Review Article

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Recent Advances in Microspheres Technology for Drug Delivery

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ABSTRACT

Microspheres are the novel drug delivery system. A well considered controlled drug delivery system can overcome some of the problems of predictable therapy 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 approach. A Microspheres has its drug dispersed throughout the particle i.e., the internal structure is a matrix of drug and polymeric excipients. 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 without untoward effects. Microspheres are typically free flowing powders consisting of synthetic polymers which are biodegradable in nature. Microspheres are particles between 0.1 and 200 μm in size. Microspheres received much consideration not only for prolonged release, but also for targeting of anticancer drugs to the tumor. Microspheres are spherical microparticles and are used where reliable and expected particle surface area is important. A microsphere has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *in-vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS: Drug delivery systems; Controlled release; Microspheres; Therapeutic efficacy.

Introduction

In contrast to drug delivery system, the word novel is searching something out of necessity. The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance (Ghulam et al., 2009). In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration (Mathew et al., 2010). The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system (Karmakar et al., 2009).

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000 nm). Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hr still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation. Microencapsulation for oral use has been employed to sustain the drug release and to reduce or eliminate gastrointestinal tract irritation. In addition, multi particulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.

Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa. (Li et al., 1988). Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in

density and therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are two most common types of polymer microspheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments. Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials (Chaturvedi et al., 2009, Sudhamani et al., 2010). High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays. Glass microspheres are primarily used as filler for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

Ceramic microspheres are used primarily as grinding media. Microspheres vary widely in quality, sphericity, uniformity of particle and particle size distribution. The appropriate microsphere needs to be chosen for each unique application (Thanoo et al., 1992). The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration. This approach facilitates the accurate delivery of small quantity of the potent drugs, reduced drug concentration at the site other than the target site and the protection of the labile compound before and after the administration and prior to appearance at the site of action. The behavior of the drugs *in vivo* can be manipulated by coupling the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are strongly influenced by the behavior of the carrier. The exploitation of these changes in pharmacodynamics behavior may lead to enhanced therapeutic effect. However, an intelligent approach to therapeutics employing drug carrier's technology requires a detailed understanding of the carrier interaction drugs *in vivo* can be manipulated by coupling the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are strongly influenced by the behavior of the carrier (Parmar et al., 2010). The exploitation of these changes in pharmacodynamics behavior may lead to enhanced therapeutic effect. 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 (Kavita et al., 2010). To avoid these problems oral controlled drug delivery systems have been developed as they release 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 (Gholap et al., 2010). A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time thereby causing little toxicity and minimal side effects. 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. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm (Agusundaram et al., 2009. Shweta et al., 2010).

Characteristics

- Microsphere size may be critical to the proper function of an assay, or it may be secondary to other characteristics. Considering traditional diagnostic methods, the test or assay format commonly dictates particle size, such as the use of very small spheres (~0.1 – 0.4μm) to ensure satisfactory wicking in lateral flow tests or the use of larger, cell-sized spheres (~4 – 10μm) for bead based flow cytometric assays.
- Common microsphere compositions include polystyrene (PS), poly(methyl methacrylate) (PMMA) and silica. These materials possess different physical and optical properties, which may present advantages or limitations for different applications. Polymer beads are generally hydrophobic and as such, have high protein binding abilities. However, they often require the use of some surfactant (e.g., 0.01- 0.1% Tween® 20 or SDS) in the storage buffer to ensure ease of handling. During synthesis, functional monomers may be co-polymerized with styrene or methyl methacrylate to develop beads with surface reactive groups. Functional groups may be

used in covalent binding reactions and also aid in stabilizing the suspension. Silica microspheres are inherently hydrophilic and negatively charged. Consequently, aqueous silica suspensions rarely require use of surfactants or other stabilizers. Carboxyl and amine functionalized silica spheres are available for use in common covalent coating protocols and plain silica microspheres may be modified using a variety of silanes to generate functional groups or alter surface properties.

- Microspheres may be coated with capture molecules, such as antibodies, oligonucleotides, peptides, etc. for use in diagnostic or separation applications. Microsphere coatings are typically optimized to achieve desired specific activity, while minimizing nonspecific interactions. Consideration should also be given to the required stability, development time frame and budget and the specific biomolecule to be coated. These factors will aid in determining the most fitting coating strategy for both short and long-term objectives. Standard microsphere products support three ***basic coating strategies:*** adsorption, covalent coupling and affinity binding.
- Many applications in the life sciences demand added properties, such as fluorescence or a visible color or iron oxide inclusions for magnetic separations. Polymer spheres (and polymer based magnetic spheres) are often internally dyed via organic solvent swelling and many standard products are available. Dye concentrations can be adjusted to produce beads with different intensities to meet special needs, such as Quantum Plex™ for multiplexed flow cytometric assays, or our Dragon Green or Flash Red Intensity Standards, which support imaging applications and associated instrument QC. Many surface or internally labeled fluorescent beads are also available as specialized flow cytometric standards.

