table 1 summarizes the main features of nanoparticles prepared from a polymer solution using the Ouzo effect. Various polymers containing charged groups in their backbone—for example, carboxylate^[2] and quaternary ammonium groups,^[6] or nonionic hydrophilic groups, such as polyethylene glycol^[18,19]—were successfully emulsified without the need of stabilizers. In all instances, the particles thus formed were smaller than those prepared by means of the solvent evaporation technique (i.e. by dissolving the polymer in dichloromethane prior to emulsification). These particles, however, could not be freeze-dried, presumably because the solvent was not removed completely (thus plasticizing the polymer during water sublimation).^[6]

Other polymers required the use of partially hydrolyzed polyvinyl alcohol or triblock copolymers as dispersants (at concentrations similar to those of the polymer). Also, in some instances, an ionic surfactant, such as a phospholipid or a sulfate or sulfonate surfactant (see Table 1), was required. For poly(DL-lactide) (PLA)^[2,16] and poly(DL-lactide-co-glycolide) (PLGA),^[7,23] particle sizes, which were typically on the order of 200 nm, were obtained. In ref. [23], the authors used a mixture of two

substances, ethanol and acetone, which were good solvents for the polymer (PLGA) and for the surfactant (PVA), respectively. Their study shows the limitations of the process, particularly regarding the polymer content that can be precipitated or the ratio of solvent necessary not to precipitate the PVA in the final water/solvent phase. Other polymers, which include small polystyrene chains end-capped with TEMPO, could also be emulsified; they then served as seeds for further radical-controlled polymerization in (mini)emulsions.^[22]

Fessi and co-workers^[24] also successfully prepared nanocapsules from preformed polymers using the Ouzo emulsification technique. They used a variety of polymers (Rhodopas AX 85–15, polyisobutyl-cyanoacrylate, poly(DL-lactide)) together with a commonly used excipient (benzyl benzoate) for oral administration of various encapsulated drugs. Capsule sizes ranged between 200 and 500 nm, with a quite narrow polydispersity. A rather striking example was the preparation of “empty nanocapsules”—in other words, hollow particles—by replacing the excipient with a volatile solvent, such as ethyl ether.^[24] Unfortunately, micrographs which would have provided information on the structure of the capsule walls, were not included in this patent.

The above authors proceeded by “trial and error” to find the emulsification operating window. We know from several studies that, in all instances, the phase separation occurred by Ouzo emulsification. In two studies,^[25,26] a phase diagram was derived, including both the binodal and spinodal lines; it should be emphasized that the nanoprecipitation was performed in the absence of surfactant. Furthermore, some authors showed that, upon pouring an excess of an acetone solution of polystyrene^[22] or poly(ϵ -caprolactone)^[25] in water, large particles arising from spinodal decomposition were formed in addition to the Ouzo pseudolatex. Finally, another evidence that suggests that the emulsification process is directed by the Ouzo effect is established by the almost-constant

Table 1. Main features for nanosphere preparation using the spontaneous polymer precipitation process.

Polymer ^[a]	\bar{M}_w [kg mol ⁻¹]	Stabilizer ^[a]	Solvent	Particle size [μm]	Dispersity	Ref.
Eudragit	–	–	Acetone, Ethanol	0.09–0.28	0.26	[6]
Poly(PEG-PHDCA)	–	PVA	Acetone, Ethanol, DMSO, Isopropanol, Ethyl Lactate	0.052–0.25	–	[20]
	3	–	THF	0.10–0.16	< 0.1	[18]
MPEG-PLA	62.5	–	Acetonitrile	0.08–0.11	0.17–0.11	[19]
HP55	–	SDS	Acetone + Water	0.3	0.096	[19]
PCL	55	Pluronic	Acetone	0.21	0.04	[17]
	140	–	Acetone	0.11–0.15	0.12–0.2	[25]
PLA	–	Pluronic	Acetone	0.2	0.07	[2]
	94	Pluronic	Acetone	0.11	0.02	[17]
	–	Pluronic	Acetone + Water	0.09	0.18	[2]
PLGA	46.8	PVA	Ethanol + Acetone	0.26	0.34	[23]
	52, 112	Pluronic	Acetone	0.125	0.04	[17]
PS	3.3	SDBS	Acetone	≈ 2.00	–	[22]
	3.3	PVA	Acetone	0.40–0.90	–	

[a] Abbreviations: Eudragit: poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) in proportions 1:2:0.1 or 0.2; Poly(PEG-PHDCA): poly(hexadecylcyanoacrylate-co-methoxypolyethylene glycol cyanoacrylate); MPEG-PLA: poly(lactide)-co-(methoxypolyethyleneglycol); HP55: hydroxypropyl methylcellulose phtalate; PS: polystyrene; PLA: poly(D,L-lactide); PLGA: poly(lactide-co-glycolide). SDBS: sodium dodecyl benzene sulfonate; SDS: sodium dodecyl sulphate. Pluronic: block copolymers of poly(ethylene oxide) and poly(propylene oxide).

average particle size and size distribution observed, independently from the type and content of surfactant^[13,16,19] and/or solvent^[19,20,23] used.

