International Journal of Pharma Research and Health Sciences, 2022; 10(6): 3505-3510.
DOI:10.21276/ijprhs.2022.06.03
Rana *et al.*

CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Review article

Micropheres as a Promising Carrier for Controlled Relase Drug Delivery - Review

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ARTICLE INFO:
Received: 01 Dec 2022
Accepted: 23 Dec 2022
Published: 31 Dec 2022

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ABSTRACT:
The purpose of targeted drug delivery is to attempt to increase drug concentration in the tissues of interest while decreasing relative medication concentration in the other tissues. Drug is thereby concentrated at the desired location. As a result, the medication has no effect on the tissues nearby. Controlled drug delivery systems can solve the issues with traditional medication therapy and improve a drug's therapeutic effectiveness. Microspheres are typically free-flowing powders with a particle size range of 1-1000 m that are made of proteins or synthetic polymers. The variety of techniques available for the manufacture of microspheres provides a number of chances to regulate drug administration processes and improve a specific drug's therapeutic effectiveness. In order to deliver a medicinal chemical to the target region with a continuous regulated release, there are several different methods. The medicine in Microspheres is contained within a special polymeric membrane in the centre of the particle. Microspheres will play a key role in future drug delivery innovations, including diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted in vivo drug delivery, and supplements that act as miniature replicas of diseased organs and tissues in the body.
Keywords: Microspheres, Controlled release, Therapeutic efficacy, targeted drug delivery.

1. INTRODUCTION

A Small, spherical particles known as microspheres range in size from 10 m to 1000 m. Microspheres are crucial for enhancing the absorption of traditional medications and reducing negative effects [1]. The controlled release of the medicinal content is the fundamental benefit of using microspheres as a drug delivery mechanism. Microcapsules are those in which the substance that is being contained is clearly encased by a distinct capsule wall, while micrometrics are those in which the substance is being contained is dispersed throughout the matrix of the microspheres. Microencapsulation is utilized to delay drug release from dosage forms, minimize side effects, and improve patient compliance. This method uses an emulsion solvent diffusion evaporation process to coat an aqueous insoluble core (drugs) with an aqueous insoluble coat (polymer) for a sustained release drug delivery system [2]. A number of methods, such as the emulsification technique with a single or double solvent evaporation system, spray-dry technique, or phase separation technique, can be used to create microspheres. The initial ingredients can be dissolved in volatile solvents, and the starting materials can then be dispersed in a different solvent that is not miscible with the first. Later, the remaining solvent will completely evaporate, leaving behind a fine powder known as microspheres that is soluble in water [3, 4].

2. MICROSPHERE TYPES

2.1 Bio adhesive microspheres

Adhesion is the attaching of a substance to a membrane using the adhesive properties of water soluble polymers. Bio adhesion can be defined as the attachment of a medication delivery device to a mucosal membrane, such as the buccal, ocular, rectal, nasal, etc. These types of microspheres have a longer residence duration at the application site, which results in close contact with the site of absorption and improves therapeutic activity. By attaching the drug to a carrier particle, such as microspheres, nanospheres, liposomes, or nanoparticles, carrier technology provides an intelligent method for drug administration by modulating the drug's release and absorption [5, 6, 7,].

2.2 Magnetic microspheres

This type of delivery mechanism, which targets the drug to the site of the ailment, is crucial. In this case, a smaller amount of a medicine that is magnetically targeted can replace a larger amount of a drug that is freely circulating. Materials utilized for magnetic microspheres such as chitosan and dextran are integrated into magnetic carriers, which receive magnetic responses to a magnetic field.

Therapeutic magnetic microspheres and diagnostic microspheres are the many varieties [8].

2.3 Floating microspheres

Because the bulk density of floating kinds is lower than that of gastric fluid, they float unaffected by the rate at which the stomach empties. If the system is floating on stomach content, the drug is released slowly at the desired rate, which increases gastric residence and causes plasma concentration to fluctuate. Additionally, it lessens the likelihood of striking and dose dumping and generates a sustained therapeutic impact. Another approach is that it prolongs the therapeutic impact, which lowers the frequency of dose [9, 10].

2.4 Polymeric Microspheres

The many kinds of polymeric microspheres can be divided into two categories: Synthetic polymeric microspheres and biodegradable polymeric microspheres [11].

2.4.1 Biodegradable microspheres made of polymers

The idea behind the usage of natural polymers like starch is that they are biodegradable, biocompatible, and naturally sticky. Due to their significant swelling capacity in aqueous media, biodegradable polymers prolong the residence time when in contact with mucous membranes, causing gel formation. The concentration of the polymer and the sustained release pattern regulate the rate and degree of medication release. The key disadvantage is that biodegradable microspheres' drug loading efficiency in clinical settings is complex, making it challenging to regulate drug release.

