Review Article

Oral Sustained Drug Release Formulation Through Microsphere

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ABSTRACT

Sustained-release oral drug delivery systems (SRDDS) have come to the rescue to solve the shortcomings of traditional dosage forms. Conventional oral medications are characterized by variable plasma concentrations and result in low therapeutic efficacy and patient adherence. Systems based on microspheres are able to offer a sustained drug delivery system with greater levels of control, and systems achieve a steady concentration of drugs. These systems involve the use of biodegradable natural and synthetic polymers that contain drugs and can be controlled to release them by diffusion, degradation or swelling process. Microspheres improve bioavailability, decrease dosage rate and diminish side effects. Their properties depend on different methods of preparation like emulsion methods, spray drying and phase separation. Drug release is dependent on key formulation factors such as polymer concentration, drug-polymer ratio and solvent system. More sophisticated microspheres such as bio adhesive, floating systems and stimuli responsive enhance targeting and therapeutic effects. Even though burst release and scale-up problems exist, current research studies are alleviating these constraints. Altogether, it can be concluded that SRDDS with the use of the microsphere are a high-risk perspective of better and patient-centered drug treatment.

Keywords: Sustained-release pharmaceutical delivery, Microspheres Controlled drug release, Biodegradable polymers, Drug encapsulation, Polymer-based delivery, Drug release kinetics and pharmaceutical formulation.

1. INTRODUCTION

Oral route remains the most preferred and highly acceptable approach to drugs administration because of its convenience, safety, cost-effectiveness, and high compliance by the patient. Nevertheless, traditional oral dosage forms like tablets and capsules are limited to some extent. A large number of drugs administered orally have a low biological half-life, travel rapidly through the gastrointestinal tract, and cause great variation in plasma drug concentrations, which is sometimes known as the peak-valley effect. This has necessitated a repetitive dosing to sustain the therapeutic concentrations thus decreasing patient compliance particularly in the chronic illnesses of long-term treatment. Moreover, the differences in drug concentration can lead to the risk of experiencing some adverse effects and reduced overall treatment outcomes[1,2].

1.1 Sustained-release oral drugs delivery is necessary

The weaknesses associated with the traditional oral formulations have led to the development of sustained-release oral drug delivery systems (SRDDS) that preserve therapeutic drug concentrations in the body over extended periods of time. These systems are specifically aimed at freeing out the drug in a controlled and predictable pattern, hence minimizing administration frequency, fluctuations in plasma drug level, and overall therapeutic response. Microsphere based delivery systems have been very popular due to its versatility, effectiveness, and capacity to deliver a wide variety of drugs, with great attention being drawn to this type of sustained delivery system among the other types of delivery systems.

Microspheres are small, round, spherical particles with a diameter of between 1 and 1000 um. They are cooked in biodegradable polymers either natural or synthetic. When used in oral sustained-release forms, the drug can be held in the polymer, or can be uniformly dispersed throughout the polymer. The drug is usually released upon release of microspheres by either diffusion, erosion of polymer, or biodegradation. This modified release mechanism assists in extending the duration of action of the drug and helps in avoiding degradation in the environment of the gastrointestinal tract which is harsh[3].

1.2 Limitation of traditional dosage preparations

Conventional oral dosage therapies are limited in a number of ways.

- They usually need several doses daily especially with drugs that have short half-lives which lower patient compliance.
- They cause large variation in plasma drug levels causing intervals of insufficient therapeutic action or possibly toxicity.
- The common peaks and troughs ensure that it is hard to have constant and steady levels of drug in the blood.

1.3 Sustained-release dosage forms

These dosage forms are not intended to be rapidly absorbed by the body but instead to maintain a specific level of a drug in the body

Sustained-release dosage forms are made to change the rate of drug release such that the therapeutic effect lasts longer. Such formulations absorb the drug into the systemic

circulation in a slow manner; hence, stable plasma concentrations with time. Sustained-release systems increase efficacy of therapy and adherence by patients by keeping the drug concentration relatively constant. In comparison to the traditional formulations, where the patient might have to take three or four doses a day, sustained-release tablets are usually taken once or twice a day and still provide the same clinical result. Such a prolonged act decreases the dosing frequency and enhances the convenience of patients[4,5].

1.4 Reason why sustained-release drugs delivery systems should be developed

The necessity to use sustained-release drug delivery systems is grounded on numerous important reasons:

- To minimize the number of doses that need to be taken whilst maintaining the constant supply of the drug at its required location.
- To enhance therapeutic outcome through regularity of the drug levels.
- To reduce the cost of overall treatment through reduction of repetition doses.
- To reduce chances of toxicity in case of high peak plasma levels.

1.5 Advantages of Sustained-release dosage form

The sustained-release formulations have several advantages such as:

- Less frequent administration of the drug.
- Reduced frequency of side effects because of constant plasma drug levels.
- Regulated and steady drug delivery[6].

2. MICROSPHERES IN DRUG DELIVERY

Microspheres are tiny, free flowing spherical particles which are derivatives of natural proteins or synthetic biodegradable polymers. Their size is normally between 1 to 1000 um. Microspheres find most applications in drug delivery applications where they are used as sustained-release systems to regulate the rate of drug release during a long period. They can maintain comparatively stable plasma drug levels, thereby minimizing the frequency of dose and the side effects.

