A NOVEL BIODEGRADABLE MICROPARTICULATED DRUG DELIVERY SYSTEM: ON REVIEW

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ABSTRACT

A well designed controlled drug delivery system can overcome some of the problems of convention therapy and enhance the therapeutic efficacy of a given drug. There are various approach in delivering a therapeutic substance to target site in a sustained controlled release manner. Targeting of drug to the particular site is an important aspect of drug delivery system. One such approach is using biodegradable microparticles as delivery for various drugs. This review presents the outstanding contributions in the field of biodegradable microparticulate system used as drug delivery systems including process technology for preparation of microparticles, drug release systems with drug release mechanism and the most important past, current and future strategies using drug loaded microparticles to improve the efficiency of various medical treatments. There are a number of techniques available for microencapsulation of drugs for Microparticle formulations such as the emulsion solvent evaporation/extraction method, spray drying, milling of films, and solvent extraction/evaporation methods, phase separation-coacervation, interfacial deposition, and in situ polymerization. There are several methods are available for drug release but current methods fall into three broad categories, viz., dialysis bag diffusion, sample & separate, and flow through cell technique. The review embraces various aspects of microparticle application in delivery of drug molecules and therapeutic genes.

Keywords: Microparticles, Microencapsulation, Process technology of Microparticles, Drug Release Profile.
INTRODUCTION
From time immemorial, drug has been used in the treatment of various acute and chronic diseases. Although the drug delivery system concept is not new, great progress has recently been made in this field of research and development. The word ‘new’ or ‘novel’ in the relation to drug delivery systems is a search for something out of necessity[1]. Over the last few decades, the field of controlled drug delivery has been faced with two major challenges. Once has been achieving sustained zero-order release of a therapeutic agent over a prolonged period of time and second of these challenges is controlled delivery of a therapeutic molecule or protein in a staggered fashion[2].

In the recent past, the development of targeted drug delivery systems have received an increasing interest not only for a better treatment of specific local pathologies, but also for the systemic therapy of both conventional and labile molecules as well as a means of achieving chronotherapy for diseases[3]. The ability to deliver and have a controlled release of therapeutic agents at injured or targeted disease sites is an important aspect in drug development and regenerative medicine. Such system avoid unnecessary health side effects due to burst effect or overdose, ensuring optimum supply of drug that is required by the biological system for a prolonged period, and cutting down wastage of expensive drugs[4].

![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)](image)

The efficacy of a drug in a specific application requires the maintenance of appropriate drug blood level concentration during a prolonged period of time (Figure 1, thick curve). However the conventional administration of drugs, gives a poor control of the concentration of these substances in plasma because of variations in the concentration of the bioactive product, once
a specific dose has been administered (Figure 1, thin curve). The conventional dosage systems can give rise to alternative periods of inefficacy or toxicity. These difficulties have been called for the development of new administration techniques for bioactive compounds, directed towards attaining the steady state plasma concentration\textsuperscript{5, 6}.

In the recent years, considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS). The reason for this paradigm shift is due to the low development cost and time required for developing a NDDS for the existing drugs rather developing a new drug molecule\textsuperscript{7}. In the form of NDDS, existing drug molecule can get a new life, thereby increasing the market value and product patent life\textsuperscript{8}. The therapeutic benefits of new systems include increased efficacy of the site-specific delivery, decreased toxicity/side effects, increased convenience, shorter hospitalizations, variable treatments for previously incurable diseases, potential for prophylactic applications and lower healthcare costs in long term and better patient compliance\textsuperscript{9, 10}. In a majority of studies the homo and copolymer have been used for drug delivery application because they can be fabricated into a variety of morphologies, including films, rods, and microparticles by compression molding, solvent casting, solvent evaporation technique and phase separation technique\textsuperscript{8}.

Controlled drug delivery systems can be extremely helpful to optimize the effects of pharmacotherapies. 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. 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\textsuperscript{11, 12}.