2.4.2 Synthetic microspheres made of polymers

In addition to being employed as bulking agents, fillers, embolic particles, drug delivery vehicles, etc., synthetic polymeric microspheres are also frequently used in clinical applications and have proven to be both safe and biocompatible. The main drawback of these microspheres is that they have a propensity to migrate away from the injection site, increasing the risk of embolism and subsequent organ damage.

3. METHOD OF PREPARATION OF MICROSPHERE:

This is dependent on the type of polymer or medicine used and the length of the treatment. The following are the methods for preparing microspheres:

1. Single emulsion techniques
2. Double emulsion techniques
3. Phase separation coacervation technique
4. Spray drying
5. Solvent extraction
6. Solvent evaporation
7. Polymerization

a)Normal polymerization

b)Inter-facial Polymerization

3.1 Single emulsion method

Using a single emulsion method, micro-particulate carriers for drug delivery are created. The natural polymers must first be dissolved in an aqueous medium before being dispersed in a non-aqueous solvent, such as oil or cross-linking agent. The process can be carried out using heat or chemical crosslinkers. By integrating the dispersion into heated oil, heat is employed to cross-link materials; however, thermolabile medications cannot be used in this way [12, 13, 14].

3.2Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is exposed then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). The results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction [15].

3.3 Phase separation coacervation technique

A thick coacervate layer, which is relatively condensed in macromolecules, and a distilled layer of equilibrium are the two immiscible forms of material that are separated using this procedure from the macromolecular fluid. Basic coacervation is the name given to this process when there is only one macromolecule present. Complex coacervations are those that involve two or more opposite-charge macromolecules. The former is brought on by particular factors, such as temperature change, utilizing non-solvents or micro-ions causes dehydration in macromolecules by facilitating interactions between polymers through interactions with the polymer solvent. This can be programmed to produce various microsphere qualities [16].

3.4 Spray drying

A suitable volatile organic solvent that the polymer dissolved in. It diffused in the polymer solution during rapid homogenization. It then underwent atomization in a warm air stream, resulting in the development of tiny droplets and solvent evaporation, which resulted in the development of microspheres. Utilizing a cyclone separator to remove microparticles from hot air and vacuum drying to remove any remaining liquid [17].

3.5 Solvent evaporation

Aqueous protein solution and polymer-containing organic solvent are both added in this phase. Following that, the material is sonicated to combine. To make the solution

uniform, homogenization is next carried out. An additional aqueous phase emulsifier is then introduced**.** Subsequent hardening occurs and then harvest it. After harvesting freeze drying technique is used. This is also called lyophilization. preserve the material by freezing it very quickly and then subjecting it to a vacuum which removes ice. And then microsphere is getting [18, 19].

3.6 Solvent extraction

The process of solvent evaporation has also been widely employed to create PLA and PLGA microspheres that contain a wide range of medications. There are a number of factors that have been found to have a substantial impact on microspheric properties, including drug solubility, internal morphology, solvent type, diffusion rate, temperature, polymer composition, viscosity, and drug loading. With medications that are either insoluble or just partially soluble in the liquid medium that makes up the continuous phase, the solvent evaporation system's ability to generate microspheres depends on the effective incorporation of the active material into the particles.er [20, 21].

3.7 Polymerization technique: Preparation of Microspheres by Polymerization technique can be classified as [22]:

a) Normal polymerization
b) Interfacial polymerization

Both are carried out in liquid phase.

a) Normal polymerization

It can be accomplished utilising a variety of methods, including bulk, suspension, precipitation, emulsion, and micellar polymerization. To begin polymerization, a monomer or mixture of monomers, along with the initiator or catalyst, are typically heated in bulk. The resulting polymer can be moulded into microspheres. During the polymerization process, drug loading might take place.

b) Interfacial polymerization

It is the process by which different monomers react at the boundary between two immiscible liquids to produce a polymer film that basically encases the dispersed phase.

1. Advantages of microspheres:

- Microspheres provide prolonged and constant therapeutic effect.
- Microspheres reduce the dosing frequency and therefore improve the patient compliance, reduce dose dumping.
- Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
- Microspheres increase the bioavailability and biological half-life.
- •Microspheres lessen the possibility of GI discomfort.

2. Disadvantage of Microsphere

- Variations in rate of discharge from one dosage to the next [23].
- Potentially dangerous
- These dosing types must not be broken or chewed.