Knowing that the Ouzo effect can be used to cause the emulsification of polymers, we examined the most recently published data to **determine the key experimental conditions**, where the emulsification process switches from Ouzo effect to spinodal decomposition. Figures 3a and 3b report the amount of polymer lost into spinodal aggregation as a function of the

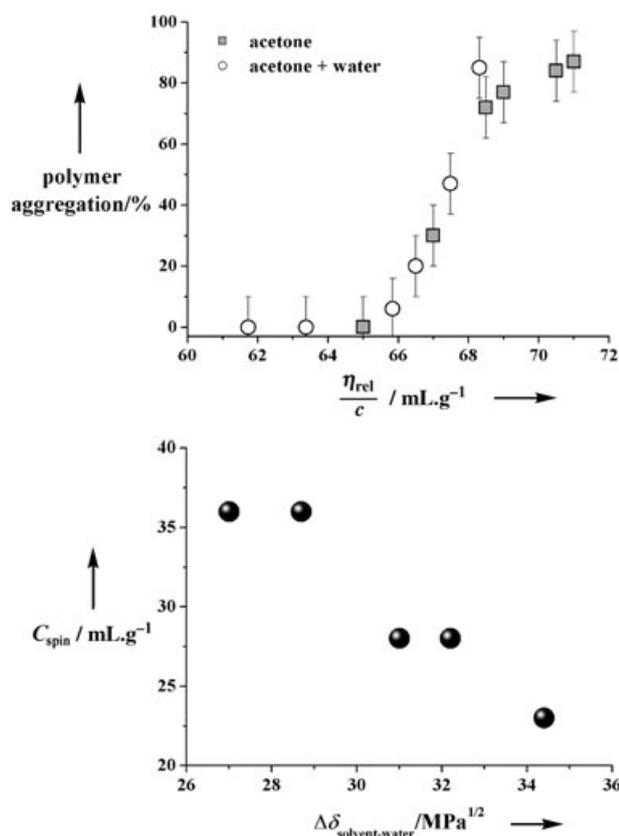
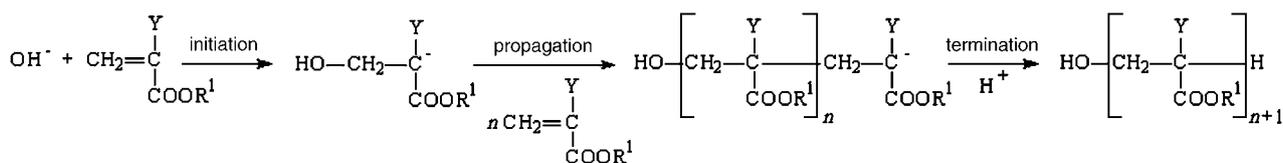


Figure 3. Transition from Ouzo effect to spinodal decomposition: polymer aggregation by spinodal decomposition during the emulsification of two different polymers: a) emulsification in water of HP55 (see chemical structure in Table 1) dissolved in acetone or acetone/water ($\approx 30\%$ v/v). The plot was reprocessed from the data in Figures 1 and 3 of ref. [21] using a viscosity for the acetone/water solution of 0.823 mPa.s; b) concentration at which polymer aggregation occurs by spinodal decomposition (C_{spin}) plotted versus the difference in solubility parameters between water and different solvents. This plot was reprocessed from data taken from Figure 5 and Table 2 of ref. [20].



