IJPSR (2022), Volume 13, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 August 2021; received in revised form, 26 October 2021; accepted, 17 November 2021; published 01 June 2022

MICROSPHERES: A NOVEL APPROACH FOR DELIVERY OF ANTIHYPERLIPIDEMIC DRUGS

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Keywords:

Coronary Heart Disease, Low-Density Lipoprotein, High-Density Lipoprotein, Microspheres, Improves systemic bioavailability, Controlled drug release

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ABSTRACT: Microsphere drug delivery is a novel drug delivery approach for sustaining and controlling the rate and release of active pharmaceutical ingredients. Microspheres are the choice of drug delivery for delivering the drug at a specific site to release the encapsulated drug to treat various diseases. Microspheres drug delivery is an attractive dosage form in terms of its flexibility and sustaining the release as compared to other sustained and controlled formulations. Most of the antihyperlipidemic drugs come under BCS class-II, which leads to poor solubility but higher permeability, the oral bioavailability of statins categories drug possess less bioavailability due to the poor solubility; hence microspheres are the best candidate for delivering antihyperlipidemic drugs to the systemic circulation and improving the systemic bioavailability of drug for a longer period with lesser adverse effects. Therefore microspheres can be used in various medical departments like oncology, gynecology, radiology, pulmonary, cardiology, diabetes, vaccine therapy, *etc*. this review article focuses on recent different methods of preparation. The microspheres formulated can be later evaluated and characterized by a different procedure.

INTRODUCTION: Cardiovascular diseases, particularly coronary heart disease (CHD) and stroke, are the leading reason behind death and permanent incapacity within the Western World. Hyperlipidemia is a leading cause of the development of atherosclerosis and a major factor for cardiovascular disease. Alterations in the lipid profile are qualitative and quantitative, representing the high level of plasma triglycerides, low level of high--density lipoprotein (HDL), cholesterol, low-density lipoprotein, and other fatty molecules responsible for cardiac diseases [1, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(6).2294-02

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(6).2294-02

Estimation of Cardiovascular Risk: Several charts and algorithms are developed to try the arrange to accurately estimate the entity of coronary and cardiovascular risk on the idea of individual risk factors and conditions; most charts include, as determinants of cardiovascular morbidity or mortality, age and gender, smoking status, cardiovascular disease, and polygenic disorder, additionally to plasma cholesterol.

The adult treatment panel-III (ATP-III) of the National sterol Education Program stratifies completely different risk levels about LDL cholesterol goals for treatment (160 mg/dL for low-risk, a 130 mg/dL for medium-risk and100 mg/dL for bad patients); this is often supported a categorical analysis of risk conditions, the presence or absence of CHD or diabetes and in borderline cases, on an estimation of absolute cardiovascular risk in keeping with the Framingham score.

The presence of the metabolic syndrome is additionally underscored as a high-risk condition. A newer revision of the ATP-III panel places even larger stress on the association of CHD and diabetes, distinguishing a 'very high-risk' population with an LDL cholesterol target of 70mg/dL [1, 3].

Pathogenesis of Hyperlipidemia: In the duration of the arteries happens once Low-Density Lipoprotein (LDL) get altered in plasma and become oxidized-LDL, this oxidized-LDL get engulfed by the macrophages that result in type foam cells that get adhere to the epithelial tissue layer of blood vessels and inflicting accumulation of the platelets. Additionally, macrophages lead to secrete cytokines and protein, which is responsible for the deposition of the animal tissue which leads to form fatty tissue 'plug', which is that the reason behind narrowing the blood vessels and elevation of blood pressure so increase in the chances of cardiovascular diseases *e.g.*- Heart attack, Angina pectoris and stroke *etc* [2].

Treatment Strategies: Diet control by increasing intake of fruits, vegetables & unsaturated fatty acids (*e.g.* fish oil, &olive oil) since they're not oxidized easily like saturated fatty acids. Additionally to exercise, weight reduction, avoid alcohol & smoking.

Antihyperlipidemic Drugs Lipid-Lowering Drugs:

1. Statins (*e.g.* lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin & rosuvastatin), which are HMG-CoA reductase inhibitors that modify cholesterol synthesis.
2. Ezetimibe, which is cholesterol absorption inhibitor.
3. Niacin "nicotinic acid that decreases secretion of lipoproteins.
4. Fibrates (*e.g.* clofibrate, fenofibrate, & gemfibrozil), that increase peripheral clearance of lipoproteins.
5. Resins (*e.g.* cholestyramine, colestipol & colesevelam), that are steroids equestrants that scale back steroid absorption [2, 3].