4. EVALUATION OF MICROSPHERES

4.1 Angle of Repose

The microspheres were permitted to exit the funnel orifice onto a piece of paper that was stored on a level surface. On the paper, it forms a mound of microspheres. By changing the base radius (R) and pile height (H) variables in the following equation, the angle of repose was determined as seein in Equation 1 [24].

Tan Θ = h /r…..(Equation 1)

Where, h - Pile Height,

r- the pile's radius.

4.2 Density determination

The density of microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of microsphere carriers is determined [25].

4.3 Determination of particle size Particle size can be determined by optical microscopy with the help of calibrated eyepiece micrometer [26]. The size of around 100 microspheres is measured and their average particle size is calculated as in Equation 2.

D mean = ∑ n d/∑ n…..(Equation 2)

Where, n = number of microspheres checked; d = Mean size

4.4 Isoelectric point

The isoelectric point can be measured by using micro electrophoresis apparatus by measuring electrophoretic mobility of microspheres. The mean velocity at different pH value from 3-10 is calculated by measuring the time of particle movement over a distance of 1 nm [27].

4.5 Electron spectroscopy for chemical analysis

The surface chemistry of microspheres can be determined by using electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of atomic composition of the surface. The spectra obtained using ESCA can be used to determine the surface degradation of biodegradable microspheres [28].

4.6 Fourier transforms infrared spectroscopy

Drug polymer interaction and degradation of microspheres can be assessed by FTIR [29, 30].

4.7 Drug entrapment efficiency

Weighed amount of microsphere are taken and crushed. Then dissolved in buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at particular wavelength by using calibration curve (Equation 3) [31, 32].

$$\text{Drug Entrapment efficiency} = \frac{\text{Acutual weight of microspheres}}{\text{Theoretical weight of drug and polymer}} * 100$$

…...(Equation 3)

4.8 Percentage yield

It is calculated as the weight of microspheres obtained from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100 [33].

4.9 Swelling index

It is determined by measuring the extent of swelling of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by swelling of 5 mg of dried microspheres poured in 5 ml of buffer solution overnight in a measuring cylinder [34]. It is calculated by given formula (Equation 4).

$$Swelling\ Index = \frac{Mass\ of\ swollen\ microspheres - Mass\ of\ dried\ microspheres}{Mass\ of\ dried\ microspheres}$$

…..(Equation 4)

4.10 *In vitro* methods

This method allows the determination of release characteristics and permeability of a drug through membrane. *In vitro* method is employed as a quality control procedure in pharmaceutical production and in product development etc. Sensible and reproducible release data derived from physically, chemically and hydro dynamically defined conditions are necessary [35, 36].

4.11 *In vivo* method

Method for studying the permeability of intact mucosa comprises of technique that gives the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at their surface. The most widely used methods of *in vivo* studies include using animal models, buccal absorption tests [37].

5. APPLICATIONS OF MICROSPHERES [38, 39, 40]

- Microspheres in vaccine delivery.
- Targeting using micro particulate carriers.
- Monoclonal antibodies facilitated microspheres targeting.
- Diagnostic Imaging.
- Intratumoral and local delivery.
- Nasal drug delivery.
- Gastroretentive controlled delivery system.
- Implantable devices.

PHARMACEUTICAL APPLICATIONS [41, 42, 43]

- Currently available pharmaceutical microencapsulated products include aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensive, potassium chloride, progesterone, and combinations of contraceptive hormones.
- To avoid the gastrointestinal side effects of potassium chloride, utilise microencapsulated KCL. Local high salt concentrations that can cause ulceration, haemorrhage, or perforation are less likely due to the microcapsules' dispersibility and the regulated release of the ions.
- Additionally, microspheres have potential uses as injectable or inhalation products.

6. CONCLUSION

Compared to many other forms of medication delivery systems, microspheres are a better option. Microspheres will eventually take centre stage in novel drug delivery by fusing a variety of other techniques, especially in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, precise, and effective in vitro delivery, and supplements as miniature replicas of diseased organs and tissues in the body [44, 45]. Compared to current technology, microspheres provide a number of advantages. The use of these approaches in the study of biomolecule interactions and cellular processes has emerged as an attractive new platform for biologists. More research using microspheres in more varied applications have been conducted in recent years, and it is clear that the variety of possible uses is expanding. Microspheres will play a key role in novel drug delivery systems by fusing multiple approaches, with a focus on cell sorting, diagnostics, and genetic engineering. According to the study, microspheres serve as efficient carriers for the cutting-edge drug delivery method.