Biodegradable particulate drug delivery systems may contain an intimate mixture of the drug and core material or the drug may be dispersed as an emulsion in the carrier material or the drug may be encapsulated by the carrier materials. Micro, nano, vesicular, colloidal and lipid based carriers have the advantage of easy administration and efficacy over their long residence time, better targeting etc. 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, various colloidal vesicles, nanoparticles and microparticles. The latter have significant advantages over the other types of dosage forms, such as\textsuperscript{11}. 
1. The possibility to avoid the gastrointestinal tract (certain drugs lose their activity upon oral administration) by intramuscular or subcutaneous injection;
2. Easy administration using standard needles (in contrast to alternative controlled release parenteral dosage forms, such as macrosized implants);
3. 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);
4. The possibility to reach target tissues, which are normally not accessible for the drug (e.g., the Central Nervous System); and
5. No need of surgical removal of empty remnants, if biodegradable matrix formers are used.

Development of these carriers is a novel area of science that provides, with a new hope, the tools and technology to work at atomic, molecular and supramolecular levels leading to creation of devices and delivery systems with fundamentally new properties and functions. These carriers offer a number of advantages making it an ideal drug delivery vehicle[13]

1. Better drug delivery to certain stubborn or impermeable sites of body.
2. Owing to their small size, chemistry and distribution these carriers have better bridged the gaps between the structure and function of biomolecules.
3. Better targeting to body tissues and sites where action is required, elimination of side effects and adverse effects.
4. Owing to size, nature and chemistry, these systems give better drug permeability from biological membranes and helps in solubilization of some practically insoluble drugs and hence solve bioavailability problems of many drug.
5. It involves overlap of biotech, nanotech, and information technology, might result in many important applications in life sciences including areas of gene therapy, drug delivery, imaging, biomarkers, biosensors and novel drug discovery techniques[14,15,16].
6. It also offers an attractive solution for transformation of biosystems, and provides a broad platform in several areas of bioscience[17,18].
7. Targeted drug carriers reduce drug toxicity and provide more efficient drug distribution[19].
8. The surface properties of carriers can be modified for targeted drug delivery\textsuperscript{[20,21,22]}, for e.g. small molecules, proteins, peptides, and nucleic acids loaded nanoparticles are not recognized by immune system and efficiently targeted to particular tissue types\textsuperscript{[23]}. 

9. Drug carriers better penetrate tumors due to their leaky constitution, containing pores ranging from 100—1000 nm in diameter.

10. Drug carriers holds promise to deliver biotech drugs over various anatomic extremities of body such as blood brain barrier, branching pathways of the pulmonary system, and the tight epithelial junctions of the skin etc.

MICROPARTICULATE DRUG DELIVERY SYSTEM

Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long periods of time. They are small particles of solids or small droplets of liquids surrounded by walls of natural & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance\textsuperscript{[24]}. Microparticulates in the size range of about 1-100 micrometer consisting of biodegradable or bioerodible solids with embodied therapeutic agent represent a prominent class of drug delivery systems. Their administration is most commonly by local injection of suitable dispersions but applications to the respiratory tract or peroral delivery are equally interesting\textsuperscript{[25]}. 

In particular, there is much interest currently in the use of biodegradable polymers for the preparation of microparticles containing a wide range of therapeutic agents which can, of course, be used for parenteral administration. Solid biodegradable microparticles incorporating a drug dispersed throughout the particle matrix have the potential for the controlled release of the drug from this system after i.m. injection. Microparticles designed for parenteral drug delivery can be composed of a variety of materials with different physical characteristics such as biocompatible, biodegradable, injectable, sterile, compatible with diluents, and pharmaceutically stable. Depending on the used microparticulate material, its size distribution and degradation or erosion kinetics, various delivery profiles are feasible\textsuperscript{[25,26]}. 

To date, the biomedical potential of microparticulate formulations is far from being fully exploited, and future steps may lead to further and better products and offer novel therapeutic and economic opportunities. For future development, the following prospects for this class of drug delivery systems are envisaged:\textsuperscript{[25]}
Innovations for novel biodegradable and biocompatible materials and additives for better control of delivery kinetics;

Improvements of manufacturing techniques in terms of narrow particle size distribution, high loading efficiency, aseptic manufacturing technologies and drug stability;

Development of microparticulates as tools in tissue engineering, for example, to establish localized gradients of mitogenic or morphogenic agents and support organised tissular development;

Exploration of novel therapeutic opportunities through the use of microparticulates for systemic and localised delivery;

Innovations regarding novel materials and surface modifications to improve on biocompatibility and targeting features of microparticulates;

Design of microparticulates for optimised delivery of antigens to professional antigen-presenting cells.

