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FORMULATION OF MICRO BEADS: A REVIEW

Mullaicharam Bhupathyraaj *, Alka Ahuja, Jayasekher and Sushama Pole

Professor of Pharmaceutics, College of Pharmacy, National University of Science and Technology, Muscat, Oman.

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Correspondence to Author:
Prof. Dr. Mullaicharam Bhupathyraaj

Professor of Pharmaceutics, College of Pharmacy, National University of Science and Technology, Muscat, Oman.

E-mail: mullaicharam@nu.edu.om

ABSTRACT: The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired drug concentration. This could be achieved through multiparticulate dosage form like beads which are divided into many individual units, so, called subunits, each exhibiting some desired characteristics. Micro particulate drug delivery systems have various well-known advantages over single unit dosage form. Preparation of microbeads drug delivery system is one of the alternatives which involve neither use of harsh chemical nor elevated temperature. The conventional techniques involve the use of ionotropic gelation method, emulsion gelation method, polyelectrolyte complexation method, *etc*. The majority of work has been done on the preparation of microbeads by ionotropic gelation method rather than other methods owing to its ease of preparation. The ionotropic gelation method is based on the ability of polyelectrolytes counter ions to crosslink to form a hydrogel sustained release formulation.

INTRODUCTION: The goal in designing delayed release sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained-release, sustained action, prolonged action, extended action are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile.

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Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. For many decades treatments of an acute disease or a chronic illness have been mostly accomplished by delivery of drugs to patients using various conventional pharmaceutical dosage forms like tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as drug carriers.

A sustained release drug delivery system is known to provide a prompt release of the drug. So to achieve and maintain the drug concentration within a therapeutically effective range needed for treatment, it is often essential to take this type of drug delivery system several times a day, which results in a significant fluctuation in drug levels. For many drug substances, conventional immediate - release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. Micro-particulate drug delivery systems have various well-known advantages over single unit dosage forms [1, 2].

In addition, oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost-effective manufacturing process. Multiple unit dosage forms such as micro-spheres or micro beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastro-intestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form [6, 10].

One of the most exploited techniques to formulate microparticulate drug delivery is micro-encapsulation. However, it offers many significant advantages but has some drawbacks also. Some of the important drawbacks of these techniques include the use of more or less harsh conditions in the formulation process, which limits many substances such as protein, enzyme, *etc*. as core material for encapsulation. Preparation of microbeads drug delivery system is one of the alternatives to overcome the above problem, which involves neither use of harsh chemical nor elevated temperature. The conventional techniques involve the use of Ionotropic gelation method, Emulsion gelation method, Polyelectrolyte Complexation method [3, 4, 5, 8]. Majority of the work has been done on the preparation of micro beads by ionotropic gelation method rather than other methods owing to its ease of preparation for the treatment of various diseases. Studies are done to assess the release pattern of the drug from microbeads [13].

Multiple Unit Dosage forms used in the Drug Delivery are as follows: [6, 10, 13]

Micro Granules / Spheroids: In this drug is wet granulated alone or incorporated into inert granules and then coated to control the release pattern.

Pellets: Pellets are prepared by coating inert drug pellets with film-forming polymers. The release depends upon the coating composition of polymer and the amount of coatings.

Microcapsules: Microencapsulation is the process of enclosing a substance inside a miniature called capsule. Microcapsules are a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core/ internal phase, whereas the wall is sometimes called a shell/coating. The microcapsule size ranges from 1 µ -7mm[32].

Microspheres: Microspheres are small spherical particles, with diameters ranging from 1 µm to 1000 µm. They are free-flowing spherical particles consisting of proteins or synthetic polymers which are biodegradable. There are two types of microspheres; microcapsules and micrometrics. Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall, and micromatrices are those in which entrapped substance is dispersed throughout the matrix. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microspheres play an important role in improving conventional drugs' bioavailability and minimizing side effects [3, 7, 11, 12].

Ideal Characteristics of Microspheres are listed as: [3, 7, 11, 12]

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of the active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable bio-degradability

Advantages of Microspheres: They are listed as follows [3, 7, 11, 12].

- Particle size reduction for enhancing solubility of the poorly soluble drug.
- Provide constant and prolonged therapeutic effect.
- Provide constant drug concentration in blood, thereby increasing patent compliance, decrease dose, and toxicity.
- Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.

