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Microparticles Used as Drug Delivery Systems

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Abstract Microparticles offer various significant advantages as drug delivery systems, including: (i) an effective protection of the encapsulated active agent against (e.g. enzymatic) degradation, (ii) the possibility to accurately control the release rate of the incorporated drug over periods of hours to months, and (iii) an easy administration (compared to alternative parenteral controlled release dosage forms, such as macro-sized implants). Desired, pre-programmed drug release profiles can be provided which match the therapeutic needs of the patient. This article gives an overview on the most important past, current and future strategies using drug-loaded microparticles to improve the efficiency of various medical treatments. Special emphasis is laid on the different types of preparation techniques that are commonly used, the physicochemical properties of the devices and practical examples illustrating the considerable benefits of this type of advanced drug delivery systems. But also the major challenges and obstacles to be overcome during the development and production of these pharmaceutical dosage forms are pointed out.

Keywords Advanced drug delivery · Controlled drug release · Microencapsulation · Release mechanism · Solvent extraction/evaporation

Controlled Drug Delivery

Controlled drug delivery systems can be extremely helpful to optimize the effects of pharmaco-therapies [1–3]. Each drug has a characteristic so-called "minimal effective concentration", below which no therapeutic effects occur, and a characteristic "minimal toxic concentration", above which undesired toxic side effects occur (Fig. 1). The range in-between is the so-called "therapeutic range", or "therapeutic window". Depending on the type of drug, this window can be rather narrow. To be able to optimize the therapeutic effects of a medical treatment it is of major importance to maintain the drug concentration within the therapeutic range over prolonged periods of time. This is particularly true for highly potent drugs, such as anticancer drugs. If the entire drug dose is administered at once using conventional pharmaceutical dosage forms, e.g. standard tablets, the whole amount is rapidly released into the stomach, absorbed into the blood stream and distributed throughout the human body. Consequently, the rate at which the drug reaches its site of action is often high. Depending on the therapeutic range and administered dose, the risk of toxic side effects can be considerable. Subsequently, as no continuous drug supply is provided and as the human body eliminates the active agent, the concentration of the latter decreases again. In some cases, the therapeutic range is attained during only very short time periods (Fig. 1, thin curve).

To overcome these restrictions, to be able to control the resulting drug concentration-time-profiles at the site of action, controlled drug delivery systems can be used. The idea is to incorporate/surround the drug within/by a ma-

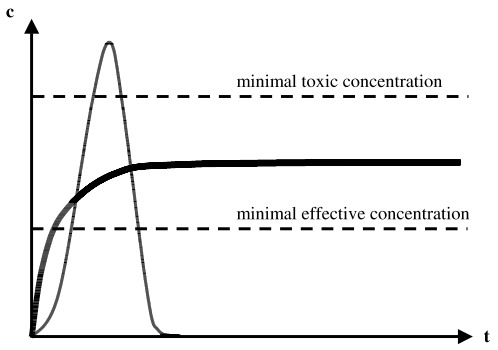

Fig. 1 Schematic presentation of the "therapeutic window" of a drug and possible drug concentration time profiles upon administration of oral immediate (*thin curve*) and parenteral controlled release dosage forms (*thick curve*) (*c* denotes the drug concentration at the site of action in the human body, *t* the time after administration)

trix former (very often polymer are used), which controls the resulting release rate. Various processes, such as diffusion, erosion and/or swelling can be involved in the control of the overall drug release rate, resulting in a broad spectrum of possible release patterns. For example, a continuous drug supply can be provided, compensating the elimination of the active agent out of the human body, thus, resulting in about constant drug concentrations at the site of action over prolonged periods of time (Fig. 1, thick curve).

