Review Article

Chitosan and its Use as a Polymeric Drug Carrier Material in Dosage Form Design - A Critical Review

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ABSTRACT

The prime goal in the drug therapy of any disease is to attain the desired therapeutic concentration of the drug in plasma or at the site of action and maintain it for the entire duration of treatment. To minimize drug degradation/loss, prevent harmful side effects and to increase drug bioavailability various drug delivery and drug targeting systems are presently under investigation. Chitosan has been the subject of interest for its use as a polymeric drug carrier material in dosage form design due to its appealing properties such as biocompatibility, biodegradability, low toxicity and relatively low production cost from abundant natural sources. Microspheres are the choice of drug delivery system for the controlled release of drugs, vaccines, antibiotics, and hormones for specific target sites. There are various methods that can be used to encapsulate drugs within chitosan matrixes such as ionotropic gelation, spray drying, emulsification-solvent evaporation, co-acervation, double layer coating and many more. Combinations of these practices are also used in order to obtain micro-particles with specific properties and performances. Double-layer coating method is used to prevent the loss of encapsulated materials in the acidic medium. The microspheres should be coated with another polymer that forms a membrane on the surface. Due to the bilayer properties, the micro carriers additionally protected against acidic conditions of the stomach and drug releases in the intestine in a better controlled manner. This review focused on the techniques applied directly to chitosan micro-particulate systems and their role in novel drug delivery systems.

Keywords: Chitosan, controlled release, microspheres, spray drying, double-layer coating.

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INTRODUCTION

Modern drug delivery skill has been made possible with the advances in polymer science. These advances facilitated the polymers with their unique properties. Polymers are used as additives, solubilizers and to stabilize drugs or as mechanical supporters for the dosage's forms. Furthermore, the role of polymers is improved continuously and engaged as central position in controlling drug release as well as in the fabrication of drug delivery system. Today numerous polymers with their innovative properties are available, selection of the appropriate polymers for certain applications became critically important. This led to utmost demands for more efficient and more functional drug delivery vehicles. It is most desirable to develop micro particulates of advanced properties of polymers with specific functions designed for drug delivery, such as drug solubilization, drug targeting and for resolving emerging problems. Microcapsules or micro particles are small and are made of natural or synthetic polymers. The diameters of these flowing free particles are ranging from 1 to 1000µm. 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. For this reason, it is beneficial to understand the current drug delivery technologies and the unique roles of polymers[1].

Chitosan: as a Polymeric Drug Carrier

Extensive use of natural polymers is now in trend to deliver active pharmaceutical ingredients (API) in pharmaceutical industry due to excellent properties such as biocompatibility, biodegradability and nontoxicity. Chitosan is the second topmost naturally occurring polysaccharide next to cellulose which is currently being explored intensively for their applications in pharmaceutical, cosmetics, biomedical, biotechnological, agricultural, food, and non-food industries[1,2]. Chitosan is derived from alkaline N-deacetylation of chitin, which is a supporting material of crustaceans, insects, and fungal mycelia. Among the different species of crustaceans, shrimp and crab shells have been widely used for the isolation of chitin[4]. It is obtained after processing of the removal of proteins and the dissolution of calcium carbonate from crustacean shells[5]. The resulting chitin is deacetylated with 40% NaOH at 120°C for 1 to 3 hours to produce 70% deacetylated chitosan. It is also obtained from fungi by applying fermentation processes with *Aspergillus niger*, *Mucorrouxii*, *Saccharo mycescerevisae*

and *Streptomyces* sp.[4,6]. Chitin is a white, hard, inelastic nitrogenous mucopolysaccharide and it can be degraded by chitinase enzyme also. It is a linear cationic hetero polymer of randomly distributed 2-N-acetyl-2-deoxy-glucose (N-acetyl glucosamine) and 2-amino-2-deoxy-glucose (glucosamine) residues with *β*-1, 4-linkage. Moreover, chitosan is a copolymer of 2-acetamido-2-deoxy-*β*-D-glucose and 2-amino-2-deoxy-*β*-D-glucose units (Fig.1). Chitosan is a product derived from alkaline N-deacetylation of chitinand this *N*-deacetylation are almost never completed[7,8].