Advantages

- Microspheres provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence on intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release (Kavita et al., 2010).

Limitations

Some of the disadvantages were found to be as follows:

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
- Differences in the release rate from one dose to another.
- 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.
- Dosage forms of this kind should not be crushed or chewed. (Kavita et al., 2010).

Basic of gastrointestinal tract physiology

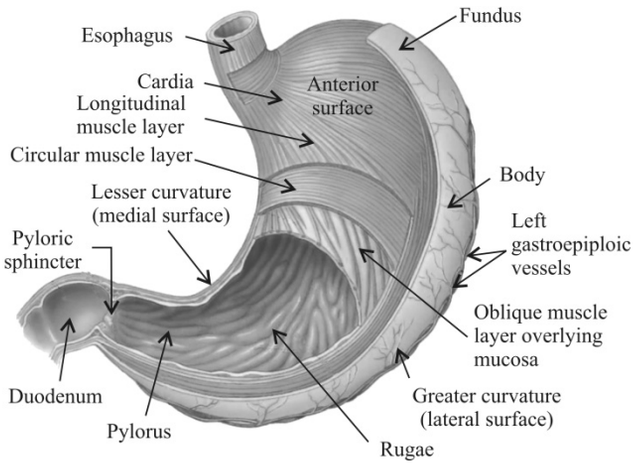


Fig. 1. Anatomy of stomach.

Anatomically the stomach is divided into three regions: fundus, body and antrum. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Desai et al., 1993). Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours (Ventrapen et al., 1979). This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases as described by Wilson and Washington (Wilson et al., 1989).

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

- Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, that of short gastric residence time and unpredictable gastric emptying rate.

Factors affecting gastric retention

Density: GRT is a function of dosage form buoyancy that is dependent on the density.

Size: Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes

Biological factors: Diabetes and Crohn's disease.

Fed or unfed state: under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content: GRT can be increased by 4-10 hours with a meal that is high in proteins and fats.

Frequency of feed: The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender: Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age: Elderly people, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Single or multiple unit formulation: Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units, allow co administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage form (Grubel et al., 1987).

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. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action (Patel et al., 2006).

Magnetic microspheres

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 is Therapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system. ***Diagnostic microspheres:*** Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides (Shanthi et al., 2010).

Floating microspheres

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 gasteric content, increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form (Najmuddin et al., 2010).

Radioactive microspheres

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. These conditions radioactive microspheres delivered 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 (Hafeli, 2002).

Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to it's 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. However they provide wide range of application in microsphere based treatment (Yadav et al., 2008).

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 kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage (Saralidze et al., 2010).

Preparation Method of Microsphere

Preparation of microspheres should satisfy certain criteria-

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability (Hafeli, 2004).

Preparation of microspheres can be done by suitable methods.

Protein gelation technique

The preparation of Pilocarpine nitrate loaded egg albumin microspheres by thermal denaturation process and obtained albumin microspheres in the size range of 1-12 μm. Drug loaded microspheres so obtained were evaluated for their size, entrapment efficiency, release rate and biological response. The entrapment and encapsulation of pilocarpine after process optimization was found to be 82.63% and 62.5% respectively shown in Table 1.

Single Emulsion polymerization technique:

Developed sustained release ethyl cellulose-coated egg albumin microspheres of Diltiazem Hydrochloride to improve patient compliance. The microsphere were prepared by the w/o emulsion thermal cross-linking method using different proportion of the polymer to drug ratio (Jeevana et al., 2009) shown in Table 2.

TABLE 1

Preparation of microspheres by protein gelation technique.