Scheme 1. Anionic polymerization of electron-deficient vinyl monomers (alkylcyanoacrylates, $Y = \text{CN}$, and methylenemalonates, $Y = \text{COOR}^1$, where R and R^1 are variable alkyl chains) proceeding in water.

viscosity of the initial polymer solution and of the affinity of the solvent for water. These plots present recalculations (or re-drawings) carried out using the data in refs. [21] and [20], respectively (see the Figure caption for details). Figure 3a shows that, for an efficient emulsification to happen, the polymer should be diluted enough so that the viscosity of the solution is sufficiently low. Another trick to depress the viscosity consists in including a small concentration of the nonsolvent (either water^[2,21] or ethanol^[25,27]) in the acetone prior to emulsification. Both procedures are believed to suppress entanglements between polymer chains, which, when present, are enough to fail the emulsification process. Figure 3b confirms the finding of the Ouzo effect that the solvent should not partition significantly into the polymer, since, otherwise, badly defined dispersions would be generated. This may also be the reason why all polymer emulsification trials made using dimethyl acetamide generated large and porous particles (on the order of a few tens of microns) instead of nanodispersions.^[28]

A quick conclusion on this part is that the pseudolatex preparation using the Ouzo effect will be efficient if the solvent (or the mixture of solvents): i) is a theta solvent for the polymer, ii) is fully miscible with water, and iii) has a solubility parameter close to that of water.

4. Spontaneous Polymerization

Since the pioneering paper of Couvreur,^[29] many articles have proposed the synthesis of nanospheres or nanocapsules of biodegradable polyalkylcyanoacrylates or polymethylenemalonates (for a recent review on the subject, see ref. [30]). These nanocapsules were prepared by “spontaneous” anionic polymerization of the (extremely reactive) corresponding monomers in the presence of water, as is presented in Scheme 1.

The preparation of nanospheres using a conventional suspension polymerization process requires careful control of the experimental conditions to avoid aggregate formation. For the polymerization of alkylcyanoacrylates, the pH is kept between two and three, since the presence of only a few OH^- molecules is sufficient to start the polymerization.^[31] A rapid dispersion of the monomer in the water phase is achieved by dropwise addition of the corresponding monomer into a beaker, which contains a surfactant solution that is being stirred at a high rate (1000 rpm); nonetheless coagulation still occurs. The polymer that forms the nanospheres has low molar mass (typically

2000 g mol^{-1}),^[32] a result that we recently explained to be caused by the interfacial control of polymerization.^[33] For methyldiene malonate derivatives, a pH as high as five can be used, but a cycle closure reaction limits the oligomer chains to molar masses of about 700 g mol^{-1} , which are too small to clearly favor particle formation.^[34,35]

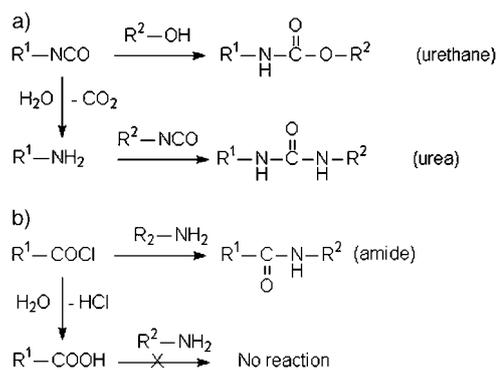
An alternative process, which we now recognize as the Ouzo effect, was used as driving mechanism. Stable dispersions were prepared, in an easier and much more reproducible way than that mentioned above, simply by dissolving one of the above monomers—with or without an inactive oil (typically fatty esters such as Miglyol)—in excess hydrophilic solvent prior to water addition.^[36] For alkylcyanoacrylates, only nanocapsules were prepared, that is, in the presence of Miglyol. The absence of oil caused the formation of “flakes”, as could be observed by electron microscopy.^[12] On the other hand, the preparation of nanospheres of poly(methyldiene malonates) by spontaneous emulsification was patented recently.^[37]

Again, several clues indicate that this emulsification occurred via the Ouzo effect. The researchers stated that: i) neither pH nor stirring rate had to be adjusted to control the size of the dispersion;^[38] ii) no formation of macroscopic aggregates occurred, although the final polymer had high molar mass;^[12,37] iii) the particle size did not depend on the type of solvent, the nature of the surfactant, or the monomer concentration;^[39] iv) the only variable that had an influence on the average capsule size was the oil/solvent ratio.^[12,24,36] Their observations are exactly what one would expect for emulsifications that occur via the Ouzo effect.^[1] After evaporation, the capsules retained their diameters (from 200 to 500 nm),^[38] as expected in liquid-liquid nucleation processes when using a solvent that does not swell the oil droplets.