Microsphere Drug Delivery: Microspheres are characterized as small spherical particulate and free-flowing powders consisting of perishable polymers mostly. They ideally have a particle size starting from1µm to 1000µm] [4, 5, 8, 25]. Microspheres are often loaded with drugs and used for targeted drug delivery. Because the drug is loaded in polymeric microspheres, it shows therapeutic action on targeted tissue only. Microspheres are designed to reinforce the drug's therapeutic effectiveness and bring home the bacon higher bioavailability, thereby minimizing the toxicity and stripped aspect effects.

There are Two Types of Microspheres, Reservoir Type and Matrix Type:

- **Reservoir Type:** In this type, the drug is entrapped as a core within a water-insoluble polymer that controls the speed of drug unleash. The usually used polymers in such devices are ethylcellulose or polyvinyl acetate. This sort is additionally referred to as microcapsules.
- **Matrix type:** The drug is homogeneously distributed during a polymeric matrix, which controls the drug release rate. The commonly used polymers for matrix types are sodium alginate or hydroxyl propyl methylcellulose. This type is additionally referred to as micromatrices.

There is two Mechanism of Drug Release from the Microspheres:

Dissolution: During the drug, dissolution rate is controlled by the polymer decreasing its wet ability or getting dissolved in GI fluid at a slower rate.

Diffusion: The drug diffuses from a neighborhood of upper concentration to lower concentration of the drug.

Advantages:

Better Patience Compliance: As microspheres provide a slow release of drug for an extended period of your time, there is a reduction in dosing frequency, thanks to which it's better for patient compliance, mainly pediatrics, geriatrics, psychology patients, *e.g.*, Karan Razdan *et al*. formulated sustained-release microspheres of cefixime [4, 6, 39].

Enhance Bioavailability: Microspheres are micron in size, *i.e.,* less size gives more area to extend the solubility of poorly soluble drugs, increasing the systemic bioavailability of the drugs. *e.g.,* Karan Razdan *et al*. formulated microspheres of cefixime with enhanced bioavailability [4, 6, 39].

Constant Drug Plasma Concentration: Microspheres showed controlled drug release for a protracted time; as a result, there's no fluctuation of drug concentration in circulation, and a continuing C_{max} is achieved [39].

Reduce Adverse Effects: Biodegradable polymeric microspheres are biocompatible with the body environment; they are not required to be removed surgically. Because the drug is controlled released, the systemic toxicity is additionally reduced [39].

Enhance Stability: Liquid drugs are often converted into solid microspheres to extend the drug's steadiness and maintain its clinical period [4, 6, 39].

Parenteral Formulation: Microspheres are spherical; a high drug dose is often given as microsphere parental depot [53].

Targeted Drug Delivery: Microspheres are designed to target disease sites, specifically tumor tissues, while the concentration remains low at remaining normal tissues [5, 11, 12, 36].

Disadvantages:

Production Cost: The cost of producing the controlled drug dosage form is much higher than conventional forms [5].

Reproducibility: Microspheres are challenging to formulate as specialization and technologies are required for manufacturing microspheres.

Potential Toxicity: As microspheres are loaded with a high drug concentration, there are chances of dose dumping resulting in potential toxicity.

Polymeric Toxicity: Polymeric additives like plasticizers, stabilizers, antioxidants, *etc*., also are used counting on the formulation design; these polymers can undergo hydrolysis, oxidation, or react to biological agents, causing toxicity.

Swallowing: The microsphere intended for oral administration should be swallowed and not chewed or crushed because they 'redesigned for prolonged release of medicine.

Maintaining Conditions: The processing conditions of microspheres like pH, temperature, agitation, solvent evaporation, heating *etc*. can influence the steadiness of the drug to be encapsulated.

Composition of Microspheres:

Polymers: In microsphere formulation, most ordinarily biodegradable and no biodegradable sort of polymers are employed by researchers. The polymers which are utilized in microspheres preparation are classified into different types:

A. Natural

B. Synthetic

Before choosing the polymer for the microsphere formulation, we would like to consider a few parameters like non-toxicity, biocompatibility, biodegradability, and straightforward availability of polymers. It should be biocompatible, biodegradable, nontoxic, and simply available. These polymers that pass all parameters for their selection have many advantages. They increase the duration of the drug within the body, due to which we recover bioavailability of drug compared to standard drug delivery system. Polymers that are utilized in microsphere formulation are of two types.