Within the broad category of microparticles, “microspheres” specifically refers to spherical microparticles and the subcategory of “microcapsules” applies to microparticles which have a core surrounded by a material which is distinctly different from that of the core. The core may be solid, liquid, or even gas. Despite the specific and logical subcategories, many researchers use the terms interchangeably, often to the confusion of the reader. It is usually assumed that a formulation described as a microparticle is comprised of a fairly homogeneous mixture of polymer and active agent, whereas microcapsules have at least one discrete domain of active agent and sometimes more. Some variations on microparticle structures are given in Figure 2. As the domains and subdomains of active agent within microcapsules become progressively smaller, the microcapsules become microparticles[27].

![Fig. 2: Variations of microparticle formulations](image-url)
ADVANTAGES OF MICROPARTICLES:
Recently, controlled release has become a very useful tool in pharmaceutical area, offering a wide range of actual and perceived advantages to the chronic diseases such as rheumatoid arthritis, osteoarthritis, and musculoskeletal disorders including degenerative joint conditions still demand long-term therapy.

With the advent of microparticles following advantages were noted in the dosage forms:[28]
- Effective delivery of agents which are insoluble or sparingly soluble in water.
- They give the products which exhibit immediate release properties & can give 80% or more of active agent in about 10 minutes or less. Ex. Nimesulide
- They increased the relative bioavailability of drugs.
- The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.
- The microparticles hold great potential in reducing the dosage frequency & toxicity of various drugs.
- Microparticles in the form of microcapsules can also be used as carrier for drugs & vaccines as diagnostic agents & in surgical procedures.
- They can also be used to produce amorphous drugs with desirable physical properties.
- They also caused the reduction of the local side effects ex. GI irritation etc of drugs on oral ingestion.
- They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
- The PH triggered microparticles are used in immunization, transfection & gene therapy.
- Parenteral microparticles have the advantage of administering high concentration of water soluble drugs without severe osmotic effects at the site of administration.
- They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.
- They are useful in administration of effervescent dosage form of medicaments to individual unable to chew. Ex. Debilitated patients having difficulty in swallowing solids & the elderly.
- In contrast, smaller microparticles need to be prepared for application to other sites such as the eye, lung, and joints[29].
POLYMERS USED IN MICROPARTICULATE DRUG DELIVERY SYSTEM

Polymers have been used as a main tool to control the drug release rate from the formulations and they play an important role in drug delivery systems. They can be fabricated to act as reservoirs of the total amount of drug. Also their properties can be suitably modified to control the rate of release to the desired level. For the regulatory approval of controlled release products, three critical issues in polymer formulation are involved,\(^\text{[30]}\)

a) Non-toxicity and non-immunogenic
b) Bio-degradability
c) Controlled release of drug

Biodegradable polymers have long been of interest in controlled release technology because of the ability of these polymers to be reabsorbed by the body. As these polymers hydrolyse in the body into low molecular degradation products, which are either metabolised or excreted, biodegradable delivery systems do not have to be removed after completion of release\(^\text{[30,31]}\). Knowledge and skill in the field of biodegradable polymer technology is progressing rapidly enough that researchers have at their disposal a substantial number of degradable polymers with a range of degradation rates. Not only may researchers use a single polymer, copolymer, or blend, but they may also use a combination of polymers. These polymers, which have been prepared as films, microparticles, rods, and other forms, display a bulk erosion hydrolysis\(^\text{[32]}\). The release rates and profiles of both hydrophilic drugs and hydrophobic drugs have been shown to be significantly changed when the biodegradable microparticles containing these drugs are incorporated into silicone (nondegradable) or gelatin (degradable) films. The drug release from the microparticles within the silicone films does not exhibit the initial high burst of release in vitro from free microparticles\(^\text{[33]}\). Naturally derived polymers are abundant and usually biodegradable. Their principal disadvantage lies in the development of reproducible production methods, because their structural complexity often renders modification and purification difficult. Additionally, significant batch-to-batch variations occur because of their ‘biopreparation’ in living organisms\(^\text{[34]}\).