Various types of controlled release dosage forms are available on the market, including tablets, capsules, pellets (spherical devices with a diameter of about 0.5–1.5 mm), patches and microparticles. The latter have significant advantages over the other types of dosage forms, such as: (i) the possibility to avoid the gastrointestinal tract (certain drugs loose their activity upon oral administration) by intramuscular or subcutaneous injection; (ii) easy administration using standard needles (in contrast to alternative controlled release parenteral dosage forms, such as macrosized implants); (iii) the possibility to directly administer the drug into the target tissue (thus, reducing the drug concentrations in the rest of the human body and the risk of related undesired side effects); (iv) the possibility to reach target tissues, which are normally not accessible for the drug (e.g., the Central Nervous System); and (v) no need of surgical removal of empty remnants, if biodegradable matrix formers are used. Poly(lactic-co-glycolic acid) (PLGA) is a frequently used biodegradable matrix former, because it is biocompatible and degraded into lactic and glycolic acid, two naturally occurring substances in the human body. However, the pH within PLGA-based microparticles can significantly decrease due to the accumulation of acidic degradation products and some drugs (especially proteins) can consequently loose their biological activity (upon denaturation).

Process Technology

Very different technologies can be used to prepare drug-loaded, controlled release microparticles, such as milling of films, spray-drying of drug-matrix former solutions, coacervation techniques and solvent extraction/evaporation methods. The latter are frequently used, especially at the lab scale. An excellent recent review on the current state of the art of this preparation technology is given by Freitas et al. [4]. At a small scale, the most frequently applied technique is the so-called "beaker method", which is illustrated in Fig. 2. The principle steps for the preparation of microparticles using a water-in-oil-in-water (W/O/W) technique are shown: (1) The drug is either dispersed or dissolved within an inner aqueous phase; (2) The latter is emulsified into an organic solution of the matrix forming polymer. Droplet formation is caused by mechanical stirring, e.g. using a propeller. (3) The obtained water-in-oil (W/O) emulsion is dispersed within an outer aqueous phase, resulting in a water-in-oil-in-water (W/O/W) emulsion. Again, droplet formation is caused by mechanical stirring, e.g. using a propeller. As soon as the organic solvent comes into contact with the outer aqueous phase, it diffuses into the latter. Due to convection and diffusion, the organic solvent reaches the surface of the W/O/W emulsion, at which it evaporates. Thus, the concentration of the polymer in the organic phase continuously increases. At a certain time point, the macromolecules start to precipitate and encapsulate the drug: The microparticles are formed. As steps (1)–(3) are all performed in beakers, this preparation technique is called "beaker method". (4) Subsequently, the microparticles are separated by filtration and

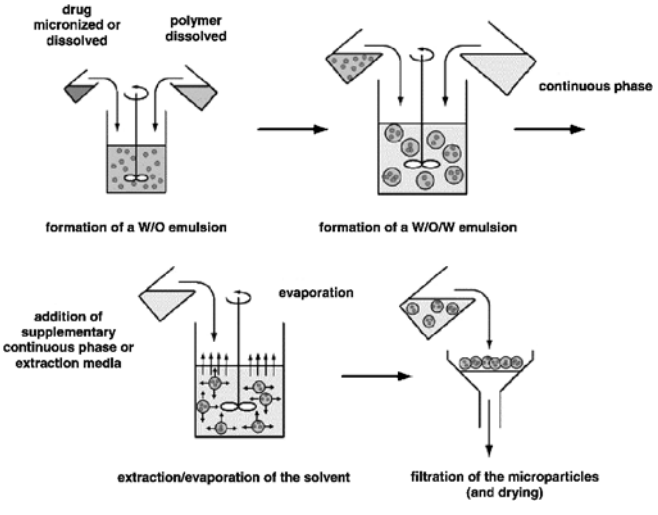

Fig. 2 Schematic illustration of the "beaker method", the most frequently used technique to prepare drug-loaded microparticles by solvent extraction/evaporation at the lab scale (adapted from [4], with permission). As an example, the preparation of microparticles using a water-in-oil-in-water (W/O/W) technique is shown

dried. A major advantage of this technique is that it does not require particularly cost-intensive equipment. However, the upscale of this process technology is not straightforward (in particular, because the "volume : surface ratio" is very important) and often the microparticle size distribution is relatively broad.