A. Natural Polymers: Carbohydrates, protein, and chemically modified carbohydrates are the various sources from wherever we tend to get natural polymers.

B. Synthetic Polymers:

1. Non-biodegradable Polymers: Polymethyl methacrylate (PMMA) Acrolein, Glycidyl methacrylate, epoxy polymers [4, 5, 6, 25, 34, 36].

2. Biodegradable Polymers: Lactides, their glycolides, and their copolymer, polyalkyl cyanoacrylate, polyanhydride [4, 5, 6, 25, 34, 36].

Surfactant: In microsphere, formation surfactants play a necessary role throughout the emulsification and extrusion process.

Surfactants play an important role by lowering the interfacial surface tension between Hydrophilic and hydrophobic molecules, due to which stable emulsion is formed. The use of surfactants results in the formation of distinct microspheres by preventing the emulsion droplets from coalescing. HLB indicator is employed for the choice of correct emulsifier. Deliquescent (Hydrophilic) surfactants have an HLB value within the range of 8-18 and are used for oil in water emulsion. In contrast, emulsifiers with HLB values within the range of 3.5 to 6 are understood as lipophilic surfactants. The particle size of microspheres is decreased by increasing the concentration of surfactant due to the smaller size and size distribution of microspheres being formed.

Oil: Particle size, size distribution, and uniformity of microspheres are affected byte the ratio of the viscosity of the oil phase to the viscosity of the water phase. For *e.g.*, it's reported that the particle size of microspheres is more prepared by using vegetable oil than microspheres prepared by using liquid paraffin because the viscosity of vegetable oil is higher than liquid paraffin. Various sorts of oils are utilized in the fabrication of microspheres throughout the emulsification/gelation method.

Cross Linkers: Most ordinarily used crosslinkers for microspheres preparation are Ca_2^+, $Sr_2^+$and Ba_2^+ ions. However, Sr_2^+ and Ba_2^+ions are gently ototoxic and Ca_2^+ ions are nontoxic, due to which Ca_2^+ions are wide used crosslinkers for the preparation of microspheres.

At low concentration of Ca_2^+ ions, agglomeration of microspheres takes place by increasing Ca_2^+ ions concentration demurrer potency of microsphere slightly increases. However, when the optimum concentration of crosslinker if the additional crosslinker is extra, the entrapment efficiency decreases thanks to the overloading of the crosslinker.

Solvent: Solvents are principally used when microspheres are ready by the solvent evaporation method, solvent acts as a carrier for dispersing the polymers and the drug.

Method of Preparation:

Spray Drying: During this technique, coating polymer is first to dissolve/dispersed in an organic solvent like acetone, methylene chloride, and so on; the drug is then incorporated into polymeric solution along with high-speed homogenization. The resultant mixture is then atomized in the stream of hot air. Atomization results in the formation of fine mist or droplets from that organic solvent evaporates like a shot, leading to the formation of microspheres during a size vary of 10um - 100um. Pavan *et al.* (1993) fabricated microspheres of vitamin D3 by using spray drying techniques [4, 6, 7, 21, 34].

Solvent Evaporation: This technique involves using organic parts as producing vehicles; this method consists of two parts. First, the liquid innovates that the drug is incorporated along with stabilizing agent or without stabilizing agent. Also, the different phase is the organic phase, which carries polymers in volatile organic solvent admire acetone, dichloromethane, and aqueous. The organic phase ought to be mixed with high-speed homogenization, which results in the formation of w/o emulsion. Then, this emulsion is extra in the massive aqueous phase to make w/o/w emulsion if necessary. The resultant mixture is heated along with continuous stirring, which leads to evaporation of the organic phase, shrinking the coating polymer across the core material, and results in information of microspheres. Sagar Balaso Sangale *et al*. formulated floating felodipine microspheres using solvent evaporation technique [4, 6, 13, 14, 22, 32].

Single Emulsion Technique: During this technique, the microsphere is ready by emulsification technique, coating polymer is dissolved in a volatile organic solvent that leads to the formation of a polymeric solution. The resultant polymeric solution extra into the liquid part containing emulsifying agent leads to the formation of o/w emulsion. This emulsion is stirred for a few hours underneath constant environmental conditions, filtered, and dried into a desiccator. Yuksel *et al.* (1997) fabricated polymeric microspheres containing Nicardipine using single emulsion techniques [5, 6, 7, 16, 22, 26, 34].

