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REVIEW ARTICLE

Floating Microsphere: A Novel Approach Used to Develop Gastroretentive Drug Delivery System

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. The range of Techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs also known as microparticles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest.

Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS

Microspheres, Controlled Release, Therapeutic Efficacy, Novel Drug Delivery

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they releases the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time.

However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry.

As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed.[1]

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Advantages[2]

a) Microspheres provide constant and prolonged therapeutic effect.

b) Reduces the dosing frequency and thereby improve the patient compliance.

c) They could be injected into the body due to the spherical shape and smaller size.

d) Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

e) Microsphere morphology allows a controllable variability in degradation and drug release.

Limitation[2]

a. Some of the disadvantages were found to be as follows:

   The modified release from the formulations.

b. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.

c. Differences in the release rate from one dose to another.

d. Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.

e. Dosage forms of this kind should not be crushed or chewed.

Types of Microspheres

Bioadhesive Microspheres: Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bioadhesion. The term "bioadhesion" describes materials that bind to biological substrates', such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.[3]

Magnetic Microspheres*[4]*: This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Diagnostic microspheres. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. The accumulation of the carrier at the target site allow them to deliver the drug locally.

Floating Microspheres*[5]*: In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form.

Radioactive Microspheres*[6]*: Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped

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in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Mucoadhesive Microspheres*[7]*: Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

Polymeric Microspheres*[8]*: The different types of polymeric microspheres can be classified as

***a. Biodegradable Polymeric Microspheres*:** Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

***b. Synthetic Polymeric Microspheres*:** The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Polymer used in microsphere[9]

Polymers used in the microsphere are generally classified into two types:

a. Synthetic polymers

b. Natural polymers

Table 1: Classification of Polymer

Polymer	Sub Types	Examples
Synthetic polymer	Biodegradable	Lactides, Glycolides & their co polymers Poly alkyl cyano acrylates Poly anhydrides
	Non–biodegradable	Poly methyl methacrylate Acrolein Glycidyl methacrylate Epoxy polymers
Natural polymer	Proteins	Albumin Gelatin Collagen
	Carbohydrates	Agarose Chitosan Starch
	Chemically modified Carbohydrates	Poly dextran, Poly starch

Table 2: Various types of polymers and their application[10-12]

Polymer	Mechanism
Modified starch, HPMC, Carbopol 974P	Slower release of drug.
Ethyl Cellulose	Controlled release for longer period of time
PLGA, Chitosan	Vaccine delivery
Chitosan coated PLGA microspheres	Targeted drug delivery
Polyvinylalcohol, Polyacrylamide	Adsorption of harmful substances in blood

Mechanism behind Floating of Microspheres[13]

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, Eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and floating granules are the recent developments.

Method of Preparation

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by microencapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release, method of cross linking, evaporation time and co-precipitation, etc. The various methods of preparations are:

A. Emulsion Solvent Evaporation Technique.
B. Emulsion Cross Linking Technique.
C. Emulsion-Solvent Diffusion Technique.
D. Emulsification Heat Stabilizing Technique.
E. Co-acervation Phase Separation Technique.
    a. Thermal Change.
    b. Non-Solvent Addition.
    c. Polymer Addition.
    d. Salt Addition.
    e. Polymer-Polymer Interaction.
F. Spray Drying Technique.
    a. Polymerization Technique.
    b. Normal polymerization.
    c. Interfacial polymerization.
G. Ionic Gelation Technique.
H. Hydroxyl Appetite (HAP) Microspheres in Sphere Morphology.
I. Hot Melt Micro encapsulation technique.

Emulsion Solvent Evaporation Technique[14]

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with de-mineralised water and desiccated at room temperature for 24 hrs.

Emulsion Cross Linking Method[15]

In this method drug was dissolved in aqueous gelation solution which was previously heated for 1 hr at 400c. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35^0c, results in w/o emulsion then further stirring is done for 10 min at 15^0c. Thus the produced microspheres were

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washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 37^0c for 10 min to block un reacted glutaraldehyde. Examples for this technique is Gelatin A microspheres.