An interesting technique allowing to obtain very narrow microparticle size distributions is the so-called "jet excitation method" [5], illustrated in Fig. 3. As an example the preparation of microparticles using an oil-in-water (O/W) extraction/evaporation method is shown. The idea is to dissolve the drug together with the matrix forming polymer in an organic solution. This solution is pumped through a nozzle (nozzle #1), creating a continuous liquid stream. The latter is periodically disrupted into individual droplets due to vibration, caused for example by ultrasound. The droplets are falling into a collection/extraction fluid bath, containing an aqueous phase into which the organic solvent can diffuse. To prevent coalescence of the droplets and deformation upon impact on the surface of the fluid bath, generally an outer aqueous liquid stream of "stealth fluid" [being pumped through a second nozzle (nozzle #2)] surrounds the organic drug-polymer solution (Fig. 3). Thus, a biphasic stream is disrupted into biphasic droplets, the organic phase being in the center. As the disruption of the stream can be well controlled and is very reproducible, similar-sized droplets can be generated, resulting in microparticles with very narrow size distributions (Fig. 3).

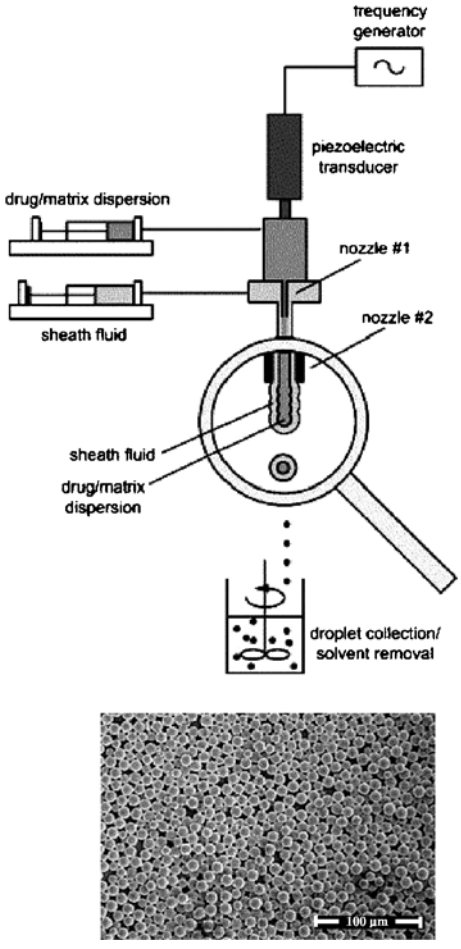

Fig. 3 Schematic illustration of the "jet excitation method" to prepare drug-loaded microparticles with a very narrow size distribution using an oil-in-water (O/W) extraction/evaporation technique (adapted from [4], with permission)

The principle of the so-called "static mixture method" to prepare microparticles by solvent extraction/evaporation is illustrated in Fig. 4 for an oil-in-water (O/W) solvent extraction/evaporation technique. The idea is to pump an organic drug-polymer solution (future inner phase) together with an aqueous phase (future outer phase) through columns containing static obstacles, e.g. baffles. Upon impact with these obstacles the liquid stream is disrupted and droplets of the organic phase are formed within the aqueous phase. If necessary, additional outer aqueous phase can be added afterwards to assure complete polymer precipitation and microparticle formation. One of the major advantages of this method is the possibility to relatively easy upscale the process by putting several static mixtures in parallel (Fig. 4). However, attention has to be paid that all mixing columns are fed with a liquid stream of identical composition. Thus, an efficient pre-blending unit is mandatory.