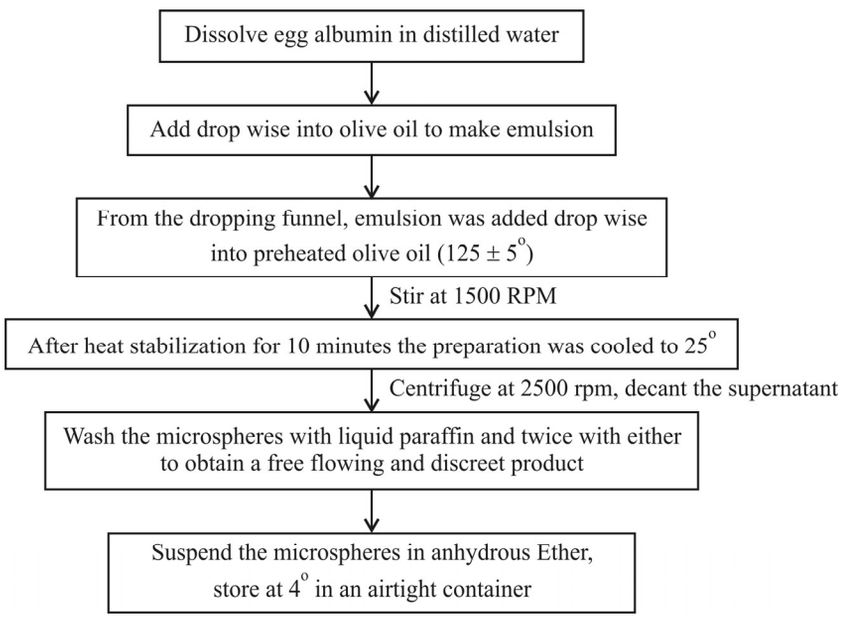
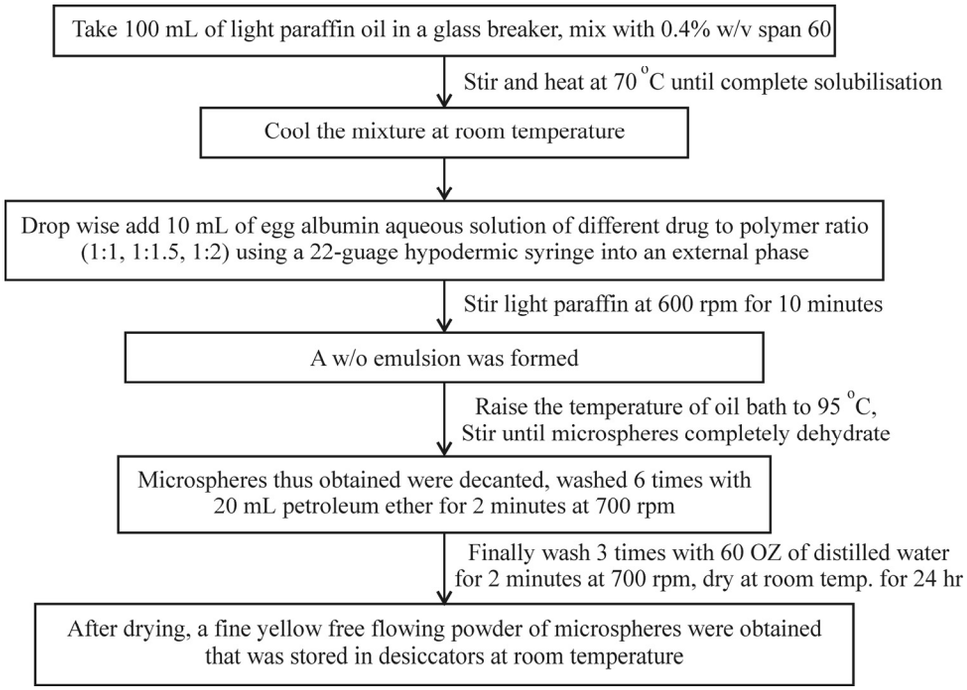


TABLE 2

Preparation of microspheres by single emulsion polymerization technique



Double emulsion polymerization technique

A double emulsion is usually prepared in two main modes-

Mode 1: One-step emulsification

Mode 2: Two-step emulsification

In one step emulsification mode a strong mechanical agitation is used for the water phase containing a hydrophilic surfactant and an oil phase containing large amounts of hydrophobic surfactant. Due to this a W/O emulsion is formed which quickly inverts to form a W/O/W double emulsion. A two-step procedure is reported where the primary emulsion can be formed as a simple W/O emulsion which emulsion can be formed as a simple W/O emulsion which is prepared using water and oil solution with a low HLB (hydrophilic-lipophilic balance) surfactant. In the second step, the primary emulsion (W/O) is reemulsified by aqueous solution with a high HLB surfactant to produce a W/O/W double emulsion (John et al., 1968).

Multiple emulsion polymerization technique

Multiple emulsion method involves formation of (o/w) Primary emulsion (non aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of cross linking agent (glutaraldehyde) and evaporation of organic solvent. This method of preparation is ideal for incorporating poorly aqueous soluble drug, thus enhancing its bioavailability. Sam T et al., carried out the formulation and evaluation of Ketorolac Tromethamine-loaded Albumin Microspheres for Potential Intramuscular Administration. The microspheres were prepared by multiple emulsion technique to make the poorly aqueous soluble drug ketorolac tromethamine more bioavailable (Khar et al., 2001).