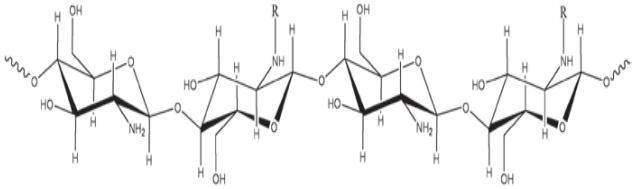

Figure 1: Chemical structure of chitosan showing the repeating subunits

Where, R = Ac or H depending on the degree of acetylation.

Commercially, chitosan is available in the form of dry flakes, solution and fine powder. Depending on the source and preparation procedure, the number of glucosamine residues meant as the degree of deacetylation in isolated chitin ranges from 5 -10% and the molecular weight of this linear polysaccharide can be as high as 1-2x10^6 Da corresponding to a degree of polymerization of ca. 5,000-10,000. In chitosan, degree of deacetylation is found above 60% and the molecular weight ranges from 2,000 Da (oligomers) to 10^4 - 2x10^6 Da[9,10]. The molecular weight and degree of deacetylation strongly affects chitosan properties, particularly during the development of micro and nanoparticles. The first study on this characteristic property was carried out by Lehr *et al.*,[11]. Chitosan is characterized by their mucoadhesive properties due to the electrostatic interaction between the positive charge on ionizable RNH_3^+ group and the negative charge on the mucosal surfaces[12]. The interaction of the protonated amine groups with the cell membrane results in a reversible structural reorganization in the protein associated tight junctions, which is followed by opening of these tight junctions. Sinha *et al.*, showed that the molecular weight, strong electrostatic interaction, chitosan chain flexibility, possibility of hydrogen bond formation due to availability of bonding groups such as carboxylic and hydroxyl groups, and ease of spreading into the mucus owing to surface energy properties are factors that attribute to this character. Another advantage that makes chitosan superior to other polysaccharide polymers is the ease of chemical modifications in the structure, especially in the C-2 position, which provide derivatives with different characteristics with potential use in different applications[3,13].

In general, the mucoadhesive nature which increases the time of attachment at the absorption site, the easy availability of free amino group for cross-linking, ease of fabrication of polymeric particles without using hazardous solvents, the cationic nature that promoteionic cross-linking with multivalent anions, and finally the ability to control the release of the administered drug makes chitosan the polymer of choice for developing the polymeric particle.

Controlled release system has additional advantages than conventional dosage forms, as they minimize side effects, improve prolonged delivery of drugs, macromolecules and targeted drug delivery. This release pattern regulates the drug release rate and can reduce the frequency of administration of the drug, with assuring better patient compliance[14]. The use of chitosan as a novel excipient in pharmaceutical products has been highlighted in several reports[15].

Chitosan shows insolubility at higher pH values > 6.5 that prevail in the jejunum and the ileum of the gut[16]. Thus, chitosan microspheres would erode slowly in phosphate buffer, and this prevents the burst effect of the release in the first segments of the gastrointestinal tract. Furthermore, there are some studies in which chitosan have been used for the specific delivery of the drug in the colon, where the pH range is 6.5-7.0[17,18]. When the drug is prone to degradation in the stomach or the upper region of the intestine, the drug is required to deliver into the colon. A microsphere-based therapy allows the drug to be released to the specific target site through the choice and formulation of different drug polymer combinations. By using innovative microencapsulation technologies and by varying the drug-polymer ratio, molecular weight of the polymer, density and viscosity etc., microspheres may achieve the optimal release profile. Microspheres may increase the life span of active drugs and control the release of bioactive agents too[19].

In this review chitosan is studied as a carrier for microsphere based drug delivery. Chitosan microspheres allow drug release such as antibiotics, anticancer agents, antiulcer drugs, proteins, peptide drugs and vaccines to the specific treatment. Chitosan microspheres are used to provide controlled release of many drugs and to improve the bioavailability of degradable substances such as protein, as well as to improve the uptake of hydrophilic substances across the epithelial layers. These microspheres are being investigated both for parenteral and oral drug delivery[20].

