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RESEARCH ARTICLE

MICROSPHERES: A RECENT UPDATE

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ABSTRACT

Microspheres are free flowing powder that consist of proteins or synthetic polymers that are biodegradable in nature ranging between 1-1000nmin size. 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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. Among them microspheric drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. Microsphere are spherical micro particles, and are used where consistent and predictable particle surface area is important. A microspheres has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. The purpose of the review is to compile various types of microspheres, different methods to preparation, its applications and also various parameters to evaluate their efficiency.

INTRODUCTION

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. [1,2] 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 protein or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. [1,3] 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. [4] 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. [5] 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 do sage form in novel drug delivery system. 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. [6] It has a particle size of (1-1000nm).[7]

Further, currently available slow release oral dosage forms, such as enteric coated/ double-layer tablets which release the drug for 12-24 hours 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, multiparticulate 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. [6] Thus, microencapsulation technique has been used to modify and retard drug release. There are various Marketed microsphere products available in market that are listed in Table1 and various patents described in Table 2.

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Table 1 List of Marketed Microsphere Drug Products

Drug	Commercial Name	Company	Technology
Risperidone	RISPERDAL® CONSTA®	Janssen®/Alkermes, Inc.	Double emulsion (oil in water)
Naltrexone	Vivitrol®	Alkermes	Double emulsion (oil in water)
Leuprolide	Lupron Depot® Enantone Depot® Trenantone®	TAP Takeda Takeda	Double emulsion (water in oil in water)
Octreotide	EnantoneGyn Sandostatin® LAR	Takeda Novartis	Phase separation
Somatropin	Nutropin® Depot[a]	Genentech/Alkermes	AlkermesProLease® Technology (Cryogenic spray-drying)
Triptorelin	Trelstar™ depot Decapeptyl® SR	Pfizer Ferring	Phase separation
Buserelin	Suprecur® MP	Sanofi-Aventis	N/A
Lanreotide	Somatuline® LA	Ipsen-Beafour	Phase separation
Bromocriptine	Parlodel LAR ™	Novartis	Spray dry
Minocycline	Arestin®	Orapharma	N/A

Table 2 Patents of Microspheres

S.No	Patent No.	Drug Used	Reference
1	CN 201110142359	Ketoprofen	[8]
2	CN 201110313846	Paclitaxel	[9]
3	CN 201210025085	5-fluorouracil	[10]
4	US08455091	Ganciclovir	[11]
5	EP19980924438	Cimetidine	[12]
6	EP20070808011	Risperidone	[13]
7	CA 2217462	Cyclosporin	[14]
8	CA 2579533	Irinotecan	[15]
9	DE1999609777	Levonorgesterel	[16]
10	DE1994632867	Doxorubicin	[17]

Advantages [18]

Various advantages can be found as follows:

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

Limitation [18]

Some of the disadvantages found to be as follows:

1. The modified release from the formulations.
2. 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.
3. Differences in the release rate from one dose to another.
4. 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.
5. Dosage forms of this kind should not be crushed or chewed.

Materials Used

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatin, starch, collagen and carrageenan.

Classification of polymer [19]

A) Synthetic Polymers: *divided into two types;*

1. Non-biodegradable:4,5- Acrolein, Glycidyl methacrylate, Epoxy polymers, etc. [20,21]
2. Biodegradable: (6)-Polyanhydrides, Polyalkylcyanoacryalates Lactides and glycolides and their copolymers.

B) Natural materials*: They are obtained from different sources like:[22,23]*

- Proteins (albumin, gelatin, collagen)
- Carbohydrate (starch, agarose, carrageenan)
- Chemically modified carbohydrates [poly (acryl dextran), Poly (acryl starch)]

Pre-requisites for ideal micro particulate carriers [19]

The material utilized for the preparation of micro particulates should ideally fulfill the following prerequisites.

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Target ability
- Polyvalent

Types of Microspheres

Bioadhesive microspheres[24]

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 bio adhesion. 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.

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. [25] The different type are

Therapeutic magnetic microspheres: These are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.[24]

Diagnostic microspheres: They 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. [26]

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 gastric content and 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) is given through this form. [27]

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. So in all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. [28] 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.[29]

Polymeric microspheres

The different types of polymeric microspheres can be classified as:

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 its high degree of swelling property with aqueous medium, resulting in 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.[30]

Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover they are also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible.[30]But the main disadvantage of these kind of microspheres are, they tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.[31]

Methods of Preparation [32]

Single emulsion technique

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di -acid chloride etc. Heat denaturation is not suitable for thermo labile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

Double emulsion technique

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulate the protein contained in dispersed aqueous phase. The primary emulsion is then subjected to homogenization or sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA).This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/ extraction.

Polymerization techniques

The polymerization techniques convention ally used for the preparation of the microspheres are mainly classified as:
I. Normal polymerization
II. Interfacial polymerization.
Both are carried out in liquid phase.