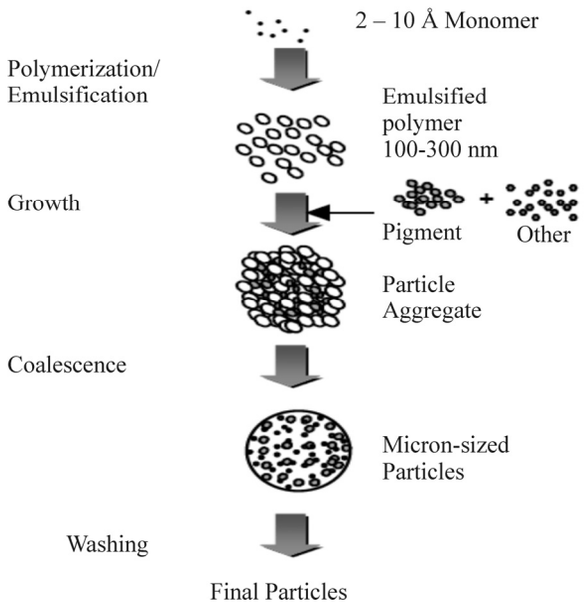


Fig. 2. Microsphere preparation by multiple emulsion method.

Solvent evaporation technique

This process is carried out in a liquid manufacturing vehicle. The albumin microspheres are dispersed in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid

manufacturing vehicle phase to obtain the appropriate size microsphere. The mixture is then heated if necessary to evaporate the solvent. The solvent evaporation technique to produce microspheres is applicable to wide variety of core materials. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. Microspheres were prepared by solvent evaporation method. The prepared microspheres were pale yellow, free flowing and spherical in shape. The mean particle size of the microspheres was found in the range of 150 to 400 μm. The drug-loaded microspheres showed 70-86% of entrapment and release was extended (Lopez et al., 1998)

Sonication technique

As the technique name itself is self explanatory, it just involves a simple sonication for certain period of time till a desired size of albumin microspheres are obtained. The albumin solution of desired concentration is taken which is sonicated. To this add the drug which will then form intra-chain cross-link with cysteine residues of albumin chains. A stable preparation of air filled human albumin microspheres (Albunex) can be prepared by sonication technique. The microspheres ranged in size from 1-10 μm with 99% of particles smaller than 10 μm. The mean size was 5 μm, which is small enough to pass freely through the pulmonary capillary circulation (Remington, 2006).

Spray drying technique

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air Fig. 3. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 μm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and leads to the formation of porous microparticles. Developed albumin microspheres of Fluticasone propionate inclusion complexes for pulmonary delivery by using spray and freeze drying technique. 2-hydroxypropyl-β-cyclodextrin inclusion complex of Fluticasone propionate was prepared by the spray drying and freeze drying technique in the molar ratio 1:1. Spray drying came of age during World War II, with the sudden need to reduce the transport weight of foods and other materials. This surge in interest led to developments in the technology that greatly expanded the range of products that could be successfully spray dried. It has been used in pharmaceutical technology studies to produce pharmaceuticals excipient with improved compressibility, such as lactose, to improve flow properties, to prepare free-flowing granules for tablet production, to improve the drug aqueous solubility and consequently, their bioavailability. In addition, a number of formulation processes can be accomplished in one step in a spray dryer; these include complex formation and micro encapsulation (Venkatesan et al., 2009).

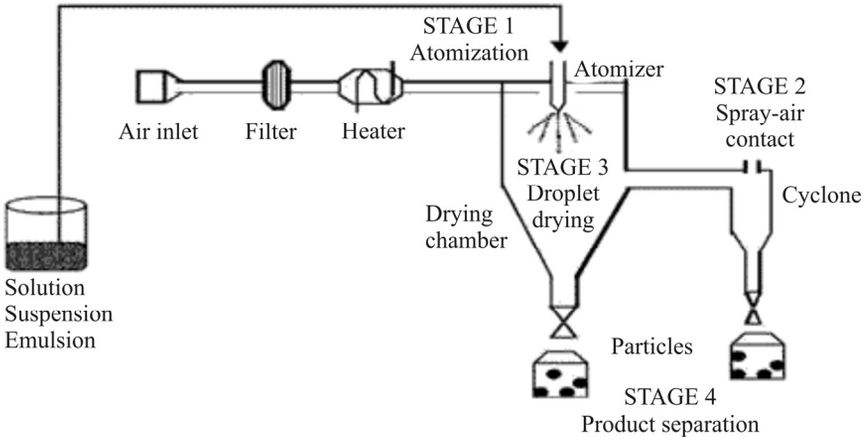


Fig. 3. Main process stages involved in spray drying process.

