Natural excipients in controlled drug delivery systems

Dhara B. Patel*1 and Madhabhai M. Patel2
1Department of Pharmacy, Nootan Pharmacy college, visnagar, Gujarat.
2Department of Pharmacy, Kalol institute of pharmacy, Kalol, Gujarat.
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ABSTRACT
The emergence of controlled release (CR) technology as an effective way to enhance patient compliance and extend the life cycle of a drug has led to the need for novel ways of controlling the drug release profiles. Polymers present a logical and simple approach to control the release of drugs. Natural and synthetic polymers serve as key excipients in oral and parenteral CR formulations. The use of natural excipients for controlled delivery of the bioactive agents has been hampered by the synthetic materials. However, advantages offered by these natural excipients are their being non-toxic, less expensive and freely available. The performance of the excipients partly determines the quality of the medicines. The traditional concept of the excipients as any component other than the active substance has undergone a substantial evolution from an inert and cheap vehicle to an essential constituent of the formulation. This article gives an overview of natural excipients which are used in controlled drug delivery systems.

Keywords: Chitosan, alginate, natural gums

INTRODUCTION
Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. As the establishment of toxicity and approval from regulatory authorities poses a problem with synthetic excipients, of late more interest is being shown by researchers in natural excipients. The drawback posed by heavy metal contamination often associated with some natural excipients is superseded by their lack of toxicity, easy availability, and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Present day consumers look for natural ingredients in food, drugs, and cosmetics as they believe that anything natural will be more safe and devoid of side effects. The traditional view that excipients are inert and do not exert any therapeutic or biological action or modify the biological action of the drug substance has changed and it is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug. As natural excipients are non-toxic and compatible, they have a major role to play in pharmaceutical formulation. Some natural excipients have specific characteristics to control the drug release from the formulations to some extent. Hence, this paper is an attempt to review natural excipients used in CDDS.

POLYSACCHARIDES IN PHARMACEUTICALS
Natural polysaccharides are extensively used for the development of solid dosage forms. These polymers of monosaccharides (sugars) are inexpensive and available in a variety of structures with a variety of properties. They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. Pectins, chitosan, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in controlled release dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon which make them potentially useful in targeted delivery systems to the colon1.

Chitosan:
Chitosan is a hydrophilic biopolymer and linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (crabs, shrimp, etc.). It is a natural, non-toxic, biodegradable polysaccharide available as solution, flake, fine powder, bead and fibre. The amino group in chitosan has a pKa value of ~6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the degree of deacetylation. This makes chitosan a bioadhesive which readily binds to negatively charged surfaces such as mucosal membranes. Chitosan enhances the transport of polar drugs across epithelial surfaces, and is biocompatible and biodegradable.

Sahasathian et al.,2 developed Sustained release systems in the forms...
Shreenatha et al.3 prepared and evaluates chitosan beads for extended release of ciprofloxacin. This study shows that the release of ciprofloxacin from chitosan beads depends on its concentration in beads, chitosan and cross-linking agent concentration. The drug release was reduced with decrease in ciprofloxacin concentration and increase in chitosan and cross-linking agent concentration. The result shows that the drug release after 6 hrs for the formulation having 1%, 2% and 3% w/v chitosan were 90.57%, 78.82% and 68.18% respectively. Jayvadan et al.4 investigated the suitability of mucoadhesive microsphere of chitosan to sustain the release of the glipizide more than 12 hrs. In this study the drug to polymer ratio affect the percentage mucoadhesion, entrapment efficiency and drug release. The t50% value obtained with polymer to drug ratio 1:1, 3:1 and 6:1 were 236mins, 207 mins and 476 mins respectively shows that higher level of polymer to drug ratio fever the crosslinking reaction and thus higher t50% is obtained. Bioadhesive chitosan microspheres of pentazocine for intranasal systemic delivery significantly improved bioavailability with sustained and controlled blood levels profiles compared to intravenous, oral administration.5 Directly compressible bioadhesive tablets of ketoprofen containing chitosan and sodium alginate in the weight ratio 1:4 showed sustained release 3 hours after intraoral (sublingual site of rabbits) drug administration.6 Buccal tablets based on chitosan microspheres containing chlorhexidine diacetate showed a prolonged release of the drug in the buccal cavity. The buccal bilayered devices (bilaminated films, bilayered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic crosslinking polymers (polycarboxphil, sodium alginate, gellan gum), demonstrated that these devices show promising potential for use in controlled delivery of drugs to the oral cavity.7 The chitosan-coated nanosphere reduced significantly the blood calcium level compared with uncoated nanospheres, and the reduced calcium level was sustained for a period of 48 hours.8 Nifedipine embedded in a chitosan matrix in the form of beads showed prolonged-release of drug compared to granules.9 Chitosan/calcium alginate microcapsules containing nitrofurantoin (NF) showed sustained release of drug. Drug release into the gastric medium is found to be relatively slow compared to that into the intestinal medium.10 Chitosan-alginic acid and Chitosan-carrageenan poly electrolyte complex (PEC) has been prepared in situ in beads and microspheres for potential applications in controlled release of drug.11