Methods of Chitosan Microspheres Preparation

Chitosan microspheres can be prepared by reacting chitosan with controlled amounts of multivalent anion resulting in cross-linking between cationic chitosan molecules. The cross-linking may be achieved in acidic, neutral, or basic environments depending on the applied method. Chitosan microspheres are prepared by various methods such as solvent evaporation, emulsification solvent evaporation, multiple emulsion, emulsification phase separation, ionotropic gelation, wet phase inversion, spray drying, coacervation precipitation, spray

hardening, reverse micellar, emulsion-droplet coalescence, sieving methods, double layer coating and many more[21,22].

Fundamentally, almost all the methods involves in rigidization (crosslinking/denaturation) of the chitosan polymer. Selection of any of the method depends upon various factors such as particle size requirement, thermal and chemical stability of the active drug molecule, reproducibility of the release kinetic profiles, stability of the final product and residual toxicity associated with the final product[17,18,23]. Various methods used in the preparation of chitosan micro/nanoparticles along with their role in the drug delivery system will be discussed in this review. However, selection of any particular method for preparing chitosan microspheres depends upon the nature of the active drug molecule that is to be encapsulated as well as the type of the delivery device.

1. Solvent evaporation method:

The solvent evaporation method involved preparation of emulsion with different external phases which depends on the nature of the polymer and the drug[24]. Bogataj *et al.,* was prepared microspheres by solvent evaporation method. The drug solution was dispersed in chitosan solution and then this mixture was emulsified in liquid paraffin and stirred. The suspension of microspheres was filtered, washed and dried. Addition of magnesium stearate an agglomeration preventer showed that average particle size decreased with increasing amount of magnesium stearate used for microsphere preparation[25].

2. Emulsification solvent evaporation method:

In emulsification solvent evaporation method emulsion was prepared with different external phases which depended on the nature of the polymer and the drug used for the encapsulation, microspheres obtained after evaporating solvent[26]. El-Hameed and Kellaway developed chitosan microspheres by the w/o emulsification solvent evaporation technique for nasal administration by insufflations[27]. This method was not found suited for hydrophilic drug prepared with chitosan due to low entrapment of the drug[28]. For the hydrophobic drugs the method is changed, an organic internal phase must have taken in emulsion formation. Genta *et al*., prepared ketoprofen loaded chitosan microspheres by applying this method[29]. The other authors investigated cross linking which can be achieved by heating or by means of chemical cross linking agents including glutaraldehyde, formaldehyde, and citric acid[30,31]. Chitosan is dissolved in an acidic medium, the drug is dispersed by ultra-sonication and magnetic stirrer in it. Consequently, aqueous phase is dropped into an oil phase (liquid paraffin) with a dispersing agent Span-80 and stirred it. After formation of emulsion cross linking agent (glutaraldehyde-saturated toluene) is added and stirred in order to harden the microspheres. Microspheres must be washed with petroleum ether, distilled water and isopropanol. To remove glutaraldehyde, the microspheres must be once washed with a 5% solution of metabisulphite to avoid harmfulness on administering into the body[32-34]. Indomethacin microspheres also can be prepared by using Citric acid, as a cross-linking agent. Many investigators studied and explored the proportion of various cross linking agents and found that density of the microspheres depends on addition of percentage of cross linking agent[35-38].

3. Multiple emulsion method:

Multiple emulsion method is the choice of methods used to encapsulate water soluble drugs, peptides, proteins and vaccines with higher entrapment efficiency. Ogawa *et al.,* prepared poly lactic-glycolic acid (PLGA) microspheres for controlled release drug delivery. Primary water-in-oil (w/o) emulsion is prepared to permit the dispersion of the protein in the wall material containing organic phase. In second step a water-in-oil-in-water (w/o/w) emulsion is prepared in an aqueous phase containing a surface-active agent. Finally, the organic solvent is extracted and leading to the formation of solid microspheres. The exposure of a protein to various factors unfavourable for stability such as organic solvents and polymer degradation may promote deactivation during this process[39]. Crotts & Park found that encapsulated enzyme severely hydrolysed with fast degrading PLGA due to an acidic microenvironment generated from polymer degradation[40].