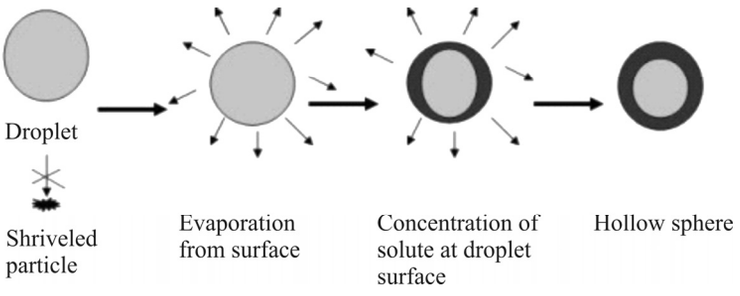


Fig. 4. Formation of product in spray drying.

Concept of spray drying technique

The production of particles from the process of spraying has gained much attention in recent years. These efforts have resulted in spray technology being applied to the manufacture of particles to generate products ranging from pharmaceutical direct compression excipients and / or granulations to microencapsulated flavors. The two main spray techniques are spray drying and spray congealing. The action in spray drying is primarily that of evaporation, whereas in spray congealing it is that of a phase change from a liquid to a solid. The two processes are similar, except for energy flow. In the case of spray drying, energy is applied to the droplet, forcing evaporation of the medium resulting in both energy and mass transfer through the droplet. In spray congealing, energy only is removed from the droplet, forcing the melted to solidify Fig. 4. Spray drying is the most widely used industrial process involving particle formation and drying. It is highly suited for the continuous production of dry solids in either powder, granulate or agglomerate form from liquid feed stocks as solutions, emulsions and pumpable suspensions. Therefore, spray drying is an ideal process where the end-product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density and particle shape (Vidgren et al., 1992).

Principle

There are three fundamental steps (figure 1) involved in spray drying

1. Atomization of a liquid feed into fine droplets.
2. Mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids.
3. Dried powder is separated from the gas stream and collected.

   Spray drying involves the atomization of a liquid feedstock into a spray of droplets and contacting the droplets with hot air in a drying chamber. The sprays are produces by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Powder is discharged continuously from the drying chamber. Operating conditions and dryer design are selected according to the drying characteristics of the product and powder specification (Vyas et al., 2002).

Emulsification-heat stabilization technique

The preparation and characterization of albumin microspheres encapsulated with propranolol HCl by emulsion heat stabilization technique. Bovine serum albumin microspheres (BSA) containing propranolol HCl were prepared by emulsification-heat stabilization technique. Briefly, a 5% solution of BSA containing 0.1% Tween80 was made, to which 4% propranolol HCl was added and used as the aqueous phase. The oil phase composed of 30 ml maize oil and 10 ml petroleum ether with 1% Span 80 as emulsifier were mixed together and allowed to stir for 10 min at 1000 rpm. The aqueous phase was added drop wise to the oil phase and stirred on a magnet stirrer at 1000 rpm for 30 min to form the initial emulsion. This emulsion was then added to 40 ml of maize oil preheated to 120 °C and stirred at 1000 rpm for 15 min to allow the formation and solidification of microspheres. The microsphere suspension was centrifuged at 3500 rpm for 30 min and the settled microspheres were washed three times with ether to remove traces of oil on microsphere surfaces. The microspheres were vacuum dried in a desiccator overnight and stored were vacuum dried in a desiccator overnight and stored at 4°C in dark. The microspheres had diameter of 1-25 μm of which more than 50 percent were below 5 μm. The encapsulated drug was found to be about 9% w/w of that initially added to microspheres and the superficial drug was 25% of the total amount of the encapsulated drug. Also albumin microspheres were noted to possess good bioadhesion in such a way that about 70% of microspheres remained adherent on the surface mucosa of rat jejunum. The total amount of drug released from microspheres after 12 hour was 70%.

Quasi-emulsion solvent diffusion method of the spherical crystallization technique

Development and characterization of sustained release microspheres by quasi emulsion solvent diffusion method. The microspheres were prepared using the quasiemulsion solvent diffusion method of the spherical crystallization technique. Ketoprofen and Eu RS were dissolved completely in the acetone-dichloromethane mixture. Then Aerosil was suspended uniformly in the drug-polymer solution under vigorous agitation. The resultant drug-polymer-Aerosil suspension was poured into the distilled water (150 ml) containing 0.08% of SDS (i.e., poor solvent) under a moderate agitation (450-750 rpm) and thermally controlled at 0-38 °C. The suspension was finely dispersed into quasi-emulsion droplets immediately under agitation and the drug and polymers co-precipitated in the emulsion droplets. After agitating the system for 20 min, 150 ml of poor solvent was added slowly to promote the diffusion of the good solvent from emulsion droplets into poor solvent resulting in enhancement of the solidification of quasiemulsion droplets. Agitation was extended for another 40 min until the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water and the resultant products were dried in an oven at 50 °C for 6 hr. The average diameters were about 104-108 μm and the drug contents in the microspheres were 62-96% (Widder et al., 1978).