Microspheres are divided into two broad categories depending on their internal structure microcapsules and micrometrics.

Microcapsules are substances that contain a clear outer layer of polymer that fully covers and envelops the drug core.

Micrometrics (or matrix microspheres) have the drug evenly dispersed in the polymer matrix as opposed to being enclosed in another shell[7].

2.1 Advantages of Microspheres

Drug delivery systems using microsphere have a number of advantages:

- Their low particle size enhances the surface area that can give a boost to solubility and efficacy of poorly hydrophilic drugs.
- They lower the rate at which dosing is done and assist in minimizing the adverse effects through controlled delivery of the drug.
- With increased convenience, there is increased patient compliance.
- The drug is encapsulated in a polymeric matrix which shields it against enzyme in the body.

2.2 Distinction between Microspheres, Microcapsules and Nanoparticles

Table 1: Distinction Between Microspheres, Microcapsules and Nanoparticles

Parameter	Microspheres	Microcapsules	Nanoparticles
Basic Structure	Solid, spherical matrix system in which drug is uniformly dispersed throughout the polymer	Reservoir-type system consisting of a drug-containing core surrounded by a distinct polymeric shell	Solid colloidal particles that may exist as nanospheres (matrix type) or nano capsules (core–shell type)
Internal Architecture	Monolithic structure (no separate core)	Clearly defined core and outer coating	Either homogeneous matrix or core enclosed within nanometric membrane
Size Range	Typically, 1–1000 µm (micrometer range)	Typically, 1–1000 µm (micrometer range)	Generally, 1–1000 nm (nanometer range), commonly 10–500 nm in pharmaceuticals
Drug Distribution	Drug is molecularly dispersed or entrapped within polymer matrix	Drug is confined to central cavity/core	Drug may be dissolved, encapsulated, adsorbed, or conjugated on surface
Mechanism of Drug Release	Controlled mainly by diffusion, polymer erosion, or swelling	Controlled by membrane diffusion, osmotic pressure, or rupture of shell	Release occurs through diffusion, degradation, surface desorption, or stimulus-responsive mechanisms
Surface Area	Moderate surface area	Moderate surface area	Very high surface area-to-volume ratio
Targeting Ability	Limited passive targeting	Limited targeting; mainly protective	Can be surface-modified for active targeting and site-specific delivery

3. ORALLY ADMINISTERED SUSTAINED-RELEASE WITH POLYMERS

The polymers are very important in creating oral sustained-release microspheres, since they regulate the rate of drug release and determine the stability of the formulation. These polymers are broadly categorized into two broad categories namely natural polymers and synthetic polymers. Issues of biodegradability, biocompatibility, mechanical strength, and compatibility of drug and polymer are some of the factors that determine the selection of an appropriate polymer.

3.1 Natural Polymers

Natural polymers are sourced naturally and primarily of plants and animals. They are popular in pharmaceutical preparations due to their biocompatibility, biodegradability, low-toxicity, and low-environmental-impact.

a) Carbohydrates:

Natural polymers that are used in sustained-release formulations are polysaccharides. These are chitosan, starch, agarose and carrageenan. The materials have good film-forming characteristic and are able to regulate drug release by means of swelling and gel formation.

b) Modified Carbohydrates:

Chemical modifications of certain carbohydrates are undertaken to enhance mechanical strength, release properties. The polymer like polydextran and polystarch provides superior stability and control of drugs release in contrast to their natural counterparts.

c) Proteins:

Microsphere preparation is also done using protein-based polymers such as albumin, gelatin and collagen. These are biodegradable materials that can be used in making stable matrices thus they can be used in sustained-release applications.

3.2 Synthetic Polymers

Synthetic polymers are unnaturally produced materials that may be subdivided into biodegradable and non-biodegradable.

Non-biodegradable polymers develop when carrying out reactions in the presence of aromatic compounds.

a) Non-biodegradable Polymers:

These are: Glycidyl methacrylate, Epoxy polymers, Acrolein, Polymethyl methacrylate.

These are polymers that are not easily degraded in the body. Parenterally, they can be stored in tissues despite full release of the drug and cause long-term toxicity (4,5).

b) Biodegradable Polymers:

They are: Polylactic acid (PLA), Poly (lactic-co-glycolic acid) (PLGA), Polyalkyl cyanoacrylates, Polyanhydrides.

Biodegradable polymers decompose to non-toxic by-products in the biological environment. They are usually preferred due to safe degradation profile particularly in cases of parenteral and controlled-release .

3.3 Polymer Criteria to be used during oral use.

- The polymer must have the capacity to extend release of drug and sustain therapeutic concentration over a long period.
- It must ensure that the drug is not broken down enzymatically and in intensive gastrointestinal environments.
- The polymer should be able to sustain sterilization without being deprived of its properties.
- It has to be non-toxic and safe to be treated orally.
- It must be biocompatible and unable to cause irritation and other unfavorable biological reactions[8,9,10].