Microbeads: Microbeads are nearly spherical, small with diameter of 0.5- 1000 μm. The solid and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. Additionally, the microbeads maintain functionality under physiological conditions, can incorporate drugs to deliver locally at high concentration, ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low.

The microbeads are produced from several polymers such as cationic polymers, *e.g.*, chitosan, anionic polymers, *e.g.*, sodium alginate, and binding components, *e.g.*, gelatin, chondroitin sulfate, avidin in a predetermined ratio. Microencapsulation has become a common technique in the production of controlled release dosage forms. One approach for the controlled release formulation of different therapeutic agents in the production of polymeric gel beads. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads. Beads can provide sustained-release properties and a more uniform distribution of drugs within the gastrointestinal tract. Furthermore, the bioavailability of drugs formulated in beads has been enhanced. Numerous studies have been reported concerning the use of alginate beads as a controlled release carrier [14, 15, 16, 17].

The advantages of microbeads are as follows:

- Limiting fluctuation within therapeutic range.
- Reducing side effects.
- Decreasing dosing frequency.
- Improving bioavailability.
- Improving patient compliance.

Criteria for Formulation of Sustained Release Microbeads Dosage forms: [3, 5] A number of formulation methods have been developed to overcome the barrier seen with immediate release oral dosage forms. These processes include inert insoluble matrices, use of coatings, hydrophilic matrices, as well as the combinations of hydrophilic and hydrophobic polymers, embedding of the drug in plastic matrix, ion exchange resins, osmotic pumps and microencapsulation.

The physiology of the gastrointestinal tract, the physicochemical property of the drug, the drug release pattern, the pharmacological action of the drug are the parameters that must be considered too. The physicochemical properties of the drug involve parameters like aqueous solubility, stability, pKa, and permeability values.

The Biopharmaceutical Classification System (BCS) involves placing a drug into four classifications:

- High solubility and high permeability
- Low solubility and high permeability
- High solubility and low permeability
- Low solubility and low permeability

Class 1 is considered the preferred category, while Class 4 is the worst category. A drug having high solubility in the intestine is a good drug for a controlled oral dosage form. The drug permeability value must also be considered and should be more than the prescribed value. A biological half-life of a required drug is between two and six hours is the best choice of formulation because this type of criteria of the drug is avoiding the accumulation of the drug in the body.

Drug Release Kinetics Criteria: [3, 5, 47] The purpose of a sustained-release system is to deliver a drug at a necessary rate to achieve and maintain a constant drug blood level. It means that the rate of drug delivery should be independent of the amount of drug remaining in the dosage form and constant over a certain time. It implies that the rate should follow zero-order kinetics. Zero-order release may be theoretically desirable. Non zero-order release rates may be clinically equivalent to constant release in many cases. In order to achieve a therapeutic level promptly and maintain that level for a given period of time, the dosage form generally should consist of two parts. With the controlled oral dosage forms, the total drug in the dosage form should consist of two portions, a loading dose and a maintenance dose. The initial loading dose is released immediately on its administration.

The release of the drug is characterized by a first-order kinetic process. The loading dose immediately obtains the acceptable therapeutic plasma levels. The remaining dose is released at a slow and a controlled rate to maintain the constant plasma concentration of the drug. The release pattern has to follow zero-order kinetics.

Therefore, the rate of release of the drug is independent of the remaining fraction of the dose. The controlled oral dosage form involves releasing the maintenance dosage at a rate that is equivalent to the elimination rate of the drug.

Drug Release Mechanism: [5, 47, 48] Drug release from the microbeads formulation occurs by a general mechanism including dissolution, diffusion, polymer degradation, and hydrolysis/erosion.

Dissolution Controlled System: In this system, the rate-controlling step is dissolution. The drug is embedded in slow-dissolving or erodible matrix or by coating with a slow dissolving substance. It is of two types is Encapsulation and Matrix

Encapsulation: The drug particle is coated or encapsulated by microencapsulation techniques with slow dissolving materials like cellulose, polyethylene glycol, polymethacrylates, waxes, *etc*. The dissolution rate is dependent upon the solubility and thickness of the coating.

Matrix: It is also called monoliths. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, which controls drug dissolution by controlling the rate of fluid dissolution penetration into the matrix by altering porosity of rate. The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same.

