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Review Article

REVIEW ON SUSTAINED RELEASE BLEND MICROSPHERES

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ABSTRACT

Sustained release drug delivery systems have emerged as an advanced approach in pharmaceutical technology to maintain therapeutic drug concentrations over an extended period, thereby enhancing efficacy and reducing dosing frequency. Among various delivery systems, microspheres have gained considerable attention due to their ability to encapsulate drugs and provide controlled release. The present study focuses on the formulation and evaluation of sustained release blend microspheres using a combination of polymers to overcome the limitations of single-polymer systems. Polymer blending plays an important role in modulating drug release by combining hydrophilic and hydrophobic polymers, which provide a synergistic effect in controlling drug diffusion, swelling behavior, and matrix integrity. Various preparation methods such as solvent evaporation, spray drying, coacervation, and ionic gelation are employed to develop microspheres with desired characteristics. Among these, the solvent evaporation method is widely used due to its simplicity and reproducibility. The performance of microspheres is influenced by formulation and process variables such as drug-to-polymer ratio, type and concentration of polymers, solvent system, stirring speed, and emulsifier concentration. These factors significantly affect particle size, entrapment efficiency, surface morphology, and drug release kinetics. Drug release from microspheres typically follows mechanisms such as diffusion, swelling, erosion, and polymer degradation, and can be analyzed using kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Evaluation parameters such as particle size analysis, scanning electron microscopy, drug entrapment efficiency, percentage yield, buoyancy studies, *in-vitro* drug release, and zeta potential are essential to assess the quality and performance of microspheres. Sustained release blend microspheres offer numerous advantages including improved bioavailability, reduced side effects, enhanced patient compliance, and protection of drugs from degradation. Despite certain challenges such as scale-up difficulties and variability in particle size, advancements in polymer science and formulation techniques continue to improve the efficiency and applicability of microsphere-based drug delivery systems.

Keywords: Sustained release, Microspheres, Blend polymers, Cannabidiol, Ethyl cellulose, HPMC, Drug delivery system, Solvent evaporation, Entrapment efficiency, Drug release kinetics, Buoyancy, Zeta potential, Controlled release.

INTRODUCTION

Sustained release drug delivery systems represent a significant advancement in pharmaceutical technology, aiming to deliver drugs at a predetermined rate for an extended period of time (Kumar *et al.,* 2017). These systems are designed to maintain constant drug concentrations in the bloodstream, thereby improving therapeutic efficacy while minimizing side effects and dosing frequency (Chugh *et al.,* 2012). Among the various approaches developed for sustained drug delivery, microspheres have gained immense attention due to their versatility, stability, and ability to encapsulate a wide range of drugs.

Microspheres are free-flowing, spherical particulate systems with sizes typically ranging from 1 to 1000 µm. They can be formulated using a variety of polymers and are capable of entrapping drugs either within the polymer matrix or on the surface (Gurung and Kakar, 2020). Sustained release microspheres are specifically designed to release the drug gradually over a prolonged duration, ensuring controlled delivery and improved patient compliance (Jantzen and Robinson, 2002). The concept of blend microspheres involves the use of two or more polymers in combination to overcome the limitations of single-polymer systems and to achieve desired release characteristics.

The use of polymer blends in microsphere formulation offers several advantages. Different polymers possess distinct physicochemical properties such as hydrophilicity, hydrophobicity, swelling behavior, and degradation rate (Jantzen and Robinson, 2002). By combining these polymers, formulators can fine-tune the drug release profile, mechanical strength, and stability of the microspheres. For instance, hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) absorb water and swell, forming a gel layer that controls drug diffusion, while hydrophobic polymers such as ethyl cellulose (EC) act as barriers that slow down drug release. Natural polymers like guar gum, xanthan gum, and alginate further enhance biocompatibility and mucoadhesive properties (Dixit *et al.,* 2013). The synergistic effect of these polymers in blend microspheres results in a more controlled and predictable drug release pattern.

Various techniques are available for the preparation of sustained release blend microspheres (O'Donnell and McGinity, 1997). Among these, the solvent evaporation method is one of the most commonly used due to its simplicity, reproducibility, and adaptability.

In this method, the drug and polymers are dissolved in a suitable organic solvent, which is then emulsified into an aqueous phase containing a stabilizer such as polyvinyl alcohol (PVA). Continuous stirring leads to the evaporation of the solvent, resulting in the formation of solid microspheres (Song and Cho, 2024). Other methods include spray drying, coacervation-phase separation, emulsion-solvent diffusion, and ionic gelation. Each method has its own advantages and limitations, and the choice of technique depends on the nature of the drug and polymers used.

The performance of sustained release blend microspheres is influenced by several formulation and process variables (Dhakar *et al.,* 2010). These include the type and concentration of polymers, drug-to-polymer

ratio, solvent system, stirring speed, temperature, and emulsifier concentration. These factors affect key characteristics such as particle size, drug entrapment efficiency, surface morphology, and drug release behavior. Optimization of these parameters is essential to achieve microspheres with desired properties.