4. DRUG CANDIDATES ACCEPTABLE IN MICROSPHERES-BASED SUSTAINED RELEASE

4.1 Physicochemical Requirements

There are physicochemical requirements, namely:

- Physicochemical properties of a drug candidate greatly determine whether it is selected as a viable drug candidate in the microsphere-based sustained release. These properties affect the encapsulation efficiency, stability and release behavior.
- The preference is to use drugs with greater lipophilicity (large log P value) due to the ability to interact with the polymer matrix and, thus, reduce initial burst release and increase drug release.
- It is better to use poorly water-soluble drugs since highly soluble drugs can be rapidly diffused and produce an unwanted initial burst effect.
- The drug should be compatible with the polymer. Likewise, solubility parameters (as are the case with PLGA) enhance the encapsulation efficiency and aid in controlled release.
- Drugs that are in a crystalline form and that are contained within the microsphere tend to have a slower and more prolonged release than the drugs that are in an amorphous form.
- The diffusion depends on molecular weight and particle size; the smaller the molecular weight and particle size, the faster the diffusion out of the polymer.
- The best candidates are highly potent drugs since smaller doses can be used in sustained-release systems to have effective therapy.

4.2 Biopharmaceutics Classification System (BCS)

Biopharmaceutics Classification System (BCS) is a classification system that ranks drugs according to their

pharmacokinetic attributes. The Biopharmaceutics Classification System (BCS) is a classification of drugs, which organizes drugs according to their solubility and intestinal permeability into four categories. In the case of microsphere based sustained release systems, the drugs most suitable are those with shorter biological half-life and those that require a long-acting duration. High solubility, high permeability (BCS Class I) and low solubility, high permeability (BCS Class II) drugs are normally regarded as appropriate since they are readily absorbed and the rate at which they are released can be readily regulated. The perfect candidate must be stable at the gastrointestinal site, be at a moderate dose, and be capable of a relatively broad index of therapeutic use so that toxicity becomes unlikely. The sustained-release microspheres are used to achieve a constant plasma level, increase bioavailability, and patient compliance, especially in chronic therapies.

4.3 Drugs with Narrow Therapeutic Index

Drugs whose NTI is narrow implies that their dosage is highly sensitive and needs meticulous control. Narrow therapeutic index drugs are drugs whose plasma concentrations need thorough regulation because a little variation in the level can lead to toxicity or failure of the treatment. Sustained-release systems based on microsphere, in particular, are useful in case of such drugs. Such systems offer regulated and homogenous release of drugs and reduce peak plasma concentrations that can lead to adverse effects and also avoid sub-therapeutic levels. The microspheres increase safety and effectiveness in treatment through the minimization of deviations between peak and trough levels. They are especially useful in the case of drugs that are applied to the cardiovascular disorders, epilepsy, and cancer treatment.

4.4 Peptides and Proteins

Proteins and peptides are prospective microsphere-based delivery systems. These molecules are very vulnerable to enzyme destruction particularly in the gastrointestinal tract. Microspheres encapsulation is used to prevent their degradation and enhance their stability. Microspheres in the sustained-release formulation enhance patient compliance in chronic therapies because of the elimination of frequent dosing, particularly frequent injections. PLGA is a biodegradable polymer that is usually employed in the delivery of proteins and peptides[11-15].

5. MICROSPHRESES PREPARATION

The various methods of producing microspheres are based on the polymer type, drug characteristics, particle size required, route of delivery and duration of drug release that is required. There are basic formulation variables that affect the end characteristics of microspheres; the speed of stirring (rpm), the nature of cross-linking method, solvent [16].

5.1 Single Emulsion Technique

The single emulsion technique is mostly employed in creating microspheres with natural polymers. During this, the polymer is first dissolved in water to create a solution. This solution is gradually introduced into a non-aqueous solution during stirring, and this results in the creation of an emulsion. The cross-linking of the polymer is done to stabilize the microspheres, which is done through heating or through chemical cross-linking reagents like formaldehyde or diacid chloride. Consequently, solid and stable microspheres are developed.

5.2 Double Emulsion Technique

This is especially the case with the double emulsion process that can be applied in the incorporation of water-soluble drugs like proteins, peptides, and vaccines. The method used in this technique involves initially dissolving the drug in water after which it is followed by the addition of an organic solution that contains the polymer. This is the major water-in-oil (W/O) emulsion. Then, the primary emulsion is introduced to a second aqueous solution which has a stabilizer such as polyvinyl alcohol (PVA), to form a water-in-oil-in-water (W/O/W) two-level emulsion. The solvent used here is organic, so it is usually removed through evaporation under low pressure. The step will result in hardening of the polymer and creation of solid microspheres. Lastly, the microspheres are filtered and washed to remove all the solvent.