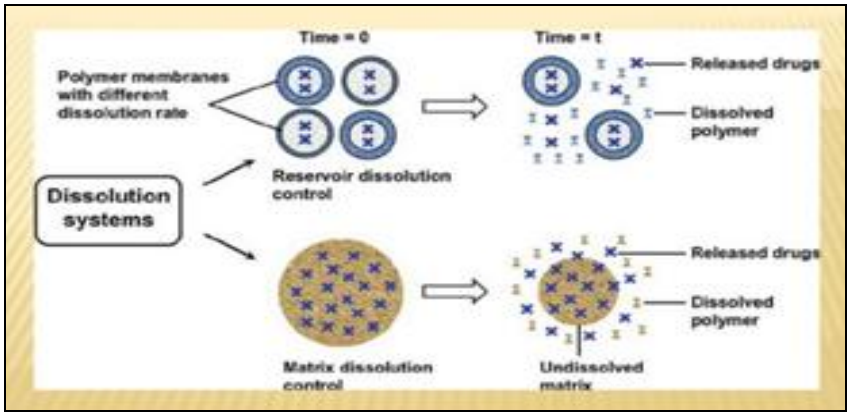

FIG. 1: RELEASE MECHANISM DISSOLUTION CONTROLLED SYSTEM [49]

Diffusion Controlled System: Rate limiting step is diffusion of drug through inert water-insoluble membrane barrier. In the case of a polymer matrix, the diffusion of the active ingredient can be through the intact polymer network or through the pores filled with water. Water-soluble drugs may also dissolve in the aqueous pore networks. Water uptake causes polymer chains to swell, indicating the formation of new pores and/or osmotic pressure.

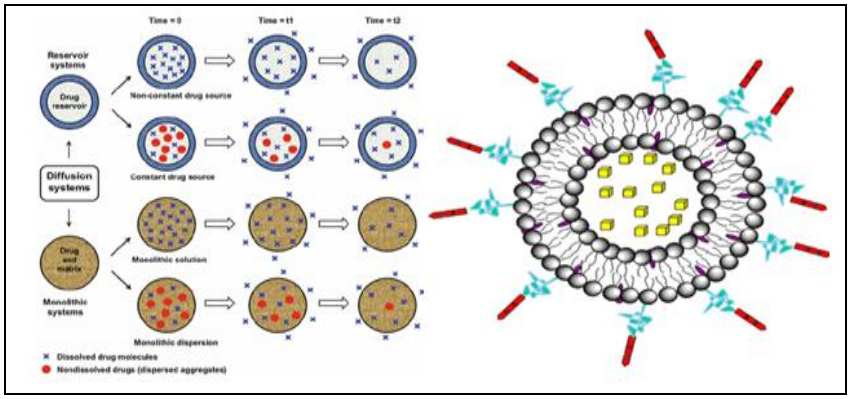

FIG. 2: RELEASE MECHANISM DIFFUSION CONTROLLED SYSTEM [50]

During swelling, the volume increases, the effective diffusion coefficient of the drug is increased, and more pharmacon molecules enter the aqueous part. The rate of release also depends upon where the polymer degradation by homogeneous or heterogeneous mechanism. The drug release depends on the rate of drug dissolution in the dissolution fluid, rate of penetration of dissolution fluid to the microbeads, and rate at which the dissolved drug escapes from the microbeads.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, *i.e.* loss of polymer, is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as the water penetrates within it leading to the plasticization of the matrix.

Techniques used for Formulation of Microbeads:

Ionotropic Gelation Method: It involves the interaction of an ionic polymer with oppositely charged ions to initiate crosslinking. Unlike simple monomeric ions, the interaction of polyanion with cations cannot be completely explained by the electro-neutrality principle. The three-dimensional structure and presence of other groups influence the ability of cations to conjugate with anionic functionalities or vice-versa. There are two sub-methods by which beads can be generated using ionotropic gelation technique. The methods differ from each other in the source of the crosslinking ion [19, 21, 23]. In one of the methods, the cross-linker ion is positioned externally, whereas, in the other method, the cross-linker ion is incorporated within the polymer solution in an inactive form. Ionotropic gelation methods classified into two types: External gelation method and internal gelation method.

External Gelation Method: The external gelation method involves the use of a metal ion solution as a source of the crosslinking ion. The polymer solution containing the drug is extruded through a needle into this solution with mild agitation. As soon as the polymeric drop comes in contact with the metal ion solution, instant gelation occurs, resulting into self-sustained bead formation. The beads are cured for a specified time period into the gelation medium following which, they are removed and dried. The external gelation occurs as a result of rapid diffusion of the cross-linker ions into the partially gelled beads [19, 21, 23].

