Core-shell coacervation in drug delivery

WHITE PAPER

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The term coacervation derives from the Latin verb "coacervare", meaning "to crowd together". The technique of coacervation was first characterised by Bungenberg de Jong in 1931, although the earliest reports of this technique go back to Tiebackx in 1911. Over the last 2-3 decades complex coacervation has been deployed in industries as diverse as food, cosmetics, agriculture and functional materials, as well as, more recently, generating an increasing interest in the pharmaceutical industry as a drug delivery mechanism. This White Paper focuses on drug delivery using complex coacervation.

Complex coacervation

There are two methods for coacervation.

- Simple coacervation occurs when a selected polymer for microcapsule preparation is salted out or desolvated.
- Complex coacervation involves complexation between two oppositely charged polymers in a solvent, usually water.

Complex coacervation commonly refers to the liquid-liquid phase separation that results when solutions of two oppositely charged macromolecules/colloids are mixed, resulting in the formation of a dense macromolecule-rich phase, the precursors of which are soluble complexes[1]. The process depends on the formation of salt bonds associated with macromolecules to bring about coacervation. There are usually three preparative steps in complex coacervation

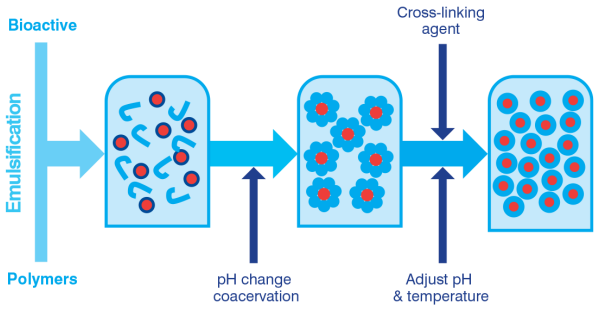


Fig 1: Schematic complex coacervation method.

- Preparation of the dispersion or emulsion.
- Encapsulation of the core – the coacervation step.
- Stabilization of the encapsulated particle, most commonly by cross-linking.

Complex coacervation is manifest in many microencapsulated products. The first recorded major use was in the 1950s in the carbonless copying paper industry. Microcapsules consist of a core surrounded by a wall or barrier of a designed thickness. The thickness of this shell ranges from several to hundreds of micrometres (2 - 300 µm) and protects the core against degradation and enables control over payload delivery under specific conditions.

Despite the wide uptake of complex coacervation, the fundamental science has been poorly understood until recently. The limitations of the earliest theory, by Voorn–Overbeek, have long been acknowledged and alternative models are now being advanced[2]. This is opening up the field to novel systems.

A wide range of naturally derived polymers are suitable candidates for complex coacervation. The commonest of these include gelatin, chitosan, alginates, pectin and albumin although, with a plethora of grades for each product it is easy for the inexperienced to struggle to achieve their desired product performance. Some drugs formulated by complex coacervation include

There have been demonstrations of the ability to tune the shell to release under certain conditions. Examples include

- Gastro-intestinal tract release is when pectin was chemically modified to make it suitable for use as a pH sensitive matrix for colon targeted delivery of drugs. In vitro drug release studies from metronidazole-loaded formulations were carried out which showed no significant release of the drug at gastric pH. However,

Category	Drug	Polymer
Anticancer	Fluorouracil Cisplatin Mitoxantrone Oxantrazol	Glutaraldehyde, Chitosan Chitosan, Chitin Glutaraldehyde - saturated toluene Chitosan
Antiinflammatory	Aceclofenac Indomethacin Diclofenac sodium Ketoprofen	Eudragit Chitosan Chitosan, chondroitin sulphate Chitosan
Cardiology	Nifedipine Propranolol Dilitazam	Chitosan Chitosan Casein, chitosan
Steroidal	Progesterone	Glutaraldehyde, chitosan
Diabetes	Insulin	Chitosan
Diuretics	Furosemide	Chitosan

Fig 2: Summary of encapsulated drugs.

[1] Kizilay 2011. "Complexation and coacervation of polyelectrolytes with oppositely charged colloids". *Adv Colloid Interface Sci. 167 (1–2): 24–37.*
[2] Sing & Perry 2020, "Recent progress in the science of complex coacervation", *Soft Matter, 16, 2885--2914*

at colonic pH, sustained release of the drug was observed[3]. Micropore Technologies has been able to achieve something similar with yeast[4].

- Targeting asialoglycoprotein receptors located on the surface of human hepatoma cells for the treatment of liver cancer through the delivery of siRNA to enhance gene silencing[5]
- Selective encapsulation of therapeutic nucleotides, such as miRNA mimics, small interfering RNAs, and transcripts to accommodate a wide range of therapeutic strategies including inhibition of atherogenic miR-33a in atherosclerosis[6].

Overall, complex coacervation has shown greater potential, compared with spray drying because the process does not involve high temperature, so the bioactive components remain secure. Along with controlled release of bioactive components, the process provides high core loading capacity and elevated encapsulation efficiency.

