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A review on recent advantages and evaluation of microparticles and their applications

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Abstract

Microparticles are free spherical dust between 1 and 1000 microns made of synthetic, non-biodegradable, and non-biodegradable polymers. There are two types of microparticles: microcapsules and micro matrix. The main types of microparticles are magnetic microparticles, polymer microparticles, bio-adhesive microparticles, biodegradable polymer microparticles, synthetic polymer microparticles, floating microparticles, and radioactive microparticles. The advantage of microcarriers over nanoparticles is that they do not cross the 100 nm interstitium during lymphatic transport and therefore act locally. Toxic substances can be solidified in the form of micro-encapsulated and dried particles. Moreover, methods to characterize numerous physicochemical parameters like drug release, thermal properties, and particle size are introduced, along with new tests like in vitro leaching tests and floating tests.

Keywords: Microparticles; Micrometrics; Polymer; Antibiotic; Microcapsules; Applications of microparticles

1. Introduction

Regulated drug delivery systems can alleviate some of the shortcomings of conventional therapies while enhancing therapeutic effects. To achieve maximum therapeutic efficacy, chemicals must be delivered to the right site in the right amount and at the right time with minimal toxicity. Therapeutic agents can be delivered to target areas in a variety of controlled and systematic ways. Some of these ideas include the use of microparticles as drug carriers [1].

Microparticles are free-flowing spherical dust composed of synthetic, biodegradable, and non-biodegradable polymers with particle sizes ranging from 1 to 1000 microns **(Figure 1)**. The main goal of such a revolutionary drug delivery system is to overcome the limitations of conventional dosage forms by increasing bioavailability, increasing patient compliance, and more precisely targeting drugs or other active ingredients [2].

There are two types of microparticles;

- Microcapsules
- Micrometrics

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Microcapsules have a recognizable capsule wall around the coating material, while microspheres have components dispersed in a particle matrix that can be controlled [3].

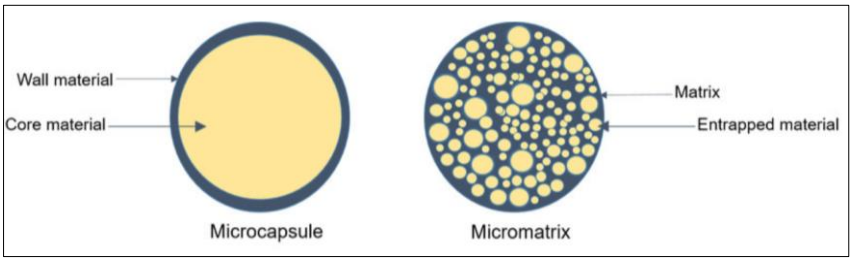

Figure 1 Micro particles (Microcapsule and Micromatrix)

1.1. Advantages of Microparticles

The advantage of microcarriers over nanoparticles is that they do not cross the interstitium at a size of 100 nm and are transported by lymph and thus act locally [4]. Toxic substances can be solid in the form of micro-encapsulated and dried particles.

- Drug encapsulation with polymers prevents enzymatic cleavage when compatible with drug delivery systems.
- Administering large amounts of drugs can improve patient performance.
- Dose and risk reduction.
- Effective use of drugs can increase bioavailability and reduce the incidence or severity of side effects.
- Helps protect the GIT from opioid stimulants.
- A shorter dosing duration results in higher patient survival.
- Reducing the size contributes to the increased surface area and can increase the strength of hard-to-dissolve materials.
- Turn the liquid into a solid and cover the unpleasant taste [5].

1.2. Disadvantages of Microparticles

The rate of release of the regulated dose varies depending on several parameters such as food and the degree of intestinal absorption.

Variation of flow rate from one dose to another.

Since the release-administration formulation has a higher dose, any defects in drug release can cause problems.

- Potentially dangerous.
- This dosage form should not be crushed or chewed [6].

1.3. Preparation of microparticles

Suspended microparticles containing active drugs were prepared by the emulsion solvent evaporation method. The drug (1g) was dispersed in a 10% w/v solution of cellulose acetate phthalate (in acetone: ethanol 8:2 solvent mixture). The resulting solution was stirred at 1000 rpm to dissolve the mixture added as well as fine droplets and slowly passed through a 250 ml beaker with 100 ml of liquid paraffin at a constant rate. The system was stirred at room temperature for 4 hours to evaporate the solvent and form microparticles of Metronidazole. The prepared microparticles were collected by filtration and washed with cyclohexane to remove non-sticky liquid paraffin. They are dried at room temperature, filtered, and stored in a closed container. [7,8].