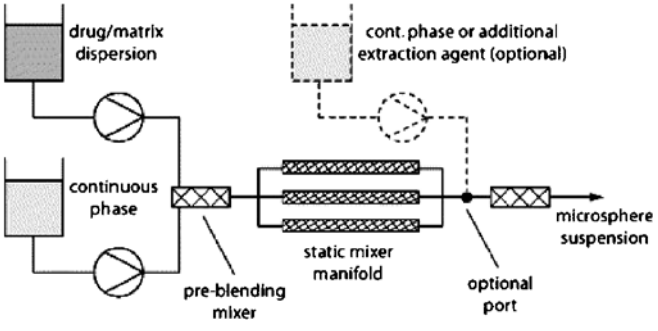

Fig. 4 Schematic illustration of the "static mixture method" to prepare drug-loaded microparticles using an oil-in-water (O/W) extraction/evaporation technique (reprinted from [4], with permission)

Practical Examples

Drug-loaded microparticles (in particular biodegradable ones) can be very useful to improve the efficiency of the treatment of various types of diseases [6–9]. Table 1 gives examples for products, which are commercially available on the market. Since 1989, Lupron® Depot containing the anticancer drug leuprorelin acetate [embedded within a poly(lactic-co-glycolic acid) (PLGA) matrix] is used for

Table 1 Examples for pharmaceutical products based on drug-loaded, biodegradable microparticles available on the market

Drug	Trade name	Company	Application
Leuprorelin acetate	Lupron Depot	Takeda	Prostate cancer
Leuprorelin acetate	Trenantone	Takeda	Prostate cancer
Recombinant human growth hormone	Nutropin depot	Genentech-Alkermes	Growth hormone deficiency
Goserelin acetate	Zoladex	I.C.I.	Prostate cancer
Octreotide acetate	Sandostatin LAR depot	Novartis	GH suppression anticancer
Triptorelin	Decapeptyl	Debiopharm	Cancer
Recombinant bovine somatropin	Posilac	Monsanto	Milk production in cattle
Risperidone	Risperdal Consta	Janssen	Schizophrenia

the treatment of prostate cancer [10]. Scanning electron micrographs of surfaces and cross-sections of these microparticles are given in Fig. 5. Clearly, the particles are spherical in shape and slightly porous. Leuprorelin acetate is a superactive luteinizing hormone-releasing hormone (LH-RH) agonist. Its biological activity is tenfold that of LH-RH. When administered chronically at a higher dose, it paradoxically produces antagonistic inhibitory effects on pituitary gonadotropin secretion and testicular or ovarian steroidogenises ("chemical castration"). These effects, attributable to a down-regulation of the receptors, are temporary and reversible. Importantly, they can be used for the treatment of hormone-sensitive tumors, such as prostate [10] and breast cancer [11] and endometriosis [12], with minimized side effects and avoiding surgical castration. The in vivo efficiency of this type of biodegradable microparticles is illustrated in Fig. 6. At the top, the serum concentration of the drug leuprorelin acetate is indicated, at the bottom the resulting testosterone levels upon monthly subcutaneous injection of the microparticles into rats. Testosterone stimulates the growth of sensitive prostate cancers. Clearly, high initial drug concentrations were observed upon each administration and about constant drug levels in-between. Importantly, the testosterone level is effectively lowered during the entire observation period (except for early time points). Thus, the growth of hormone-sensitive prostate cancers can be reduced. Trenantone® (Takeda) is a similar product, releasing the drug leuprorelin acetate over a longer period of time (during 3 month), being commercially available since 1995.