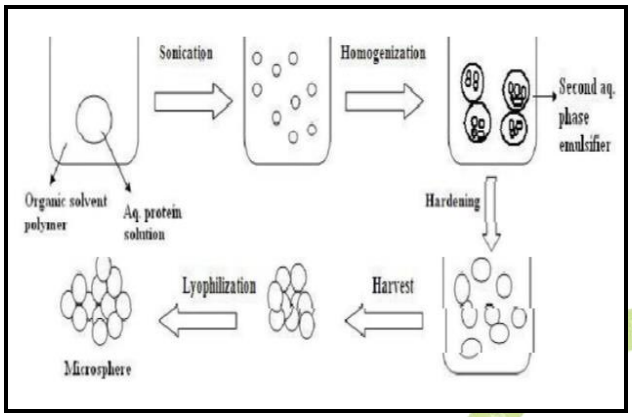

Figure 1: Solvent evaporation method for preparation of microsphere

Emulsion-Solvent Diffusion Technique[16]

In order to improve the residence time in colon floating microparticles of drug is prepared by emulsion solvent diffusion technique. The drug polymer mixture is dissolved in a mixture of ethanol and dichloromethane (1:1) then the mixture is added drop wise to sodium lauryl sulphate (SLS) solution. The solution is stirred with propeller type agitator at room temperature at 150 rpm for 1 hr, washed and dried in a desiccator at room temperature.

Emulsification Heat Stabilizing Technique[17]

In this method, drug and polymer are dissolved in 20 ml of deionised water and 5 ml of egg albumin solution and 0.1% of Tween 80 are added stirred it for 30 min. The prepared solution is used as aqueous phase. The oil phase is prepared by mixing 20 ml of sunflower oil and 5ml of diethyl ether with 1% span 80 (as emulsifier) and stirred it for 20 mins at 800-1000 rpm on a magnetic stirrer. The primary emulsion is prepared by adding the oil phase drop wise to the aqueous phase followed by stirring it for 30 mins at 800-1000 rpm. The prepared primary emulsion is added to preheated (65 to 70^0c) sunflower oil (80 ml) by using 21 No. needle and stirred at 1000-1200 rpm for 2 hrs till the solidification of microspheres takes place. The suspension then allowed to cool to room temperature with continuous stirring using a magnetic stirrer. On cooling, 100 ml of anhydrous ether is added. The suspension containing the microspheres is centrifuged for 15 mins and the settled microspheres are washed three times with ether to remove traces of oil on microspheres surfaces. The obtained microspheres are then vacuum dried in a desiccator overnight and stored at 4^0c in dark.

Co-acervation Phase Separation Technique[18]

a) Thermal Change: Microspheres are formed by dissolving polymer (ethyl cellulose) in cyclohexane with vigorous stirring at 80^0c by heating. Then the drug is finely pulverized and added to the above solution with vigorous stirring. The phase separation is brought about by reducing temperature using ice bath. The product is washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

b) Non Solvent Addition: Microspheres are formed by dissolving polymer (ethyl cellulose) in toluene containing propyl-isobutylene in a closed beaker with stirring for 6 hrs. at 500 rpm and the drug is dispersed in it. Stirring is continued for 15 mins., then phase separation is brought about by petroleum benzene with continuous stirring. The microcapsules washed with n-hexane and air dried for 2 hrs, and kept in an oven at 50^0c for 4 hrs.

c) Polymer Addition*:* Microspheres are formed by dissolving polymer (ethyl cellulose) is dissolved in toluene, then1 part is added to 4 parts of crystalline methylene blue hydrochloride. Co-acervation is accomplished by adding liquid polybuta-diene. Then the polymer coating is solidified by adding a nonsolvent (hexane). The resulting product is washed and air dried.