The choice of the solvent appears to be crucial in these experiments.^[12,39,40] Protic solvents, such as ethanol, were able to start the polymerization of alkylcyanoacrylates and generate oligomers prior to emulsification.^[12] During the emulsification process, competition between polymer precipitation and monomer polymerization produced, respectively, nanospheres and nanocapsules.^[12,40] Prepolymerization can be inhibited either by adding an acid, typically SO_2 ,^[38] or by working with a nonprotic solvent, such as acetone.^[39]

5. Spontaneous Polycondensation

Interfacial polycondensation in water suspensions has been thoroughly addressed in the literature (for a comprehensive review, see ref. [41]). Capsules of typically a few hundred microns are routinely prepared nowadays, even with water-sensitive monomers, such as epoxides,^[42] isocyanates,^[43,44] or acid chlorides.^[45,46] The latter two, are used, respectively, in the synthesis of polyurethanes and polyamides (they hydrolyze rapidly upon addition of water, while the former generates amino groups that are still able to react with isocyanate moieties, Scheme 2). The synthesis of small-sized particles (less than 1 μm) by polycondensation in miniemulsions has been exten-



Scheme 2. Main reactions in the preparation of polyurethanes (a) and polyamides (b) by polycondensation in an aqueous environment.

sively addressed in recent publications,^[47–49] although not for fast-hydrolyzable systems such as polyamides.

Fessi and co-workers^[50,51] used spontaneous emulsification to produce submicron crosslinked polyamide capsules of controlled sizes (ranging from 100 to 700 nm for increasing contents of Miglyol), which had wall thicknesses that depended on the ratio of organic (phthaloylchloride) to hydrophilic (diethylentriamine) monomers. A surfactant (lipoid S75) and a dispersant (a triblock copolymer) were used to ensure that both electrostatic and steric stabilization occurred upon emulsification. The same authors applied the Ouzo effect for preparing polyurethane and poly(ether-urethane) nanocapsules, using isophorone diisocyanate and various diols as organic and hydrophilic monomers, respectively.^[51,52] While 1,2-ethanediol and 1,4-butanediol produced monomodal particle-size distributions (with sizes typically under 400 nm), with long PEG chains, a second population (average $\approx 2 \mu\text{m}$) was observed. Presumably, the amphiphilic molecules did not diffuse readily enough from the water phase towards the interface of the droplets to react with the isocyanates, thus causing some coalescence prior to interfacial reaction. An example from our lab, obtained

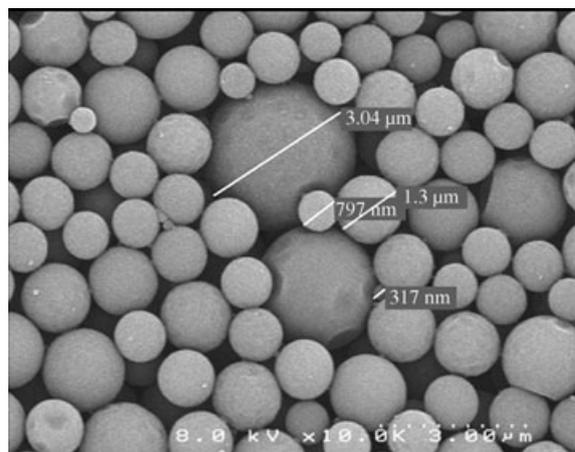


Figure 4. Polyurethane capsules containing miglyol oil obtained by spontaneous polycondensation. Small bumps confirm the fact that the capsules are hollow beyond the polymer wall.^[53]

using isophorone diisocyanate and ethylene glycol, is presented in Figure 4.^[53]

6. Spontaneous Oligomer Precipitation and Postcondensation

A third class of dispersion is obtained through the preparation of oligomers prior to emulsification and postreaction in contact with water or with water-soluble monomers. This process has the advantage that the oligomer chains are small and thus quite soluble in the polar solvent, and that the post-interfacial hardening of the prepolymer allows a quite easy preparation of robust nanocapsules; for example, water-borne polyurethane dispersions are extensively prepared by the so-called "acetone process" (for a comprehensive review, see ref. [54]). Basically, polyurethane oligomers containing polar groups are prepared by polycondensation in acetone, before pouring the mixture into excess water. In most of the articles published in this field, including some recent references,^[55,56] the emulsification was probably not caused by the Ouzo effect, in view of the high polymer concentration in the acetone (30–70 wt%) prior to emulsification. Instead, we suppose that these emulsifications proceed by spinodal decomposition, which explains why larger particles are obtained when acetone is used than those obtained in the absence of a solvent. Some examples of the application of the Ouzo effect to water-borne polyurethane latex preparation probably exist in the abundant patent literature reviewed by Dieterich,^[54] but a systematic investigation to pinpoint these has not been made here.

Sol-gel reactions of tetraethoxysilane (TEOS) in mixtures of ethanol and water are widely used nowadays to prepare synthetic silica nanoparticles. They are based on the initial work of Stoeber et al.^[57] who showed that TEOS molecules, which are initially soluble in the continuous medium, rapidly hydrolyze and polycondense to produce particles of controlled shape and size. Minehan and Messing^[58] reported that, by initiating the polycondensation of TEOS in a concentrated ethanol/water solution (i.e. below the binodal curve) and then pouring excess water, capsules with sizes typically under 1 μm could be obtained; the morphology of these capsules depended on the amount of catalyst used in the first step, that is, on the extent of the polycondensation reaction.