In addition to the possibility to accurately time-control the release rate of an incorporated drug, microparticles offer the major advantage to be directly injectable into the target tissue. Thus, the concentration of the drug in other parts of the human body (and related undesired side effects) can be minimized. In addition, potential natural barriers, which might normally hinder the drug to reach its site of action, can be overcome. For example, the Blood-Brain-Barrier (BBB) very well protects the Central Nervous System (CNS) against potential toxins and, thus, renders the treatment of brain diseases often extremely difficult. Only low molecular weight lipid-soluble molecules and a few peptides and nutrients can cross this barrier to a significant extent, either by passive diffusion or using specific transport mechanisms. Thus, for most drugs it is difficult to achieve therapeutic levels within the brain tissue. In

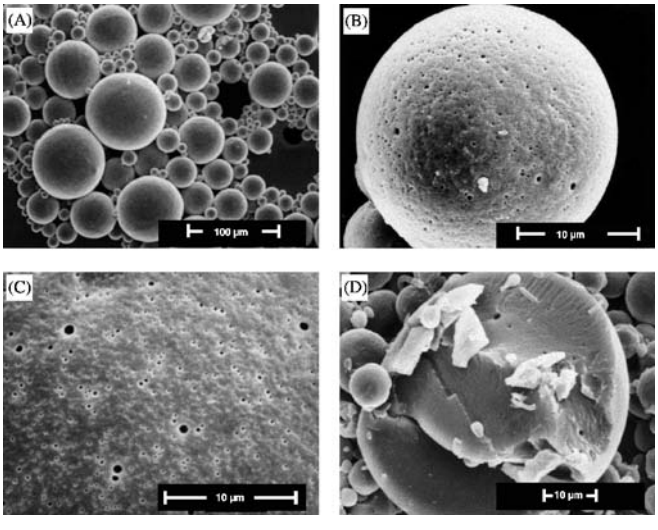

Fig. 5 Scanning electron micrographs of leuprorelin-loaded, poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles (Lupron Depot®) used for the treatment of prostate cancer (adapted from [7], with permission): **A** overview on an ensemble of microparticles, **B** surface of a single (*smaller*) microparticle, **C** surface of a single (*larger*) microparticle, **D** partial cross-section of a single microparticle

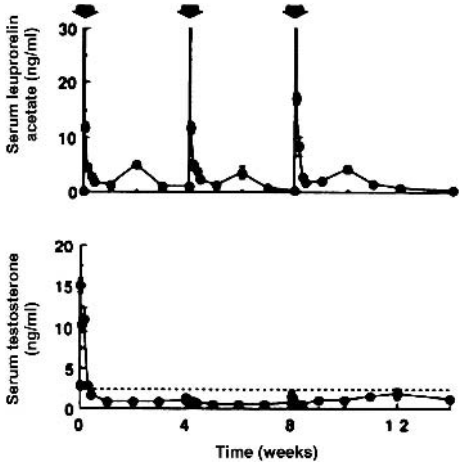

Fig. 6 In vivo efficiency (in rats) of poly(lactic-*co*-glycolic acid) (PLGA)-based, leuprorelin-loaded microparticles used for the treatment of prostate cancer (adapted from [7], with permission)

addition, highly potent drugs (e.g., anticancer drugs and neurotrophic factors) that may be necessary to be delivered to specific areas in the CNS, often cause serious toxic side effects in other parts of the human body (especially if high systematic concentrations are required to assure sufficient drug levels in the target tissue).

The stereotaxic injection of drug-loaded, biodegradable microparticles directly into the brain tissue (intracranial administration) offers a very promising possibility to overcome this restriction (Fig. 7). Optimized drug concentrations at the site of action can be provided over prolonged periods of time, improving the efficiency of the pharmacotherapy. An example for this type of treatment method is illustrated in Fig. 8. The black circle represents a brain tumor. As is can be seen, the surrounding environment has already been infiltrated by single tumor cells (Fig. 8A). If possible (if operable), the surgeon removes the tumor (Fig. 8B). However, due to the risk to affect vital functions, the surgeon cannot remove large parts of the surrounding tissue. Thus, the risk is very high that single tumor cells remain within the brain, leading to local recurrences of the cancer. In the case of malignant glioma, the average life-time expectancy is only about 11 months after diagnosis [13]. To reduce the risk of local tumor recurrences, anticancer drug-loaded, biodegradable microparticles can be injected into the walls of the resection cavity during the same operation, when the crane is still open (Fig. 8C). These microparticles release the drug in a pre-determined, time-controlled manner, assuring optimized drug concentrations over prolonged periods of time at the site of action. Recently, a phase II clinical trial with 5-fluorouracil (5-FU)-loaded, poly(lactic-co-glycolic acid) (PLGA)-based microparticles has shown promising results [14].