Spray congealing

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of cold air. The

atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm (Kreuter et al., 1983).

Phase separation coacervation technique.

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Polylactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment (Margel et al., 1984).

Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

I. Normal polymerization.
II. Interfacial polymerization.

Both are carried out in liquid phase.

I. Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

II. 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 (Acikgoz et al., 1996)

Solvent extraction

The contaminants are separated from the solvent either by changing the pressure and temperature, by using a second solvent to pull the first solvent out of the solvent/contaminant mixture or by other physical separation processes. At the completion of this step, concentrated contaminants result Fig. 5. Concentrated contaminants are removed during the separation process, and the solvent is sent to a holding tank for reuse. The contaminants are then analyzed to determine their suitability for recycle/reuse or need for further treatment before disposal (Bodmeir et al., 1988).

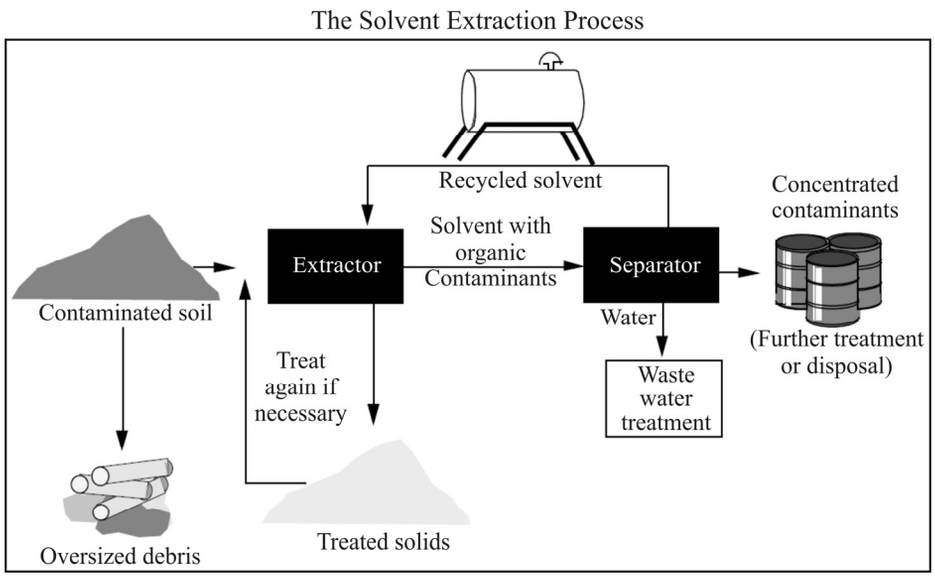


Fig. 5. Microsphere preparation by solvent extraction.

Materials used in Microsphere Preparation

Adjuncts used in microsphere preparation can be classified into two types:

(a) synthetic polymers and
(b) natural polymers.

Synthetic polymers

Poly alkyl cyano acrylates is a potential drug carrier for parenteral as well as other ophthalmic, oral preparations. Poly lactic acid is a suitable carrier for sustained release of narcotic antagonist, anti cancer agents such as cisplatin, cyclo phosphamide and doxorubicin. Sustained release preparations for anti malarial drug as well as for many other drugs have been formulated by using of co-polymer of poly lactic acid and poly glycolic acid. Poly anhydride microspheres (40 μm) have been investigated to extend the precorneal residence time for ocular delivery. Poly adipic anhydride is used to encapsulate timolol maleate for ocular delivery. Poly acrolein microspheres are functional type of microspheres. They do not require any activation step since the surfacial free CHO groups over the poly acrolein can react with NH_2 group of protein to form Schiff's base.

Synthetic polymers are divided into two types.

(a) Non-biodegradable polymers

e.g., Poly methyl methacrylate (PMMA) Acrolein, Glycidyl methacrylate Epoxy polymers

(b) Biodegradable polymers

e.g., Lactides, Glycolides and their co polymers, Poly alkyl cyano acrylates, Poly anhydrides

Natural polymers

Albumin is a widely distributed natural protein. It is considered as a potential carrier of drug or protiens (for either their site specific localization or their local application into anatomical discrete sites). It is being widely used for the targeted drug delivery to the tumour cells. Gelatin microspheres can be used as efficient carrier system capable of delivering the drug or biological response modifiers such as interferon to phagocytes. Starch8 belongs to carbohydrate class. It consists of principle glucopyranose unit, which on hydrolysis yields D-glucose. It being a poly saccharide consists of a large number of free OH groups. By means of these free OH groups a large number of active ingredients can be incorporated within as well as active on surface of microspheres. Chitosan is a deacylated product of chitin. The effect of chitosan has been considered because of its charge. It is insoluble at neutral and alkaline pH values, but forms salts with inorganic and organic salts. Upon dissolution, the amino groups of chitosan get protonated and the resultant polymer becomes positively charged (Li et al., 1994). Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. e.g.,

Proteins: Albumin, Gelatin and Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates: Poly dextran, Poly starch.