A variety of drugs, regardless of their molecular weights and water solubility, can be loaded into the biodegradable microparticles using different manufacturing techniques. A few examples of biodegradable polymers used in microparticle preparation include polyesters, polyanhydrides, poly(ortho esters), polyphosphazenes and polysaccharides. Figure 3 shows the chemical structures of some biodegradable polymers\(^\text{[35,36]}\).
PROCESS TECHNOLOGY FOR PREPARATION OF MICROPARTICLES

For preparation of microparticles using biodegradable polymers, it is important to choose an appropriate encapsulation process which meets the following requirements:\[^{37}\]:

1. The chemical stability and biological activity of the incorporated drugs should be maintained during the encapsulation process.
2. The encapsulation efficiency and the yield of the microparticles should be high enough for mass production.
3. The microparticles produced should have the reasonable size range (< 250 µm) that can be administered using the syringe needle via the parenteral pathway.
4. The release profile of the drug should be reproducible without the significant initial burst.
5. The process employed should produce free-flowing microparticles, thus making it easy to prepare uniform suspension of the microparticles.

There are a number of techniques available for microencapsulation of drugs for Microparticle formulations such as the emulsion solvent evaporation/extraction method, spray drying, milling of films, and solvent extraction/evaporation methods, phase separation-coacervation, interfacial deposition, and \textit{in situ} polymerization. Each method has its own advantages and disadvantages. The choice of a particular technique depends on the attributes of the polymer and the drug, the site of the drug action, and the duration of the therapy\[^{38, 39}\]. Most commonly, organic solvent evaporation and/or extraction methods are applied. Depending on the solubility of the drug simple or multiple emulsion technique, oil-in-water (o/w) and water-in-oil-in-water (w/o/w) methods are used\[^{40}\] (Figure 4).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Chemical structures of several biodegradable polymers.}
\end{figure}
At a small scale, the most frequently applied technique is the so-called “beaker method”, which is illustrated in Figure 5. 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 to 3 are all performed in beakers, this preparation technique is called “beaker method”.

4. Subsequently, the microparticles are separated by filtration and dried. A major advantage of this technique is that it does not require particularly cost-intensive equipment.
An interesting technique allowing to obtain very narrow microparticle size distributions is the so-called “jet excitation method”\cite{41}, illustrated in Figure 6. 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. 6). 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. 6: 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

The principle of the so-called “static mixture method” to prepare microparticles by solvent extraction/evaporation is illustrated in Figure 7 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. 7). 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. 7: Schematic illustration of the “static mixture method” to prepare drug-loaded microparticles using an oil-in-water (O/W) extraction/evaporation technique

EMULSION-SOLVENT EVAPORATION/EXTRACTION METHODS

SINGLE EMULSION METHOD

This method has been primarily used to encapsulate hydrophobic drugs through oil-in-water (o/w) emulsification process. The polymer is dissolved in a water-immiscible, volatile organic solvent such as dichloromethane, and the drug is dissolved or suspended into the polymer solution. The resulting mixture is emulsified in a large volume of water in the presence of an emulsifier. The solvent in the emulsion is removed by either evaporation at elevated temperatures or extraction in a large amount of water, resulting in formation of compact microparticles\(^ {37, 42}\).

In an attempt to encapsulate hydrophilic drugs (e.g., peptides and proteins), an oil-in-oil (o/o) emulsification method has recently received considerable attention. In this method, the water miscible organic solvents are employed to dissolve the drug and polymer, whereas hydrophobic oils are used as a continuous phase of the o/o emulsion. The microparticles are obtained by removing the organic solvents through evaporation or extraction process\(^ {43, 44, 45}\).

DOUBLE EMULSION METHOD

Most water-soluble drugs have been encapsulated by water-in-oil-in-water (w/o/w) methods. The aqueous solution of the water-soluble drug is emulsified with polymer-dissolved organic solution to form the water-in-oil (w/o) emulsion. The emulsification is carried out using either high speed homogenizers or sonicators. This primary emulsion is then transferred into an excess amount of water containing an emulsifier under vigorous stirring, thus forming a w/o/w emulsion. In the subsequent procedure, the solvent is removed by either evaporation or
extraction process. One advantage of this method is encapsulation of hydrophilic drugs in an aqueous phase with the high encapsulation efficiency\(^{[46, 47, 48]}\).