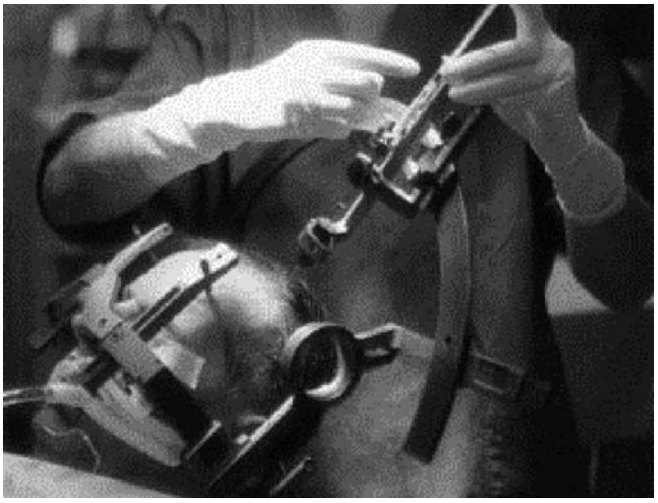

Fig. 7 Stereotaxic implantation of drug-loaded, biodegradable microparticles into human brain tissue. This procedure allows an accurate and well-controlled injection into the targeted brain regions (adapted from [15], with permission)

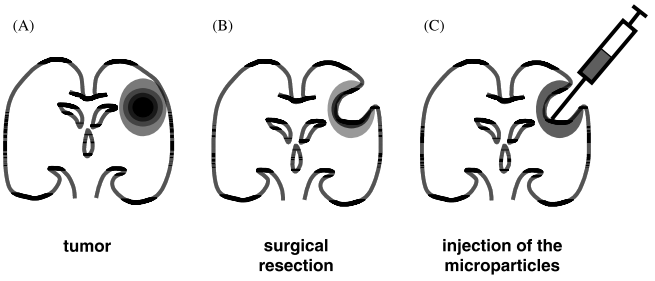

Fig. 8 Schematic cross-sections through human brains illustrating the treatment of brain cancer by surgical removal and subsequent stereotaxic injection of anticancer drug-loaded, biodegradable microparticles into the walls of the resection cavity: **A** before surgery, the *black circle* represents the tumor, **B** after surgical tumor resection, **C** during microparticle administration

Furthermore, the stereotaxic administration of anticancer drug-loaded microparticles allows the treatment of *in*operable brain tumors. In these cases, the tumors are located in brain regions that are not accessible for the surgeon without significant damage of major vital functions. Figure 9 shows a magnet resonance image and computed tomography (CT) scans of a human brain before and after microparticle injection into such tumors. Clearly, the controlled drug delivery systems could effectively be administered into the target tissue (Fig. 9C), releasing the drug in a time-controlled manner directly at the site of action. A clinical phase I trial showed first promising results with this novel treatment method [15].

Another example for the use of controlled release microparticles is the optimization of the growth and differentiation of cells used for cell therapy (living cells are implanted into human tissue). Main restrictions of this type of therapy include limited cell survival, differentiation and integration into the host tissue. The time-controlled release of drugs that can stimulate the growth and differentiation of the implanted cells can help to overcome these restrictions. For example, Tatard et al. [16] incorporated nerve