Double Emulsion Technique: This method involves the preparation of double emulsion either w/o/w or o/w/otype. The solution, which contains a drug it disseminates in the organic phase, which is

hydrophobic. The organic part containing the coating chemical compound encapsulates the drug available within the spread liquid phase and results in the formation of primary emulsion.

Then this primary emulsion undergoes homogenizing or sonicating before adding into a solution of polyvinyl alcohol (PVA) to make a secondary emulsion; then, ready microspheres are filtered and dried in a desiccator. Das *et al.* (2007) fabricated microspheres containing Zidovudine by using double emulsion techniques [5, 6, 7, 16, 34].

Phase Separation Coacervation Technique: This technique is usually used to fabricate a reservoir variety of microspheres. Principally this method wont to encapsulate the deliquescent drugs; during this method, coating polymer is dissolved in a volatile organic solvent, and then an aqueous solution of the drug is extra to allow the chemical compound to coat the drug, then phase separation can be initiated by ever-changing the close conditions like changing temperature, changing PH, the addition of salt and so on. Arunachalam *et al.* (2010) fabricated gelatin microspheres of ofloxacin by using phase separation conservation technique [4, 6, 7, 23].

Spray Congealing: During this technique, the drug is dissolved/disseminated in polymeric solution, *i.e.,* oleophilic polymer like wax. The hot liquefied solution was then sprayed to make fine droplets into a vessel that had already cooled in CO_2 ice bath [7, 24].

Solvent Extraction: This technique involves the removal of the organic phase by extraction of the organic solvent *via* exploitation of deliquescent organic solvents like iso-propyl-alcohol. The organic phase is then extracted using water; this method decreases the hardening time of microspheres [5, 34].

Quasi Emulsion Solvent Diffusion: Microsponges may well be prepared by exploitation (this technique / this system). It involves two parts one is internal, and also the difference is external. The external phase consists of polyvinyl alcohol and distilled water. The internal phase carries polymer, drug, and ethanol with it. The internal phase is hot to 60°C, then extra to the external phase main. It is then maintained at area temperature. Resultant emulsion is then homogenized up to a pair of hours and fictional into microsponges, then filtered, washed and dried in a vacuum oven for twenty-four hours [4].

Cross-Linking Agent Method: In this method, the cross-linking agent is employed for the fabrication of the microspheres. The first specific, focused polymeric solution has been created in a liquid medium then extra in continuous part containing oil and specific concentration of surfactant to make w/o emulsion. Then dropwise solution of crosslinker added alongside continuous stirring and permitted for rigidisation of the surface of microspheres. Resultant microspheres were then washed and dried [4].

Hot Melt Microencapsulation: In this method coating polymeric solution homogenized with drug, the resultant mixture is then suspended in oleophilic solvent admire semiconducting material oil along with continuous agitation/stirring and heating the solution at 5°C up to the melting point of the polymer, when the emulsion get stabilized, it is cooled to solidify the polymeric microspheres.[6,28]

Ionic Gelation Technique: In this method, suspension of deliquescent polymer alongside drug is complexed with multivalent ion, *i.e.,* salt ensuing into the formation of extremely viscous gel spheres. An iridescent suspension is obtained. This suspension is centrifuged to induce a uniform size of microspheres. Microspheres are then washed and dried at a temperature for twenty-four hours. Selveraj *et al.,* (2011) prepared microspheres of acyclovir by using ionic elation technique [4, 20, 29, 30].

Evaluation Techniques Characteristics: It is important to develop these microparticulate carriers, which helps design a sustainable and suitable carrier for proteins, drug, or antigen delivery. Every microsphere has different microstructures. These microstructures determine the release and stability of the carrier.

Particle Size and Shape: The most common ways to picture microspheres are conventional light microscopy (LM), confocal fluorescence microscopy and scanning electron microscopy (SEM). These techniques can be used to determine the shape and outer structure of microspheres [4, 6, 11, 13].

Conventional Light Microscopy: Conventional light microscopy provides control over coating parameters in the case of double-walled microspheres. The microsphere's structures can be visualized before and after coating, and the change can be measured microscopically. SEM provides higher resolution in distinction to lightweight microscopy.

