Sphere of Influence

Biodegradable PLGA-based microspheres present a valuable vehicle for drug transportation, and their use in controlled release opens doors for developers and manufacturers

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In recent decades the use of biodegradable and biocompatible microspheres (typically constituted with a backbone of lactic and glycolic acid) has become one of the most attractive drug delivery platforms. The advantages of these systems include the ability to tune biodegradability, with its wide range of erosion times, to a less frequent administration (with consequent reduction in the total dose); improved patient compliance; and the potential to microencapsulate from small molecules to peptides and proteins.

Microsphere Characteristics

Polylactic-co-glycolic acid (PLGA) based microspheres are typically characterised by a bulk-eroding profile. Due to water permeation into the polymer matrix, a 'burst' effect (release of a large quantity of drug within the first few hours of incubation) is typically observed followed by a slow (typically zero-order), diffusion-controlled release of the drug. This is controlled by the hydrolysis/biodegradability of the polymer. Sometimes a third phase occurs in which the remaining drug is released quickly as a result of severe and complete erosion of the polymer matrix. Factors such as the size of microspheres, polymorphic form, polymer molecular weight and the ratio of lactic glycolic acid are fundamental in the control of this type of release profile.

There are currently an increasing number of PLGA-based microsphere products on the market. These microspheres are being used in delivery systems for small molecules, proteins, vaccines and DNA. Table 1 compiles a number of such FDA approved controlled-release products (1-4). One of the most successful products so far has been Risperdal Consta from Jansen, with sales of more than $1.5 billion in 2011. Risperdal Consta is a PLGA-based product for the treatment of schizophrenia, enabling a sustainable release of risperidone (the active ingredient) over a two-week time-frame.

Despite the high market potential of PLGA-based microspheres, their widespread adoption is being hindered by a difficult scaling-up of existing processes, as well as by the high costs associated to their manufacturing. An example of the significant resources required for manufacturing of PLGA-based microspheres was the discontinuation of Nutropin Depot – a decision made by Genentech and Alkermes in 2004, based solely on a financial basis.

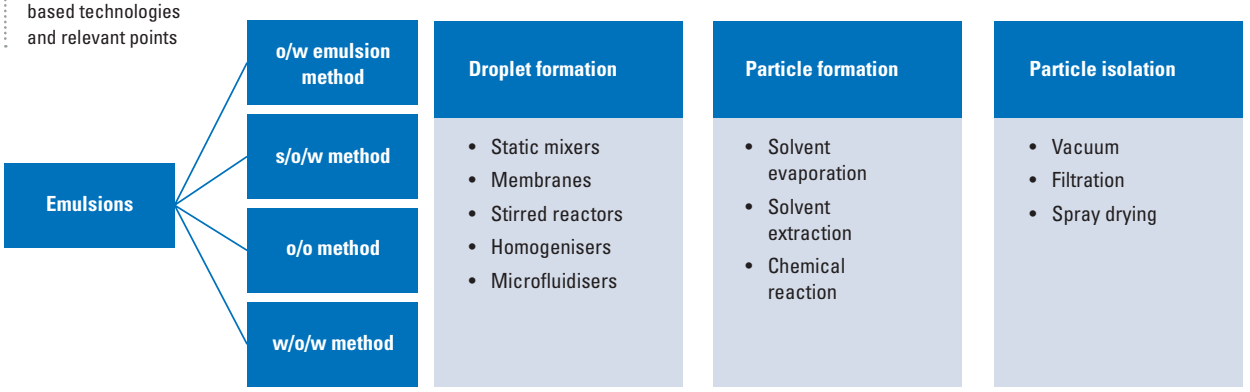
The production of PLGA-based biodegradable microspheres is a topic of increasing interest to both industry and academia. The main drivers for this are twofold. On the one hand, drug delivery based on microsphere technology provides important enhancements and flexibility in the way drugs are released in the human organism, and therefore enables a therapeutic gain for the patient. On the other hand, the clear commercial potential of microspheres for drug delivery means that the industry and its technological partners will strive to develop manufacturing processes that are both scalable and low cost.