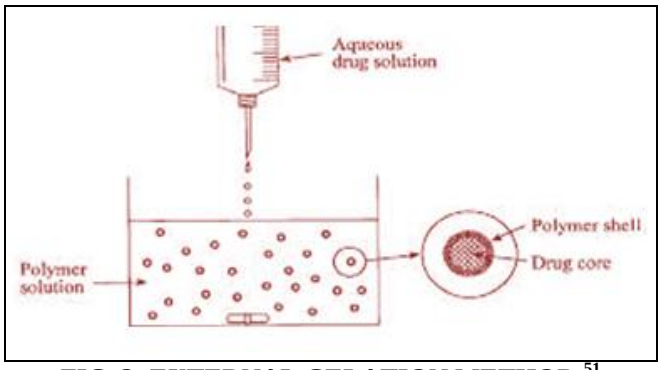

FIG. 3: EXTERNAL GELATION METHOD [51]

Internal Gelation Method: The internal gelation method involves the generation of the cross-linker ion 'in situ'. This method involves the use of insoluble metal salt (such as calcium carbonate and barium carbonate) as a source of crosslinking cation. The cation is released, *in-situ*, by lowering the pH of the solution, thereby solubilizing the metal salt and releasing the metal ion [19, 21, 23].

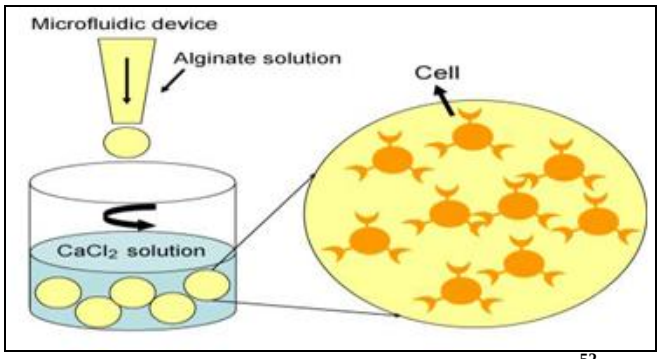

FIG. 4: INTERNAL GELATION METHOD [52]

Emulsion Gelation Method: Another method of microbead preparation is emulsion gelation techniques. The sodium alginate solution is prepared by dispersing the weighed quantity of sodium alginate in deionized water. An accurately weighed quantity of drug is added to the polymeric solution of Sodium alginate, and the drug is stirred magnetically with gentle heat to get a homogenous drug polymeric mixture.

A specific volume of the crosslinking agent is added to form a viscous dispersion, which is then extruded through a syringe with a flat-tipped needle of size no. 23 into oil containing span 80 and 0.2% glacial acetic acid being kept under magnetic

stirring at 1500 rpm. The microbeads are retained in the oil for 30 min to produce rigid discrete particles. They are collected by decantation, and the products thus separated are washed with chloroform to remove the traces of oil. The microbeads are dried at 400 ºC for 12 h [18, 22].

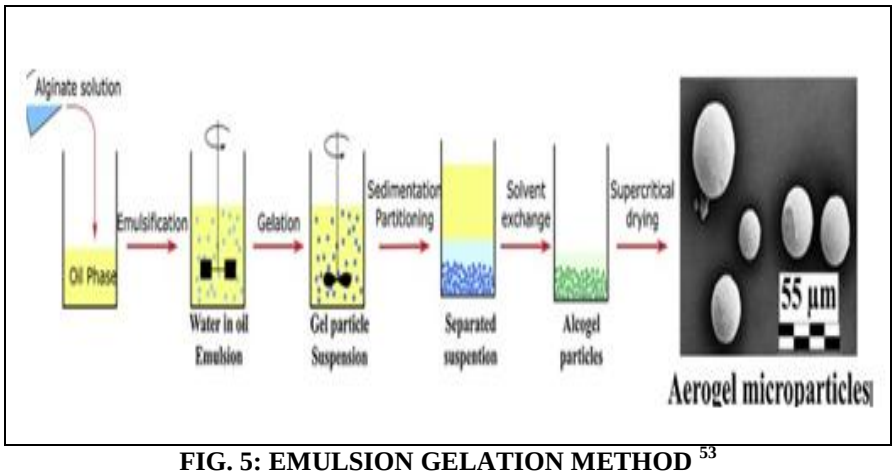

FIG. 5: EMULSION GELATION METHOD [53]