**PHASE SEPARATION METHOD**

This method involves phase separation of a polymer solution by adding an organic non-solvent\(^{[49, 50]}\). Drugs are first dispersed or dissolved in a polymer solution. To this mixture solution is added an organic nonsolvent (e.g., silicon oil) under continuous stirring, by which the polymer solvent is gradually extracted and soft coacervate droplets containing the drug are generated. The rate of adding nonsolvent affects the extraction rate of the solvent, the size of microparticles and encapsulation efficiency of the drug. The commonly used nonsolvents include silicone oil, vegetable oil, light liquid paraffin, and low-molecular-weight polybutadiene. The coacervate phase is then hardened by exposing it into an excess amount of another nonsolvent such as hexane, heptane, and diethyl ether. The characteristics of the final microspheres are determined by the molecular weight of the polymer, viscosity of the nonsolvent, and polymer concentration\(^{[51, 52]}\).

**Fig. 8:** Formation of mononuclear reservoir-type microcapsules by interfacial phase separation. Two different liquid droplets produced from ink-jet nozzles collide each other in the air. The solvent exchange occurs at the interface between two liquids to form a polymer layer on the aqueous core. The formed microcapsules are collected in the water bath.

Recently, a novel method of preparing reservoir-type microcapsules, based on interfacial phase separation, was developed\(^{[53]}\). Two different types of liquid droplets (i.e., a polymer solution and a drug solution) were separately produced using a dual microdispenser system consisting of two ink-jet nozzles, and the produced droplets were allowed to collide each other in the air (Figure 8). Upon collision, the drug-containing aqueous core remains spherical due to its high surface tension while the polymer-containing droplet spreads over
the aqueous core. As a result, a reservoir-type microcapsule is generated due to the interfacial phase separation by the mutual mass transfer of two solvents (i.e., solvent exchange). Successful formation of microcapsules depends on the polymer concentration and the properties of the solvents, such as surface tension, interfacial tension, and the solvent exchange rate.

**SPRAY DRYING METHOD**

Compared to other conventional methods, spray drying offers several advantages. The drug is dissolved or dispersed in the polymer solution, in which volatile solvents (e.g., dichloromethane and acetone) are preferred. The resulting solution or suspension is sprayed in a stream of heated air to produce microparticles. The size of the microparticles is determined depending on the atomizing conditions. The main disadvantage of this technique is a loss of a significant amount of product, primarily due to adhesion of the microparticles to the inner wall of the spray-drier (Figure 9). In addition, large aggregates are frequently obtained because the microparticles are very sticky before the complete removal of the solvent\[54,55\].

**Fig. 9:** Spray-drying apparatus A) Schematic drawing of apparatus for fabricating microspheres portraying acoustic excitation with carrier stream B) Schematic drawing indicating the variables used for acoustic excitation theory development\[54\]

In an attempt to minimize aggregation of the microparticles, a double-nozzle spray-drying technique was developed\[56\]. While the polymer/drug solution is sprayed from one nozzle, aqueous mannitol solution is simultaneously sprayed, which enables the surface of the microparticles to be coated with mannitol. The results indicated that the coating of the microsphere with mannitol reduces the extent of aggregation and augments the yield of the
product. In this technique, the liquid droplets of the polymer/drug solution are produced through the spraying nozzle, collected in liquid nitrogen containing frozen ethanol, and hardened by placing them at -80°C where the solvent extraction occurs\[57].

DRUG RELEASE FROM MICROPARTICULATE SYSTEMS

Microencapsulated and particulate systems for drug delivery have found wide application in pharmaceutics; initially for external use as creams and ointments, later for subcutaneous drug delivery, and in oral and intravenous administration\[58]. The release of drugs from microencapsulated systems, including micro- and nanocapsules, micro- and nanospheres, micro- and nanoparticles, and emulsion droplets, has been extensively reviewed. Drug release mechanisms are commonly inferred from kinetic measurement data of microencapsulated drug delivery systems by indirect methods based on the effects of solvent, buffer, agitation rate, or other variables\[59,60].