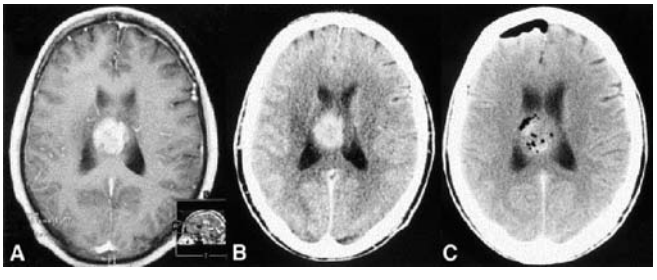

Fig. 9 Administration of anticancer drug-loaded, biodegradable microparticles into human, *in*operable brain tumors: **A** pre-operative magnetic resonance image showing a malignant glioma, **B** pre-operative computed tomography (CT) scan, **C** CT scan after implantation of the microspheres (reprinted from [15], with permission)

growth factor (NGF) in PLGA-based microparticles and obtained promising results. Figure 10A shows a schematic representation of this treatment method: Cells adhere to the microparticles, which release the growth factor in a time-controlled manner. This leads to improved cell survival and differentiation. Figure 10B,C shows optical and scanning electron microscopy pictures of PLGA-based microparticles containing NGF, with PC12 cells adhering to their surfaces. These systems are intended to be implanted into human brains: The differentiated cells can produce dopamine, which is needed to treat Parkinson's disease.

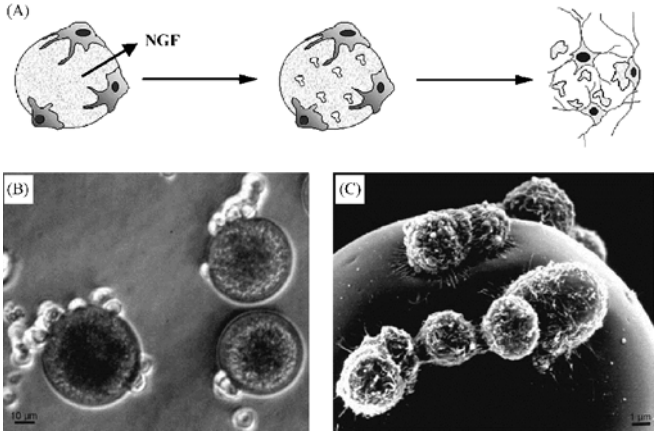

Fig. 10 Drug-loaded microparticles used to optimize cell growth and differentiation in cell therapies: **A** schematic illustration of the concept; **B** optical microscopy picture; and **C** scanning electron microscopy picture of cells adhering to the surfaces of the microparticles (adapted from [16], with permission)

Drug Release Mechanisms from PLGA-based Microparticles

Despite of the steadily increasing practical importance of poly(lactic-co-glycolic acid) (PLGA)-based microparticles as advanced drug delivery systems, yet only little knowledge is available on the underlying physical and chemical processes controlling the resulting drug release rates [17]. This can be attributed to the complexity of the occurring phenomena [18, 19]. Upon contact with aqueous body fluids water diffuses into the system (Fig. 11). Due to concentration gradients the drug subsequently diffuses out of the device. Importantly, the matrix forming polymer PLGA (being a polyester) is cleaved into shorter chain acids and alcohols upon contact with water. This significantly alters the conditions for drug diffusion with time. With decreasing macromolecular weight, the mobility of the polymer chains increases and, thus, the apparent drug diffusivity increases. As water imbibition into PLGA-based microparticles is rapid compared to the subsequent polymer chain cleavage, polymer degradation occurs throughout the entire system ("bulk erosion").