1.4. Types of microparticles

- Magnetic microparticles.
- Polymer microparticles.
- Bio-adhesive microparticles.
- Biodegradable polymer micro-particles.

- Synthetic polymer micro-particles
- Flowable microparticles.
- Radioactive microparticles.

1.5. Magnetic microparticles

The drug is directed to the disease site using magnetic microparticles. The magnetic carrier collects the magnetic response of the integrated material and transfers it to the magnetic field. These magnetic microparticles, shown in **Figure 2**, are made of chitosan, dextran, and other polymers. Magnetic microparticles allow the replacement of large amounts of freely dispersible drugs with small amounts of magnetically targeted drugs [9,10].

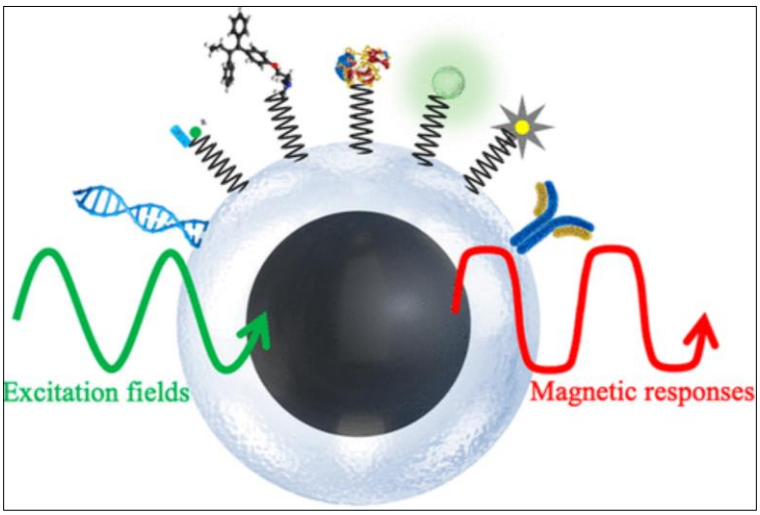

Figure 2 Magnetic Microparticle

1.6. Polymeric Microparticles

The polymer microparticles shown in Figure 3 are classified as follows:

1.7. Synthetic polymers

Synthetic polymer microparticles have been proven to be safe and biocompatible in medical applications such as embolic particles, bulk agents, drug carriers, and other applications. The main disadvantage of these microparticles is their migration away from the injection site, increasing embolism and tissue injury [11].

1.8. Biodegradable Polymers

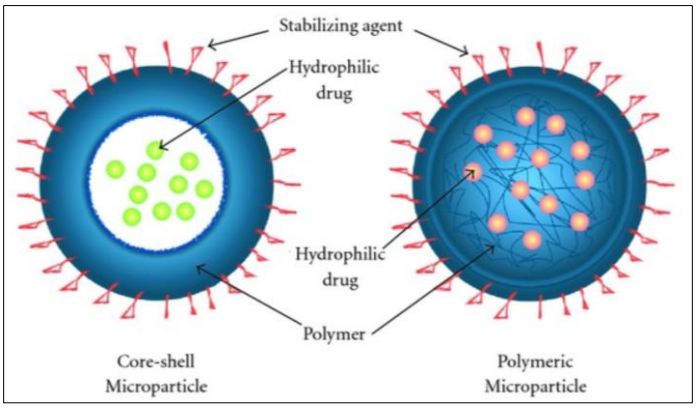

Figure 3 Polymeric Microparticle

Natural polymers such as starch are biodegradable, biocompatible, and bioadhesive. Due to the high degree of swelling in aqueous media, biodegradable polymers extend their shelf life when in contact with the mucosa and cause gel

formation. The amount and amount of drug released can be adjusted by changing the polymer concentration and drug release profile. The main problem is that the ability to load drugs from biodegradable microparticles is difficult in medical applications, making drug release difficult [12].

1.9. Bio-adhesive Micro Particles

The ability of a drug to attach to a membrane through its ability to adhere to a water-soluble polymer is called adhesiveness. Adhesion of the drug carrier to the mucous membrane such as nasal, rectal, axillary, or buccal mucosa is called bioadhesion. These microparticles, shown in Figure 4, spend more time at the application site, resulting in close contact with the absorption site and increasing pharmacological action. [13,14,15].