Microsphere drug delivery systems have been fabricated by a variety of

Table 1: Marketed products produced with biodegradable microspheres

Trade name	Drug	Company	Release period	Application
Lupron Depot	Leuprolein acetate	Abbott	1, 3 or 4 months	Prostate cancer
Nutropin Depot	Reombinant human growth hormone	Genentech-Alkermes	1 or 2 months	Prostate cancer
Zoladex	Goserelin acetate	AstraZeneca	1 or 3 months	Prostate cancer
Decapeptyl	Triptorelin	Ipsen	1 month	Prostate cancer
Prostap	Leuprorelin acetate	Takeda	1 or 3 months	Prostate cancer
Sandostatin LAR Depot	Octrotide acetate	Novartis	1 month	GH suppression anti-cancer
Risperdal Consta	Risperidone	Jansen	2 weeks	Schizophrenia
Vivitrol	Naltrexone	Alkermes	1 month	Alcohol and opioid dependence
Posilac	Recombinant bovine somatropin	Eli Lilly	2 weeks	Milk production in cattle
Arestin	Minocycline	Orapharma	2 weeks	Periodontal disease

Figure 1: Emulsion based technologies and relevant points

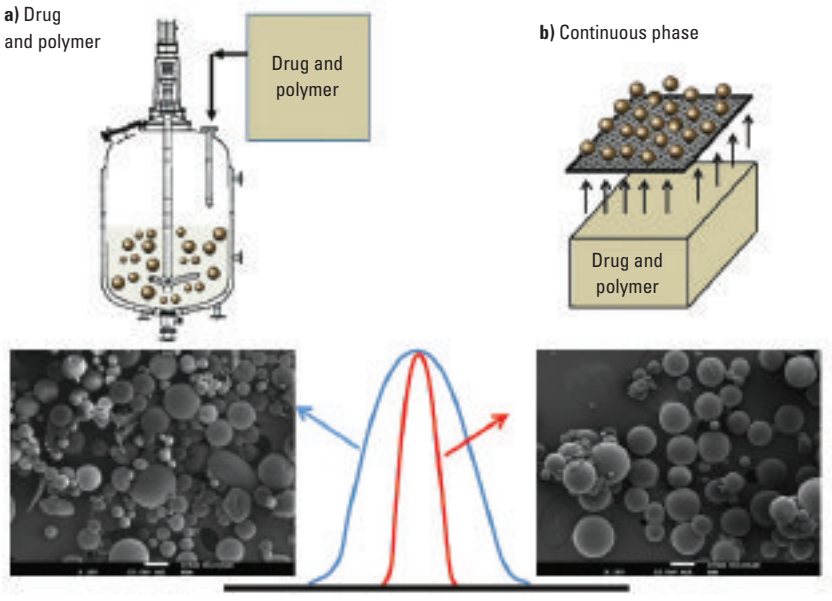


techniques, where those showing the most potential are the preparation of emulsions (a dispersion of one phase in the other, in which it is immiscible) and spraying methods. A number of classes of emulsion may be distinguished, namely oil-in-water (o/w), water-in-oil (w/o), oil-in-oil (o/o) or complex systems, such as multiple emulsions (or double emulsions) – for example, water-oil-water (w/o/w) or oil-water-oil (o/w/o) emulsions.

Several procedures may be applied for emulsion preparation, ranging from simple stirrers (low to medium energy) or high-speed mixers, static mixers, high pressure homogenisers, microfluidisers, or ultrasound generators. These methods all rely on a strong shear to disperse one phase into the other. Another method is membrane emulsification, where emulsion production relies mostly on surface tension forces rather than on shear. In all emulsification methods the presence of a third component – a surfactant – is typically necessary to address the long-term stability of the resulting emulsion droplets.