**Pectins:**

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. They are predominantly linear polymers of mainly (1-4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50 000 to about 1 80 0002. Being soluble in water, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine. It was found that a coat of considerable thickness was required to protect the drug core in simulated in vivo conditions1. Hence the focus was shifted to the development of less soluble derivatives of pectin which get degraded by the colonic microflora. Calcium salts of pectin reduced their solubility by forming an egg-box configuration. To overcome the drawback of high solubility of pectin, mixed films of pectin with ethyl cellulose were investigated as a coating material for colon-specific drug delivery. These films combined the colon specific degradation properties of pectin with the protective properties of the water insoluble polymer ethyl cellulose2. Polymeric hydrogels are widely used as controlled release matrix tablets. Sungthongjeen et al.12 investigated the high-methoxy pectin for its potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the in vitro release studies showed that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and the type of pectin in the matrix tablets. In relation to cosmetics, using citronellal as a model compound, pectin gel formulations were evaluated for controlled fragrance release by kinetic and static methods. These formulations showed a prolonged duration of fragrance release and limitation of fragrance adsorption to the receptor skin layers. The increase in pectin concentrations suppressed the fragrance release by a diffusion mechanism, thereby proving that pectin/calcium microparticles are promising materials for controlled fragrance release13.

**Alginates:**

Alginates are natural polysaccharide polymers isolated from
the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. A linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain, these homogeneous blocks (composed of either acid residue alone) are separated by blocks made of random or alternating units of mannuronic and guluronic acids. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications (fig. 1). Bioadhesive sodium alginate microspheres of metoprolol tartrate for intranasal systemic delivery were prepared to avoid the first-pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris. The microspheres were prepared using emulsification-crosslinking method. In vivo studies indicated significantly improved therapeutic efficacy of metoprolol from microspheres, with sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with oral and nasal administration of drug solution. A new insert, basically consisting of alginates with different hydroxyethylcellulose content was developed to maintain a constant drug level over a certain period in the eye, which cannot be achieved by conventional eye drop application. This study showed good tolerance of the new calcium-alginate-insert applied to the ocular surface for controlled drug release.

In order to achieve 24 h release profile of water soluble drugs, sodium alginate formulation matrices containing xanthan gum or zinc acetate or both were investigated.

The release of the drug from the sodium alginate formulation containing only xanthan gum was completed within 12 h in the simulated intestinal fluid, while the drug release from the sodium alginate formulation containing only zinc acetate was completed within 2 h in the same medium. Only the sodium alginate formulation, containing both xanthan gum and zinc acetate achieved a 24 h release profile, either in the simulated intestinal fluid or in the pH change medium (pH 1.2). The helical structure and high viscosity of xanthan gum possibly prevent zinc ions from diffusing out of the ranitidine HCL sodium alginate-xanthan gum-zinc acetate matrix so that zinc ions react with sodium alginate to form zinc alginate precipitate with a cross-linking structure. The crosslinking structure might control a highly water-soluble drug release for 24 h. In a comparative study, alginate formulation appeared to be better than the poly lactide-co-glycolide (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs - clotrimazole and econazole. The nanoparticles were prepared by the emulsion-solvent-evaporation technique in case of PLG and by the cation-induced controlled gelification in case of alginate.