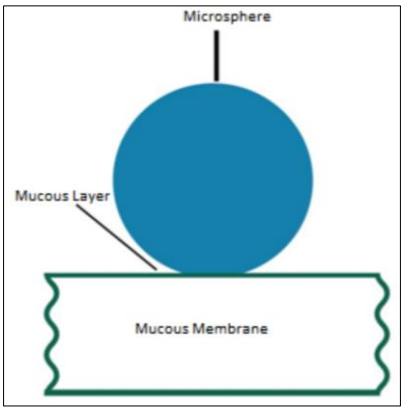

Figure 4 Bio-adhesive Microparticles

1.10. Floating Micro Particles

The microparticles shown in Figure 5 float in the stomach because of their apparent lower density than gastric fluid. As the entire system flows with the contents of the stomach, the drug is released slowly and ideally. This increases gastric emptying and changes in plasma concentration. This method has a longer therapeutic effect and reduces the required dose. With each successive gastric emptying, absorbed particles spread over a wide absorption area, increasing the likelihood of drug absorption and diffusion profile. Also, since each dose consists of several parts, there is a small chance of the dose slipping [16-18].

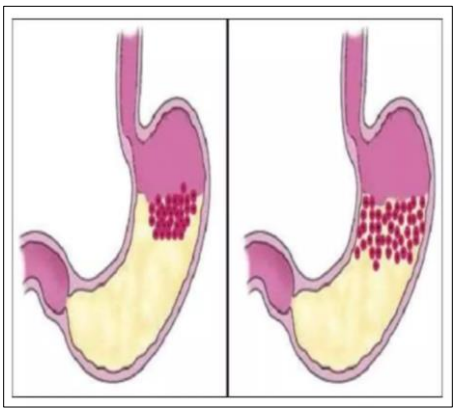

Figure 5 Floating Microparticles

1.11. Radioactive Micro Particles

Radiofrequency immobilization (RFI) is a treatment that uses radio waves to immobilize the patient. When microparticles with a diameter of 10-30 nm come into contact with the capillary, they hit the capillary bed first. The tumor is injected into an artery that supplies oxygen and nutrients. In all of these scenarios, the radioactive microparticles shown in Figure 4 deliver targeted doses of radiation to areas without causing damage to nearby healthy tissue. Different radioactive microparticles are called α emitters, β emitters, and γ emitters [19,20].

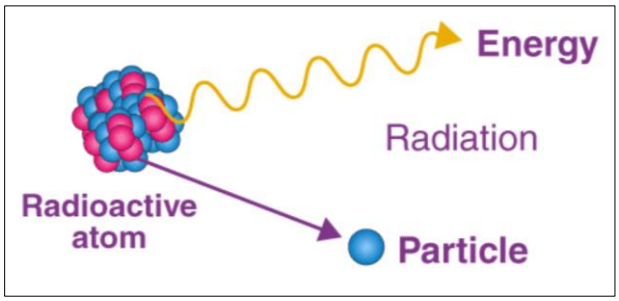

Figure 6 Radioactive Microparticles

2. Evaluation of microparticles

2.1. Physicochemical Evaluation

2.1.1. Particle shape and size

Conventional scanning light microscopy and electron microscopy are the most widely used techniques for observing microparticles. Both methods can be used to determine the structure of external microparticles. Optical microscopy on double-walled micro particles enables precise monitoring of coating conditions. The architecture of the microparticles can be seen before and after washing, and changes can be observed with a microscope.

The resolution of scanning electron microscopy (SEM) is better than that of light microscopy. After the microparticles are cut, scanning electron microscopy (SEM) can be used to examine the surface and the double wall system. The structure of multi-walled microparticles was investigated by confocal fluorescence microscopy. In addition to experimental approaches, the shape, morphology, and size of microparticles can be determined by laser light scattering and multidimensional counter coating [21,22].

The average particle size was determined

$$D\ mean = \Sigma\ n\ d/\Sigma\ n$$

Where n = number of microparticles checked; d = Mean size [23].