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d) Salt Addition: Microspheres are formed by dissolving oil soluble vitamin in corn oil and is emulsified by using pig skin gelatin under condition of temperature 50^0c, coacervation is induced by adding sodium sulphate. Stirring is necessary for uniform coating of gelatin. The resultant microspheres product is collected and washed with water, chilled below gelation temperature of gelatin and dried by using spray drying.

e) Polymer-Polymer Interaction: In this process, aqueous solution of gum Arabica and gelatin (isoelectic point 8.9) are prepared, the homogeneous polymer solutions are mixed together in equal amount, diluted to about twice their volume with water, adjusted to pH 4.5 and warmed to 40- 45^0c. The oppositely charged macromolecules interact at these conditions and undergo co-acervation. While maintaining the warm temperature, the liquid core material (methyl salicylate) is added to polymer solution and stirred well. Then the mixture is cooled to 25^0c and coating is rigidised by cooling the mixture to 10^0c.

Spray Drying Technique[19]

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystallinity due to fast drying process.

Polymerization Techniques[20]

Mainly two techniques are used for the preparation of microsphere by polymerization technique:

(a) Normal Polymerization: Normal polymerization classified as:

a) Bulk polymerization

b) Suspension/ pearl polymerization

c) Emulsion polymerization

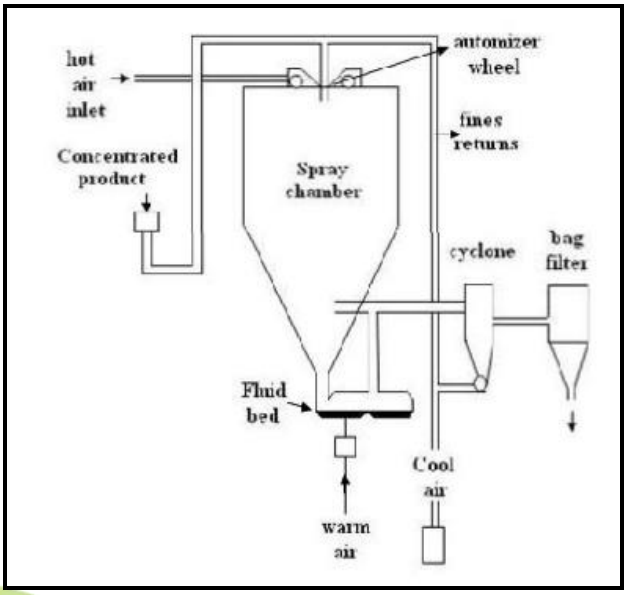

Figure 2: Spray drying method for preparation of microsphere

In bulk polymerization a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients.

Suspension polymerization is carried out at lower temperature and also referred to as pearl polymerization in which the monomer mixture is heated with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less the 100 μm.

Emulsion polymerization differs from the suspension polymerization due to presence of initiator in aqueous phase and also carried out at low temperature as suspension. External phase normally water in last two techniques so through which heat can be easily dissipated. The formation of higher polymer at faster rate is possible by these techniques but sometimes

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association of polymer with the un- reacted monomer and other additives can occur.

(b) Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolved in continuous phase while other is dispersed in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of the solubility of formed polymer in the emulsion droplet. The formation is Monolithic, if the polymer is soluble in droplet and the formation is Capsular type if the polymer is insoluble in droplet.

Ionic Gelation[21]

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

Hydroxyl Appetite (HAP) Microspheres in Sphere Morphology[22]

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

Hot Melt Microencapsulation Technique[23]

The polymer is first melted and then mixed with solid particles of the drug that has been sieved to less than 50 µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, *e.g.* polyanhydrides. Microspheres with diameter of 1-1000 µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

Table 3: List of drugs which are given as microspheres[24]

S. No	Drug	Polymer	Category
1.	Metformin HCl	Sodium alginate	Antidiabetic
2.	Amoxicillin Trihydrate	Ethyl Cellulose	Antibiotic
3.	Ibuprofen	Sodium alginate	Analgesic
4.	Pioglitazone HCl	Carbopol 934	Antidiabetic
5.	Trimetazidine HCl	Chitosan	Antianginal
6.	Furosemide	Sodium alginate Carbopol	Diuretic