In vitro drug release studies are generally performed to accomplish one or more of the following aims\[61,62]:

1. As an indirect measurement of drug availability, especially in preliminary stages of product development
2. Quality control to support batch release and to comply with specifications of batches proven to be clinically and biologically effective
3. Assess formulation factors and manufacturing methods that are likely to influence bioavailability
4. Substantiation of label claim of the product
5. As a compendial requirement

An in vitro release profile reveals fundamental information on the structure (e.g., porosity) and behavior of the formulation on a molecular level, possible interactions between drug and polymer, and their influence on the rate and mechanism of drug release and model release data. Such information facilitates a scientific and predictive approach to the design and development of controlled delivery systems with desirable properties\[63].

CONSIDERATIONS IN METHOD DEVELOPMENT

As with conventional release testing, selection of media and temperature are important. Media selection is governed by drug solubility and stability over the duration of the study,
whereas the temperatures employed may be physiological, 37°C, or elevated. Additionally, the following should be considered prior to studying drug release:\cite{64, 65}

1. **Sink conditions:** Although sink conditions may not exist at the in vivo site of injection, it is wise to employ sink conditions during in vitro testing. In the event that a small volume of media can be used (based on the method employed and assay sensitivity), total media replacement may be used to ensure drug solubility, maintain sink conditions, and prevent accumulation of polymer degradation products.

2. **Burst release:** The release method employed should be able to identify a high initial release or “burst” from the formulation. Additionally, the method should provide information about the onset and duration of burst to assess its influence on the in vivo efficacy and safety window of the drug being studied.

3. **Robustness of technique:** The in vitro release method employed should be able to assess the influence of changes in the manufacturing procedure on the formulation. This would be useful from a quality-control standpoint and could also aid in the design and development of microparticulate drug delivery systems.

**OTHER ADDITIONAL CONSIDERATIONS**

Currently, *in-vitro* release testing of controlled and sustained release parenterals is primarily for quality-control purposes. However, as with controlled release oral and transdermal formulations, the outcome of in vitro release tests should be to ensure clinical performance, i.e., safety and efficacy of the product. To achieve *in-vivo* relevance, physiological variables at the site need to be considered including body temperature and metabolism (factors that affect blood flow), muscle pH, buffer capacity, vascularity, level of exercise, and the volume and osmolarity of the product. Other considerations include tissue response (inflammation and/or fibrous encapsulation of the product). The lack of such information has prompted the FDA to exercise caution in establishing regulatory guidelines. Some guidelines that have been suggested for *in vitro* method development include\cite{62}:

1. Identification and selection of release media and conditions that result in reproducible drug release rates
2. Preparation of formulation variants that are expected to have different behaviour *in-vivo*
3. *In-vitro* and in vivo release testing of formulation variations
4. Modification and/or selection of an *in-vitro* release method that discriminates between formulation variants that exhibit different *in-vivo* release profiles
Ideally, an *in-vitro* test method should mimic *in-vivo* conditions and release mechanism as much as possible.

The measurement of drug release from microencapsulated systems poses many difficulties which are not encountered for larger particulate systems, which can be carried out using basket and paddle methods as described in the United States Pharmacopeia (USP) or other monographs\(^{[66, 67]}\). The main difficulty arises when an attempt is made to separate the released drug in the continuous phase from the suspended microparticulate carriers. This becomes increasingly difficult and slow as the particles become smaller; however, the release rates become faster for smaller particles, as one reaches a limiting lower size for which the separation cannot be carried out on a timescale that is faster than the release profile. Under these circumstances, any useful kinetic information in the release profile is lost\(^{[68, 69]}\). The methods available to evaluate drug release from colloidal carriers fall into the following groups:

**1. Dialysis Bag Diffusion Techniques**

The dialysis bag diffusion technique is widely used to evaluate drug release from macro and nanosized carriers. A small volume of the concentrated drug–particle suspension is contained in a dialysis bag, which is immersed in a larger volume of continuous-phase acceptor fluid. Preferably, both compartments are stirred, and the drug then diffuses out of the particulate carrier into its local continuous phase, and then through the dialysis membrane into the acceptor phase, which is periodically sampled and assayed\(^{[70, 71, 72]}\).

**2. Sampling and Separation Methods**

Examples of this method normally start by preparing a concentrated suspension of the particulate carrier and rapidly diluting it into a much larger bulk of acceptor phase. Samples of this diluted system are then removed at intervals, and the particles are separated so that the continuous phase may be assayed for the released drug. This technique is perfectly adequate for larger microparticles using filtration or centrifugation techniques, when the release times are measured in hours\(^{[73]}\).