2.2. Isoelectric Point

The isoelectric point is calculated by microelectrophoresis, which is used to evaluate the electrophoretic behavior of microparticles. The time taken by the particles to travel a distance of 1 mm at different pH values from 3 to 10 was used to calculate the average velocity. This information can be used to calculate the electrical conductivity of the particles. Surface charge, ionizable mobility, and ion absorption properties of microparticles can all influence electrophoretic behavior [24].

2.3. The angle of Contact

The wetting behavior of the microparticle carrier is determined by the contact angle. Microparticles are classified according to their hydrophobicity or hydrophobicity. Adsorbed components control the thermodynamic properties of these solids. The contact angle is calculated at the solid/air/water interface. The advancing and receding contact angles are determined by placing points in the circular cell of the circular microscope objective. The contact angle was measured at 2000°C for one minute after microparticle deposition [25].

2.4. Percentage Yield

The amount of drug and polymer used in each batch was divided by the number of microparticles recovered from that batch and then divided by 100 [26].

2.5. Determination of density

A multivolume pycnometer can be used to determine the density of microparticles. Properly weighed samples were placed in a cup in a multivolume pycnometer. This chamber is filled with helium and allows expansion at constant

pressure. As a result of the expansion, the pressure inside the chamber decreases. Two consecutive pressure readings are taken at different initial pressures. The carrier density and volume of the microparticles were determined using two pressure readings [27].

2.6. Swelling index

It is calculated by determining how many microparticles swell in a given solution. The degree of equilibrium swelling of microparticles can be calculated by immersing 5 mL dry microparticles in 5 mL buffer solution overnight in a measuring cylinder. It is determined using the given formula [27,28].

Swelling index = mass of swollen microparticles, the mass of dry microparticles multiplied by 100 minus dry microparticles.

2.7. Chemical Analysis Using Electron Spectrometry

ESCA [electron spectroscopy for chemical analysis] can be used to determine the surface chemistry of micro-particles. In chemical analysis, electron spectroscopy can be used to determine the atomic structure of a substance. Degradation of the surface of biodegradable microparticles can be determined using spectra produced by an electron spectrometer for chemical analysis [29].

2.8. Fourier Transform Infrared Spectroscopy

The polymer matrix dispersion of the carrier system was measured by Fourier transform IR spectroscopy. The surface of microparticles is checked by ATR (alternative total reflectance). Infrared light passing through variable total reflection cells is reflected multiple times on the sample, resulting in the dominant IR spectrum of the surface material. Total reflectance FTIR spectroscopy can detect microparticle surfaces depending on the manufacturing method and conditions [26].

2.9. Entrapment Efficiency

A specific number of microparticles are weighed and crushed. It is then dissolved in a buffer solution and filtered using a mixer. A UV spectrophotometer was used to evaluate the filter at different wavelengths using a calibration curve [26]. The percentage of the experimental drug concentration multiplied by 100 to the theoretical drug concentration is the drug efficacy.

2.10. In vitro method

This method can be used to determine the drug release profile and drug barrier penetration. The in-vitro approach is used as a product testing method in drug development and manufacturing. The availability of consistent and reproducible release data from chemical, physical, and hydrodynamic conditions is important [26].

2.11. Beaker Method

In this procedure, the dosage form is attached to the base of the central hook and stirred by a continuous mixer. The average volume used in literature studies is between 50 and 500 mL, with a mixing speed of 60–300 rpm [26,28].

2.12. Interface Diffusion Method

Dearden and Tomlinson advance this approach. There are four different parts in total. Part A, which is initially filled with the drug concentration in the buffer, represents the oral cavity. The buccal membrane is represented by compartment B with 1 octanol, and the body fluid by compartment C with HCl 0.2 M. Protein binding is indicated by subunit D, which is 1-octanol. The aqueous phase must be saturated with 1 octanol before use. The syringe collects the sample from the A compartment and returns it to the A compartment [26,28].

2.13. Modified Keshary Chien Cell Method

Advanced laboratory technology is essential. At 37 degrees Celsius, use distilled water (50 ml) as a solvent containing Keshari Chien cells. TMDDS (Trans Membrane Drug Delivery System) is placed in a 10 # mesh glass tube under which the medium is pumped 30 times per minute [26,28].

2.14. Dissolution Apparatus Method

Paddle and basket bending elements are used to evaluate release characteristics in vitro using standard BP dissolution or USP apparatus. The study dispersant ranged from 100 to 500 ml, and the rotation speed ranged from 50 to 100 rpm [26,28].