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7.	Insulin	Sodium alginate, Chitosan	Antidiabetic
8.	Furazolidin	Eudragit RS100, Carbopol 974P, HPMC	Antiulcer
9.	Aceclofenac	Sodium alginate HPMC, Chitosan, Carbopol.	Analgesic
10.	Acyclovir	Sodium alginate	Antiviral
11.	Atenolol Propranolol	Polyacrylic acid, Polyvinyl pyrrolidine	1 Blockers
12.	Rantidine HCl	Sodium alginate	Antacid
13.	Glipizide	Chitosan	Oral Hypo-glycemic
14.	Captopril	Sodium alginate, HPMC, Chitosan, Carbopol 934P, Cellulose acetate phthalate	ACE Inhibitor
15.	Ketoprofen	Sodium alginate, Chitosan, Pectin, Xanthum gum	Analgesic
16.	Salbutamol Sulphate	Carbopol, HPMC	Bronchodilator
17.	Torsemide	Sodium alginate , HPMC	Diuretic
18.	Ketorolac	Eudragit RS100, Eudragit RL100	Antiinflammatory and Analgesic
19.	Acetazolamide	Eudragit RS, Eudragit RL	Diuretic
20.	Metronidazole	Guargum, Sodium alginate	Antiamoebic
21.	Famotidine	Sodium CMC, Sodium alginate	Antiulcer
22.	Monteleukast Sodium	HPMC, Eudragit, Carbopol	Antiallergic
23.	Salbutamol Sulphate	HPMC, Carbopol	Broncho-dilator

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Table 4: Floating Microspheres with their achievements

Researcher	Drug	Method	Polymer	Achievements
Punitha et al.[25]	Ranitidine hydrochloride	Solvent Evaporation	HPMC K15M, Eudragit E 100	The present novel drug – floating microsphere approach for ranitidine HCl proposed that with both acrylic and hydrophilic polymers the GI retention can be enhanced
Srivastava et al.[26]	Cimetidine	Solvent Evaporation	HPMC, ethyl Cellulose	In vitro studies demonstrated diffusion controlled drug release from microspheres.
Tanwar et al.[27]	Verapamil hydrochloride	Diffusion evaporation	Cellulose acetate, Acrycoat S100, Eudragit S100	The prepared microspheres exhibited prolonged drug release and remained buoyant for more than 12 h.
Karthikeyan et al.[28]	Cefpodoxime proxetil	Solvent evaporation	HPMC K4M, ethyl cellulose	The floating microspheres showed better result and it may be useful for prolong the drug release in stomach and improve the bioavailability.
Gattani et al.[29]	Aceclofenac	Solventevaporation	Eudragit RS	The prepared microspheres exhibited prolonged drug release (>12hr) and remained buoyant.
Garg et al.[30]	Silymarin	Emulsion solvent Evaporation	HPMC, ethyl cellulose (EC) ,Eudragit® S 100 (ES), Eudragit® RL	The microspheres exhibited prolonged drug release for 12 h while still remained buoyant.

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Najmuddin et al.[31]	Ketoprofen	Emulsion solvent diffusion	Eudragit S 100, Eudragit L 1	Floating microspheres of ketoprofen are promising for sustained drug delivery which can reduce dosing frequency.
Patel et al.[32]	Glipizide	Emulsification phase separation	Chitosan	The drug release was sustained for more than 12 h. *In-vivo* testing of the mucoadhesive microspheres to Albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.
Naggar et al.[33]	Ketoprofen	Emulsion solvent diffusion	Eudragit S100 (ES), Eudragit RL (ERL).	The formulation containing ES:ERL (1:1) exhibited high percentage of floating particles in all examined media
Barhate et al.[34]	Ketorolac trometamol	Emulsion solvent diffusion	Ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100	The optimized formulation shows good buoyancy and *in vitro* controlled release of ketorolac trometamol.
Yasunori et al.[35]	Aspirin, Salicylic acid, ethoxybenzamide, indomethacin, riboflavin	Emulsion solvent diffusion	Enteric acrylic Polymers	The release properties of five different drugs exhibiting distinct water solubilities (aspirin, salicylic acid, ethoxybenzamide, indomethacin, riboflavin entrapped within microballoons were investigated.

Factors to be considered during Formulation[36]

Addition of Polymer Solution

As reported that, the high surface tension of water caused the solidification and aggregation of polymer on the surface of aqueous phase. To minimize the contact of polymer solution with the air-water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of

water. This method improved the yield of microspheres and reduced the extent of aggregate formation. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase. The microspheres, which overflow from the top of the vessel, can be collected in a container with an appropriate sieve size at the bottom.