4. Emulsification Phase Separation Method:

In this method microspheres are prepared by addition of drop wise polymer solution into the liquid paraffin containing emulsifying agent and stirred. Cross-linking agent is added in the prepared emulsion, centrifuged at 4000 rpm, washed with diethyl ether for several times and finally with acetone and obtained microspheres dried at room temperature. These microspheres show sustained release kinetics > 10 h with greater encapsulation efficiency[41]. Emulsification cross-linking is a one of the remarkable methods, used for the formulation of microsphere. Chitosan solution was prepared in 1% (v/v) acetic acid; drug was dispersed in polymer solution. This dispersed phase was added to the continuous phase (light liquid paraffin and heavy liquid paraffin in the ratio of 1:1) containing surfactant (span 80) through a disposable syringe (10 ml). After 20 min of stirring, cross linking agent aqueous gluteraldehyde (25% v/v) was added drop wise. The formulation was centrifuged at 3000 rpm; obtained microspheres were washed 4 times with petroleum ether and then air dried at room temperature, collected and stored in desiccators. The drug loaded microspheres showed higher 72-94% of entrapment and extended release up to 12h[42].

5. Ionotropic Gelation Method:

Many authors utilized ionotropic gelation method for formulating chitosan beads. This method comprises preparation of emulsion and subsequent cross-linking of the chitosan present in inner aqueous phase of the emulsion. This method involves ionic interaction between a cross-linking agent with negative charge (e.g. sodium

dioctylsulphosuccinate) and chitosan polymer. This technique also involves the ionic cross-linking of chitosan with low molecular weight counter ions (pyrophosphate, tri polyphosphate, tetra polyphosphate, octa polyphosphate, hexametaphosphate and, hydrophobic counter ions e.g. alginate, carrageenan, poly-1-hydroxy-1-sulphonate-propene-2, polyaldehydro-carbonic acid) and high molecular weight ions (octyl sulphate, lauryl sulphate, hexadecyl sulphate, cetylstearyl sulphate. Sodium tripolyphosphate (TPP) is commonly used to aggravate the ionotropic gelation of chitosan. In the year 1989 Bodmeier *et al.,* developed chitosan beads by ionotropic gelation method with TPP[43]. Moreover, Anal *et al.,* developed multilayer beads with improved properties for controlled delivery of the antibiotic ampicillin by ionotropic gelation method with TPP. These beads encapsulate higher concentration of ampicillin. During incubation in simulated gastric fluid, the beads swelled and started to float but did not show any sign of erosion[44].

A combination of the ionotropic gelation method and emulsification method was described by Ko*et al*., in this method lipophilic drug felodipine was dissolved in methylene chloride and emulsified it with chitosan. The resulting o/w emulsion was then dropped through a spray gun into a 10% TPP solution[45].

6. Wet Phase Inversion:

In this method of preparation, chitosan solution in acetic acid was dropped into an aqueous solution of a counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1 h, washed and cross linked with 5% ethylene glycol diglycidyl ether. Finally, the microspheres were washed and freeze-dried to form porous chitosan microspheres[46].