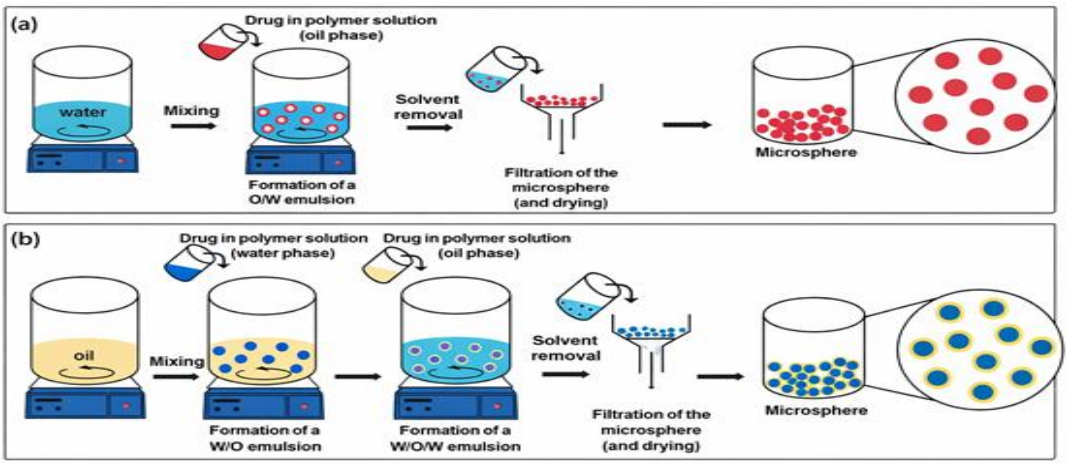

Figure 1: Schematic representation of a single and double emulsion technique

5.3 Spray Drying Technique

Under the spray drying technique, the polymer is dissolved in an organic solvent that is volatile like acetone or dichloromethane. This polymer solution either dissolves or disperses the drug. This is then atomized in a stream of hot air in a spray dryer. The droplets are evaporated rapidly to form solid microspheres that are gathered at the bottom of the chamber[24].

5.4 Phase Separation (Coacervation) Process

This technique finds application primarily in encapsulation of water-soluble proteins and peptides. The solvent is then used to dissolve the polymer and the drug is dispersed into the solution. Separation is then caused by varying system conditions, e.g. addition of salts, non-solvents, incompatible polymers, or ph change. This leads to the creation of droplets of polymer surrounding the drug particles to create microspheres.

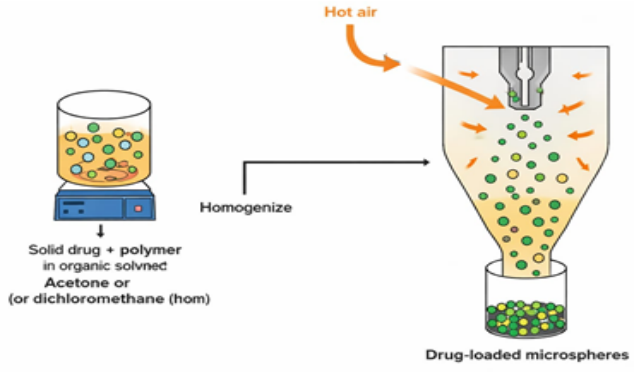

Figure 2: Schematic Representation of a Spray Drying Technique

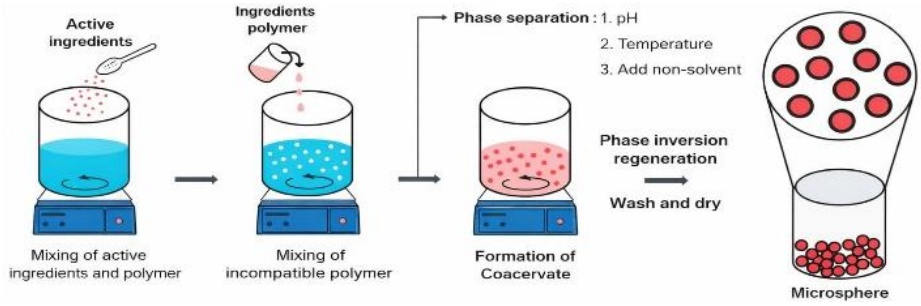

Figure 3: Schematic representation of a phase separation process

5.5 The Solvent Extraction Technique

In the solvent extraction technique, the solvent is removed by separating the emulsion system by an aqueous solvent to form microspheres. As the organic solvent can be partially dissolved in water it diffuses slowly into the aqueous phase and is extracted. Polymer solubility, solvent volume, temperature, and ratio of water and emulsion have an effect on the solvent removal and formation of microsphere efficiency[17-21].

6. INFLUENCING FACTORS OF MICROSPHERES CHARACTERISTICS

Some formulation and process parameters determine the properties of microspheres including particle size, drug loading, and release behaviour. These factors should be appropriately controlled in order to attain the desired therapeutic performance.

6.1 Polymer Concentration

The quantity of polymer in the formulation is a significant factor in defining the size of the microsphere, entrapment and release of the drug. As the concentration of polymer rises the viscosity of the inner phase rises. This causes the emulsification to form the bigger droplets hence the formation of the bigger microspheres. An increase in polymer level normally increases the encapsulation of the drug since the drug is encased in a thicker polymer layer. Nonetheless, extremely high polymer concentrations can create a dense structure, thereby slowing down drug diffusion and release too slowly. Thus, the concentration of polymer has to be well optimized in such a way that to maintain the balance between the size of particles and the continuous drug release.