7. REFERENCES

1. Jain NK. Controlled and Novel drug delivery, 04 Edition, CBS Publishers New Delhi, India; 21, 236-7.
2. Agusundaram M, Madhu SC. Microsphere, as a novel drug delivery system a review. Int J ChemTech Res. 2009;1:526-34.
3. Chein YW. Oral Drug Delivery Systems: In Novel drug delivery systems. Vol.50, Marcel Dekker, Inc., New York. 1992, 139-77.
4. Bunty ChanuIrom, Kavitha K, Rupeshkumar M, SD. Jagadeesh Singh, Natural Polymeric Microsphere for Drug Delivery: A Review. International Journal of Pharmaceutical Research and Development. 2012;4: 31-7.
5. Hardenia SS, Jian A, Patel R, Kaushal A. Formulation and evaluation of mucoadhesive microsphere of ciprofloxacin. Journal of Advanced Pharmacy Education and research. 2011; 1(4): 214-24.
6. Chinna Gangadhar B, Shyam Sunder R, Vimal Kumar Varma M, SleevaRaju M, Sai Kiran M. Formulation and Evaluation of Indomethacin Microspheres using natural and synthetic polymers as Controlled Release Dosage Forms. International Journal of Drug Discovery. 2010; 2: 8-16
7. Hafeli U. Physics and Chemistry Basic of Biotechnology: Focus on biotechnology. Review: Radioactive Microspheres for Medical Application 2002; 7: 213-48.

8. Imran Abdul KayyumTadwee, Sadhana Shahi, Thube M, Ankit S. Review on Microspheres. International Journal of Pharmaceutical Research Allied Sciences, 2012; 1: 24-33.
9. Freitas S, Merkle HP, Gander B. Microencapsulation by solvent Extraction/Evaporation: reviewing the state of the art of microsphere preparation process technology. J Control Rel. 2004; 102: 313–32.
10. Purnachandra Reddy Guntaka, Lankalapalli S. Solid Dispersion-A Novel Approach for Bioavailability Enhancement of Poorly Water-Soluble Drugs in Solid Oral Dosage Forms. Asian Journal of Pharmaceutical and Clinical Research. 2019,7:17-26.
11. Gholap SB, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. Hollow microsphere: a review. Int J Pharm Sci Rev Res. 2010; 1:10-5.
12. Jayaprakash S, Halith SM, Mohamed Firthouse PU, Kulaturanpillai K. Preparation and evaluation of biodegradable microspheres of methotrexate. Asian J Pharm 2009; 3: 26-46.
13. Kadam NR, Suvarna V. Microsphere a brief review. Asian J Biomed Pharm Sci. 2015; 5: 13-9.
14. Kalyan S, Sharma PK. Recent advancement in chitosan best formulation and its pharmaceutical application. Pelagia Res Library 2010; 1:195-210.
15. KalyanShweta, Sharma Parmod Kumar et al. Recent Advancement In Chitosan Best Formulation And Its Pharmaceutical Application. Pelagia Research Library. 2010; 1: 195-210.
16. Meghna KS, Krishna MP, Giridas S, Sreelakshmi C, Vijayakumar B. Microsphere a drug delivery system–a review. Int J Novel Trends Pharm Sci. 2017; 7:109-18.
17. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: A Review, International Journal of Research in Pharmacy and Chemistry. 2011; 1: 1184-98.
18. Akiful Haque M, Chinmaya Keshari Sahoo. A review on in situ gel: a novel drug delivery system. Int J Pharm Sci Rev Res. 2018; 50: 175-81.
19. Kumar A, Mahajan S, Bhandari N, Microspheres: a review. World J Pharm Pharm Sci. 2017; 6:724-40.
20. Mathew Sam T., Devi Gayathri S., PrasanthV.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology. 2008; 6: 67-73.
21. Nair R, Reddy B. Application of chitosan microspheres as drug carriers: a review. J Pharm Sci Res. 2009;1:1-12.
22. Orienti I, Aiedeh K, Gianasi E, Bertasi V, Zecchi V. Indomethacin loaded chitosan microspheres correlation between the erosionprocess and release kinetics. J Microencapsul 1996;13:463-72.
23. Roy H, Nayak BS, Maddiboyina B, Nandi S. Chitosan based urapidil microparticle development in approach to improve mechanical strength by cold hyperosmotic dextrose solution technique. J Drug Deliv Sci Technol. 2022;76:103745.
24. Dutta p, Struti j, Niranajanpatra CH, Bhaojirao ME. Floating Microsphere: Recents Trends in the Development of Gastroretentive Floating Drug Delivery System. International Journal of Pharmaceutical Science and nanotechnology. 2011; 4: 1293-306.
25. Parmar H, Bakliwal V. Different method of evaluation of mucoadhesive microsphere. Int J ApplBiol Pharm Technol 2010; 1:1164-5.
26. Pradeesh TS, Sunny MC, Varma HK, Ramesh P. Preparation of microstructured hydroxyapatite microspheres using oil in water emulsions. Bull Materials Sci. 2005; 28:383-90.
27. Roy H, Nayak BS. Formulation and Design of Microparticles based Drug Delivery System of Selective Anti-Retroviral Drug by Chitosan. Scholars Academy Journal of Pharmacy 2017; 6: 34-9.
28. Prasanth VV, Moy AC, Mathew ST. Microsphere: An Overview. International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2: 335 - 6.
29. Swapna S, Ananthnag V, Meena B, Manikya Veena A, Snigha A, Prasanna A. Formulation and Evaluation of floating microspheres of Diacerein by Ionic Gelation method. World Journal of Pharmaceutical and Life Sciences. 2018; 4: 117-23.
30. Rajput S, Agrawal P, Pathak A, Shrivasatava N, Baghe SS, Baghe RS. A review on microspheres: methods of preparation and evaluation. World J Pharm Pharm Sci. 2012;1:422-38.
31. Purnachandra Reddy Guntaka, Lankalapalli SR. Solubility and dissolution enhancement of Ivacaftor tablets by using solid dispersion technique of hot-melt extrusion-a design of experimental approach. Asian Journal of Pharmaceutical and Clinical Research. 2019; 7:356-63.
32. Munwar S, Roy H, Abdul Rahaman Sk. Antioxidant and Free Radical Scavenging Activity of Citrus Medica. Int J Pharma Res Health Sci. 2015; 3: 810-6.
33. Rana mazumder, Lila K. Nath, Anwarul, Haque, Tarasankar Maity, Prasant K. Choudhary et al. Formulation and in vitro evaluation of natural polymers based microsphere for colonic drug delivery, International journal of pharmacy and pharmaceutical sciences. 2010; 2: 211-9.
34. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B, Microsphere: a review. Int J Res Pharm Chem. 2011; 1: 2231-781.
35. Saravana Kumar K., Jayachandra Reddy P., Chandra Sekhar KB. A Review on Microsphere for Novel drug delivery System. Journal of Pharmacy Research. 2012; 5: 420-4.
36. Purnachandra Reddy Guntaka, Lankalapalli S. Design and Development of Spray Dried Telaprevir For Improving The Dissolution From Tablets. International