Drug release from blend microspheres occurs through a combination of mechanisms, including diffusion, swelling, erosion, and polymer degradation. Initially, a small amount of drug present on the surface may be released rapidly (burst release), followed by a sustained release phase governed by diffusion through the polymer matrix (Dasan and Rekha, 2012). Hydrophilic polymers swell upon contact with biological fluids, forming a gel barrier that controls drug release, while hydrophobic polymers slow down the penetration of the dissolution medium. The release kinetics can be analyzed using mathematical models such as zero-order (constant release), first-order (concentration-dependent release), Higuchi (diffusion-controlled release), and Korsmeyer–Peppas model, which provides insight into the mechanism of drug release.

Sustained release blend microspheres offer numerous advantages in drug delivery. They improve bioavailability by maintaining therapeutic drug levels for longer durations, reduce dosing frequency, and enhance patient compliance (Manish and Abhay, 2012). These systems also protect drugs from degradation, minimize gastrointestinal irritation, and reduce systemic side effects. Furthermore, blend microspheres can be engineered for targeted delivery, floating drug delivery systems, and site-specific release, making them highly versatile.

Despite these advantages, there are certain challenges associated with the development of microspheres. These include the use of organic solvents, potential drug instability during processing, difficulty in scale-up, and variability in particle size distribution. However, advancements in formulation techniques, polymer science, and process optimization are continuously addressing these challenges (Bhalala *et al.,* 2026).

Concept of Blend Microspheres

Blend microspheres involve the use of two or more polymers in combination to achieve improved drug delivery characteristics. Single-polymer systems often have limitations such as uncontrolled release or poor mechanical strength (Dhadde *et al.,* 2021). The use of polymer blends allows modification of drug release kinetics, enhancement of stability, and better control over physicochemical properties. This approach provides flexibility in formulation design and optimization.

Types of Polymers Used

Synthetic Polymers

Synthetic polymers such as ethyl cellulose (EC), polyvinyl alcohol (PVA), and polymethacrylates are widely used due to their controlled release properties and stability. These polymers generally provide a hydrophobic matrix that retards drug release.

Semi-Synthetic Polymers

Semi-synthetic polymers like hydroxypropyl methylcellulose (HPMC) are commonly used for their swelling and gel-forming properties, which help in controlling drug diffusion (Gurung and Kakar, 2020).

Natural Polymers

Natural polymers such as guar gum, xanthan gum, alginate, and chitosan are biodegradable, biocompatible, and eco-friendly. They enhance mucoadhesion and improve patient safety.

Advantages of Polymer Blending

Polymer blending plays a vital role in the development of sustained release microspheres by providing improved control over drug release rate. By combining polymers with different physicochemical properties, it becomes possible to tailor the release profile of the drug according to therapeutic needs (Ghasemiyeh and Mohammadi-Samani, 2021). Hydrophilic polymers tend to swell and facilitate drug diffusion, whereas hydrophobic polymers act as barriers to slow down drug release. The synergistic effect of these polymers helps in achieving a more predictable and sustained release pattern.

Another important advantage of polymer blending is the enhancement of mechanical strength of microspheres. Single polymers may sometimes produce fragile or brittle microspheres, but blending improves structural integrity and durability. This ensures that the microspheres can withstand handling, processing, and storage conditions without breaking or deforming, thereby maintaining their functional properties.

Polymer blends also contribute to better stability and reproducibility of the formulation. The combination of polymers can minimize variability in drug release and physical characteristics, leading to more consistent batch-to-batch performance. This is particularly important in pharmaceutical formulations where uniformity and reliability are essential for therapeutic effectiveness.

One of the significant challenges in microsphere formulation is the initial burst release of the drug. Polymer blending helps in reducing this burst effect by forming a more uniform and dense matrix, which prevents rapid release of the drug from the surface. This controlled release behavior enhances the safety and efficacy of the formulation.

Additionally, polymer blending allows the combination of hydrophilic and hydrophobic properties within a single system. This dual nature helps in modulating drug release mechanisms, improving swelling behavior, and controlling the interaction with biological fluids. Such versatility makes polymer blends highly suitable for designing advanced drug delivery systems.

Methods of Preparation of Blend Microspheres

Solvent Evaporation Method

This is the most commonly used technique where drug and polymers are dissolved in an organic solvent and emulsified in an aqueous phase. Upon solvent evaporation, solid microspheres are formed (Chai *et al.,* 2003).

Emulsion-Solvent Diffusion Method

Involves diffusion of solvent from dispersed phase to continuous phase, leading to microsphere formation (You *et al.,* 2006).

Spray Drying Method

A rapid and scalable technique where the polymer-drug solution is atomized into a hot chamber to form dry microspheres (He *et al.,* 1999).

Coacervation Phase Separation

Involves separation of polymer-rich phase to encapsulate the drug.

Ionic Gelation Method

Commonly used for natural polymers like alginate, where cross-linking occurs in the presence of multivalent ions.

Factors Affecting Microsphere Formulation

The formulation of microspheres is influenced by several critical parameters that determine their physicochemical properties and performance. One of the most important factors is the drug-to-polymer ratio. An appropriate ratio is essential to achieve optimal drug loading and controlled release (Clelik and Maganti, 1994). A higher polymer concentration generally leads to better encapsulation and slower drug release due to the formation of a thicker matrix, whereas a lower polymer content may result in faster drug release and reduced entrapment efficiency.

The type and concentration of polymers also play a significant role in microsphere formulation. Different polymers exhibit varying properties such as hydrophilicity, hydrophobicity, swelling behavior, and degradation rate. Hydrophilic polymers tend to swell and facilitate drug diffusion, while hydrophobic polymers retard drug release by forming a barrier. The concentration of these polymers further influences the density and integrity of the microspheres, thereby affecting drug release kinetics and mechanical strength.

The solvent system used during preparation is another key factor that impacts microsphere characteristics. The choice of solvent determines the solubility of the drug and polymers, as well as the rate of solvent evaporation. A suitable solvent system ensures proper emulsification and formation of uniform microspheres. Inappropriate solvent selection may lead to irregular particle formation, low encapsulation efficiency, or drug leakage.

Stirring speed and time during emulsification significantly affect the particle size and distribution of microspheres. Higher stirring speeds generally produce smaller and more uniform particles due to increased shear force, whereas lower speeds may result in larger particles. Adequate stirring time is necessary to ensure complete solvent evaporation and proper formation of microspheres.

Temperature during preparation also influences the formulation process. Elevated temperatures can accelerate solvent evaporation and affect polymer solidification, leading to changes in particle size and surface morphology. However, excessive temperatures may cause degradation of heat-sensitive drugs or polymers, making temperature control essential during microsphere preparation.

The concentration of emulsifier, such as polyvinyl alcohol (PVA), is another important parameter. Emulsifiers stabilize the emulsion system and prevent aggregation of microspheres. An optimal concentration is required to achieve uniform particle size and high entrapment efficiency. Too little emulsifier may lead to particle aggregation, while excessive amounts can affect drug release and surface characteristics.

Evaluation Parameters of Microspheres

Particle Size and Size Distribution

Particle size is a critical parameter that influences drug release, bioavailability, and stability of microspheres. It is usually determined using optical microscopy, laser diffraction, or dynamic light scattering

techniques (Szlek *et al.,* 2016). Uniform particle size distribution ensures reproducibility and predictable drug release behavior. Smaller particles generally provide faster drug release due to increased surface area, whereas larger particles tend to sustain drug release over a longer duration.

Surface Morphology (SEM)

Surface morphology of microspheres is commonly analyzed using scanning electron microscopy (SEM). This technique provides detailed information about the shape, surface texture, and structural integrity of microspheres. Ideally, microspheres should be spherical with a smooth and uniform surface (Ramadan and Tawashi, 1990). Any cracks, pores, or irregularities can influence drug release and stability.

Drug Entrapment Efficiency

Drug entrapment efficiency indicates the percentage of drug successfully encapsulated within the microspheres relative to the total drug used in formulation. It is an important parameter that reflects the effectiveness of the formulation process (Dhakar *et al.,* 2010). Higher entrapment efficiency ensures better drug loading and minimizes drug loss during preparation.

Percentage Yield

Percentage yield represents the efficiency of the microsphere preparation process. It is calculated as the ratio of the practical yield to the theoretical yield of microspheres (Patel *et al.,* 2005). A high percentage yield indicates minimal material loss during formulation and efficient processing conditions.

Buoyancy Studies

Buoyancy studies are particularly important for floating microsphere systems intended for gastro-retentive drug delivery (Pandey *et al.,* 2016). This parameter evaluates the ability of microspheres to float on gastric fluids for an extended period. It includes measurement of floating lag time and percentage buoyancy. Good buoyancy ensures prolonged gastric residence time and sustained drug release.

***In-vitro* Drug Release**

In-vitro drug release studies are conducted to evaluate the release profile of the drug from microspheres over time (Gaur *et al.,* 2014). These studies help in understanding the release kinetics and mechanism, whether diffusion-controlled, erosion-controlled, or a combination of both. Sustained release formulations are expected to show a controlled and prolonged release pattern.

Zeta Potential and Stability

Zeta potential is a measure of surface charge of microspheres and is used to predict the stability of the system. Higher absolute values of zeta potential indicate better stability due to electrostatic repulsion between particles, which prevents aggregation. Stable microspheres maintain their size, shape, and drug release properties over time, making this parameter fundamental for formulation evaluation (Sun *et al.,* 2016).

CONCLUSION

The study highlights that sustained release blend microspheres are a promising and effective drug delivery system for achieving controlled and prolonged drug release. The use of polymer blends, combining hydrophilic and hydrophobic polymers, provides better control over drug release, improved stability, and enhanced formulation performance compared to single-polymer systems. The solvent evaporation method proved to be a reliable and reproducible technique for the preparation of microspheres with desirable

physicochemical properties. Various formulation and process parameters significantly influence the characteristics and performance of microspheres, including particle size, entrapment efficiency, and drug release behavior. Sustained release blend microspheres offer advantages such as improved bioavailability, reduced dosing frequency, and better patient compliance. Despite some challenges like scale-up and variability, continuous advancements in formulation strategies make microsphere-based systems a valuable approach for modern drug delivery applications.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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