Polyelectrolyte Complexation Method: Another method of microbeads preparation is the complex coacervation of oppositely charges poly-electrolytes, polycation, and polyanion materials. Alginate chitosan microcapsules with bio-compatibility and biodegradability may be prepared under mild conditions. Even physiological conditions, so they are suitable for application in biomedical fields. In recent years, there has been an increasing interest in the study of the use of alginate– chitosan microcapsules as the drug-delivery systems of proteins and polypeptides. With this method, specific conditions of polyion concentration, pH and ionic strength, the mixture will separate into a dense concretive phase containing the microbeads and a dilute equilibrium phase. For example, complex coacervation between alginic acid and chitosan was achieved by spraying the sodium alginate solution into the chitosan solution, producing strong microbeads that remained stable over a large range of pH. For the best yield with coacervative bead preparation, conditions should be set to a pH of 3.9, ionic strength of 1 mm, and a 0.15% w/v total polyion concentration [24, 25, 27].

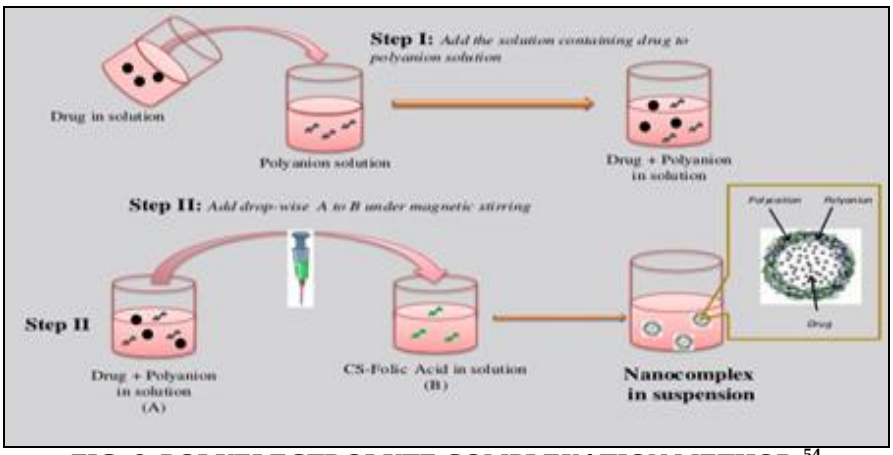

FIG. 6: POLYELECTROLYTE COMPLEXATION METHOD [54]

Polymers used for the Preparation of Micro-beads: A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microbeads. These materials include polymers of natural and synthetic origin and also modified natural substances. Some examples of polymers are Albumin, Gelatin, Sodium alginate, Chitosan, Starch, Dextran, Polylactide, and olyglycolide Polyanhydride, Polyphosphazene, *etc*. Sodium alginate micro Beads are one of the multiparticulate drug delivery systems and are prepared to obtain

prolonged or controlled drug delivery, to improve bioavailability or stability, and to target the drug to specific sites. Multiple unit dosage forms such as microspheres or beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastro-intestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material when compared to non-disintegrating single unit dosage form [20, 22, 23, 30].

Alginates: Alginates are natural polysaccharide polymers isolated from the brown seaweed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used.

Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in a liposome, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications. The bioadhesive character of alginates makes them useful in the pharmaceutical industry.

The application areas of sodium alginate-based drug delivery systems are many, and these systems can be formulated as gels, matrices, membranes, nanospheres, microspheres, and microbeads, *etc*.

Alginate beads can be administered by filling in capsules or by compressing them into a tablet. A new approach of alginate polymer in the pharmaceutical field is the development of systems that are capable of adjusting drug release according to physiological needs (*e.g*., pH-responsive systems based on polymer swelling, magnetically triggered delivery systems). Alginate also possesses the physic-chemical properties required to make it an important contributor to this area of future research [26, 28, 29].

Chitosan: Chitosan is a cationic natural poly-saccharide that is derived from the chitin of crustaceans, with crabs and shrimp-shell wastes as its principal source.