The simplest applied technique to produce emulsions is the so-called 'stirred reactor method', in which droplet formation is caused by mechanical stirring, usually by using a propeller. As the speed of the motor is increased, the size of the dispersed droplets decreases as a result of the high shear induced by the propeller. A major advantage of this method is that it does not require particularly cost-intensive equipment. However, scale-up is not straightforward (in particular, due to the importance of the volume:surface ratio) and the particle size distribution is often relatively broad (4). To address scalability issues, static mixers and homogenisers have been used with success; nevertheless, they present other drawbacks, including high mechanical stress due to fluctuating forces in the flow field and poor batch-to-batch reproducibility (5).

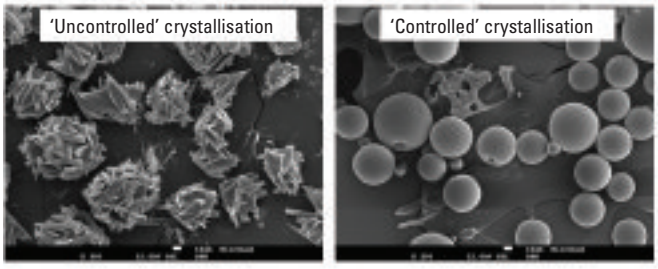
Figure 2: Emulsion based technologies: **a)** stirred reactor **b)** membrane emulsification process examples



Membrane emulsification is a relatively new technology (the first reference in literature appeared in 1991), which allows for the production of emulsion droplets with fine-tuned properties through a rigorous control over process conditions (6). Membrane emulsification has important advantages over traditional emulsification methods (stirring apparatus, rotor-stator systems and high-pressure homogenisers), namely its potentially lower energy demand, the better control of droplet size (typically in the range between 0.5µm and 100µm) and droplet size distribution, and the lower shear stress that is needed (typically lower than 20 Pa) (7).

On a typical membrane emulsification process, the dispersed phase is pressed and forced to permeate through a porous membrane into a continuous phase where fine droplets are formed at the membrane/continuous phase

Figure 3: Crystallisation control impact on the morphology/polymorphs of the PLGA microspheres loaded with 40 per cent API. Left image: particle formation induced by solvent evaporation; Right image: particle formation induced by solvent extraction



interface. An important aspect is that the choice of membrane material and porous structure has a decisive impact in the droplet size and droplet size distribution, in contrast with conventional methods in which emulsification is mainly assured by turbulent droplet break-up effects. In order to ensure a regular droplet detachment from the pores, shear stress is generated at the membrane/continuous phase interface by recirculating the continuous phase using a pump. This is achieved by agitation in a stirring vessel or by using vibration systems. The benefits of membrane emulsification are more evident in the production of larger (greater than 20 micrometres) droplets, where low shear rates allow a fine control of the emulsion droplet size and produce a narrow size distribution (8).

Membrane emulsification inherits the features that characterise membrane systems, in particular their easy scaling-up and effective control over operating parameters. As a result, there is clear potential for large scale production of emulsions in the pharmaceutical industry. Figure 2 (see page 29) presents a general scheme with emulsions prepared using two of these technologies (stirred reactor and a membrane emulsification process) dispersing a liquid phase, such as an organic solvent, into a second immiscible liquid phase (water). In both processes the API can be incorporated into the matrix that is to be dispersed by co-dissolving drug and polymer in a solvent such as methylene chloride or ethyl acetate.