6.2 Drug-Polymer Ratio

The drug-polymer ratio influences the rate of drug loading, encapsulation and release kinetic. In case of large drug content and low polymer content, the entrapment of drug can be poor and some drug can be available on the surface of microspheres. Enhancing the polymer content will tend to increase the encapsulation capacity and the formation of the matrixes, but can decrease the content of drug loading. The release behaviour is also determined by this ratio. An increased polymer content normally leads to slower and regulated drug release. It is thus important to choose the right drug-polymer ratio to achieve the optimal therapeutic effect.

6.3 Stirring Speed and Type of emulsifier

The rate of stirring during the preparation influences the diameter of microspheres. An increase in the stirring rates generates greater shear forces that result in smaller droplets and smaller microspheres. Reduced stir rates tend to give large particles. Very high speeds however can lead to shapes of particles or aggregation. The kind and amount of emulsifier is also significant. The emulsifiers stabilize the

emulsion and lower the tension between phases. The correct choice can be used to achieve homogeneous particle size, smooth surface morphology, and avoid fusion of droplets during preparation[22,23].

6.4 Solvent System

Solvents have a strong impact on the formation of microspheres and the entrapment of drugs. The speed of the solidification of the polymer is defined by solvent properties like volatility, polarity, and miscibility with the external phase. Solvents that are very volatile evaporate rapidly and could yield porous microspheres. Easy to mix solvents with the external phase may result in diffusion of the drug much faster, and hence lower entrapment efficiency. Thus, it requires a suitable solvent system to allow formation of a proper matrix, decrease losses of drugs and obtain a desired release profile.

6.5Cross-Linking Agents

Cross-linking agents aid in augmenting the polymer framework and enhance mechanical steadiness of microspheres. The increased degree of cross-linking decreases swelling and retards diffusion of drugs leading to long-term drug release. Reduced levels of cross-linking give rise to soft matrices that discharge the drug faster. The nature and the quantity of cross-linking agent should be regulated with great care to prevent toxicity and retain biocompatibility. The microsphere system has a greater structural integrity and stability over proper cross-linking[24-27].

7.Drug Release Prolongation Mechanisms of Microspheres.

Various controlled processes allow drug release of microspheres. The pattern of release varies with the nature of the polymer employed, properties of the drug and the environmental factors. A combination of one or more of the mechanisms is used in most instances to offer lasting drug action.

7.1 Diffusion-Controlled Release (DCR)

Diffusion-Controlled release is a depiction of the diffusion process whereby a substance diffuses to the surface through diffusion. One of the most widespread drug release processes in microsphere systems is diffusion. During this process, the drug is gradually released out of the polymer matrix into the biological fluids. Microspheres dissolve the drug on or around the surface first when put in a dissolution medium. Subsequently, the drug entrapment in the matrix diffuses slowly through small pores and channels. The rate of release is affected by drug solubility, polymer porosity and concentration gradient. Hydrophilic polymers tend to permit faster diffusion of drugs than hydrophobic polymers. The drug is also released faster by smaller microspheres as they have a greater surface area. Diffusion-controlled systems are usually of Higuchi release kinetics and are typical of matrix-type microspheres[28].

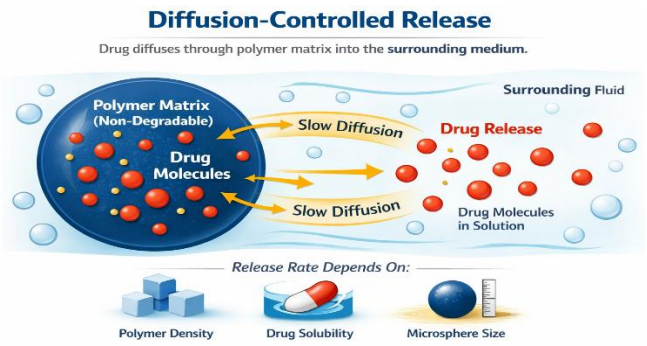

Figure 4: Schematic Representation of a Diffusion-Controlled Release

7.2 Dissolution-Controlled Release

In biological systems, the dissolution of proteins can be influenced by the electric potential, ionized solutes, and ionized solvents, among other factors. The rate of drug release in the dissolution-controlled systems is determined by the rate of dissolution of the drug or polymer. When the drug is not soluble in water, the solubility is low and thus the release will be delayed. In other formulae, a polymer coating dissolves slowly, and the drug can be released gradually. Dissolution rate depends on the thickness of the polymer layer and other factors in the environment like pH. Its mechanism is effective in the case of drugs that dissolve poorly and assist in producing slow and controlled release of drugs.

7.3 Degradation-Controlled (Erosion-Controlled) Release.

The release of drugs in this mechanism takes place by the slow breakdown of the polymer matrix with time. PLGA, PLA, and gelatin are biodegradable polymers that are hydrolyzed or attacked by enzymes. As polymer goes away, releasing of the captured drug is done gradually. Polymer composition, molecular weight, and environmental conditions such as pH and temperature influence rate of degradation where surface erosion leads to a more homogeneous release pattern in comparison to bulk erosion which could cause rapid release. It is a mechanism applied in long-acting injectable microspheres, where the mechanism does not require surgical removal at the end of therapy.