**3. Continuous-Flow Methods**

The continuous-flow method most commonly uses an ultrafiltration cell to recover samples of clean continuous phase; this is fed from a pressurized reservoir and flows continuously through a detector for a direct continuous measurement of drug release\(^{[74]}\).
4. In Situ Methods
In situ methods depend on the use of analytical techniques, which are only sensitive to the drug in the solution and not to that which is in the solid particles or that is bound to their surface, so that the assay of the released drug may be performed without any separation step\[^{75}\].

**MECHANISMS OF DRUG RELEASE**
In microencapsulated matrix systems, a drug is incorporated into a polymer matrix by either particulate or molecular dispersion. The diffusional release of drug from carrier has been assumed to be the controlling step, and usually can be described by Fick’s first and second laws. Release is influenced by a range of factors, such as diffusion and partition coefficients, drug loadings and solubilities, boundary surface areas, layer thickness, and shape factors\[^{76}\]. Several of the drug properties, such as solubility, pK value, and partition coefficient, are closely dependent upon the properties of sink medium into which the drug diffuses (Fig. 10). As a measure of the important Fickian parameter surface area, the size distribution will undoubtedly be relevant to the release profile provided it is measured under realistic conditions, as there may be time dependency involving differential swelling, degradation, erosion, or splitting\[^{77}\].

![Drug Release Mechanism](image)

**Fig. 10:** Schematic illustration of drug release from microparticulated systems. Release mechanisms will imply a range of release rates, with the smaller particles showing rapid release and the larger ones a slower component. In theory, it is straightforward to integrate the release rate expression over the *particle size distribution* if this is known. However, this relationship may not be straightforward, as the structure of the particle may vary with size\[^{64,77}\].

*Shape* variation is a further complicating factor. The particles may be non-spherical; many papers show electron micrographs of “spherical” particles which show minor or gross distortions; these can be induced or augmented by freeze-drying, so that the dried formulation shows very different release profiles to the suspension formulation.
Wall–core ratios also vary in populations. Increasing the core versus wall ratio will increase the drug content of particles and consequently the release rate. Decrease of the core versus wall ratio leads, as expected, to a reduction in release rate. Porosity and cross-linking density have a direct relationship with drug release. In macroporous systems, where the polymer is hydrophilic, the drug release may occur in two phases: first by desorption from the polymer to pores, then by emptying of the drug from pores to the medium. The drug diffusion coefficient is slower through the beads with a higher degree of cross-linking, thus, cross-linking treatment on a porous matrix causes a modification of the pore tortuosity and the drug-release rate[78].

Drug location in microencapsulated systems also influences the drug-release rate and/or pattern. If the drug is surface active, it will adsorb to the outside of the particles during preparation, and may provide a burst effect on dilution. The release profiles depend on the number of washing steps carried out prior to the actual release measurement, because of the removal of the loosely deposited drug near the surface[79].

Many variables that have been studied in microparticulate controlled release devices, and in the field of polymer science, are also relevant to release from microencapsulated systems. Important factors include drug diffusivity and solubility in polymers and solutions, molecular weights of polymer and diffusant, diffusant size, degree of polymer crystallinity or cross-linking, presence of diluents, plasticizers and fillers, geometry and dimensions of polymer matrix and/or membrane thickness, degree of polymer swellability, polymer degradation, polymer erosion, thickness of aqueous boundary layer, porosity and tortuosity, partition coefficient of a drug between polymer and aqueous medium, drug loading, pH value of medium and pK value of drug, drug polymorphism, and the interplay among these variables[80].