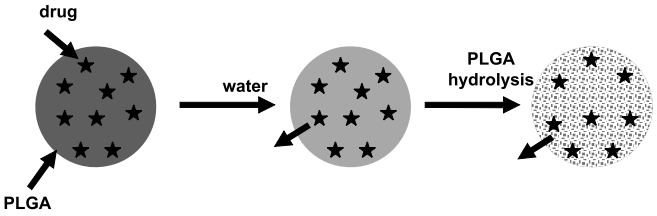

Fig. 11 Schematic illustration of a bulk-eroding, poly(lactic-*co*-glycolic acid) (PLGA)-based microparticle. Water penetration into the system is much faster than polymer hydrolysis

Often, three-phasic drug release patterns are observed with PLGA-based microparticles. An example is illustrated in Fig. 12, showing the release of 5-FU-loaded systems in phosphate buffer pH 7.4. The three phases can essentially be attributed to: (i) pure diffusion at early time points (the very short diffusion pathway lengths lead to high initial drug release rates, so-called "burst effects"); (ii) a combination of drug diffusion, polymer chain cleavage and the limited solubility of 5-FU, leading to approximately constant drug release rates (the increase in the diffusion pathway lengths is compensated by an increase in drug diffusivity); and (iii) to the breakdown of the polymeric network as soon as a critical threshold value is reached, resulting in the disintegration of the microparticles. Consequently, the surface area available for diffusion significantly increases and the diffusion pathway lengths decrease. Both effects result in a pronounced increase in

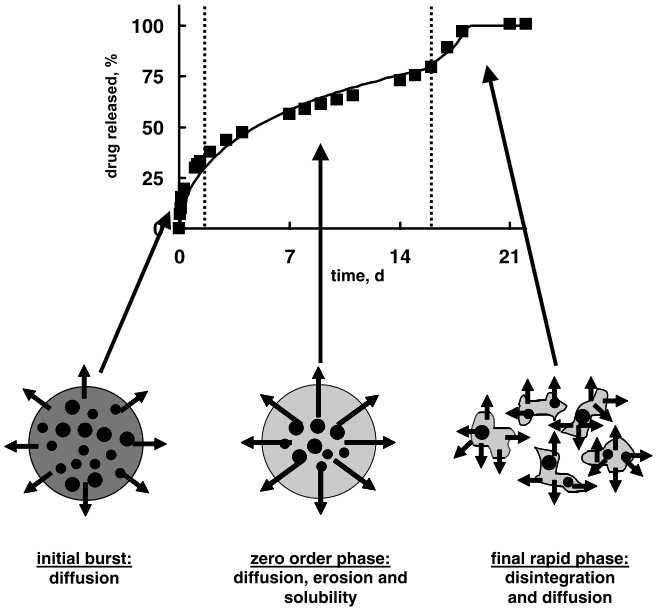

Fig. 12 Drug release from and drug release mechanisms in 5-fluorouracil (5-FU)-loaded, poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles

the resulting drug release rate (final rapid drug release phase), leading to complete drug exhaust.

It has to be pointed out that the composition, inner and outer structure (e.g., porosity), size and preparation technique of the microparticles can significantly affect the underlying drug release mechanisms. Depending on various parameters, including the type of drug and matrix former, drug loading, presence of additional excipients and dimension of the systems, different physical and chemical phenomena can be dominating and control the resulting drug release kinetics. To be able to assure a secure pharmacotherapy, it is obviously highly desirable to know which processes are of importance in the particular product. Furthermore, based on this knowledge the optimization of this type of controlled drug delivery system can be significantly facilitated.

Conclusions

Microparticles can effectively be used as controlled drug delivery systems, allowing to optimize the resulting drug concentration-time-profiles at the sites of action in the human body and, thus, the therapeutic effects of the medical treatments. Furthermore, they can be directly injected into the target tissues. This reduces the drug concentrations in the other parts of the human body (and consequently the risk of undesired side effects) and permits to reach target tissues, which are normally not accessible for the drug (e.g., the Central Nervous System). Various process technologies can be used for the preparation of these advanced drug delivery systems and broad ranges of drug release patterns can be provided, matching the therapeutic needs of the patient. However, the development and production of drug-loaded microparticles is not straightforward, because many physical and chemical processes can be involved in the control of drug release. Thus, great care has to be taken when identifying the optimal system design (composition and dimension) and preparation procedure.

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