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A review on micro beads: Formulation, technological aspects, and extraction

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Abstract

Any drug delivery system's purpose is to deliver a therapeutic amount of medicine to the appropriate place in the body while also achieving and maintaining the correct drug concentration. This could be accomplished by using numerous unit dosage forms such as microgranules/spheroids, pellets, microcapsules, and beads, which are divided into many separate units, referred to as subunits, each of which possesses certain desired features. The advantages of micro particle drug delivery systems over single unit dose form are well documented. One of the solutions that does not entail the use of harsh chemicals or elevated temperatures is the production of microbeads medication delivery systems. The traditional procedures require the use of ionotropic gelation methods, which include internal and external gelation methods, emulsion gelation methods, polyelectrolyte complexation methods, and so on. Because of the ease of preparation, the majority of work has been done on the preparation of microbeads using the ionotropic gelation process rather than alternative approaches.

Keywords: Microbeads; Formulation; Coventional Techniques; Extraction

1. Introduction

Microbeads have a diameter of 0.5-1000 µm and are almost spherical in shape. Treatment with different active agents can be carried out with numerous release profiles or a sustained release with minimal adverse effects thanks to the solid and free-flowing particulate carriers that contain dispersed drug particles in crystalline or solution form. Furthermore, under physiological settings, the microbeads remain effective. They can also be modified to include medications and deliver them locally at high concentrations, ensuring that therapeutic amounts are achieved at the target site and minimising negative effects by maintaining low systemic concentrations. A variety of polymers, including cationic polymers like chitosan, anionic polymers like sodium alginate, and binding components like gelatin, chondroitin sulphate, and avidin, are combined in a preset ratio to create the microbeads [1-2]. A typical method for creating controlled release dosage forms is microencapsulation. A method for producing polymeric gel beads using a controlled release formulation of various medicinal ingredients. The medicine is coated or encapsulated in the centre of the beads, which are distinct spherical microcapsules that function as a solid substrate. Drugs can be distributed more uniformly throughout the gastrointestinal tract and have sustained-release qualities thanks to beads. Additionally, medications packaged in beads have improved in terms of bioavailability. Alginate beads have been the subject of numerous reported investigations regarding its usage as a controlled release carrier [3].

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In cosmetics and personal hygiene products including toothpaste, body scrubs, and face wash, microbeads—minuscule plastic microspheres—are employed as exfoliating agents [Figure 1]. The natural exfoliating ingredients pumice, oats, and walnut husks are substituted with these beads. Our lakes, rivers, and ocean are filled with these little particles that wastewater treatment systems are unable to filter out. What's worse is that these microplastics may act as microscopic chemical and toxin transfer stations [4].

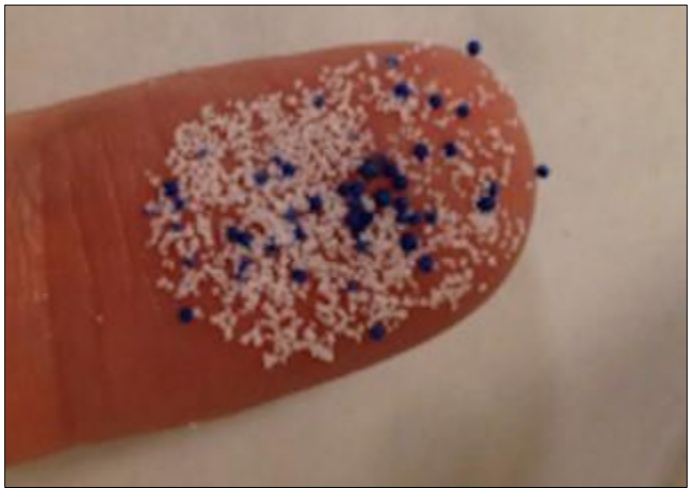

Figure 1 Image of Micro beads

Among other methods, microbeads have piqued the curiosity of researchers all around the world. They haven't proven as effective, though, because of how quickly they enter the gastrointestinal (GI) system after oral delivery. Increasing the microbeads' close contact with the biological barrier membrane is one way to prolong the GI residency period. medication release rate can be precisely controlled and medication bioavailability can be improved by using mucoadhesive technologies that lengthen the GI residence time of the dose form [5].

1.1. Types

Microbeads, which are made of solid plastic particles with a maximum dimension of less than one millimetre, are commonly made of polyethylene (PE), polyethylene terephthalate (PET), nylon (PA), polypropylene (PP), and polymethyl methacrylate (PMMA). Polyethylene or other petrochemical polymers like polypropylene and polystyrene are the most commonly utilised materials. Commercial microbeads range in particle size from 10 micrometres (0.00039 in) to 1 millimetre (0.039 in). They are particularly well-suited for forming porous patterns in ceramics and other materials due to their low melting temperature and quick phase transitions [6-7].

1.2. Use

In order to provide exfoliation, microbeads are added to toothpaste, face scrubs, soaps, and other cosmetics and personal hygiene items. To make over-the-counter medications simpler to swallow, they could be added. Microbeads are utilised in fluid visualisation, process troubleshooting, microscopy techniques, and fluid flow analysis in biological and health science research [8].

Creams and lotions have a smooth texture and are easily spread because of the ball-bearing effect caused by sphericity and uniform particle size. Roundness and smoothness can act as lubricants. Cosmetic goods look more appealing when they contain coloured microspheres [9].

2. Preparation of Micro beads

The Ionotropic External Gelation process was utilised to create micro beads. Here, distilled water was used to dissolve sodium alginate, HPMC, and Eudragit L-100 in a 1:0.5 and 2:0.5 ratio with stirring.This solution was mixed with the medication, and after 15 minutes, the drug suspension was added to the mixture that contained varying percentages of $CaCl_2$ and $AlCl_3$. Using a needle-equipped syringe, the drug suspension was gradually added to this mixture. Following two rounds of deionized water washing, the resultant beads were filtered through Whatman paper filters and dried for 48 hours at 45°C. A dosage of eight milligrammes of dried beads was placed into the capsules.

Table 1 Various formulations of micro beads drug delivery system

S.No	Ingredients	Quantity
1	Hydrocortisone	1.0g
2	Sodium alginate	3g
3	Eudragit L-100	1.0g
4	HPMC K15	-
5	Calcium chloride	3%w/v
6	Aluminium chloride	-

2.1. Multiple unit dosage form includes

2.1.1. Micro granules/spheroids

The drug was either wet granulated on its own or combined with inert granules, and then coated to regulate the release pattern.

2.1.2. Pellets:

Pellets are made by applying a film-forming polymer coating to inert medicament pellets. The polymer coating composition and coating quantity determine the release [10].

2.1.3. Microcapsules

Small solid particles, liquid droplets, and dispersions are coated with a comparatively thin layer to create microcapsules.

2.1.4. Beads

Microbeads are solid, free-flowing particulate carriers with nearly spherical, 0.5-1000µm diameter, and dispersed drug particles in crystalline or solution form. As the name implies, they allow for multiple release profiles of treatment with different active agents, either in solution or in a sustained release mode, all without causing significant side effects. [11] To ensure that therapeutic amounts are achieved at the target site, the beads can also incorporate drugs and continue to function normally under physiological settings. This helps to minimise side effects by maintaining low systemic concentrations. The cationic polymers, like chitosan, the anionic polymers, such sodium alginate, and the binding components, like gelatin, chondroitin sulphate, and avidin, are combined in a certain ratio to create the microbeads.

3. Techniques of Microbeads

3.1. Ionotropic Gelation Method

To begin cross-linking, an ionic polymer interacting with an oppositely charged ion is all that is required. The electro-neutrality principle cannot fully account for the interaction of polyanion with cations, in contrast to simple monomeric ions. The capacity of cations to conjugate with anionic functions or vice versa is influenced by the three-dimensional structure and the presence of other groups [12].

The ionotropic gelation technique has two sub-methods for producing beads. The cross-linking ion source varies throughout the approaches. One of the techniques places the crosslinker ion outside, whereas the other technique incorporates it inactively into the polymer solution. Two categories of ionortopic gelation methods exist:

3.2. External Gelation Method

As a source of the cross-linking ion in the external gelation process, a metal ion solution is employed. A needle is used to gently stir the drug-containing polymer solution before it is extruded into the mixture. Self-sustaining bead formation is the result of instantaneous gelation that takes place as soon as the polymeric drop comes into contact with the metal ion solution. Before being taken out and dried, the beads are cured for a predetermined amount of time in the gelation medium. The cross-linker ions diffuse quickly into the partially gelled beads, causing the external gelation to happen [13].

3.3. Internal Gelation Method

In the internal gelation process, the cross-linker ion is created "in situ." Using an insoluble metal salt (such calcium or barium carbonate) as a source of crosslinking cation is the technique used in this procedure. By decreasing the pH of the solution, the cation is liberated in situ along with the metal ion and the metal salt [14].

3.4. Emulsion Gelation Method [15]

Emulsion gelation procedures are another way to prepare microbeads. By dispersing the weighed amount of sodium alginate in deionized water, the sodium alginate solution was created. To obtain a homogenous drug-polymeric mixture, a precisely weighed quantity of drug was introduced to a polymeric solution of sodium alginate and the drug was magnetically agitated with low heat. A certain amount of cross-linking agent was added to create a viscous dispersion, which was then extruded into oil containing span 80 and 0.2% glacial acetic acid using a syringe fitted with a flat-tipped needle of size no. 23 while being stirred magnetically at 1500 rpm. To create stiff, distinct particles, the microbeads are left in the oil for thirty minutes. They were collected by decantation and the products thus separated was washed with chloroform to remove the traces of oil the microbeads were dried at 400ºC for 12 h.

3.5. Polyelectrolyte Complexation Method [16]

An additional technique for creating microbeads is the complex coacervation of polyelectrolytes with opposing charges, polycation and polyanion materials, and alginate-chitosan microcapsules that are biocompatible and biodegradable. These microcapsules can be produced in mild or even physiological conditions, making them appropriate for use in biomedical fields. The use of alginate–chitosan microcapsules as drug-delivery vehicles for proteins and polypeptides has drawn more attention in recent years. Using this technique, the mixture will split into a dilute equilibrium phase and a dense coacertive phase that contains the microbeads, depending on the pH, ionic strength, and polyion concentration. By spraying the sodium alginate solution into the chitosan solution, for instance, complicated coacervation between alginic acid and chitosan was accomplished, resulting in robust microbeads that remained stable over a wide pH range. The optimal yield when using coacervative beads requires preparation conditions of pH 3.9, ionic strength of 1 mM, and total polyion content of 0.15% w/v.

Table 2 Microbeads of Different Drugs, Different Polymers, Methods, and Importance

S. No	Type	Drug	Polymer	Method	Significance
1	Microbeads	Ibuprofen (Anti Inflammatory)	Sodium alginate	Ionotropic gelation method.	Higher drug entrapment and delayed release characteristics were demonstrated by prepared Rioprostil micro beads.
2	Microbeads	Theophylline (Respiratory system)	Chitosan and Sodium alginate	Ionotropic gelation method	Reduce the cross-linking time and the gel bead diameter.
3	Microbeads	Nifedipine (Anti-Anginal)	Sodium alginate and pectin	Ionotropic gelation method	The mean microbead particle size grew considerably as the concentration of pectin increased.
4	Microbeads	Norfloxacin (Antibacterial Drug)	Sodium alginate and pectin	Ionotropic gelation method	An increase in the sodium alginate % was associated with sustained release.
5	Microbeads	Zaltoprofen	Gellan-chitosan and calcium chloride	Ionotropic gelation method	Zaltoprofen-entrapped microbeads showed an improved drug delivery method for a prolonged release of medication.

4. Biodegradability of microbeads

When it comes to the creation of new materials, biodegradability—the process of breaking down plastic material via microbial technology—has emerged as a creative way to address the issue of disposing of plastic waste. Biodegradability is a problem with several state and local microbead bills and laws. Several state and local laws now in effect either don't define "biodegradable" precisely or permit the usage of biodegradable microbeads. In its bill 75, Ontario described microbeads as "nonbiodegradable solid particles measuring >1 mm in diameter which are used in soaps, cosmetics, and other similar products." These definitions allow producers to create another type of "biodegradable plastic" to replace artificial plastic microbeads. Additionally, research indicates that biodegradable microplastics may be just as hazardous to the environment as traditional microbeads, which presents another obstacle. In order to speed up deterioration, biodegradable plastics are typically composites of synthetic polymers with vegetable oils, starch, or other specialised compounds. They will break down in industrial composting facilities with adequate airflow if they are disposed of appropriately. Plastics can undergo photodegradation when exposed to sunlight for an extended length of time. UV radiation oxidises the polymer matrix, which breaks bonds. However, as a result of this degradation, the chemicals that are applied to the plastics to increase their durability and corrosion resistance may start to seep out of them [17-18].

5. Toxicology of microbeads

Possibility of bioaccumulation along the nutritional chain When swallowed, plastics can lead to internal bleeding, abrasions, ulcers, and obstructions in the digestive system in people. Heavy metals and persistent organic pollutants (POPs) are among the contaminants that plastic particles can carry. It has been demonstrated that the absorption of plastic slows down the biodegradation of pollutants, raising their environmental persistence. [19] Multiple non-native species can be carried by plastic waste, and they can get colonised by harmful bacteria. It follows that plastic waste can affect freshwater, marine, and terrestrial environments in a variety of ways, both ecologically and economically. A worldwide evaluation of the origin, destiny, and impacts of microplastics in the ocean was provided by GESAMP in its study. There are still a lot of unanswered questions that need to be answered even though their comprehension of the issue has increased. They have therefore made two sets of suggestions pertaining to policy. Recommendations to enhance future assessments and action-oriented suggestions to address marine microplastics are the first and second, respectively. Report and study No. 90 from GESAMP The polymer of acrylamide, polyacrylamide, one of the main components of microbeads, has been discovered to be a major cause of toxicity in laboratory animals. It is apparently present in 110 distinct cosmetic formulations at concentrations ranging from 0.05 to 2.8%. Polystyrene microbeads with diameters of 0.05, 0.5, and 6 μm have been found to have a genotoxic effect on the growth and fecundity of the copepod Trigriopus japonicus.[20] Acute and chronic toxicity tests have been used to examine the effects of acrylamide, which may not be absorbed through the skin, but has neurotoxic effects on both the central and peripheral nervous systems, possibly via microtubule disruption. When given phytoplankton, T. japonicus did not show any preferential feeding behaviour despite ingesting and egestion of all three sizes of microbeads. Polystyrene microbeads may negatively impact marine copepods, according to their findings. Additionally, zebra fish treated with polystyrene microplastics showed increased levels of catalase and superoxide dismutase, indicating that oxidative stress had been generated. Furthermore, it's been proposed that exposure to microplastics changed the metabolic profiles of fish liver. These results shed new light on the harmful consequences of microplastics on fish.

Due to the possibility of entanglement and severe ingestion, a number of further studies have demonstrated that microplastics present a health concern to birds and aquatic animals. Examining the harmful impacts of polystyrene microbead consumption in monogonont rotifers is being done. Significant size-dependent consequences were brought about by microplastic exposure, including slowed growth, shorter life spans, and longer reproductive times. These results indicated that the toxicity of microbeads was size dependent, meaning that the more tiny the microbead, the more harmful it was to the organisms. In a size-dependent manner, exposure to microplastics activated antioxidant-related enzymes and mitogen-activated protein kinase (MAPK) signalling pathways, suggesting severe forms of cellular shock to organisms [21].

6. Microbead extraction from the cosmetics [22-23]

5 g of cosmetic product was dissolved in 100 mL of warm water (450C) to extract microbeads. Five duplicate samples of each product were obtained using the same process. A cotton cloth was used to filter the microbeads. To be sure that every microparticle had been collected, the filtrate was then passed through a Whatman filter paper (ashless, grade 42, 2.5 mm pore size). For fourteen hours, the particles were dried at 370C in an Ecocell oven (MMM-group). After product A27 was discovered to contain a high amount of organic components, the organic matter was dissolved using Fenton reagent (FeSO4 ÷ H2O2) prior to filtering. In order to separate out additional organic components like parabens, the microbead-containing solids in A23 and A25 were extracted using organic solvents including ethyl acetate and

chloroform. When multiple types of microplastic were found in a product, the particles were manually sorted using a stereoscope model SZ2-ILST microscope. With A25, the blue and white microbeads were separated by flotation using solvents with varying densities (ethanol and CHCl3). Microbeads were present in just 28 of the 37 items. The 1 g product sample was treated with 1 mL of 30% (v/v) H2O2 and 0.5 mL of catalyst for the Fenton reagent treatment.The result was a pH 5 solution. Iron (II) sulphate heptahydrate (FeSO4. 7H2O) weighing 20 g in 1 litre of distilled water made up the catalyst solution. After allowing the sample and solution to react for about ten minutes at room temperature. Following filtration using a Whatman filter paper, the solution was then mixed with 10 mL of water. A 3-10 mL solution of distilled water was used to rinse the filter paper. Next, an Ecocell oven (MMM-group) was used to dry the filter paper containing the sample of beads at a temperature of 37.0°C.

7. Microparticles extracted from facial/body scrubs [24]

After filtering, the beads were cleaned with distilled water, dried, and their weight, size, and form were examined. An ABT 220-5DM electronic balance (detection limit: 0.01 mg) was used to weigh the beads. A stereoscope (Model SZ2-ILST) was used to obtain microphotos of the beads. For the purposes of the quantitative study and pictures, five replicate samples of each product were used. The size, shape, and Feret's diameter of the microphotos were examined using the Fiji Image J software. Microbead size was represented by the Feret's diameter. The longest distance along the bead boundary between any two sites is represented by the diameter of the Feret. To ascertain the makeup of the microbeads removed from each product, Fourier Transform Infrared (FT-IR) spectroscopy was performed using a Thermo Nicolet Nexus 670 FT-IR spectrometer. To determine the kind of polymer or other material present, the acquired spectra were compared using OMNIC 9 software.

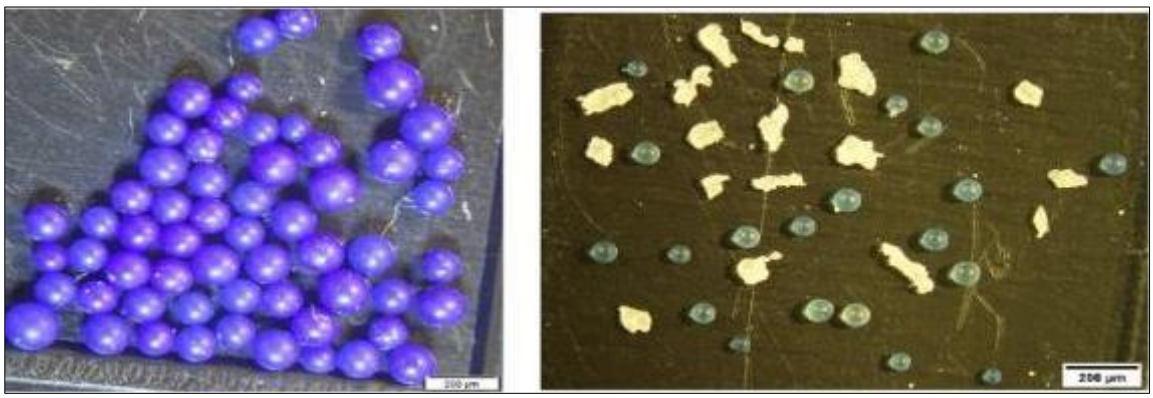

Figure 2 Microplastics isolated from products as they are viewed under a stereoscope

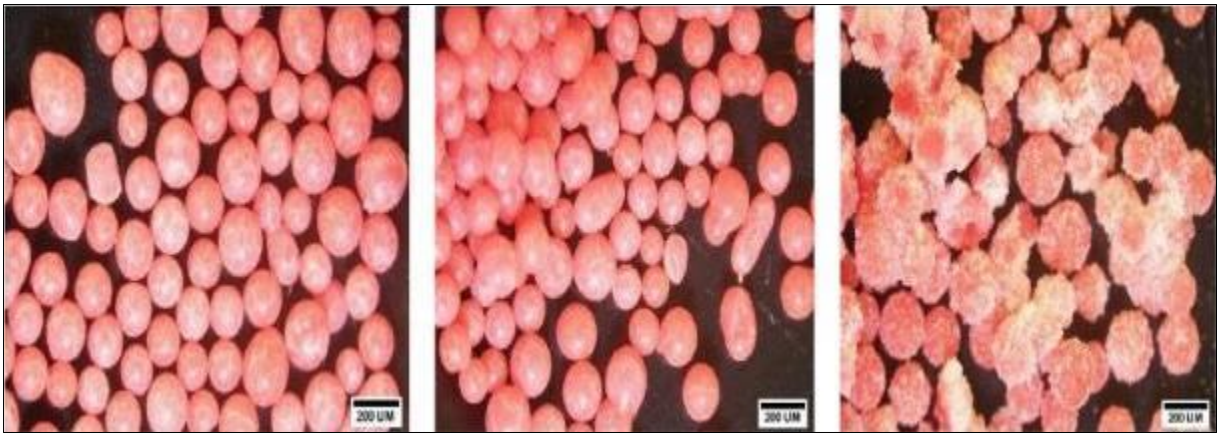

Figure 3 Microbeads of product (A16) heated at 60^0C, 80^0C and 100^0C

8. Thermal stability of extracted microbeads

Differential scanning calorimetry (DSC-60, Shimadzu) was used to examine the thermal stability behaviour of the microbeads in five products that contained microplastics (A16, A24, A2, A23, and A18). Although lower than 2000C is expected for phase transitions of the products, 5000C was set as the maximum heating temperature for the DSC tests. In order to test the microbeads' physical stability in the presence of a material that resembled soil, the microbeads extracted from products A16 and A23 were heated in an oven at three different temperatures (600C, 800C, and 1000C) on silica gel (Merck grade 9385) and on alginite (Terra Natural Resources). The microbeads' tendency to float in a water column was examined both before and after the heat treatment. To see if there were any surface abrasions, 300 mg of product A16 and product A23 microbeads in 15 mL Sterilin plastic centrifuge tubes were shaken for 24 hours (using an Incu-Shaker 10 L) at 21.50C and 178 rpm in both air and water (6 mL each) [25].

9. Conclusion

According to the current review article, microbeads are a more effective drug delivery mechanism than several other kinds. According to research, the preparation of microbeads using the ionotropic gelation approach improves bioavailability and lowers dose frequency, resulting in an oral controlled release of the medication. In the future, microbeads will play a key role in novel drug delivery by combining a number of other strategies. These include sorting diseased cells, diagnostics, gene & genetic materials, safe, targeted, specific, and effective in vivo delivery, and supplements that act as tiny replicas of the body's diseased organs and tissues.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of inter-est for this study.

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