Its properties include the extent of deacetylation and the average molecular weight of the polymer and low toxicity, and good bioavailability makes it a novel excipient in a pharmaceutical formulation as relatively new development. Chitosan is a biopolymer that could be used for the preparation of various polyelectrolyte complex products with natural polyanions such as xanthan, alginate, and carrageenan. Many formulations were recently prepared and evaluated within different dosage forms such as ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal as well as gene carrier, which is based on the application of chitosan and its derivatives.

Chitosan is biocompatible and shows anti-microbial and antifungal activities, which makes it a favorable option for biomedical applications. In many researches, researchers proved that the chitosan is very useful in tissue growth, tissue repair, and accelerating wound-healing and bone regeneration therapies [31, 32].

Pectin: Pectin is used as a thickening agent and a gelling agent. Basically, it is a polymer of a-D-galacturonic acid with 1-4 linkages. The chemistry and gel-forming characteristics of pectin have enabled this naturally occurring biopolymer to be used in the pharmaceutical industry.

It has also been used potentially in pharmaceutical preparation and drug formulation as a carrier of a wide variety of biologically active agents, not only for sustained release applications but also as a carrier for targeting drugs to the colon for either local treatment or systemic action [33, 34, 35].

Xanthan Gum: Xanthan gum is a natural, biosynthetic, edible gum, and extracellular polysaccharides. Xanthan gum consists of glucose, mannose, and glucuronic acid. Xanthan is highly soluble in cold and hot water, and this behavior is related to the polyelectrolyte nature of the xanthan molecule.

Xanthan gum is mainly considered to be a nongelling agent and is used for viscosity. It hydrates rapidly in cold water without lumping to give a reliable viscosity. Xanthan gum is used as a thickener stabilizer, emulsifier, and foaming agent. Xanthan has the potential advantage of drug release with zero-order release kinetics. However, its major drawback is that the drug release is influenced by the pH and the presence of ions in the medium [37,38].

TABLE 1: FORMULATION OF MICROBEADS OF DIFFERENT DRUGS AND DIFFERENT POLYMERS [39, 40, 41, 42, 43, 44, 45]

S. no.	Type	Drug	Polymer	Method	Significance
1	Microbeads [39]	Ibuprofen (Anti Inflammatory)	Sodium alginate	Ionotropic gelation method.	Prepared Rioprostil micro beads shown higher drug entrapment and prolonged release characteristics.
2	Microbeads[40]	Diclofenac (Anti Inflammatory)	Sodium-Loaded Alginate-PVP K 30	Ionotropic gelation method	Oral alginate-PVP K 30 microbeads for controlled delivery system of DS was successfully developed by alginate-PVP K 30 blending using ionotropic gelation
3	Microbeads	Theophylline (Respiratory system)	Chitosan and Sodium alginate	Ionotropic gelation method	As conc. Of polymer increased, size of beads also increased. -Lower cross linking time, lower the size diameter of gel beads.
4	Microbeads[42]	Venlafaxine HCL (Anti Depressant)	Sodium alginate and calcium chloride	Ionotropic gelation method	Good encapsulation efficiency and micron sized alginate spheres.
5	Microbeads[43]	Nifedipine (Anti-Anginal)	Sodium alginate and pectin	Ionotropic gelation method	Mean particle size of microbeads increased significantly with increasing pectin concentration
6	Microbeads[44]	Norfloxacin (Antibacterial Drug)	Sodium alginate and pectin	Ionotropic gelation method	Sustained release was observed with the increase in percentage of sodium alginate.
7	Microbeads[45]	Ibuprofen (Anti Inflammatory)	Agar sodium carboxy- methyl cellulose	Extrusion and dispersed phase congealing technique	Ibuprofen-loaded agar microbeads are found to be potential, cost-effective and satisfactory in vitro release studies
8	Microbeads[46]	Zaltoprofen	Gellan-chitosan and calcium chloride	Ionotropic gelation method	Zaltoprofen entrapped microbeads demonstrated a better delivery system for the sustained release of a drug

CONCLUSION: The present review article shows that microbeads are a better choice of drug delivery system than many other types of drug delivery systems. Research shows that microbeads are prepared by Ionotropic Gelation technique to improve bioavailability and reduce dose frequency, thereby achieving an oral controlled release of the drug. In the future, by combining various other strategies, microbeads will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific, and effective *in-vivo* delivery, and supplements as miniature versions of diseased organ and tissues in the body.

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