APPLICATIONS OF MICROPARTICLES IN DRUG DELIVERY[28]
1. Application areas of microcapsules include pharmaceutical and biotechnology products, cosmetics, diagnostic aids, biological filtration devices, veterinary and zoo technical products, foods and food additives, flavors, fragrances, detergents, paints, agricultural chemicals, adhesives, industrial chemicals, household products, packaging, textiles, photographic and graphic arts materials.
2. These microcapsules are important in providing sustained and controlled release, improving drug stability, reducing vaporization of volatile oils, protecting
moisture/light/oxidation–sensitive drugs, masking unpleasant taste and odor, converting liquids to powders, and separating incompatible substances within a single system.
3. Amoxicillin, ampicillin, bacampicillin, cephalixin, cephradine, chloramphenicol, clarithromycin, erythromycin, potassium pheneticillin, ofloxacin, and ciprofloxacin are some examples of the encapsulated antibiotics.
4. Anti-inflammatory drugs are another group in which microencapsulation is employed. Diclofenac sodium, flufenamic acid, glafenine, hydrocortisone, ibuprofen, indomethacin, naproxen, oxyphenbutasone, and prednisone are examples of encapsulated drugs in this group.
5. Sulfadiazine, sulfamethizole, sulfamethoxazole, sulfamerazine, and sulfisoxazole are some representatives of sulfa drugs that are encapsulated.
6. Furosemide, chlorothiazide, and sulphonamide were encapsulated in order to prepare sustained release formulations that would offer the advantage of avoiding short periods of peak diuresis observed with the conventional formulations.
7. Isosorbide-5-mononitrate (IS-5-MN), dihydralazine sulfate, piretanide and propranolol HCl, captopril, nicardipin, and dipyridamole are examples of microencapsulated antihypertensives. IS-5-MN microcapsules were optimized and formulated to sustain the action and to overcome the tolerance developed in conventional preparations.
8. Vitamins A, B1, B2, B6, B12, C, D, were encapsulated to provide formation of smooth- and thick-walled microcapsules largely prevented the aggregation of microcapsules and showed low dissolution rate.
9. Converting Liquids to Free-Flowing Powders Citrus essential oil, cod liver oil, benzaldehyde, carbon tetrachloride, and oil droplets were coated and recovered as fine powders. The authors have stated that the bulk droplet size of the encapsulated material appeared to be a factor in the strong capsule wall, which protects against vaporization and oxidation.
10. Air filled micro particles are used in echocardiography & other ultrasonic imaging techniques. They are also used as opacifier or reflectivity enhancers in cosmetics.
11. Solid microspheres are of particulars used in nasal delivery of drugs including polypeptides, insulin, somatostain, metolopromide etc.
12. PH triggered micro particles have been used to deliver drugs by various means ex-by IV inject, intra dermal inj, rectally, orally, intra vaginally, inhalationally, mursoual delivery etc.
13. They are also used for administering. An antigenic epitote of a pathogen or a tumor.
14. The micro particles are useful in transficting cells & gene therapy.
15. Condensed phase micro particles are used as stable strong kit for enzymes, antibodies, dye.

**Practical Examples:** Drug loaded microparticles have been applied to improve the efficacy for various therapies. Some of the products that are commercially available in the market are listed in table 1[11].

**Table 1: Examples of pharmaceutical products based on drug loaded, Biodegradable Microparticles available on the market**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Company</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolein acetate</td>
<td>Lupron Depot, Trenantone</td>
<td>Takeda</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Recombinant growth hormone</td>
<td>Nutropin depot</td>
<td>Genetech-Alkermes</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>Zoladex</td>
<td>I.C.I</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Octrotide acetate</td>
<td>Sandostatin LAR depot</td>
<td>Novartis</td>
<td>GH suppression anti-cancer</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>Decapeptyl</td>
<td>Debiopharm</td>
<td>Cancer</td>
</tr>
<tr>
<td>Recombinant bovine somatropin</td>
<td>Posilac</td>
<td>Monsanto</td>
<td>Milk production in cattle</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal consta</td>
<td>Janssen</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

**CONCLUDING AND FUTURE REMARKS**

Biodegradable microparticles have one of the greatest ranges of utility in controlled release manner of any formulation yet studied. They can be utilized in injectable formulations, oral formulations, bioadhesive systems and as the principal release-controlling component of degradable and non-degradable implants and films. 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. For further improvement, several aspects should be considered such as process engineering, material engineering and biomedical engineering. Further, shielding the
surface of microparticles from unspecific phagocytosis and establishing a functionalised surface to allow specific receptor-mediated phagocytosis may enable more functional control.

REFERENCES


77. Donbrow M. The relation of release profiles from ensembles to those of individual microcapsules and the influence of types of batch heterogeneity on release kinetics. In:

