REVIEW ARTICLE

Microspheres as a Unique Drug Carrier for Controlled Drug Delivery: A Review

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Abstract

Comparing such systems to conventional administrative approaches, they may offer a numeral benefit. Controlled distribution of drugs can solve the problems of traditional medicine and improve medicine resources. Microspheres (MS) are generally free-flowing powders made of proteins or synthetic polymers with a particle size of 1–1000 mm. The literature search was accomplished using PubMed, Science direct, Google scholar, and the Cochrane library to recognize appropriate scientific articles. The search terms included controlled drug delivery systems, MS as drug carrier, advantages of MS, types of MS, importance of MS, different formulation techniques of MS, evaluation techniques of MS, and applications of MS.

Key words: Controlled drug delivery system, drug carrier, microspheres, novel drug delivery

INTRODUCTION

APIs can be delivered through drug delivery systems (DDS) to achieve the correct therapeutic effect. The lack of bioavailability and poor plasma properties of DDS drugs (tablets, capsules, syrups, ointments, etc.) prevent their distribution. Without a good delivery, complete treatment will not be possible. For the drug to be effective and safe, it must be controlled in the agreed amount and area. The challenges of conventional drug delivery have been addressed with the development of controlled DDS (CDDS).[1] Comparing such systems to conventional administrative approaches, they may offer a number of benefits. CDDS can solve the problems of traditional medicine and improve the resources of medicine. Microspheres (MS) are generally free-flowing powders made of proteins or synthetic polymers with a particle size of 1–1000 mm. The various methods for producing MS offer many opportunities to change delivery methods and increase the efficacy of certain drugs. The drug in the MS is contained in a special polymer matrix at the center of the particle.[2]

Human healthcare is significantly influenced by the controlled and predefined release of drug from drug carriers that direct active drug molecules to specified body regions. Innovative drug delivery technique offers an efficient method for encasing potent therapeutic medications in various unit pharmaceutical formulations, such as microparticles and nanoparticle, which changes the drug particles' kinetic and absorption characteristics.[3] A ball-bearing effect is provided by MS because of their size and morphology. The grade, roundness, homogeneity of the size distribution, and MS themselves differ. Each specific application requires and must be selected different MS. There are many methods of forming MS to alter drug delivery.[4]

It facilitates the administration of small amounts of strong drugs, reduces the amount of drugs in places other than the intended place, and prevents unstable drugs before and after by showing them in the office. The *in vivo* behavior of a drug can be altered by combining it with a carrier. Cell interactions, tissue distribution, and elimination kinetics of drugs can be affected by the behavior of the carrier. Use of pharmacodynamic variables can increase pharmacological efficacy.[5] Due to its free-flowing powder properties and biodegradable makeup, MS have recently attracted a lot of attention. There are two different types of MS, depending on how the active drug

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Received: 26-07-2023
Revised: 23-09-2023
Accepted: 30-09-2023

molecules are enclosed (microcapsules and micromatrices). In contrast to micromatrices, which evenly distribute the medication all across the polymer matrices, microparticles are multiparticulate delivery systems wherein the API molecule is enclosed and surrounded by a distinct polymeric wall.[6-8]

The present review highlights importance of MS as effective carrier of drug, different formulation and evaluation techniques and applications of MS. Second, the review has highlighted novel approaches in MS based drug delivery and novel applications of MS.

MATERIALS AND METHODS

The literature search was accomplished using PubMed, Science direct, Google scholar, and the Cochrane library to recognize appropriate scientific articles. The search terms included CDDS, MS as drug carrier, advantages of MS, types of MS, importance of MS, different formulation techniques of MS, evaluation techniques of MS, and applications of MS. The literature search included 60 scientific articles.

OVERVIEW OF MS AS A NOVEL DRUG CARRIER

Ideal characteristics of MS[9,10]

- The capacity to include pharmacological dosages that are reassuringly high
- Stability of the medication following manufacture with a life span that is clinically acceptable
- Check the particle size and injection dispersibility in the vehicle for injection
- Release of an dynamic reagent over a wide time period with great control
- Biodegradability that is manageable while maintaining biocompatibility
- Ability to be altered chemically.

Benefits of MS[3,7]

- Reducing the particle size to improve a drug's low solubility
- Offer stable drug levels in the blood, increasing the likelihood that a patent will be followed
- Reduce toxicity and dosage
- Prevent proteolytic and photolytic breakdown of the drug, making it the ideal option for drug administration
- These devices deliver a steady and prolonged therapeutic action
- Decreases the frequency of dose, which improves patient adherence
- Absorption is more reliable when using MS
- Less local allergic reaction due to inhibition of absorption in the stomach
- MS treatment can be improved with drugs with a shorter half-life
- MS can reduce drug waste (dose dumping effect)
- Additionally, MS lessen the possibility of G.I. discomfort
- In particular when used with a buffer, MS offer independence from drug and receiver problems
- Improved defences against environmental factors for medicines
- Biodegradable MS offer significant advantages over bulky polymer implants in that they can be implanted and removed without surgery
- Biodegradable MS are used in controlled-release drug delivery to control drug release frequency, reduce the risk of side effects, and counteract the effects of frequent injections.

Types of MS

1. Mucoadhesive MS
2. Radioactive MS
3. Magnetic MS
4. Floating MS
5. Polymeric MS
   a. Biodegradable polymeric MS
   b. Synthetic polymeric MS

Mucoadhesive MS

MS with a diameter between 1 and 1000 mm and made completely of a mucoadhesive and either made of polymers or possessing a covering of it are known as mucoadhesive MS.[11]

Additional benefits of incorporating mucoadhesive products with MS include drug release at the site of absorption through the combination of phytolectins, better absorption, and improved drug retention due to high surface-to-volume ratio close to and opposing the mucosal surface.[12] Mucoadhesive MS adhere to mucosal layers such as the eyes, nose, urinary tract, and gastrointestinal tract, allowing local drug and drug release.

To administer medications with a localized effect, mucoadhesive MS are applied to the mucosal tissues of the eye cavity, gastrointestinal, and colorectal epithelium. Extended release of drug and fewer doses administered to the ocular cavity can significantly increase treatment adherence.[13]

M cells in Peyer's patches in the intestinal mucosa select MS made of mucoadhesive and biodegradable polymers. Antigens for vaccination, peptide and protein drugs, and plasmids for gene therapy are all delivered through this uptake process. In addition, by putting the medications just next to the GI mucosa's absorption site. Drugs such as furosemide and riboflavin have improved oral bioavailability and absorbed well with the help of the mucoadhesive MS.[14-16]

Through mucosal immunization, the idea of a non-invasive single-dose vaccine provides regulated delivery of antigen and creates yet another exquisite application for mucoadhesive MS.[17]

Radioactive MS[18,19]

Radio embolism treatment MS between 10 and 30 nm in diameter tap in with the first vascular system (capillaries) whenever they make contact with one. In all these scenarios, radioactive MS give significant doses of radiation to the designated areas avoiding harm to the healthy tissue organs because they are infused in the arteries that flow to the tumor of concern. It differs from the DDS in that the MS does not release radioactivity; instead, it works on normal radioisotopes and different types of radio MS are alpha emitters, beta emitters, and gamma emitters body.

Magnetic MS[20,21]

This type of distribution is crucial for delivering the drug to the affected area. In this case, a small fraction of the magnetized target can replace a large amount of free flow. Materials such as chitosan and dextran used for magnetic MS are placed on a magnetic carrier that receives magnetic pulses of the magnetic field.

a. Delivery of chemotherapy to breast cancer using magnetic MS. With this technology, chemicals such as peptides and proteins can also be modified
b. MS for clinical evaluation purposes, which create nano-sized supramagnetic iron oxide nanoparticles, are used to image liver tumors and also can be utilized to identify bowel looping besides other abdominal organs.

Floating MS[22-24]

Since the density of air floats is lower than apple juice, their float is not affected by empty stomach fats. The medicine is released gradually at the required speed, and it is discovered that the mechanism is drifting on gastric fluids, which enhances stomach residence and heightens peak plasma fluctuations.

In addition, it lessens the likelihood of dosage dumping. Due to the longer pharmacological efficacy, dose frequencies are decreased. The medication (ketoprofen) is administered as floating MS.

Polymeric MS[19]

There are many types of polymer MS that can be divided into two groups: Synthetic MS and synthetic biodegradable MS.

Polymeric MS that degrade naturally[25]

The idea behind the usage of natural polymers like starch is that they could be biocompatible, biodegradable, and naturally sticky. Due to their extreme tensile properties in aqueous media, biopolymers extend the retention time whenever in contact with mucosal surfaces, causing gelation. The amount of the polymers and the extended-release mechanism control the rate and degree of medication discharge. The key disadvantage is that biodegradable MS' drug encapsulation performance in clinical settings is complex, making it challenging to regulate drug release. They do, however, offer a variety of applications in MS-based treatment.

MS made of synthetic polymers[26,27]

MS are made of synthetic polymers have a wide range of clinical applications and have been shown to be reliable and have excellent biocompatibility. However, the disadvantage of such MS is that they move away from the target site, causing more blood clotting, and more damage to the body.

Formulation techniques of MS

1. Single emulsion
2. Double emulsion
3. Spray drying
4. Solvent evaporation
5. Polymerization technique
6. Heat stabilization
7. Spray drying/spray congealing
8. Solvent extraction

Single emulsion method (SEM)

Using SEM, specific properties of natural materials such as carbohydrates and proteins can be compared. After being dissolved or dispersed in an aqueous medium, the biopolymer is dispersed in a semi-medium such as oil. The dispersed beads are then crosslinked in the next step. Alternatively, thermal or chemical crosslinkers can be used to complete the crosslinking. The cross-linking chemicals employed are glutaraldehyde, acid chloride, formaldehyde, etc. The final nanoparticulate product's shape, physical properties, specific surface area, dosage, release of drug, and biological compatibility can all be significantly impacted by the type of surfactants used to stabilize the emulsion phases.[28]

Double emulsion method

This approach works with both bio and synthetic polymers and is better suited for medicines, peptides, proteins, and vaccinations that dissolve in water. This technique for making MS calls for the creation of many emulsions. This method involves dispersing an aqueous protein solution in an organic lipophilic continuous liquid phase that contains the main ingredients. A polymer mixture that contains protein that is diffused in the aqueous phase makes up the continuous phase. After that, the primary emulsion is homogenized before being added to the poly vinyl alcohol (PVA) aqueous solution (PVA). When two emulsions are formed, the solvent is removed from the emulsion by evaporation or extraction of the solvent.[29,30]

Spray drying method

The polymer is first mixed with methylene chloride, acetone, etc. It is placed in a suitable solvent such as a solvent and then dried using the spray method. Following that, speedy

homogenization is used to disseminate the drug's solid form within the polymer solution. The dispersion is then atomized using a hot air jet. The atomization process produces a small liquid or mist where the solvent is immediately dispersed, forming MS in the size range of 1–100 μm. Heat is broken down into MS using a vacuum cleaner and these are vacuum-dried to remove any remaining solvent. One of the advantages of the system is that it can be used in a sterile environment.[19]

Solvent evaporation

The liquid manufacturing vehicles (LMV) phase is where this procedure is done out. The LMV phase and the volatile solvents are used to spread the microcapsule coatings are incompatible. Inside the coating suitable solvent, a core substance that will be microencapsulated is disintegrated or disseminated. The inner layer is mixed and dispersed in the LMV phase to produce microcapsules of the appropriate size.

When the polymers of the composite are dispersed in the polymer solution, the composition is heated, if necessary, to evaporate the solvent. The polymer shrinks around the surface. For the solvent to evaporate, the polymer mixture must form an insoluble continuous phase emulsion, whether aqueous (o/w) or non-aqueous.[19,31]

Polymerization technique

Ordinary polymerization

Mass, suspensions, precipitation, emulsified, and other methods are used to carry out this type ordinary polymerization. When polymerization occurs in mass, a monomers and catalysts are warmed to start the process. When polymerization is taking place, drugs may be loaded into the resulting polymers, which is then shaped into MS. The benefit of mass polymerization is the creation of pure polymers. Warming of monomer or a combination of monomer with API as droplets dissemination in uninterrupted aqueous phase is used in suspension cases. Suspended polymerization, which takes place at constant temperature, is also referred as pearl polymerization. When an emulsion polymerizes, an activator is available in the aqueous medium and subsequently disperses at the micelle's interface.[4]

Interfacial polymerization (IFP)[4] IFP creates polymeric film that effectively encompasses the dispersed phase by causing diverse monomer to interact at the intersection among two immiscible phases.

Heat stabilization method

Adding up dispersed phase into hot oil is done in the heat stabilization method, although thermolabile medicines should not be used with this approach.[4]

Spray drying and spray congealing

This technique is based on air drying of the polymer and solvent. The method includes two different methods (spray drying and spray coagulation), which differ in solvent removal or solution freezing, respectively. First disperse the polymer using a suitable solvent such as dichloromethane, acetone, or others. Then the drug is dissolved in the polymer solution with rapid homogenization. This dispersion is then atomized using a hot air jet.

The blasting process creates small droplets or fine air, where the solvent evaporates immediately and forms MS 1–100 m long. Cyclone separators are used to separate solids in hot air, and vacuum cleaners are used to clean solvents. The possibility of using the process in a sterile environment is one of its main features. Several penicillins are encapsulated using the drying process. Spray coagulation is used to incorporate sulfaethylthiadiazole and thiamine mononitrate into a mixture of monomeric and diacylglycerols of stearic and palmitic acids.

However, porous particles are formed due to the rapid evaporation of the solvent.[32,33]

Solvent extraction

Formulation of MS by this method involves removing the organic phase through the extracting of a watery or quasi solvent. It uses organic solvents that are water soluble, such as isopropyl alcohol. Aqueous extraction can be used to provide clarity of the organic phase. The MS' stiffening time is slashed by this procedure. Direct proteins or drug integration into an organic liquid medium is one form of the procedure. The efficiency of removing the solvent using the extraction process is affected by the water's temp, the amount of the emulsified phase in relation to the liquid, and the solubility characteristic of the polymer.[7]

Evaluation techniques of MS

Chemical examination with the help of electron spectroscopy

Chemical analysis using electron spectroscopy was to determine the surface morphology (ESCA) of MS. ESCA offers a method for figuring out the surface's atomic make-up. To ascertain the rate of complete loss of degradable MS, spectra acquired by ESCA can be employed.[4,7]

Determine density

Multi-volume pycnometers can be used to calculate the density of particles. Place the container containing the correct sample into the multi-volume pycnometer. In the chamber, a constant force and stretching ability are provided to the helium. As a direct result of the expansion, the pressure in the vessel decreases. It is worth noting that there are two consecutive shock values at different initial pressures.

Use two gauges to measure the cargo's capacity and density.[34]

Shape and size of MS

Using a calibrated optical micrometer, optical microscopy can measure particle size. One hundred MS are measured and overall mean particle size is determined.

D mean is calculated as $\sum n\,d/\sum n$

n = the number of MS examined; *d* = the mean size[34,35,36]

Isoelectric point

The electrophoretic velocity of spheres wherein the micro electrophoresis is employed to determine the isoelectric point. It is possible to identify the isoelectric point.[7,37]

Contact angle

To ascertain the, the angle of contact is measured. A microparticle shipper's capability to moisten. When measuring the impedance to particulate movement, the MS angle of relaxation is estimated using the formula tan = 2h/d.

2h/d = surface area of the spheres heaps that forms when the MS are made to flow out of the funnel.[7,38]

Approaches used in vitro[7]

Rotating paddle equipment (USP/BP) is typically used to conduct release studies for various types of particles using various suitable dissolving solutions.

Drug entrapment efficiency[7]

The effectiveness of drug encapsulation can be measured using the formula percent Entrapment = Actual content/ Theoretical content × 100.

Swelling index[7]

To determine the microsphere's swelling index, the mathematical methodology was used: Swelling index = (weight of swollen spheres - weight of dry MS/weight of dried MS) 100.

Fourier-transform-infrared spectroscopy analysis

It can also be utilized to characterize the RS-related characteristics, frequently in conjunction with other methods (thermo gravimetric analysis-TGA, and Differential scanning calorimetry- DSC).[39]

Novel approaches in MS-based drug delivery

Poly (lactide-co-glycolide) nanocomposite and nano-hydroxyapatite (HAp) MS

For *in vivo* bone repair, Wenzhi *et al*. developed poly (lactide-co-glycolide) nanocomposite and nano-HAp MS using an unique airflow shearing process. To efficiently manufacture MS with exact control over MS dimension and uniformity, an unique airflow shearing process was proposed. The MS in particular showed excellent uniformity and a distinctive "acorn" shape with two sides produced during preparation: A stiff, glossy side and a crushed, and rougher side.[40]

Hollow gelatin/HAp composite-based, FD-gelatin/ Hap, DCPD-attached gelatin/HAp MS structures

Three different kinds of hollow gelatin/HAp composite-based composites were developed by Zhu *et al*. Traditional freeze-drying was used to create FD-gelatin/HAp scaffold, whereas emulsifier method and an unique MS-packing process were coupled to create DCPD-attached gelatin/HAp MS structures, as well as HAp-stuck gelatin/HAp MS scaffold. By cultivating the osteoblast-like MC3T3-E1 cells with various scaffolding kinds, functionalization testing was carried out. The findings demonstrated that all kinds of scaffolds might promote cell adhesion and growth in a compatible manner. Yet the existence of the highly porous made the HAp-gelatin/ HAp MS scaffold' most significant finding. The porous gelatin/HAp MS-holded scaffold offer promise as cutting-edge materials for bone tissue regeneration.[41]

Infiltrated embedded rose bengal MS in titanium MS

To provide a specific biomechanics and biofunctional equilibrium, Accioni *et al*. established Infiltrated Embedded Rose Bengal MS in Titanium Alloy MS of polycaprolactone that can cling to porous titanium (PT) implantation model generated by the spacing clamp approach. A double emulsification and evaporation process was effectively used to create the microparticles that were correctly packed with the antimicrobial medicinal ingredient, rose bengal, for this objective. To create a useful prophylactic matrix, the produced MS were infused into PT substrate and heated at 60°C for 60 min. As an outcome of superior hydrophilicity of the PT substrate to encourage calcium phosphate formation, it was found that the sintering polymer-holded microparticles were essential for managing the medication dissolution rate and promoting the early healing phase.[42]

Carbon-Dot-embed MS (C-Dot-embed MS)

A unified process was built that combined the advantages of both nanomaterials and MS for continuous delivery of Cetirizine through a straight forward emulsification method. Singh *et al*. produced poly lactic acid (PLA) MS - Cetirizine with carbon dots as therapeutic agent carrier. To create medication-conjugated C-Dot-embed MS, Polyethylene glycol (PEG) C-Dot was first created, and then Cetirizine was dispersed in it. PEG C-Dot was subsequently enclosed in PLA MS. The scanning capabilities of drug-holding C-Dot-encapsulated MS targeting HEK293 cell lines were excellent. These results represent a new framework for Cetirizine's regulated drug discovery and may open the door for subsequent cancer therapy drugs.[43]

Sustained-release floated MS

Over the existing MS sustained-release floated MS were developed by Ma *et al*. Using calcium carbonate (CaCO3)

as a gas-forming representative, multi-unit floating alginate (Alg) MS of a certain type was created. Chitosan was added to the gelling solution and coated with Eudragit in an effort to increase drug entrapment efficiencies and prolong drug delivery, accordingly. Gamma-scintigraphy was used to compare the intestinal transit of optimized floated prolonged-release MS to a non-floating system made of the same materials in healthy volunteers.[44]

Application of MS

Medical application

Long-term delivery of hormones, peptides, and proteins is used for active intravenous/arterial targeting of tumor cells and antigenic cell. Moreover, utilized for passive manipulation of leaky tumor arteries. Furthermore, utilized different screening procedures for communicable diseases (viral, bacterial, and fungal infections). It is also used mostly for bone marrow cleansing and stem cell collection.[4]

Ophthalmic medication carrier in ophthalmic delivery

Polymer-based MS have advantageous biological activity, including mucoadhesive, penetrability qualities, and intriguing physicochemical properties, making them a special resource for the creation of ocular drug carriers.

The capacity of MS holding polymer to form sheets allows for its usage in the development of films for oral medication delivery.

E.g., Geletin, Alg, and chitosan.[7]

MS in oral drug delivery

The capacity of MS holding polymer to form sheets allows for its usage in the development of films for oral medication delivery. Alternatives to tablets in the form of dose forms. The reaction's reactivity and pH sensitivity make the amino group compounds, MS are more stable. Appropriate for use in oral medication administration applications.

E.g., Geletin, Alg, and chitosan.[7]

Application as radioactive

It is utilized to embolized malignancies in the spleen and liver. Used for deep venous thrombosis monitoring, local radiation, chemotherapy treatment, monitoring of the hepatic, bone marrow, spleen, and lung, as well as radiosynovectomy of arthritic joints.[45]

Application as a gene carrier

The adhesion and transport qualities of MS in the GI system make them potential oral gene carriers. A few examples include chitosan, collagen, virions, charged liposomes, and polycation complex.[7]

Delivery of vaccines using MS

The best injection should meet standards of effectiveness, safety, ease of use, and cost. Safety and risk reduction are important considerations. The cost and safety of antibiotics are directly related to treatment. The disadvantages of conventional vaccine delivery can be overcome by biodegradable delivery technologies for parenterally administered vaccines. Since they provide specific benefits, such as enhanced antigenicity through auxiliary effect, modulated antigens ejection, and antigen stabilization, injectable (transcutaneous, intramuscular, and transdermal) vehicles are of importance.[46]

Drug administration through the nose

Bioadhesive drug delivery devices are excellent for the nasal mucosa. When in interaction with the mucous membrane of nose, polymer-based drug delivery mechanisms including MS and gels have been shown to have high bioadhesive properties and quickly expand, improving the accessibility and retention time of the medications to the nasogastric tube. For intranasal controlled drug delivery of vancomycin hydrochloride, a number of polymer salts, including chitosan (hydrochloride, aspartate, and glutamate), are suitable choices.[46]

Novel applications of MS

Bone repairing potential

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Three different kinds of hollow gelatin/HAp composite-based composites were developed by Zhu *et al*. Traditional freeze-drying was used to create FD-gelatin/HAp scaffold, whereas emulsifier method and an unique MS-packing process were coupled to create DCPD-attached gelatin/HAp MS structures, as well as HAp-stuck gelatin/HAp MS scaffold. By cultivating the osteoblast-like MC3T3-E1 cells with various scaffolding kinds, functionalization testing was carried out. The findings demonstrated that the highly porous made the HAp-gelatin/HAp MS Scaffold' most significant. The porous gelatin/HAp MS-holded scaffold offer promise as cutting-edge materials for bone tissue regeneration.[41]

Microsphgeres importance in avoiding osseointegration and aggressive infections

To provide a specific biomechanics and biofunctional equilibrium, Accioni *et al*. established Infiltrated Embedded Rose Bengal MS in Titanium Alloy MS of polycaprolactone that can cling to PT implantation model generated by the spacing clamp approach. A double emulsification and evaporation process was effectively used to create

the microparticles that were correctly packed with the antimicrobial medicinal ingredient, rose bengal, for this objective. As a result of a superior hydrophilicity of the PT substrate to encourage calcium phosphate formation, it was found that the sintering polymer-holded microparticles were essential for managing the medication dissolution rate and promoting the early healing phase. With the use of this combination technology, difficulties with late osseointegration and aggressive infections can both be avoided.[42]

Anticancer targeting treatment approach BV MS

A unified process was built that combined the advantages of both nanomaterials and MS for continuous delivery of Cetirizine through a straight forward emulsification method. Singh *et al*. produced poly lactic acid (PLA) MS-Cetirizine with carbon dots as therapeutic agent carrier. To create medication-conjugated C-Dot-embed MS, PEG C-Dot was first created, then Cetirizine was dispersed in it. PEG C-Dot was subsequently enclosed in PLA MS. The scanning capabilities of drug-holding C-Dot-encapsulated MS targeting HEK293 cell lines were excellent. These results represent a new framework for Cetirizine's regulated drug discovery and may open the door for subsequent cancer therapy drugs.[43]

CONCLUSION

MS will play a key role in novel medication delivery systems in the future, especially in pathogenic cell disruption, detection, genes and genetic materials, secure, controlled, and efficient *in vivo* delivery, and supplementation as miniaturized representations of damaged organs and internal organs. In the current review, we discussed conventional as well as novel MS, formulation and evaluation, applications of MS in novel as well as conventional.

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Source of Support: Nil. **Conflicts of Interest:** None declared.