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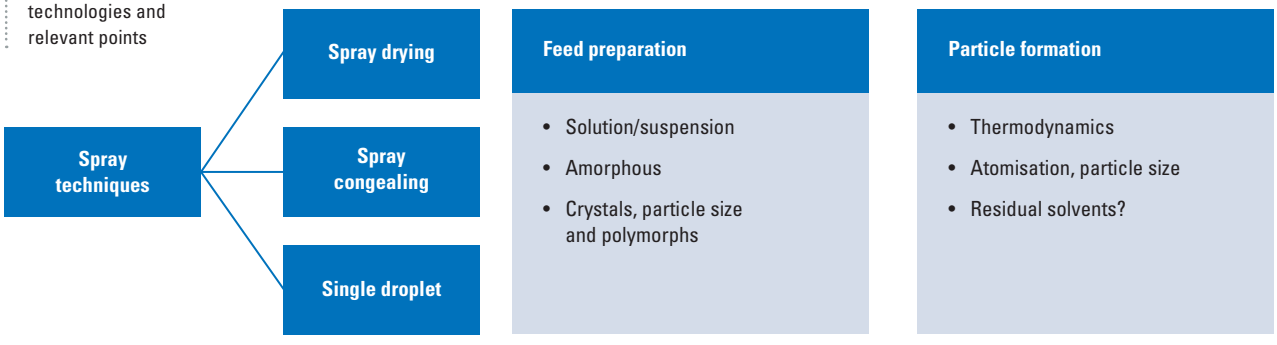
Alongside droplet formation stage in the emulsification process, particle formation is also critical to determine the microsphere properties, including release profile and stability of the API. Particle formation is generally promoted by solvent evaporation; in other words, after emulsion formation the organic solvent diffuses and partitions to the aqueous phase, and evaporates to the headspace, thereby leading to the formation of microspheres. As an alternative, the result can be achieved through solvent extraction/removal using a quench liquid such as water or other organic solvent. The solvent removal kinetic is fundamental in the control of particle size, morphology and polymorphic form. An example is shown in Figure 3, where particles/materials with the same API loading, polymer grade, solvents concentration/ratio and emulsification process were submitted both to a fast and to a slow removal of the organic phase, resulting in different polymorphic forms, different morphologies and, consequently, different release profiles. After particle formation, the microspheres are typically filtered,

Figure 4: Spray-based technologies and relevant points



washed, lyophilised and/or isolated by drying technology.

Alternative Methods

Other methods that do not rely on the formation of emulsions have been successfully used, such as spray drying, spray congealing or single droplet systems, although the latter can also be used to prepare monodisperse droplets in an emulsification process.

Spray drying is a gentle drying method (moderate temperatures are applied compared to other methods), where atomised droplets are dried within a drying chamber to produce powders with a defined particle size, starting with solutions or suspensions. The main advantages of spray drying are related to the easy processing of thermo-labile compounds – since drying takes place within milliseconds and the temperature of the product is well below the hot gas temperature due to the evaporative cooling effect – as well as manipulation of particle critical quality attributes (particle size, morphology and density), reproducibility and simple scale-up. Spray congealing may be thought of as a hybrid between hot melt extrusion and spray drying, where a melt (instead of a solution as in spray drying) is atomised with subsequent formation of particles of spherical shape by spraying the melt into a cooling chamber, through which cooled or low temperature gas (normally air or nitrogen) is circulating, typically in co-current.

Both technologies can overcome the issue of the large volumes of solvent-contaminated water phase that result from emulsion-based process. In these processes – particularly microencapsulation of small molecules – it is important to consider the potential to produce amorphous materials (related to fast solidification/particle formation processes) and the expected impact within the release profile.

Moving Forward

During the next decade an increase is expected in the number of extended release formulations, particularly in the life cycle management of proprietary drugs that have run out of patent protection. For the ones already approved, next-generation technologies may be expected to focus on the reduction of the administration frequency and in the development of more cost-effective processes capable of producing monodisperse microspheres in a controllable and reproducible way.

The characteristics of biodegradable synthetic polymers, including their safety record and biocompatibility, also make them attractive candidates for the delivery of compounds like adjuvants, rotavirus, antigens (both viral and bacterial antigens), RNAi and vaccines.

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