Characterization of Microspheres

Particle size analyzers

Microsphere (50 mg) was suspended in distilled water (5 ml) containing 2%w/v of tween 80, To prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer (Khan et al., 2000).

Optical microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK). The measurement was done under 450 × (10 × eye piece and 45 × objective) and 100 particles were calculated (Kannan et al., 2009).

Scanning electron microscopy (SEM)

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slub with the help of double sided sticking tape and coated with gold film under reduced pressure (Shaji et al., 2009).

Swelling index

This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique. Different solution (100 ml) were taken such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) were taken and alginate microspheres (100 mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37 ^oC and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper (Chaudary et al., 2003).

Entrapment efficiency

Microspheres containing of drug (5 mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by UV- spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content (Soni et al., 2010).

X-ray diffraction

Change in crystalinity of drug can be determined by this technique. Microparticles and its individual components were analysed by the help of D and discover (Bruker, Germony).Scanning range angle between 8 oc - 70 oc. Scan speed - 4o/min

Scintillation detector

Primary silt = 1mm

Secondary silt = 0.6 mm.1

Thermal analysis

Thermal analysis of microcapsule and its component can be done by using differential scanning calorimetry, thermo gravimetric analysis, and differential thermo-metric analysis. The sample is weighed and heated on

alumina pan at constant rate of 10 oc/min under nitrogen flow of 40 ml/min.1

UV-FTIR (Fourier transform infra red)

The drug polymer interaction and also degredation of drug while processing for microencapsulation can be determined by FTIR. (Surini et al., 2009).

Stability studies

By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/–2 ^{o}C)
3. Oven temperature (40+/–2 ^{o}C)
4. Refrigerator (5 ^{o}C – 8 ^{o}C).

It was carried out of 60 days and the drug content of the microsphere was analysed (Khar et al., 2001).

Zeta potential

The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement (Fischer et al., 2004).

Applications in Drug Delivery System (Shweta et al., 2010).

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 hydro gels 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. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs. In contrast, polymer based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug carrier (micro spheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan.

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. Also, polymer could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Mac Laughlin et al., showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered *in vivo* by chitosan and depolymerized chitosan oligomers to express a luciferase gene in the intestinal tract.

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 fabricated. Paclitaxel could be loaded at 31% (w/w) in films, which were translucent and flexible. polymer films containing paclitaxel 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 bioadhesive drug delivery systems. Polymer based drug delivery systems, such as micro spheres, liposomes and gels have been demonstrated to have good bioadhesive 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. Nasal administration of Diphtheria Toxoid incorporated into chitosan microparticles results in a protective systemic and local immune response against Diphtheria Toxoid with enhanced IgG production. Nasal formulations have induced significant serum IgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine. Nasal absorption of insulin

after administration into polymer powder were found to be the most effective formulation for nasal drug delivery of insulin in sheep compared to chitosan nanoparticles and chitosan solution.

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 containing 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 mucoadhesive property, a presystemic metabolism of peptides can be strongly reduced leading to a strongly improved bioavailability of many perorally given peptide drugs, such as insulin, calcitonin and buserelin. Unmodified chitosan has a permeation-enhancing effect for peptide drugs. A protective effect for polymer embedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer. The mucoadhesive property of polymer gel can be enhanced by threefold to sevenfold by admixing chitosan glyceryl mono-oleate. Drug release from the gel followed a matrix diffusion controlled mechanism. Nifedipine embedded in a chitosan matrix in the form of beads have prolonged release of drug compared to granules.

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. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly improved and this is found to increase the residence time of the vaginal mucosa tissue (26 times longer than the corresponding unmodified polymer), guaranteeing a controller drug release in the treatment of mycotic infections . Vaginal tablets of polymer containing metronidazole and acriflavine have showed adequate release and good adhesion properties.

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. Polymer gel beads are a promising biocompatible and biodegradable vehicle for treatment of local inflammation for drugs like prednisolone which showed sustained release action improving therapeutic efficacy. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anesthetic, is a good transparent system for controlled drug delivery and release kinetics.

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.

Multiparticulate delivery system

Some investigators have prepared chitosan pellets using the extrusion/spheronization technology. Micro-crystalline cellulose was used as additive in concentrations range from 0-70 %. The powder mixture was extruded using water and dilutes acetic acid in different powder to liquid ratios. The study showed that chitosan pellets with a maximum of 50% (m/m) could be produced with demineralized water as granulating fluid. The mass fraction of chitosan within in the pallets could be increased to 100% by using dilute acetic acid for the granulation step.