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.

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.

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. Poly lactic 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.

Spray drying and spray congealing

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. 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. 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.

Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulphaethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.

Solvent extraction

Solvent evaporation method is used for the preparation of micro particles, involving removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as is opropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer**.**

Evaluation of Microspheres

Particle size analyser

Microsphere (50 mg) are suspended in distilled water (5mL) containing 2%w/v of tween 80, to prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size is expressed as volume mean diameter in micrometer. [33]

Optical microscopy

This method is used to determine particle size by using optical microscope (Meizer OPTIK) The measurement i done under 450x (10x eye piece and 45x objective) and100 particles are calculated. [34]

Scanning electron microscopy (SEM)

Surface morphology is determined by the method SEM. In this microcapsule are mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure and analyzed. [35]

Swelling index

This technique is used for characterization of sodium alginate microspheres. Different solution (100mL) are taken such as [distilled water, buffer solution of Ph (1.2, 4.5, 7.4)] and alginate microspheres (100mg) are placed in a wire basket and kept on the above solution and swelling is allowed at 37^{o}C. Thus, changes in weight variation between initial weight of microspheres and weight due to swelling is measured by taking weight periodically and soaking with filter paper. [36]

Entrapment efficiency

Microspheres containing of drug (5mg) are crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content. [36]

X-ray diffraction

Change in crystalinity of drug can be determined by this technique. Micro particles and its individual components are analysed by the help of XRD Instrument. [39] Scanning range angle between 80^{o}C - 70^{o}C.

Thermal analysis

Thermal analysis of microcapsule and its component can be done by using

Differential scanning calorimetry (DSC)
Thermo gravimetric analysis (TGA)
Differential thermometric analysis (DTA)
Accurately the sample is weighed and heated on alumina pan at constant rate of 10^{o}c/min under nitrogen flow of 40 ml/min. [39]

FTTR

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR. [37]

Stability studies

Stability Studies are done by placing the microspheres in screw capped glass container and storing them at following conditions:

- Ambient humid condition
- Room temperature (27+/-2 ^{o}C)
- Oven temperature (40+/-2 ^{o}C)
- Refrigerator (5 0+/-8 ^{o}C).

It was carried out of for 60 days and the drug content of the microsphere is analysed. [40]

Zeta potential

The polyelectrolyte shell is prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles are determined by zeta potential measurement. [38]

Applications in Drug Delivery System [44]

Ophthalmic Drug Delivery

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemicalcharacteristics, 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 drugcarrier(microspheres) seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the of loxacin 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 viralvectors, 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 promotersequence and a luciferase reporter gene could be delivered in vivo by chitosan and depolymerized chitosan oligomers to expressa luciferase gene in the intestinal tract.

Intratumoral and local drug delivery

Intratumoral and local drug delivery strategies have gained momentum recently as apromising modality in cancer therapy. Inorder to deliver paclitax el 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 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 bioadhesive drug delivery systems. Polymer based drug delivery systems, such as microspheres, 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 localimmune response against Diphtheria Toxoid with enhanced IgG production. Nasal formulations have induced significant serumIgG responses similar to secretory IgA levels, which are superior to parenteral administration of the vaccine. Nasalabsorption of insulin after administration in to 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

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 amixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic cross linking 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 6.7hours 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 lead to a strongly improved bioavailability of many per-orally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has apermeation-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, animidazole 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 beadsand microspheres for potential applications inpackaging, controlled release systems and wound dressings. Polymer gel beads are apromising biocompatible and biodegradablevehicle 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 lidocainehydrochloride, a local anesthetic, is a goodtransparent 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

H.Steckel and F. Mindermann-Nogly have prepared chitosan pellets using the extrusion/spheronization technology. Microcrystalline cellulose was used as additive in concentrations range from 0-70 %.The powder mixture was extruded using water and dilute acetic acid in different powder to liquid ratios. The study showed that chitos an 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. [42]

Recent Advancements in Microspheres [43,44]

Important utilizations of chitosan polymer 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 4·3mM 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 cholestyramine. The mechanisms underlying the cholesterol lowering effect of cholestyramine were,

1. Decreased cholesterol (food) intake,
2. Decreased cholesterol absorption efficiency, and
3. 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 skinsur face, and to prevent excess scar formation. In dentalmedicine, 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 ofstudies 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 micro granules were fabricated as bone substitutes for the purpose of obtaining high bone-forming efficacy. The chitosan micro granules were fabricated by dropping a mixed solution into a NaOH/ethanol solution. TGF-pl was loaded into the chitosan micro granules 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 of50% chitosan result in rapid disintigration. The degree of deacetylation determine the extent of moisture absorption. Chitosan higher than 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 correlation for binder efficiency. Hydroxy propyl methylcellulose >chitosan> Methyl cellulose>Sodium carboxymethyl 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.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Microspheres by ionotropic gelation technique promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. 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.

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