Scanning Microscopy: Scanning lepton microscopy permits investigations of the surfaces of the microspheres. When particles are cross-sectioned, it can even be used to investigate double walled systems [31, 38].

Confocal Microscopy: Confocal visible radiation microscopy is employed to characterize the structure of multiple walled microspheres. Optical laser light scattering and multi-size colter counter except for instrumental methods, which might be used to characterize the microspheres' size, form, and morphology.

Angle of Contact: The angle of contact determines the wetting property of microspheres in terms of hydrophobicity and hydrophilicity. This physical science property is such that to a solid substance and suffering from an absorbed component. The angle of contact is measured at the solid/air/water interface. The increasing and decreasing angle of contact is measured by inserting a drop during a circular cell mounted higher than the target of an inverted microscope. The Contact angle is measured at two hundred degrees Centigrade at intervals a second of deposition of microspheres.

Attenuated Total Reflectance Fourier Transforms Infrared Spectroscopy: FT-IR determines the degradation of the carrier system's chemical compound matrix and the surface of the microspheres is investigated activity alternated total coefficient of reflection (ATR). A beam of infrared is gone through the ATR crystal in such some way that it reflects over and over through the sample to supply IR spectra principally of surface material. Along ATR-FTIR provides information concerning the surface composition of the sample microspheres [4, 6, 36].

Density Determination: The multi-volume pycnometer is employed to work out the density of microspheres. When a cup accurately weighed sample of microspheres is placed, the cup is placed within the multi-volume pycnometer in a cup is placed into the multi-volume pycnometer. At constant pressure, the noble gas is introduced in the chamber and allowed to expand. Enlargement of the noble gas decreases the pressure at intervals in the chamber and two consecutive readings of reduction in pressure at completely different initial pressure are noted. From these two pressure readings, the amount additionally the density of the sample microsphere is determined [5, 11].

Electron Spectroscopy for Chemical Analysis: Electron spectroscopy for chemical analysis (ESCA) determines the surface chemistry of the microspheres. ESCA also determines the atomic composition of the surface of the microsphere and layer degradation of the perishable microspheres by making spectra with the assistance of electron spectroscopy. It's also known as X-ray photoelectron spectroscopy (XPS) [4, 36].

Surface Carboxylic Acid Residue: Radioactive glycine is employed to live surface acid residue. Hot glycine conjugates are ready by the reaction ofC14 - glycine alkyl radical organic compound-complex with the sample microspheres. The glycine residue is coupled with the soluble compression 1- ethyl- 3 (3-dimethyl aminopropyl) carbodiimide (EDAC). Emission of the conjugate is then measured employing a liquid counter tube technique. Thus, the carboxylic acid residue is compared and correlated. Free carboxylic acid residue can be wont to measure hydrophobic or deliquescent or the other derivatized variety of the microspheres [4].

Isoelectric Point: To work out isoelectric point, equipment called micro electrophoresis is employed to measure microspheres' electrophoretic mobility. Mean velocity at every pH value starting from 3-10 is calculated by activity at the time of particle movement over a distance of one mm. The electrical mobility of the particle is determined exploitation of this data. The electrophoretic mobility can be regarding these three parameters: surface contained charge, ion sable behavior, or ion absorption nature of the microspheres [4, 36].

Surface Amino Acid Residue: The radioactive C14-acetic acid conjugate is used within the

determination of surface-associated amino acid residue. The amino acid residue is decided indirectly by the first determinant radical acid residue through the liquid scintillation counter. EDAC is employed to condense the amino and also the c14 - acetic acid, carboxylic acid residue. The indirect estimation technique is completed to work out the free amino or the free carboxylic acid residues by activity the emission of the C14 glycine alkyl radical organic compound complex having acetic acid or the glycine conjugates [4, 5, 36].

Entrapment Efficiency: Entrapment efficiency of the microspheres is decided by permitting washed microspheres to the lysate. The lysate is then subjected to the determination of active constituents as per the necessity of a monograph. The percent encapsulation efficiency is calculated by exploiting the following equations [11, 20, 36, 38].

% Entrapment = Actual content / Theoretical content × 100

Applications of Microspheres in Pharmaceutical Industries:

Oral Drug Delivery: The oral route is a simple and convenient route for administering the drug with higher patient compliance. There are massive numbers of pharmaceutical merchandise administered *via* the oral route. The principal behind oral absorption completely depends on the solubility and permeableness of the drug. Microsphere drug delivery offers sustained and controlled manner drug unleash for an extended amount of your time results in scale back dosing frequency and improve patient compliance [27, 51].