7.4 Swelling-Controlled Release:

This type has a large beam made of a brittle material that acquires a significant release when broken. Swelling-controlled release takes place in the case of hydrophilic polymers that take in water and swell. When in touch with biological fluids, the polymer expands and develops a gel like structure. Swollen polymer network diffusion takes place next, then the drug diffuses through it. The level of swelling determines the rate of release. Examples of polymers that have this behaviour are chitosan and alginate. Drug release may be slowed by raising the concentration of polymer or cross-linking density. This is a common process in the case of natural microspheres made of polymer and can be employed in oral and mucoadhesive-delivery of drugs.

7.5 Osmotically Controlled Release

The OCR is controlled by varying the osmotic pressure exerted on the gel. The OCR is regulated by the adjustment of osmotic pressure acting on the gel. Water flows into the microsphere under the influence of disparities in the osmotic pressure in osmotically controlled systems. The incoming water dissolves the drug contained within the matrix and the dissolved drug, then, is forced out by small holes. The rate of release is affected by the osmotic gradient and the permeability of the polymer membrane. This process offers a regulated and uniform release of drugs and is not affected by the external environmental factors so much. Osmotically controlled systems are used to assist in the maintenance of the stable drug concentrations and minimize the chances of the dose dumping.

7.6 Combination Mechanisms

In most formulations, the release of the drugs is not by one mechanism. Alternatively, there can be several mechanisms which combine. As an example, burst release can be followed by sustained release by diffusion and polymer degradation because of the availability of drug on the surface. The prevailing release mechanism is dependent on the type of polymer, drug loading and the mode of preparation. Mathematical formulation is usually applied to analyze release kinetics and to design the formulation. The improved control over the long-term treatment and attainment of excellent therapeutic outcomes are ensured by combination mechanisms[29,30].

8. CHARACTERIZATION OF MICROSPHERES SYSTEMS

Microspheres characterization is a crucial procedure that should guarantee quality, performance, and repeatability of the formulation. Physical and chemical analysis can be used to determine the behaviour of drugs in release and general effectiveness during the therapeutic process. The important parameters that are usually measured are the particle size, surface morphology, encapsulation efficiency, and drug loading.

The chemical composition includes the particle size and size distribution, which is defined as the proportion of particles ranging from a given minimum size up to a specified maximum size.

8.1Particle Size and Size Distribution

The chemical composition consists of the particle size and size distribution, which refers to the proportion of particles that are of a certain minimum size up to a certain maximum size.

The size of the particles is very crucial in the rate of drug release, bioavailability, and stability of microspheres. The smaller the size of microspheres, the greater the surface area and this could lead to the release of drugs at a higher rate. Contrastingly, bigger particles tend to give slower and more protracted discharge. The homogenous distribution of the particles is required to obtain the same therapeutic response and manufacturing performance. Measurement of the particle size may be made by optical microscopy, laser diffraction or sieve analysis. The size of particles is highly affected by factors such as concentration of polymer and speed of stirring during preparation.

8.2 Surface Morphology (SEM)

Surface properties of microspheres can be observed by Scanning Electron Microscopy (SEM). The accuracy of this technique is capable of giving a lot of details concerning shape, smoothness of the surface, and porosity of the particles. Strongly developed microspheres tend to be smooth in surface and are spherical. Conversely, porous or crack surfaces can cause early burst effect of the drug (porous surface). Morphological surface study is useful in interpreting the association among the structural characteristics and drug liberation conduct.

8.3 Efficiency and Drug Loading of Encapsulation

Encapsulation efficiency is a percentage of the drug that was trapped in the microspheres during preparation. Drug loading is the mass of drug as compared to the total mass of the microspheres. Significance of these parameters is that they directly influence the effectiveness of therapy and the cost of formulation. They are typically identified by leaving the drug on microspheres and analyzing the drug by methods like UV spectroscopy or High-Performance Liquid Chromatography (HPLC). Maximizing the efficiency of encapsulation and loading drug makes the microsphere system control and sustained drug release [31-34].

9. ADVANCED MICROSPHERES OF ORAL DRUGS DELIVERY

Development of advanced microsphere systems has been done to enhance drug targeting, enhance drug action and improve therapeutic response. Such microspheres are special spheres that are aimed at addressing shortcomings of traditional oral delivery systems.

9.1 Bio adhesive Microspheres

The bio adhesive microspheres are geared towards being stuck on the mucosal surface of the gastrointestinal tract. They are also adhesive in nature hence are in close contact with the site of absorption over a long time. This long time of residence enhances absorption of the drug and offers sustained release of drug. Bio adhesive microspheres decrease gastrointestinal transit, increase therapeutic outcome, and decrease the dosing frequency.

9.2 Magnetic Microspheres

The magnetic microspheres are magnetic materials that enable them to be controlled with the help of an external magnetic field. These particles can be introduced into the body; they can be targeted to any given location in the body via controlled magnetic force since they are small enough to fit through the capillaries without obstructing them. This system allows localized delivery of the drugs, so that there is less distribution of the drugs to healthy tissues and less side effects. Magnetic microspheres have been primarily investigated to be used in targeted therapy particularly in cancer treatment.