7. Spray Drying Method:

Spray drying is a relatively simple process that has been industrially used since 1927 and that consists of spraying a solution of the polymer, in which the drug is solubilized, inside a chamber at high temperature. When the liquid is fed into the nozzle through a peristaltic pump, atomization occurs by the force of the compressed air, disrupting the liquid in small droplets which with the hot air are blown into a chamber where the solvent in the droplets is evaporated and discharged through an exhaust tube. The micro particles formed this way are separated in a cyclone and collected in a collection bottle. The particles thus isolated usually show a shrunken shape due to the rapid evaporation of the solvent and the formation of an external crust during the first stages of drying. After this external crust is formed, the solvent present in the inner parts of the droplet evaporates, leading to partial shrinkage of the particle[47]. Spray drying can be combined with some other microencapsulation methods. Chitosan-Ca-alginate micro particles for the colon-specific delivery of 5-aminosalicylic acid (5-ASA) prepared by a spray drying method followed by ionotropic gelation/polyelectrolyte complexation were evaluated. A solution of sodium alginate with the model drug was spray dried into a solution of chitosan and $CaCl_2$ in acetic acid. A dispersion of micro particles of less than 10µm was achieved. This dispersion was allowed to harden for few hours, and then the micro particles were separated by centrifugation, washed and freeze dried. These micro particles released the 5-ASA at the colon due to the increased deprotonization of chitosan at pH 6.4-7.0 that provokes chitosan microspheres can also be prepared by spray drying. Chitosan solution is sprayed, air-dried followed by the addition of a crosslinking agent. He *et al.,* reported microspheres prepared by spray drying of multiple emulsions (o/w/o or w/o/w). On the other hand, chitosan microspheres with the ability to extend the dissolution period of oxytetracycline in low pH medium were prepared by the interfacial acylation method. The result indicated that the release of oxytetracycline from various acylated chitosan microspheres was decreased with increasing the molecular weight of chitosan. A lipophilic agent such as triclosan can be encapsulated in chitosan-gelatin microcores, by spray dry method. He *et al.,* described the preparation of chitosan microspheres by novel spray drying processes[48]. Investigators reported the w/o/w emulsion spray drying method to produce chitosan microspheres loaded with hydro soluble drugs. A gelatine solution, in which the drug was dissolved, was prepared and emulsified into an ethylcellulose solution in methylene chloride. This primary w/o emulsion was then dropped into a chitosan solution, and the resulting double emulsion was spray dried in order to remove the solvent (Fig. 2).

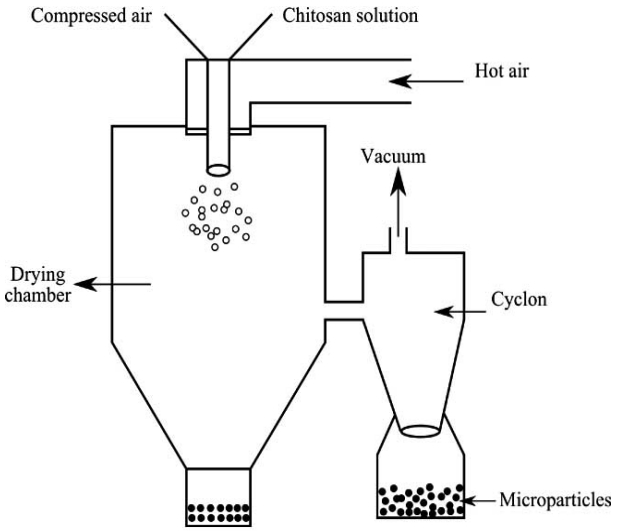

Figure 2: Diagram of spray drying process

8. Coacervation Precipitation Method:

Coacervation is the separation of a polymer solution: a dense colloid rich coacervate phase and a diluted equilibrium phase deprived of colloid or supernatant[49]. Coacervation method is of two types: simple and complex coacervation. In simple coacervation, single colloid solute is prepared while in complex coacervation aqueous polymeric solution is prepared from the interaction of two oppositely charged colloids, such as gelatin (gum arabic or silk fibroin chitosan)[50]. Microspheres are prepared without

using toxic organic solvents. Berthold *et al.,* developed prednisolone sodium phosphate loaded chitosan microspheres where sodium sulphate acted as a precipitant. It was found that on addition of sodium sulphate into the chitosan solution resulted in decreased solubility of chitosan, foremost to precipitation of chitosan[51].

It is a well-designed method for the microencapsulation of oils or solids; in the food industry, this method helps in masking a potentially bad taste and oxidation of the vitamins and/or unsaturated fatty acids[52]. Gaserod *et al*., prepared alginate-chitosan microcapsules by using two different procedures[53]. In first step homogeneous microcapsules prepared by dropping sodium alginate solution into a calcium chloride solution and these beads transferred into a chitosan solution, and in the second one sodium alginate solution directly added into a chitosan solution containing calcium ions which resulted to heterogeneous microcapsules. Chellat *et al.,* prepared microspheres from chitosan and xanthan after interaction between the two-polyionic polymers. The results proposed a better release kinetics when chitosan was complexed to xanthan[54].