Other potential applications include

- Conversion of oil and other liquids to solids for ease of handling
- Taste and odor masking
- To delay the volatilization
- Safe handling of toxic substance (Chaturvedi et al., 2010)

Recent Advancement in Microsphere

Important utilizations of chitosan polymers are as follows (Gadad et al., 2011).

Cholesterol-lowering effects

Chitosan and cellulose were used as examples of fibers with high, intermediate and low bile acid-binding capacities, respectively. The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol diet for 3 weeks increased about 2-fold to 4·3 mM and inclusion of any of these fibers at 7.5% of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibers. The three kinds of fibers showed similar hypocholesterolaemic activity; however, cholesterol depletion of liver tissue was greatest with cholesty-ramine. The mechanisms underlying the cholesterol lowering effect of cholestyramine were,

- Decreased cholesterol (food) intake,
- Decreased cholesterol absorption efficiency and
- Increased fecal bile acid and cholesterol excretion.

The latter effects can be attributed to the high bile acid-binding capacity of cholestyramine. In contrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake, but did not affect either intestinal cholesterol absorption or fecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol lowering.

Increase stability of drug

Chitosan polymer is used to increase the stability of the drug in which the drug is complexed with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no.16 and make a granules is completely stable at different condition.

Orthopaedic patients

Chitosan is a biopolymer that exhibits osteo conductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive coating to improve Osseo integration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration

Cosmetics industry

Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantial, particularly to hair keratin and prove to have hair strengthening and hair conditioning characteristics. e.g., Hair setting lotion, Oxidation Hair-coloring Composition, Hair toning Composition, Skin Cream, Hair treatment Composition, Gel-form.

Dental Medicine

Chitosan have been recognized to accelerate wound healing to attain an Aesthetically valid skin surface and to prevent excess scar formation. In dental medicine, chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis. Furthermore, it is being investigated as an absorbing membrane for periodontal surgery. Chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or care of various disorders, arthritis, cancer, diabetes, hepatitis, etc.

Chitosan as Permeation Enhancer

It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability.

Chitosan as Mucoadhesive Excipient

Bioadhesivity is often used as an approach to enhance the residence time of a drug in the GI tract, hereby increasing the oral bioavailability. A comparison between chitosan and other commonly used polymeric excipients indicates that the cationic polymer has higher bioadhesivity compared to other natural polymers, such as cellulose, xantham gum and starch.

Effect of chitosan: citric acid ratio on drug release

It has been demonstrated that polymer with appropriate viscosity and expanding property can be used as osmotic agents for the release of water-insoluble drug. Due to its high molecular weight and a linear unbranched structure, chitosan is completely biodegradable, toxicologically harmless and low cost and exhibits an excellent gelation characteristic. Hence the potential for chitosan to be used as a polymeric osmotic agent in osmotic pump is obvious. The hydration and gel formation of chitosan are very much dependent on the pH of surroundings. It is insoluble at an alkaline and neutral pH but soluble at acid condition. Upon dissolution, amine groups of the polymer become protonated, forming a resultant viscous and soluble polysaccharide. Inclusion of citric acid as pH-regulating excipient in the developed formulations was expected to decrease the micro environmental pH of the core to a suitable level at which chitosan could form appropriate viscous gelling solution and hence, to enhance the osmotic pressure of core tablets.

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Enhanced bone formation by transforming growth factor (TGF-pl)

Chitosan composite microgranules were fabricated as bone substitutes for the purpose of obtaining high bone-forming efficacy. The chitosan microgranules were fabricated by dropping a mixed solution into a NaOH/ethanol solution. TGF-pl was loaded into the chitosan microgranules by soaking the microgranules in a TGF-pl solution.

Direct compressible excipients and as binder

Chitosan has an excellent property as excipients for direct compression of tablets where the additions of 50% chitosan result in rapid disintegration. The degree of deacetylation determine the extent of moisture absorption. Chitosan higher then 5%, was superior to corn starch and microcrystalline cellulose as a disintegrant. The efficiency was dependent on chitosan crystalinity, degree of deacetylation, molecular weight and particle size chitosan is found to be excellent tablet binder as compared to other excipients with the rank order co-relation for binder efficiency: HPMC > chitosan > Methyl cellulose > Sodium carboxy methyl Cellulose.

Wound healing properties

Efficacy of chitosan in the promotion of wound healing was first reported in 1978. Chitosan acetate films, which were tough and protective, had the advantage of good oxygen permeability, high water absorptivity and slow enzymatic degradation.

Conclusion

Microspheres are used to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects. A microsphere has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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