2.15. In-vivo method

Turbidity transparency is determined by methods that include direct local examination of biological effects of organisms, either local or systemic, as well as chemical absorption or surface aggregation. Animal models and buccal absorption studies are the most commonly used in-vivo research methods [26,28].

2.16. Animal Models

It is often used to test many compounds, determine their behavior, and evaluate many formulations. Dogs, cats, pigs, and sheep are just a few types of animals. This method involves anesthetizing animals, administering doses, drawing blood at several intervals, and analyzing the results [26,28].

2.17. Buccal absorption test

For drug combinations of one or more components, it is the most appropriate and reliable approach to determine the rate of drug loss from the human oral cavity. Adult subjects swallowed 25 ml of the test solution sample 15 minutes before voiding while the drug was still in the oral cavity to measure the kinetics of drug absorption.

Determine the importance of drug structure, contact time, drug concentration, and solution pH when first used. The amount of drug remaining in the expelled volume is calculated to determine how much drug has been absorbed [26,28].

2.18. Relationship between In-vitro and In-vivo

The relationship between the extent and degree of availability of a drug or metabolite in vitro, as assessed by blood concentration and urinary excretion, is known as the "*in-vitro-in-vivo* correlation". Such correlations allow the establishment of product parameters related to bioavailability [30,31].

3. Applications of microparticles

3.1. Delivery of vaccine microparticles

Vaccines must be protected from bacteria or harmful products. These features should be included in an ideal vaccine: safety, ease of use, efficacy, and affordability. Balancing safety and minimizing adverse reactions is difficult. The degree of antibody response induced and the question of safety is closely related to the treatment strategy. Conventional vaccines have disadvantages that biodegradable vaccine systems for parenteral immunization can correct [29].

3.2. Gene delivery using microparticles

Viral vectors, nonionic liposomes, polycation complexes, and microcapsules are used to deliver genetic drugs. Viral vectors are ideal for genotype delivery because they are highly efficient and can target a wide variety of cells. However, when used *in vivo*, it causes immunological effects and causes adverse effects. Non-viral delivery methods for gene therapy have been explored to overcome the limitations of viral vectors. The non-viral delivery approach provides several advantages, including ease of preparation, cell/tissue targeting, immunosuppression, unlimited plasmid size, and reproducible large-scale output. Polymers will be used as DNA carriers in gene delivery applications [32-35].

3.3. Using Microparticle Carriers to Target

Targeted distribution, also known as targeted drug delivery, is a concept that is gaining traction. The effectiveness of drug therapy is determined by its ability to reach and attract target receptors. Drug activity mediated by the use of transporter systems is associated with an efficient, consistent, and specific ability to exit the target group [36].

3.4. Microparticle Targeted Monoclonal Antibodies Facilitated

Monoclonal antibodies that attack microparticles are called immune microparticles. This approach is used to target specific websites. Monoclonal antibodies are molecules of very limited use. Microparticles containing bioactive substances can be targeted to specific sites using highly specific monoclonal antibodies (Mabs). Mabs can bind directly

to microparticles through covalent attachment. Antibodies can bind amines, free aldehydes, or hydroxyl groups on the surface of microparticles. Attaching the card to the microparticles can be done in several ways;

- Both adsorption is non-specific and non-selective
- Live connection.
- Reagent coupling [36].

3.5. Chemotherapy and microparticles

Microparticles are one of the most promising applications as anticancer drug carriers. Microparticles are required due to increased vascular permeability and endocytic activity. Coating soluble polyoxymethylene microparticles create invisible, microparticles. Secreted microparticles that accumulate in the RES [Reticuloendothelial System] can also be used to treat cancer [37,38].

3.6. Imaging

Microparticles have been extensively studied and used in various applications. Radiolabeled microparticles can be used to image tissues, organs, cell lines, and multiple cells. When imaging discrete areas, the particle size of microparticles becomes a serious concern. Particles deposited in vessels other than the portal vein adhere to the pulmonary capillary bed. Using labeled human serum albumin microparticles, this phenomenon is used to obtain scintigraphic images of lung tumor masses. [26,28].

3.7. Micro Particles with Porous Surfaces that can be applied to the Skin

Micro-sponges are micro-porous particles that range in size from 5 to 300 microns. These porous microparticles and active compounds can be used in creams, lotions, and powders and can trap various active components such as fragrances and essential oil sands. Micro-sponges are porous multi-layered non-bending structures that slowly release active chemicals [26,28].