Effect of Rotation Speed

It is obvious that the rotation speed of propeller affects yield and size distribution of microspheres. As the rotation speed of propeller is increased, the average particle size decreases, while maintaining its morphology.

Effect of Temperature

The temperature of the dispersing medium is an important factor in the formation of microspheres as it controls the evaporation rate of the solvents. At lower temperature (10ºC), prepared microsphere has crushed and irregularly shaped morphology. The shell of the microsphere turns translucent during the process, due to the slower diffusion rate of ethanol and dichloromethane. At higher temperatures (40ºC), the shell of the microsphere becomes thin and it might be due to faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium.

Characterization of Floating Microspheres

Percentage Yield[37]

The percentage yield of the floating microspheres was determined for drug and was calculated using the following equation

% Yield = (Actual weight of product / Total Weight of excipient and drug) × 100

Particle Size[38]

Calibrate the eye piece micrometer and transfer the floating microspheres on clean slide. Add one or two drops of liquid paraffin. Disperse the sample uniformly with the help of a brush. Place the cover slip to avoid entrapment of air bubbles. Drain the excess liquid with a blotting paper. Place the slide on the stage of the microscope. Focus the slide in low magnification (10X). Observe the presence of individual particle. Shift to high power (45X) and focus the slide. Measure the size of each particle in terms of eye-piece divisions. Tabulate the particle in terms of divisions of eye-piece and number of particles. Multiply the number of eye-piece divisions by the calibrated value. Classify the diameters into size ranges and calculate the number of distribution.

Bulk Density[40]

It is the ratio of mass of the blend to bulk volume. It was measured by pouring powder in measuring cylinder and measuring the volume occupied by powder.

Tapped Density[41]

It is the ratio of mass of the blend to tapped volume. It was measured by digital tap densitometer by measuring the volume occupied by powder after 100 standard tapping.

Carr's (compressibility) Index[41]

Compressibility index (C.I.) or Carr's index value of micro particles was computed according to the following equation

% compressibility = Tapped density – Bulk density / Tapped density X 100

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Hausner's Ratio[41]

Hausner's ratio of microspheres was determined by comparing tapped density to bulk density

Using equation

$$\text{Hausners ratio} = \frac{\text{Bulk density}}{\text{Tapped density}}$$

Values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr).

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Angle of Repose[41]

Angle of repose (q) of the microspheres was measured using funnel method. The microspheres were poured through a funnel that can be raised vertically until a maximum cone of height was obtained. The radius of heap was measured and angle of repose was calculated.

$$\tan \theta = h/r$$

Where, θ = Angle of repose,

h = Height of granules above the flat surface,

r = radius of the circle formed by the granule heap.

Scanning Electron Microscopy[42]

Dry microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then picture of microsphere were taken by spectra random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV.

IR Spectroscopy[43]

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure metformin hydrochloride, Eudragit RS100, HPMC K4M, Physical mixture and floating microspheres (formulation) were recorded.

Percentage Yield[44]

The prepared microspheres with a size range of 609- 874 µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product / total Weight of excipient and drug) × 100

DEE (Drug Entrapment Efficiency)[45]

The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatman filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured at 233 nm against 0.1 N HCI as a blank. The percentage drug entrapment was calculated as follows.

DEE = (Amount of drug actually present/Theoretical drug load expected) × 100

Floating behavior of Floating Microsphere[46]

100 mg of the floating microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% of tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in desiccators overnight. The percentage of microspheres was calculated by the following equation

% Floating microspheres = (weight of floating microspheres/ initial weight of floating microspheres) × 100

In-vitro Release Studies[47]

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly 38. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm.

One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.

The collected samples were suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 233 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies

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were repeated using phosphate buffer pH 6.8 as dissolution medium.