Ocular Drug Delivery: Microspheres are sensible carriers for ocular drug delivery. By exploiting microspheres, the drug delivery bioavailability of the drug has been improved as compared to the liquid ocular preparations. Because of their sustained or controlled unleash mechanism microspheres are used for the long-lasting release of drugs that results in scaling back the dosing frequency [6, 10, 35, 42].

Intranasal Drug Delivery: This route is especially well-liked for the delivery of proteins and peptides. Typical formulations are get drained far from the nasal mucosa. Bioadhesive microspheres offer higher bioavailability by exerting their sustained/controlled mechanism [6, 9, 43].

Gene Therapy: In this technique, microspheres are fictional with viral vectors in gene-drug delivery. This method offers ease of preparation, website targeting, and enormous scale production and shows low immunogenic response as compared to the direct viral vector drug delivery [6, 44].

Buccal Drug Delivery: Mucoadhesive microspheres function as a reservoir for drug; it releases the drug from the applied site for an extended period of time. Mucoadhesive polymers reside on the cavity's mucous membrane and act as reservoir; it also improves the bioavailability of the drug by avoiding first-pass metabolism [6, 37, 40].

Percutaneous and Topical Drug Delivery: Polymers have a sensible film-forming ability to deliver the drug through the skin. For instance, chitosan, alginate, and PLGA loaded microspheres are used as percutaneous Drug Delivery. It is also used for delivering the drug for topical application. E.g., Asiatic side-loaded microspheres for wound healing show an acceleration in re-epithelization still promoting angiogenesis [45, 54].

Gastrointestinal Drug Delivery: Microspheres are used for the delivery of the potent drug to the precise website (GIT). Eudragit, alkyl radical cellulose, carbopol, and alginate microspheres are used for delivery of the drug at a specific site in GI Tract. It prevents the first-pass metabolism of the drug and will increase the bioavailability of the drug [6].

Intra-tumoral and Local Drug Delivery: Anti-tumor medicine ought to be delivered at the tumor site in applicable concentration parenthetically paclitaxel loaded microspheres. Film-forming polymers are wont to sustain the discharge at the local site *i.e.,* oral cavity [44, 47, 52].

Colonic Drug Delivery: Microspheres are used to deliver the drug at a specific site in the bowel, i.e., colon hypoglycemic agent loaded into chitosan microspheres targeted to release its drug at colon [6, 48].

Vaginal Drug Delivery: Microspheres drug delivery used for treating vaginal infections admiremycotic infection of the reproductive organ tract. Chitosan, gelatin, PLGA polymers are used

for fabricating the microspheres to treat vaginal infections [6, 49].

Radioactive Applications: Radioactive isotopes loaded microspheres6+are used to treat many diseases like liver and spleen tumors. For instance, Yttrium 90 loaded microspheres are won't to treat cancer [50].

Medical Applications: Microspheres also are employed in neutraceuticals to deliver proteins, peptides overextended amount of time. Magnetic microspheres are used to extract the stem cells and bone marrow purging.

Vaccine Drug Delivery: Microsphere Drug Delivery has been showing economical in vaccine delivery; Thiolated Eudragit Microspheres would be a higher candidate for oral vaccine delivery. It also evokes the general and tissue layer immunity [36].

CONCLUSION: Microspheres drug delivery system has been developed to improve bioavailability and sustain the release of the drug. Antihyperlipidaemic drugs suffer from poor bioavailability and solubility; hence need for a novel drug delivery system becomes essential. Microsphere drug delivery system shows a promising tool for delivery of such drugs. Subsequently, various methods of preparation of microspheres were discussed along with their application.

ACKNOWLEDGEMENT: We are thankful to the management of Hygia Institute of Pharmaceutical Education Research for providing the facilities and access to online resources for the literature survey to complete this review successfully.

CONFLICTS OF INTEREST: All authors declared that there are no conflicts of interest.

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How to cite this article:
Ahmad A and Niranjan AK: Microspheres: a novel approach for delivery of antihyperlipidemic drugs. Int J Pharm Sci & Res 2022; 13(6): 2294-02. doi: 10.13040/IJPSR.0975-8232.13(6).2294-02.