Journal of Pharmaceutical, Chemical & Biological Sciences. 2017;7 (4): 430-8.
37. Shanthi NC, Gupta R and Mahato KA: Traditional and Emerging Applications of Microspheres: A Review. International Journal of Pharm Tech Research. 2010; 2:675- 681.
38. Roy H, Brahma CK, Kumar R, Nandi S. Formulation of saquinavir mesylate loaded microparticle by counterion induced aggregation method: Approach by hyperosmotic technique. Drug Invention Today. 2013; 5 :259-66.
39. Swapna S, Anna Balaji, Uma Shankar MS. Microspheres as a Promising Mucoadhesive Drug Delivery System – Review. International Journal of Pharmaceutical Sciences Review and Research. 2013; 23: 8-14.
40. SM Ali. Radioembolization for hepatocellular carcinoma using Thera sphere. The Suadi Journal of Gastroenterology. 2011; 17: 215-17.
41. Sudha Mani T, Naveen Kumar K. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal of Pharma Research and Development. 2010; 2: 120-1.
42. Ganesan P, Johnson AJD, Sabapathy L, Duraikannu A. Review on Microsphere. American Journal of Drug Discovery and Development 2014; 4:153-79.
43. Roy H, Venkateswar Rao P, Panda SK, Biswal AK, Parida KR, Dash J. Composite alginate hydrogel microparticulate delivery system of zidovudine hydrochloride based on counter ion induced aggregation. Int J Applied Basic Med Res. 2014; 4(Sup 1): S31-36.
44. Thanoo BC, Sunny MC, Jayakrishnan A. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. J Pharm Pharmacol 1992; 44:283-6.
45. Purnachandra Reddy Guntaka, Lankalapalli S. A comparative study of ledipasvir solid dispersion technique using spray drying and hot-melt extrusion. International Journal of Pharmaceutical Sciences and Research. 2018; 9: 5145-54.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable.