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MICROBEADS – A REVIEW

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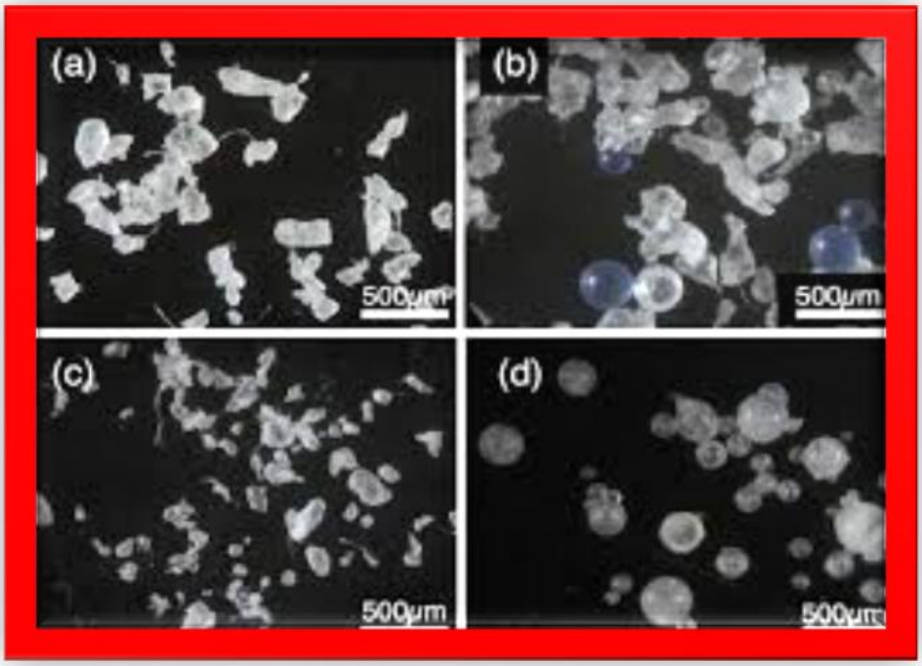
ABSTRACT
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired drug concentration. This could be achieved through multiparticulate dosage form like beads which are divided into many individual units, 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**.**

KEYWORDS: Microparticulate drug delivery, Microbeads, Preparative methods, Polymers used, Applications.

INTRODUCTION
Multiparticulate systems have been paid considerable attention since several years in controlling and sustaining of release rate of many active pharmaceutical ingredients. And use of natural biodegradable polymers as rate controlling agents also has been enormously increased. Recently, dosage forms that can precisely control the release rates and targets drugs to a specific body site have made enormous impact in the formulation and development of novel drug delivery systems. Oral multiunit dosage forms such as microcapsules and microspheres have received much attention as modified/ controlled drug delivery systems for the treatment of various diseases without major side effects. Additionally, the beads maintain functionality under physiological conditions, can incorporate drug 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. It will therefore be advantageous to have means for providing an intimate contact of the drug delivery system with microbeads. **(Jagadevappa S Patil *et al.*, 2014).** Microspheres are, in strict sense, spherical empty particles. However, the terms microcapsules and microspheres are often used synonymously. In addition, some related terms are used as well. For example, essentially "micro beads" and "beads" are used alternatively. **(Narasimha rao R *et al.*, 2013)**

Definition
Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. **(Abdul Hasan Sathali *et al.*, 2012)**

Additionally, the beads maintain functionality under physiological conditions, can incorporate drug 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. It will therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling the bioadhesive characteristics to microbeads and develop bioadhesive microbeads. Therapeutic molecules complexed by polymers capable of forming a gel may also released by diffusion hence, drug delivery system by a polymeric matrix that is non – toxic, biocompatible and biodegradable. **(Bathula Bharathi *et al.*, 2014)**



They release the active ingredients through a double mechanism: diffusion and/or biodegradation of the polymer. The cross-linked microbeads, depending on the biodegradability and biocompatibility, can be administered as long lasting medications. The use of coating substances which can dissolve either in different areas of the gastrointestinal tract (depending on pH and/or the enzymes present) or after a preset time (depending on the thickness) allows coated microbeads to be used both in a space-and-time focussed manner. **(Koranappalli S. Aswathy *et al*., 2014)**

To obtain maximum efficacy and minimum side effects it is necessary to deliver the drugs to target site in optimal amount and for required time period. Improved drug stability, optimal duration of therapeutic effect, flexibility of administration via different routes with minimum drug metabolism/degradation are some of the attributes of sustained release drug delivery system. **(Sumbul Qamar *et al*., 2014).** Alginate beads are stable in acidic media and easily depredated in alkaline media. **(Mohammad abu taher rasel *et al*., 2012)**

Polymers used (Bathula bharathi *et al*., 2014)

- **Sodium alginate**

Sodium alginate is salt of alginic acid and it is a linear polymer of $\beta^{[1-4]}$ mannuronic acid and gluccouronic acid residues in varying proportions and arrangements, bio-compatible, non-toxic, natural polysaccharide found in all species of brown algae. Alginate beads advantages are non toxic orally, high biocompatibility, inability to re-swell in acidic environment and easily re-swell in an alkaline environment there by protecting the acid sensitive drugs from gastric environment. The higher sodium alginate concentration improves the gelling capacity and lower sodium alginate concentration sustain the drug release for an extended period.

- **Chitosan**

Chitosan, obtained by alkaline deacetylation of chitin. Chitosan is non toxic, biodegradable, natural, linear polymer resembling the structure of cellulose. The more effective beads for drug delivery can be formed by using combination of both alginate and chitosan. Chitosan because of its anti-ulcer and antacid properties decreases stomach irriatation.

- **Carboxymethylcellulose**

Cellulose is a plant product in these product on carboxy methylation process it can be modified as carboxy methyl cellulose. The carboxy methyl cellulose can be cross linked with aluminium salt to get bio degradable hydrogel beads. Prepared from cellulose by treatment with alkali and monochloro-acetic acid or its sodium salt thickening agent, stabilizer, suspending agent.

- **Gellan**

Gellan gum as an excellent flavor release, stability and high gel strength, process flexibility and thermo reversible capacity obtained from fermented *Sphingomones Eloda*. The chain undergoes arrangement and rearrangement when temperature changes occurs, resulting in a conformational change in structure and entrap the drug.

- **Pectin**

Pectin is a non toxic polysaccharide extracted from citrus peel and it has been used as a thickening & gelling agent.Pectin has been used as an adsorbent and bulk forming agent, and is present in multi-ingredient

preparations for the management of diarrhoea, constipation, and obesity Pectin gel beads have been shown to be an effective medium for controlling the release of a drug within the gastrointestinal (GI) tract Pectin occurs as a coarse or fine, yellowish white, odorless powder that has a mucilaginous taste.

➢ **Karaya gum**

It is a hydrophilic naturally occur- ring gum obtained from Sterculia urens and com- posed of galactose, rhamnose and glucuronic acid. It swells in water and thus used as release rate controlling polymer in different formulations. It possessed very low hydration capacity and higher erosion. When release studies were investigated, karaya gum was found to produce zero order drug release along with erosion of matrices.

Karaya gum to develop gastric floating drug delivery system of verapamil hydrochloride and studied its effect on drug release. It was observed that it swells on contact with aqueous medium and at a specific concentration of 23.3% produced sustained drug release for 8 h.

➢ **Xanthan gum**

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent.[3–5] It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablet Controlled release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area. Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum is also used as a hydrocolloid in the food industry,and in cosmetics.

➢ **Hydroxy propyl methyl cellulose**

HPMC E3 (Hydroxy Propyl Methyl Cellulose) is a semi synthetic, inert viscoelastic polymer. As well as an excipient and controlled delivery component in oral medicaments.

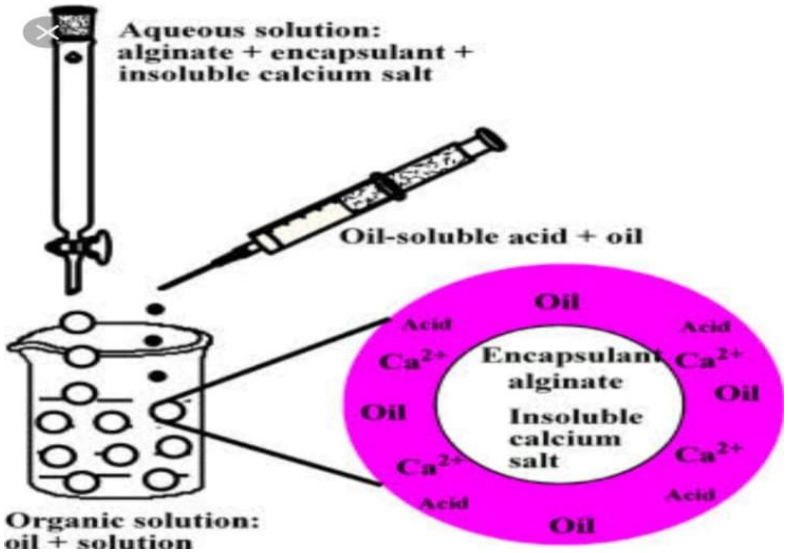
➢ **Carbopol**

Most carbopol polymers are high molecular weight acrylic acid chain usually cross linked, and are available as powder or liquid and it is also used to thickening agent, stabilizer, suspend, and control the release of pharmaceutical products.

Formulation techniques of hydrogel beads

- **Ionotropic gelation**

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Ionotropic gelation technique has been widely used for the encapsulation of drug and also cells. Inspite of having a property of coating on the drug core and release rate retardants, the natural polyelectrolytes also contain certain anions on their chemical structure. These anions form meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuse into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically cross-linked moiety. Biomolecules can also be loaded into these hydrogel beads under mild conditions to retain their three dimensional structure.



A gel, in classical colloid terminology, is defined as a system which owes its characteristic properties to a cross – linked network of polymeric chains which form at the gel point. **(Arun raj R *et al*.,2013)**

Developed suitable microparticulate system of Flurbiprofen for controlled release delivery by varying the alginate, $CaCl_2$ and HPMC concentrations. The drug loaded beads showed 83.6 – 98.2 % drug entrapment, which was found to increase with increase in sodium alginate concentration. *In vitro* drug release study of these microbeads indicated controlled release for Flurbiprofen upto 84.54 – 97.74 % release at the end of 10 hrs. They concluded that the spherical and free flowing microbeads of Flurbiprofen could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics. **Manjanna K M *et al*.2009**, prepared Diclofenac microbeads by ionotropic gelation method using sodium alginate as the hydrophilic carrier in combination with HPMC, chitosan and pectin polymers in various proportions as drug release modifiers to overcome the drug related adverse effects and to improve drug bioavailability in different GI conditions. All investigated properties showed satisfactory results.

- **Polyelectrolyte complexation**

The quality of hydrogel beads prepared by ionotropic gelation method can also be further improved by polyelectrolyte complexation technique. The mechanical strength and permeability barrier of hydrogels can be improved by the addition of oppositely charged another polyelectrolyte to the ionotropically gelated hydrogel beads. For instance, addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate beads Depending on the intended particle size, the hydrogel beads are generally formulated.

- **Syringe Dropping/Extruding method**

The hydrogel beads can be produced widely by dropping an aqueous solution of polyanion solution into a solution of cation usually calcium chloride. Although this is a simple and fast way of obtaining particulate drug carriers, the method presents a major limitation of drug loss during formulation. The matrix formed is usually very permeable and little or no drug release can actually be controlled in the core of soluble drugs. Hence, a preferential use for these hydrogel beads in the delivery of low solubility or micromolecular drugs has been suggested. This problem can also be solved by mixing with other polyelectrolytes such as alginate-pectin, alginate-chitosan, alginate-ethyl cellulose, and alginate-Eudragit. However, this technique may either cause a high degree of particle aggregation or involve the use of methanol as a solvent.

- **Air atomization method**

Beads can also be prepared by vibration system or air atomization method. Relatively smaller droplets can be formed using a vibration system or air atomization method to extrude the polyanion solution. The later involves a Turbotak air-atomizer in which pressurized air is fed to mix with the polyanion solution, and thereby forcing tiny liquid droplets out through the orifice of the nozzle. The cations cross-link the droplets of polyanions on contact to form microgel droplets which were further cross-linked by polyelectrolytes such as poly-L-lysine to form a membrane on the droplets. Microparticles obtained using this method were within the size range of 5-15 µm. This method requires special extrusion device or atomization device that can have the disadvantage of the high cost and possible clogging.

- **Novel techniques**

➢ **Emulsion gelation method [incorporation of oil]**

A new emulsion gelation technique was developed to prepare emulsion gel beads. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing polymer which was then extruded in to calcium chloride solution. The factors like concentration of oil, curing time, curing agent and drug: polymer ratio influence drug entrapment efficiency, floating lag time, morphology and drug release. In this technique, polymer was dissolved in water with stirring, oil was added to polymer solution with continued stirring to form an emulsion to which the drug was added. This homogenized mixture was extruded into calcium chloride solution with gentle agitation at room temperature. The formed beads were filtered, washed and dried.

Prepared alginate based mineral oil entrapped emulsion gel (MOEG) buoyant beads of Domperidone by emulsion gelation technique. They studied effect of different oils (castor oil, olive oil and linseed oil) and oil concentrations (10%, 15% and 20%, w/w) on uniformity, homogeneity and integrity of the beads. The results of the *in vitro* drug release indicated that linseed oil showed to be good release retardant, exhibited maximum buoyancy and minimal oil leakage compared to castor oil and olive oil. prepared Tinidazole loaded Oil entrapped floating beads by emulsion gelation method and optimized for polymer: cross linking agent ratio (sodium alginate/ Calcium chloride),oil selection (olive oil and castor oil), oil concentrations (10%, 20% and 30% w/w) and drug: polymer (D: P) ratios (1:1, 2:1 and 3:1). Developed a multi-unit gastroretentive sustained release dosage form of a water soluble drug, Verapamil hydrochloride, thus releasing the drug for a prolonged duration of time using emulsion gelation technique.

➢ **Incorporation of both oils and waxes**

Various amounts of different waxes (viz. polyethylene glycol, glyceryl monostearate, white wax, carnauba wax, spermaceti wax and stearyl alcohol) were melted in water depending on the melting ranges of the waxes used. The molten wax was dispersed in the homogenized emulsion mixture of polymer, oil and drug which is already heated to same temperature, and then mixed until

the homogenous mixture was obtained. The hot melted mixture was extruded into calcium chloride (cooled at 5°C).[44]

➢ **Impinging technology**

Alginate gel encapsulation methods have been proven to be promising for the protection of immobilized biological materials and controlled delivery of drugs. However, existing techniques to produce discrete alginate gel particles have limitations, which can result in the production of macro particles, whose use is restricted by obvious sensory detection during their consumption in food products. Other techniques to produce micron size beads are normally successful only on a laboratory scale or non-continuous operations. In addition, some of the techniques (such as the emulsion method) require solvent or oil to produce micron size alginate gel particles. To overcome, these limitations a novel impinging aerosols technique was developed. This involved the application of continuous process for producing micron sized beads without the use of any heat or solvents. This technique possesses high scale-up potential directions in a chamber. The atomised alginate solution gel droplets as soon as they come in contact with calcium chloride aerosols fall to the bottom of the chamber from where the microbeads are collected. Actives may be mixed with the alginate solution prior to atomisation or aerosol formation. Alginate microbeads (10-40 µm) containing the probiotics were produced and compared with extruded macrobeads (approximately 2 mm in diameter) produced by the conventional method. Microbeads produced by the novel aerosols technique offered comparable protection in high acid and bile environments.

Evaluation of alginate beads

❖ **Appearance**

The general appearance and elegance of the beads are identified visually, which include analyzing the beads size, shape, colour, presence or absence of odour, surface texture etc., **(Behin sundararaj *et al.*, 2012)**

❖ **Particle size measurement**

- ***Optical microscopy***

To determine bead size, 100 dry beads from each batch are measured using an optical microscope with an ocular micrometer which was calibrated using a stage micrometer. (**Inthakab Alam *et al.*, 2010)**

- ***Scanning electron microscopy***

Particle size and surface morphology of beads are determined by scanning electron microscopy (SEM), Model Quanta FEI 200F. The dried beads are coated with gold foil (100 A°) under an argon atmosphere in a gold coating unit and micrographs are obtained at both higher and lower resolutions. **(Anup Singh *et al* ., 2014)**

❖ **Disintegration of beads**

Disintegration of beads in SIF (Suitable buffer solution) is studied at different intervals of time. Beads (10mg) are preincubated with 10ml of SGF with and without pepsin for 4hours at 37° C in an incubator with 100rpm shaking. After filtering, swollen beads are transferred to another vial, containing 10ml of SIF with or without pancreatin. The samples are incubated at 37° C at 100 rpm in a shaking incubator. The physical appearance of the beads and their fragments during incubation was observed through a microscope. The time of complete disintegration was registered. All experiments are done in quadruplet. **(Anal A K & Stevens W F *et al* ., 2005)**

❖ **Buoyancy behaviour**

The time between the introduction of floating beads into the medium and its buoyancy to the upper one third of the dissolution vessel (Floating lag time) and the floating ability is determined using USP dissolution tester apparatus II (Paddle method). Fifty beads are put in the vessel and the paddles are rotated at 50 rpm in 900ml of dissolution medium maintained at 37±0.5° C for 12hours. The preparation was considerd to have a buoyancy, only when all beads floated on the test solution immediately or within a lag time. **(Venkatesh Gavini *et al* ., 2014)**

❖ **Loose surface crystal study**

It is conducted to estimate the amount of drug present on the surface of the microbeads which showed immediate release in dissolution media. 100 mg of microbeads are suspended in 100ml of buffer solution simulating the dissolution media. The samples are shaken vigorously for 15 minutes in a mechanical shaker. The amount of drug leached out from the surface can be analysed spectrophotometrically. Percentage of drug released with respect to entrapped drug in the sample is recorded. **(Thulasi V Menon *et al.*, 2013)**

❖ **GI residence time studies**

Gastro intestinal residence time associated with the administration of mucoadhesive microbeads containing Barium sulphate (Free from drug) is determined with X-ray photography. **(Tejakrishna M *et al*., 2013)**

❖ **Entrapment efficiency**

It is calculated to determine the ability of microbeads to entrap the drug. Accurately weighed drug loaded microbeads are crushed in a glass mortar and pestle and mixed with suitable buffer solution and kept for 24 hours. Then, it is filtered and the filtrate is suitably diluted and analysed by spectrophotometric methods.

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

(Koranappalli S Aswathy *et al.*,2014)

❖ **Evaluation of swelling behavior**

Swelling behavior can be studied by measuring the % water uptake by the beads. About 100mg of the beads are accurately weighed and placed in 100 ml of buffer medium. Beads are removed from their respective media after 8 hours and weighed after drying the surface water using filter paper. The water uptake is calculated as the

ratio of the increase in weight of beads after swelling to the dry weight. **(Intakhab M Alam *et al* ., 2010)**

❖ ***In vitro* release studies**

In vitro release of beads can be determined by using USP type I apparatus (Basket method). The dissolution test is performed using 900 ml of suitable buffer solution at 37±0.5° C at 100rpm. A 5ml of sample is withdrawn from the dissolution apparatus at different time intervals. The sample solution is replaced with the same ml of appropriate buffer. Absorbances of the samples are measured by using spectrophotometric methods and cumulative % drug release is calculated. **(Anup Singh *et al*., 2014).**

Applications of microbeads

- NSAID like Diclofenac micro-beads, it show reduced release in the stomach. It reduces the adverse effects and avoids direct contact between the drug and the gastric mucosa.
- The micro-beads loaded with the antibiotics (like Oxytetracycline) is useful for the oral administered for the treatment of gastric and intestinal disease.
- Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an Antiretroviral regimen for the treatment of HIV infection and it formulated in the alginate beads so that their controlled release can be obtained for the prolonged therapeutic effect.
- Ranitidine, peptic ulcer drug, it designed in micro-bead form in such a way that it will be retained in stomach for sufficient time. So, it could open new treatment of gastric ulcer and acidity.
- Sustained release of Prednisolone from chitosan gel beads, and it increses the therapeutic efficacy and decreases side effects by minimizing the reaching of the drug to the systemic circulation against inflammation.
- Theophylline, a poorly water soluble bronchodilator and the targeted drug for controlled delivery, and reduces drug release under physiologically simulated pH conditions (acidic and neutral) So, it could be formulated into modified dosage form.
- 5-Fluorouracil encapsulated alginate micro-beads for the treatment of breast cancer can be formulated in the alginate beads so that their controlled release can be obtained for the prolonged therapeutic effect.
- Metformine Hydrochloride, an antidiabetic drug, using albumin are degraded in to acidic medium when it given orally. Formulating them in the modified alginate micro- beads can deliver them in to intestinal region without degradation in the stomach region.
- Insulin, an antidiabetic drug, formulating them in the modified alginate beads can directy delivers them in the intestinal region without drug degradation in the stomach.
- Piperine was fabricated into alginate beads using sodium alginate. To achieve sustained release of profile studies were showed that the alginate beads sustained the release.
- Rifampicin, first line drug used to treat tuberculosis, formulated as alginate beads to control and prolong its release profile.
- Salbutamol sulphate is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma, so their therapeutic effect is enhanced by the use of the sodium alginate interpenetrating network beads.
- Development of calcium alginate–gelatin based microspheres for controlled release of Endosulfan act as a model pesticide. **(Ritesh Kumar Tiwari *et al*.,2013)**

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