Vincent and co-workers also utilized the polycondensation of diethoxysilanes with^[59] and without^[60] trifunctional silanes to form silicone emulsions or microgels, respectively. In ab initio systems (monomer/ethanol/water poured all together) and at low water content (typically below 30 wt%), the polycondensation of the silanes proceeded homogeneously, whereas the postaddition of excess water forced the Ouzo emulsification of the prepolymerized silicone oil into particles of 100 to 200 nm. Phase diagrams proposed for ethanol/water/silicone oil^[60] or ethanol/water/silica^[58] systems showed the clear transition between one and two phases (clear binodal curve), but did not discriminate between the Ouzo domain and the area above the spinodal curve.

7. Related Studies

Other components can also be dispersed by the Ouzo effect, particularly low HLB surfactants. Lipids were shown—quite a long time ago—to generate small unilamellar liposomes of controlled sizes when using the spontaneous emulsification process.^[61,62] Since lipids were introduced in various recipes described before,^[15,16] the bimodal population of nanodispersion sizes observed in these studies can be explained by the formation of liposomes, typically of 50 nm diameter, besides nanodroplets^[15] or nanocapsules.^[16] Special lipids, such as mono-

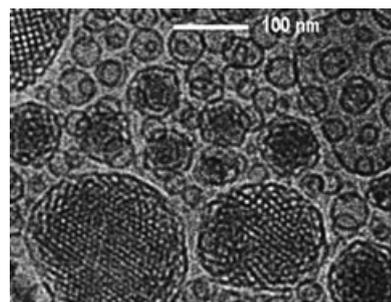


Figure 5. Cubosomes and vesicles prepared by the Ouzo effect and observed by cryo-TEM (adapted from ref. [63]).

olein, form cubic liquid crystalline phases. When a diluted ethanol solution of mono-olein is dispersed in water, so called "cubosomes", that is, nanoparticles of cubic liquid crystals, are produced, together with vesicles (see an example in Figure 5). Recent studies showed that emulsification via the Ouzo effect allows a simpler preparation of crystallites than that possible by extensive ultrasonication.^[63] Amphiphilic β -cyclodextrins modified by alkyl chains are likely able to form a new generation of nanoparticle^[64,65] or nanocapsule^[66] vectors for drug delivery by means of the Ouzo effect. Again, neither the stirring rate nor the surfactant concentration or the temperature modified the sphere sizes.^[65]

8. Summary and Outlook

This Minireview shows that the Ouzo effect can be used for preparing a variety of aqueous dispersions, which include nanospheres, nanocapsules containing an oil or a void, and even liposomes or vesicles. Note that its use is not limited to ethanol/water mixtures, but is extendable to many kinds of miscible solvents; for example, Fessi and co-workers^[2] demonstrated that a mixture of two miscible organic solvents (chloroform/heptane) spontaneously produced polymer dispersions with sizes of about 100 to 300 nm.

Beyond its use in fast polymerization processes, the Ouzo effect may become an alternative to high-shear techniques or ultrasonication, which are widely used nowadays in academia to prepare miniemulsions or microsuspensions,^[67] but are difficult to implement on an industrial scale. Ouzo emulsification presents no difficulties, as it is spontaneous, takes place over

the entire volume, and is not controlled by the choice of surfactant (except for pseudolatex preparations). In the case of the Ouzo emulsification, the particle size ranges from 100 nm to about 4 μm , independently from the surfactant concentration, whereas in the case of ultrasonication, particle sizes are controlled by the content of surfactant, and are limited to diameters smaller than 500 nm.

Note that the preparation of stable emulsion droplets by using the Ouzo effect has already been used to circumvent the sonication step, particularly in the widely studied field of radical polymerization; for example, thirty years ago, a paper describing the preparation of polystyrene surfactant-free latexes starting from an Ouzo emulsion^[68] remarked that the process of emulsification they used "differs from the technique recently proposed by Ugelstadt et al. in which both a long-chain fatty alcohol and an anionic emulsifier are used to create small, stable emulsified droplets of monomer" (i.e. miniemulsion). Another example is the very recent paper by Szkurhan and Georges,^[22] who prepared pseudolatexes of TEMPO-terminated polystyrene by means of the Ouzo effect and stated that "importantly, no high-shear device is required to form small particles".

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