9. Spray Hardening Method:

Emulsification, solvent evaporation and spray drying methods are combined in this process for the formation of microspheres. The droplets are produced by spraying while crosslinking is carried out when droplets come in contact with crosslinking agent e.g. acetic anhydride[55].

10. Reverse micellar method:

Reverse micelles prepared by mixing of water, organic solvent and surfactant. Chitosan solution, drug and cross linking agent are added with constant stirring in the prepared micelles. Transparent dry mass is obtained after evaporating organic solvent. Entrapment of drugs in reverse micelles varies from drug to drug. Mitra *et al*., encapsulated doxorubicin-dextran conjugate in chitosan nanoparticles by reverse micellar method[56]. The surfactant sodium bis(2-ethylhexyl) sulfosuccinate was dissolved in *n*-hexane. To 40 ml of surfactant solution, 100 µl of 0.1% chitosan solution in acetic acid, 200 µl doxorubicin-dextran conjugate (6.6 mg/ ml), 10 µl liquor ammonia and 10 µl of 0.01% glutaraldehyde solution were added with continuous stirring at room temperature. This procedure produced chitosan nanoparticles encapsulating doxorubicin-dextran conjugate. Solvent was removed by rotary evaporator and the dry mass was re-suspended in 5 ml of pH 7.4 Tris-HCl buffer by sonication. To this, 1 ml of 30% $CaCl_2$ solution was added drop-wise to precipitate the surfactant as calcium salt of diethylhexylsulfo succinate. The precipitate was pelleted by centrifugation at 5,000 rpm for 30 min at 48°. The pellet was discarded and the supernatant containing nanoparticles was centrifuged at 60,000 rpm for 2 h to pellet the nanoparticles. The pellet was dispersed in 5 ml of pH 7.4 Tris-HCl buffer.

11. Emulsion-droplet Coalescence Method:

The novel emulsion-droplet coalescence method was developed by Tokumitsu *et al*., which utilize the principles of both emulsion cross-linking and precipitation. However, in this method, instead of cross-linking the stable droplets, precipitation is induced by allowing coalescence of chitosan droplets with NaOH droplets. First, a stable emulsion containing aqueous solution of chitosan along with drug is produced in liquid paraffin oil and then, another stable emulsion containing chitosan aqueous solution of NaOH is produced in the same manner. When both emulsions are mixed under high-speed stirring, droplets of each emulsion would collide at random and coalesce, thereby precipitating chitosan droplets to give small size particles. Gadopentetic acid-loaded chitosan nanoparticles have been prepared by this method for gadolinium neutron-capture therapy. Since gadopentetic acid is a bivalent anionic compound, it interacts electrostatically with the amino groups of chitosan, which would not have occurred if a cross-linking agent is used that blocks the free amino groups of chitosan. Particles produced using 100% deacetylated chitosan had the mean particle size of 452 nm with 45% drug loading. Nanoparticles were obtained within the emulsion-droplet. Thus, it was possible to achieve higher gadopentetic acid loading by using the emulsion-droplet coalescence method compared to the simple emulsion cross-linking method[57].

12. Sieving Method:

Agnihotri and Aminabhavi developed a simple, innovative method to produce clozapine chitosan micro particles[58]. In this method, chitosan solution was prepared in 4% acetic acid and glutaraldehyde cross linking agent used to form a thick jelly mass. The obtained mass was sieved with a suitable mesh size to get micro particles. Un-reacted excess glutaraldehyde was removed by washing with 0.1N NaOH solution, dried overnight in an oven at 40°C. Clozapine microspheres showed high entrapment efficiency up to 98.9%. This unique method was deprive of tediousness than others but produced microparticles displayed irregularity in shape with particle sizes range from 543-698 µm. The *in vitro* release was exhibited up to 12 h, while the *in vivo* studies indicated a slow release of clozapine.