Recent Applications of Controlled Release Microspheres

Cancer Research[48]

One useful discovery made from the research of microspheres is a way to fight cancer on a molecular level. According to Wake Oncologists, "SIR-Spheres microspheres are radioactive polymer spheres that emit beta radiation. Physicians insert a catheter through the groin in to the hepatic artery and deliver millions of microspheres directly to the tumor site. The SIR Spheres microspheres target the liver tumors and spare healthy liver tissue. Cancer microsphere technology is the latest trend in cancer therapy. It helps the pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. A major disadvantage of anticancer drugs is their lack of selectivity for tumor tissue alone, which causes severe side effects and results in low cure rates. Thus, it is very difficult to target abnormal cells by the conventional method of the drug delivery system. Microsphere technology is probably the only method that can be used for site-specific action, without causing significant side effects on normal cells.

DNA Encapsulation[49]

Gene therapy holds tremendous potential for treating genetic diseases and acquired diseases including cancer, and as vaccines. A major barrier to development of gene-based pharmaceuticals is safe and efficient DNA delivery. Much research has focused on development of gene delivery vectors including viruses, liposomes, and polymers. However, parenteral administration of naked plasmid DNA (pDNA) leads to gene expression, and controlled release of p DNA from polymeric matrices, microparticle and nanoparticles has been reported recently. In particular, encapsulation and controlled release of p DNA from biodegradable microspheres may provide a number of advantages including protection from nuclease degradation, access to alternative routes of administration (e.g., nasal, pulmonary, oral, and mucosal), passive targeting to professional antigen-presenting cells, and prolonged gene expression.

Pharmaceutical Applications in Drug Delivery System[50]

Ophthalmic Drug Delivery

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydrogels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow.

Gene Delivery

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications.

Intratumoral and Local Drug Delivery

Intratumoral and local drug delivery strategies have gained momentum recently as a promising modality in cancer therapy. In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films were

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fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. polymer films containing paclitaxels were obtained by casting method with high loading efficiencies and the chemical integrity of molecule was unaltered during preparation according to study.

Oral Drug Delivery

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

Nasal Drug Delivery

The nasal mucosa presents an ideal site for bio adhesive drug delivery systems. Polymer based drug delivery systems, such as micro spheres, liposomes and gels have been demonstrated to have good bio adhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride.

Buccal Drug Delivery

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres contain chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug. Polymer microparticles with no drug incorporated have antimicrobial activity due to the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity.

Gastrointestinal Drug Delivery

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastroretentive controlled release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 hours e.g., Metoclopramide and glipizide loaded chitosan microspheres.

Peroral Drug Delivery

As polymer and most of its derivatives has a muco-adhesive property, a pre systemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many per orally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs.

Vaginal Drug Delivery

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, an imidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract.

Transdermal Drug Delivery

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings.

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Colonic Drug Delivery

Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with enteric coating (Hydroxy propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically disintegrated in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the polymer.

Diagnostic Uses of Radioactive Microspheres[51]

- Gated blood pool study.
- Thrombus imaging in deep vein thrombosis.
- Blood flow measurements.
- Investigation of bio distribution and fate of (drug-loaded) microspheres.
- Lung scintigraphy.
- Diagnostic radio embolization.
- Liver and spleen imaging.
- Bone marrow imaging.
- Infection localization.
- Tumor imaging.
- Gastrointestinal transit studies
- Local restenosis prevention in coronary arteries

Magnetically Targeted Drug Delivery Systems[52]

In targeted drug delivery, drugs are directed to cells that need therapy or repair, such as in cancer treatment. Effective treatments of cancer involve either surgery, radiation, immunotherapy, chemotherapy or a combination of these choices. Tumour targeting, Magnetic delivery of chemotherapeutic drugs to liver tumors, Locoregional Cancer Treatment with Magnetic Drug Targeting, Magnetically induced Hyperthermia for treatment of cancer, magnetic targeting of radioactivity.

Medical Application[53]

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/ intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Future Challenges

Future challenges of microspheres look bright particularly in the area of medicinal field because

of its wide spectrum of application in molecular biology, eg: microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres is used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins.

CONCLUSION

It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and better patient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours,

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detecting biomolecular interaction etc. So in future microspheres will have an important role to play in the advancement of medicinal field.

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