3.8. Nasal medication administration

Intranasal (IN) administration offers several practical and theoretical advantages for continuous and local delivery of various therapeutic agents. Intranasal delivery is painless, requires no needles, and requires no preparation. This is also self-sustaining. Numerous microvilli, permeable endothelial membranes, and highly vascular epithelium in the nasal mucosa contribute to the initiation of the therapeutic effect. This includes many methods of drug administration, tools, formulations, and nasal and nasal passages. Depending on the purpose of the treatment, intranasal medication can be used for local or systemic treatment. Incorporating bioadhesive properties into microparticles is important because of the advantages of efficient drug absorption and increased bioavailability, closer contact with mucosal layers, and reduced mucosal clearance of adherent drugs. Nasal mucosal delivery system [26,28].

3.9. Controlled Gastro Protective Delivery System

Floating systems are low-density systems that float in the stomach and stay in the stomach longer than conventional dosage forms. The ability to adjust the emptying time of a dosage form is a huge advantage for dosage forms because gastric emptying is a complex process. On the other hand, developing controlled release systems to improve absorption and bioavailability presents several obstacles.

Because the drug floats through the stomach, it is released slowly and precisely, resulting in less change in plasma drug concentration and longer gastric retention time. Polyvinyl acetate, Eudragit, Methocil, agar, polycarbonates, cellulose acetate, chitosan, and other polymers are used in gastro-protective controlled release systems [26,28].

3.10. Implantable Gadgets

In the medical field, microencapsulation has been used to encapsulate living cells. Encapsulation of artificial cells with macromolecules, such as hormones, peptides, and proteins, improves biocompatibility and prevents unwanted immunological reactions that could lead to rejection or inactivation. Microparticles are used to keep the components separate until they are needed for their function. Microparticles are used in biotechnology to help individual organisms and their recombinant products [26,28].

3.11. Oral Medication Administration

Rabbits were used to investigate the potential of polymer matrices as an oral drug delivery mechanism for diazepam. He found that a film composed of a 1:0.5 ratio of drug and polymer could be a suitable alternative to conventional tablet formulations. The ability of polymers to form films may lead to the development of film dosage forms to replace pharmaceutical drugs. Coupled with the two main processes of the amine group, the pH sensitivity of the polymer began to differentiate as a type of polymer for oral drug delivery [26,28].

3.12. Ocular Delivery Micro Particles

Most ocular device glaucoma is treated with cholinergic agonists, especially pilocarpine. Biodegradable microparticles can extend the elimination half-life of water sources from very short [1 to 3 minutes] to longer [15-20 minutes]. For example, alkyl cyanoacrylate [39,40].

3.13. Applications for pharmaceutical products

Microencapsulated pharmaceutical products on the market include progesterone, theophylline, aspirin and its derivatives, antihypertensive drugs, gastric and potassium chloride. Microencapsulated potassium chloride is used to protect against intestinal problems caused by potassium chloride. Microcapsule encapsulation and ion release reduces the risk of saline concentrations that can cause perforation, ulceration, and bleeding. Injection and inhalation therapies containing microparticles have also been proposed [41].

The amount of research done in this area or the benefits that can be achieved with this technology is not reflected in the number of commercially available products. Cost factors affect the amount of drug microencapsulated products. Most packaging processes are expensive and require significant investment in equipment. Spray or drum coatings and spray dryers are exceptions, as the necessary equipment can be found at home. Many microencapsulation methods are patent-protected, which adds value [32].

4. Conclusion

Microparticles are unique drugs that provide an effective therapeutic alternative to conventional single-dose or immediate-release formulations. Produce microparticles by filling solid gelatin or by direct pressing. Compared to conventional dosage forms, microparticles produced using different technologies change the functionality and administration of dosage forms. Microparticles have been tested with in vitro release methods including dialysis membrane bags, individual samples and devices, and USP IV. According to these method comparisons, the USP IV device is currently the preferred method. Accelerated in vitro release assays are designed to reduce the time required for quality control. In *vitro-in vivo*, correlations are generated using real-time data and are accelerated to reduce the need for *in vivo* performance analysis. Storage stability was performed to see how different environmental conditions affect the quality of the microspheres during the product's lifetime. New tests, such as the in vitro leaching test and the floating test, have also been introduced to measure various physicochemical properties such as drug release, thermal properties, and particle size.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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