13. Coating Method:

Kala M *et al.,* formulated piroxicam loaded colon specific microspheres by chitosan and coated with Eudragit S-100 which increases the bioavailability of the drug to the targeted area in a controlled manner and reduces G.I related side effects[59]. Firstly, chitosan microspheres were prepared by emulsion crosslinking method. For that a chitosan solution (2% w/v) was prepared with 20 ml of 2% v/v aqueous acetic acid in which piroxicam was added gradually upon stirring on a magnetic stirrer and kept overnight. Aqueous phase was dispersed into 100 ml of liquid paraffin and glutaraldehyde, formulated microspheres were dried at 50°C in hot air oven. Cross-

linked chitosan microspheres were dispersed in eudragit S100 coating solution, mixture was agitated, *n*-hexane was added and kept on stirring. Eudragit S100 was dissolved in ethanol containing 0.25% v/v span 80. Coated microspheres washed with *n*-hexane for 2-3 times and dried at room temperature.

It was observed that uncoated microspheres released drug slowly but independent of pH of the dissolution fluid. It might be due to the cross linking of microspheres and higher concentration of crosslinking agent. It was observed that almost 86% of the drug was released within 10 h, indicated the need for enteric coating of the formulation for colon delivery. Moreover, coated microspheres showed no drug release in simulated gastric fluid for up to 2 h whereas in pH 7 phosphate buffer drug released about 96% in 24 h. This showed that microspheres retained their integrity up to 24 h with slowly and consistent release.

14. Double Layered Coating Method:

In the double layered coating method drug loaded Ca-alginate micro beads were developed and followed with double coating. This alginate–chitosan–k-carrageenan micro particulate system is based on ultrathin double-layered external coating of the alginate matrix. Emulsification method was used to prepare 5-ASA-loaded alginate micro particles using calcium chloride as a crosslinking agent. 2.808 g Tween-85 was added to 160 ml of cyclohexane and stirred to dissolve. Then, aqueous solution of sodium alginate and 5-ASA was added drop wise in to it. The mixture was stirred at 800 rpm for about 10 min to obtain stable emulsion. 30 ml of 0.2 M calcium chloride solution was added drop wise to the mixture to obtain cross-linked alginate micro particles, again stirred for next 30 min. Emulsion was left for 1 h to harden microspheres. Resulted micro particles were obtained after filtration and washing with distilled water[60].

Formulated micro beads were coated with chitosan and k-carrageenan. Chitosan and k-carrageenan solutions of pH 5.0 were prepared in 0.02 M acetic acid with addition of 0.15 M NaCl. Solutions were filtered by using syringe filter. To obtain each layer, the microspheres were introduced into the solutions and mixed for about 30 min. After then microspheres were filtered and washed with distilled water. It has been seen that due to the bilayer properties, the micro-carriers released the drug in better controlled manner in the intestine because micro beads were additionally protected against acidic conditions of the stomach. It was observed during study that internal chitosan layer should decrease drug's release in jejunum and the ileum of the gut and outer layer should protect the internal layer from the dissolution in the stomach. At pH 1.2, the chitosan external layer of micro particles was not soluble. In phosphate medium, chitosan coating inside the micro particle promoted a quick erosion process which accelerated drug release. The investigation showed that the release behavior depended on the dissolution media and the coating of chitosan in the micro particles. The external coating of micro particles with chitosan retarded significantly the drug release in water compared with CaAl micro particles. The effect of chitosan as coating of 5-ASA on T50, depended on the concentration of chitosan solution used for coating. A higher chitosan concentration retards drug release compared with CaAl. In acid medium, additional coating was required in the micro particle for obtaining a 5-ASA delayed release formulation

CONCLUSION

Microspheres are widely used in controlled as well as sustained drug delivery due to reduced dose frequency, improved stability, bioavailability and dissolution rate. Controlled microspheres assist the accurate delivery of drug at the particular target site and acts as a potential system to increase the bioavailability of the drugs. Chitosan is a valuable excipient with specific properties for microsphere drug delivery systems. Although, a number of techniques are present but bilayer-coated method can be promising for different diseases specially associated with colon where additional protection against acidic conditions of stomach are required. In future, with the discovery of newer techniques of formulation and by combining various other strategies, microspheres will find the central place in colon drug delivery system.

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