9.3 Floating Microspheres

Gastro-retentive microspheres or floating microspheres are developed to stay in the gastric fluids. They are low density, hence surface floating without any impact on the normal gastrointestinal emptying. The extent of gastric residence ensures that the drug is released gradually over a long duration. Suspensions are especially applicable to the drugs that are absorbed mainly in the stomach or the upper section of the small intestine[36].

10. MICROSPHERES-MEDIATED DRUG RELEASE PROBLEMS

Despite the numerous benefits of the microsphere-based drug delivery systems, there are numerous issues which need to be resolved in order to make them popular in the clinical practice. Technical, biological and regulatory challenges have to be overcome to move laboratory research to patient use[37].

Table 2: Major obstacles and potential resolutions

S.NO	DIFFICULTIES	MANAGEMENT PLANS
1.	Poor in-vitro-in-vivo correlation	Development of new advanced in-vitro models and predictive mathematical modelling.
2.	Burst release	Surface coating, core-shell design, and formulation optimization.
3.	Problem of long-term stability	Stabilizers, protective coating, and correct storage conditions.
4.	Challenges in scale-up and manufacturing	Optimization of the process and adherence to GMP standards.
5.	Immunogenicity and biocompatibility issues	Use of biocompatible materials and elaborate preclinical testing.
6.	Regulatory and approval issues	Extensive preclinical and clinical trials including regulatory engagement.

10.1 Problems of in-vitro-in-vivo Correlation.

The greatest obstacle in microsphere system is the need to create a clear correlation between laboratory drug release studies (in-vitro) and the reality in the body (in-vivo). In-vivo conditions are complicated and they are dependent on the blood flow, the activity of enzymes and tissue interactions. These variables may have a big influence on drug release behaviour. Hence, it is hard to forecast on the basis of in-vitro results only clinical outcomes. Complex testing structures and mathematics to enhance the accuracy of prediction are needed.

10.2 Prevention of Burst Release

Burst release is when a huge number of drugs is released at once when the drug is administered. Such acute discharge can result in toxicity, loss of long-term efficacy, and poor future optimal therapeutic concentrations. To control burst release, formulation design, optimization of the polymer concentration, enhancement of drug encapsulation, and coating or core-shell structure control of initial release is necessary.

10.3 Stability of Microspheres over a Long Period.

The stability is necessary to make sure that the drug is released regularly within the planned shelf life. Microspheres stability can be influenced by factors like polymer degradation, drug-polymer interactions and environmental factors (temperature, humidity).

One of the major challenges is coming up with formulations which do not change when stored but do not alter their release properties.

10.4 Scale-Up and Manufacturing issues.

Recreational scale Between laboratory and industrial production of microsphere is technically challenging. It is difficult to maintain uniformity in the particle size, drug loading and product uniformity amongst a high-volume manufacturing process. To be able to achieve quality and reproducibility, process optimization and Good Manufacturing Practices (GMP) must be observed. These concerns are very important in order to achieve commercialization.

10.5 Biocompatibility and Immunogenicity.

Microspheres when introduced into the body have a risk of immunological reactions or undesired biological reactions. Inadequate biocompatibility can result in compromised patient safety and change drug release behaviour. To reduce these risks, the polymers incorporated in microspheres should be safe and well-tolerated. Exhaustive preclinical research is needed to analyze the toxicity, immune response, and general safety[38-41].

11. MECHANISMS OF SUSTAINED TARGETED DRUG RELEASE

Microspheres can be designed to react to certain internal or external stimuli which enhances targeted drug delivery. Such systems can only deliver drugs under specific conditions, which are certain to deliver the drug to the

desired location accurately. Specific strategies are external stimuli-responsive system, internal stimuli-responsive system and site-specific targeting strategies.

11.1 Microspheres of External Stimuli-Responsiveness.

These microspheres react to external environmental stimuli. When the system is subjected to a certain external stimulus, the drug release takes place.

✧ **Temperature-Responsive Systems**

The microspheres which are temperature sensitive swell or shrink as the temperature varies. As the temperature rises, the polymer swells permitting the release of the drug. Such a method is practical in situations like fever or inflammation in which the local temperature increases.

✧ **pH-Responsive Systems**

The PH-sensitive microspheres are drugs that are released when the acidity changes. The pH levels vary in different body parts. To illustrate, tumor tissues tend to be more acidic as compared to normal tissues. The acidic-reactive microspheres can also be used to release drugs that specifically release drugs to tumor locations.

✧ **Light-Responsive Systems**

Light sensitive microspheres are materials that vary their structure upon exposure to light. This rearrangement of structure causes the release of the drugs. Given that light can be manipulated externally, this technique can be used to accurately manage the timing and location of the release of the drug.

11.2 Internal Stimuli-responsive microspheres.

Such microspheres react to biological circumstances in the interior of the body. The release of drugs is possible only under particular disease conditions.