Manufacture of complex coacervates

Traditional manufacturing approaches involve dissolution of the two polymeric materials in water, with stirring. Typically an amphoteric biopolymer gelatine (porcine or piscine are preferred) and gum acacia (or alternate polymers such as sodium carboxy methyl cellulose) Dissolution is performed at elevated temperature (50°C), at high pH (~9) to ensure no unwanted interaction between the polymers. The internal phase is then added to the tank. At this point either a recirculating homogeniser or an in-tank homogeniser is used to emulsify the mix to the specified target droplet size. Careful monitoring is required at this stage as droplet size has a profound effect on final capsule mechanical stability. Oversized capsules may be fragile and smaller capsules hard to control the release properties. In addition the generation of foam from the applied high shear can be problematic, so the use of a defoamer is advised. Once the droplet size has been achieved the homogeniser can be deactivated and a lower stirrer speed can be used.

The pH is carefully adjusted to below the isoelectric point of the gelatine, (~pH 4) wherein the gelatine becomes cationic in nature and interacts with the anionic gum acacia, thus forming the coacervate phase. This polymer rich phase can be observed as droplets of clear polymer dispersed in the aqueous phase.

By reducing the temperature of the batch, slowly, over time, the coacervate comes out of solution and begins to deposit at the interface of the oil and water, making up the capsule wall. Different grades of gelatine have different 'working temperatures' where the rate of deposition is critical, allowing, by process design and formulation, differing amounts of wall material to deposit and influencing the final capsule wall thickness.

Variation in particle size distribution also affects how much coacervate deposits, with larger capsules having thinner walls than the smaller capsules. Overall droplet surface area can have an effect on how much coacervate is available.

Taking the temperature down to 10-13°C should ensure that all available coacervate have been utilised before the crosslinking step, wherein chemical or enzymatic approaches can be taken to 'set' the capsule walls. This process takes time and the batch can usually be left overnight to complete crosslinking. After the requisite time has passed, some post processing may be required, depending on the application, such as dewatering, pH adjustment or filtering and resuspension.

Alternative approaches to coacervation, broadly involve the same process steps but with some modifications, e.g. using chitosan with gum acacia, starts at low pH and is slowly increased to the isoelectric point of the gum acacia, which then forms coacervate with the cationic chitosan. This process can be done at ambient temperatures.

Whilst complex coacervation is a uniquely versatile encapsulation technique, it is often referred to the 'science and art' of encapsulation. Batch to batch variations can be challenging. Inherent differences in naturally derived biopolymers, can influence the effective pH at which coacervation occurs. A small adjustment in particle size can have a profound impact on surface area and coacervate deposition. Polymer ratios, concentration or dilution at various stages can all effect the overall quality.

The Micropore difference

Achieving an accurate target capsule size in an industrial setting can be a challenge While the homogeniser is running, samples are taken and sized via electrozone sensing (Coulter principle) or laser diffraction. These techniques take time to run, and in the meantime the homogeniser continues to reduce the size of the emulsion droplets in the batch. This makes accurate sizing unpredictable.

[3] Pramanik 2017, "formulation and evaluation of a pectin based controlled drug delivery system containing metronidazole", *Life Science Informatics Publications, RJLBPCS 3(4) Page No.24*

[4] Micropore Technologies internal document of test conducted by the Centre for Process Innovation,

[5] Oishi et al 2005. "Lactosylated poly(ethylene glycol)-siRNA conjugate through acid-labile beta-thiopropionate linkage to construct pH-sensitive polyion complex micelles achieving enhanced gene silencing in hepatoma cells" J. Am. Chem. Soc, 127:1624– 1625

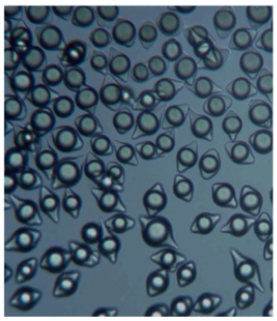
[6] Kuo et al, 2014, "Inhibition of atherosclerosis-promoting microRNAs via targeted polyelectrolyte complex micelles ", *J Mater Chem B Mater Biol Med.* 2(46): 8142–8153.

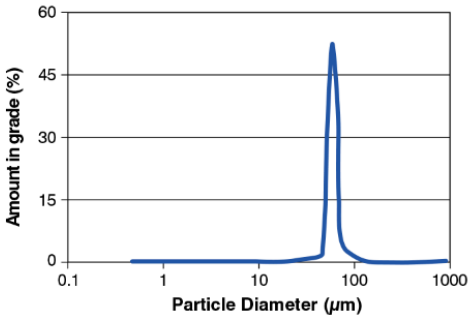
A preferred approach is a system where the desired size characteristics can be defined in advance and the emulsion produced in a single pass.

Membrane emulsification makes this possible, by injecting the internal phase through the membrane pores and, by applying a known shear force, droplet sizes can be controlled precisely. A combination of membrane design and control of the degree of shear force applied to the surface of the membrane deforms and detaches the uniform droplets as they form on the surface.

This single pass continuous technique can provide 10 µm droplets with a coefficient of variation as low as 10% at emulsion concentrations approaching 50%. The formation of this mono-dispersed emulsion ensures that every droplet will pick up a consistent volume of coacervate, will have a uniform mechanical stability and therefore a predictable release profile.

By reducing variability as much as possible a more consistent final product can be obtained. Membrane emulsification technologies now provide the repeatability, reproducibility and fine control not previously offered by historical emulsification techniques.





Volume Distribution	Diameter	Statistical Analysis	
D10	47.16µm	StDev	6.32
D50	52.26µm	Span	0.20
D90	57.59µm	CV	12.02

Fig 3: Typical coacervate capsules produced by membrane emulsification

We're ready to help you with your core-shell coacervation challenges.