✧ **Enzyme-Triggered Release**

There are other diseases such as cancer which have increased levels of some enzymes. Microspheres may be made to contain enzyme sensitive linkers which disintegrate in the presence of those enzymes. Consequently, the drug is able to be released at the location of the disease.

✧ **Redox-Sensitive Systems**

The Redox-responsible microspheres respond to variations in oxidation levels in the body. Structural changes take place on the microsphere in disease conditions characterized by high levels of oxidative stress, resulting in the release of drugs. It is especially applied in inflammatory, cancer-related diseases.

11.3 Microspheres-based Targeting to Sites.

Microspheres are also planned to be made to concentrate at particular locations within the body to enhance better therapeutic results and minimize side effects.

Passive Targeting (Enhanced Permeability and Retention Effect)

Passive targeting exploits Enhanced Permeability and Retention (EPR) effect. The tumor blood vessels are frequently leaky and they lack good lymphatic drain. These leaky vessels can deposit microspheres of the right size in tumor tissues and permit active targeting drug delivery without active targeting systems[42,43].

12. APPLICATION:

In disease treatment, microspheres have been used in the treatment of diseases like asthma, oncology, rheumatoid arthritis, and others.

Microsphere drug delivery system is a popular method of application of controlled, sustained and targeted therapy of several diseases. They assist in enhancing the efficacy of drugs and decreasing the systemic side effects. They can be used in the treatment of metabolic disorders, cancer, neurological diseases, inflammatory conditions, and bone disorders.

12.1 Diabetes

Diabetes mellitus is a metabolic disease that is associated with elevated glucose levels in the blood because of lack of enough insulin or insulin resistance. The prolonged elevation of sugar in the blood may harm body organs, including kidneys, nerves, and eyes.

Sustained release of insulin and oral antidiabetic drugs can be achieved in the microspheres and eliminate the occurrence of frequent dosing. The microspheres made of biodegradable polymers are used to stabilize the level of insulin in the bloodstream. Microspheres filled with antioxidants can also be used to prevent oxidative damage of the pancreatic beta cells. Even though there are promising factors, there are still important issues of consistency in long-term release and safety of polymers.

12.2 Breast Cancer

Breast cancer is a widely spread type of cancer in the world. The use of conventional chemotherapy normally has serious side effects because the drug is not targeted. Anticancer drugs can be transported directly to tumor tissues using microspheres prepared out of biodegradable polymers like PLGA. This enables localized and controlled drug delivery, which enhances therapeutic value and minimized systemic toxicity. Nevertheless, there is a need to standardize the distribution of drugs and carry out the long-term safety assessment prior to their extensive clinical application[44].

12.3 Alzheimer's Disease

Alzheimer is a progressive neurodegenerative disease, which is defined by impaired memory and cognitive decline. Cholinesterase inhibitors and the like are frequently employed to manage the symptoms.

Formulations based on microsphere can be used to achieve prolonged drug release as in the case of donepezil and ensure that drug levels are stable over a period of time. This decreases the dosage schedule and enhances adherence in

patients. High production costs and long-term safety of brain tissue are some of the challenges.

12.4 Rheumatoid Arthritis

Rheumatoid arthritis is a long-lasting autoimmune disorder in which there is inflammation and soreness in the joints. Systemic side effects might occur with long-term use of the conventional anti-inflammatory drugs. Anti-inflammatory and disease-modifying drugs can be delivered locally into the affected joints using microspheres. Controlled release lowers the exposure in the system and enhances the therapeutic results. To assure chronic treatment, there must be uniform release and durability of polymer safety[45-47].

13. CONCLUSION

Microspheres make oral sustained drug release systems particularly interesting because of their capability to deliver sustained and controlled therapeutic responses. Microspheres are used to provide sustained levels of drugs unlike other traditional dosage forms which make drugs enter the blood at a high rate leading to the formation of peaks and lows in the plasma. This minimizes the difference between peaks and valleys, side effects and generally the treatment outcome especially in chronic illnesses like diabetes, cancer, high blood pressure problems, and nervous system disorders. Microspheres are very flexible in their formulation. They have the ability to pack a wide range of different kinds of drugs such as hydrophilic and hydrophobic, peptides, proteins, and growth factors. Natural polymers (chitosan, gelatin, and alginate) and synthetic polymers (PLGA, PLA and PCL) are both popular. The release of drugs in microspheres can be done by diffusion, polymer degradation, swelling, and erosion. The release pattern can be modified to achieve specific therapeutic requirements by varying formulation factors, including the polymer concentration, particle size and the ratio of a compound and polymer. The oral sustained drug delivery has been expanded further by innovative systems like floating, mucoadhesive, magnetic and stimuli-responsive microspheres. The systems increase site specificity, improve bioavailability and decrease systemic toxicity. Nonetheless, there are still challenges such as burst release, storage stability, scale-up production, regulatory authorization and extended safety assessment. These limitations are being overcome by continuous improvements in the science of polymers, methods of formulation, and the integration of nanotechnology. Conclusively, oral sustained release system that is based on the microsphere is an excellent and promising drug delivery platform. As more research and technology advances, they will become significant in coming up with safer and more effective patient-friendly therapies in the future.

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