**Starches:**

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as is also the ratio of the content of the principal constituents, amylose and amylopectin. A number of starches are recognized for pharmaceutical use (fig. 2). These include maize (Zea mays), rice (Oryza sativa), wheat (Triticum aestivum), and potato (Solanum tuberosum). Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems. It was prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol. The advantages of the material include ease of tablet preparation, the potential of a constant release rate (zero-order) for an extended period of time and its ability to incorporate high percentages of drugs with different physicochemical properties. Acetylation of starch considerably decreases its swelling and enzymatic degradation. Thus, starch acetate (SA) based delivery systems were tested for controlled drug delivery. It was proved that acetylation of potato starch can substantially retard drug release by preparing and evaluating films of native starch and acetylated starch. Bovine serum albumin (BSA, mol. wt. 68 000), FITC-dextran (mol. wt. 4400), timolol mol. wt. 332, log P=1.91) and sotalol-HCl (mol. wt. 308, log P=-0.62) were used as model drugs.

**Fig. 2: Structures of (A) amylopectin or α amylase and (B) β-amylase.**

All the model drugs were released rapidly from the potato starch film in PBS pH 7.4 with and without alpha-amylase in the dissolution medium (t50% varied from 0.17 to 3.37 h). When compared to the potato starch film, all the studied drugs were released at a substantially slower rate from the SA films in the corresponding media. A comparative study was carried out to evaluate drug release from the SA microparticles (SA mps) and SA films. The average degree of acetyl substitution (DS) per glucose residue in the starch was either 1.9 (SA DS 1.9) or 2.6 (SA DS 2.6). Timolol, calcein and BSA were used as model drugs. This study demonstrated the achievement of slow re-
lease of different molecular weight model drugs from the SA mps and films as compared to fast release from the native starch preparations.

GUMS

Gums are translucent and amorphous substances produced by the plants. Usually pathological products, gums are produced when the plant is growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic acid.

Guar gum:

Guar gum derived from the seeds of cyamopsis tetragonolobus (Family Leguminosae) is a naturally occurring galactomannan polysaccharide. It is made up of a linear chain of $\beta$-D-mannopyranose joined by 1-6-(1-4) linkage with a-D-galactopyranosyl units attached by 1, 6- links in the ratio of 1:22 (p. g. 3). Guar gum is used in colon-delivery systems due to its drug release retarding property and susceptibility to microbial degradation in the large intestine. Core tablets containing 5-aminosalicylic acid (5-ASA) were prepared by wet granulation with starch paste and were compression coated with coating formulations containing different quantities of guar gum. The study confirmed that selective delivery of 5-ASA to the colon can be achieved using guar gum as a carrier in the form of a compression coating over the drug core. Further, guar gum-based matrix tablets of rofecoxib were prepared for their intended use in the chemoprevention of colorectal cancer. In vivo studies showed delayed Tmax, prolonged absorption time and decreased Cmax indicating that rofecoxib was not released significantly in stomach and small intestine, but was delivered to colon resulting in a slow absorption of the drug and making it available for local action in human colon. In an attempt to design oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets, trimetazidine dihydrochloride was chosen as a model drug because of its high water solubility. Both matrix tablets as well as three layer matrix tablets were prepared and evaluated. The three-layer guar gum matrix tablet provided the required release rate on par with the theoretical release rate for guar gum formulations meant for twice daily administration. The results indicated that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as trimetazidine dihydrochloride. The same study was carried out by using metoprolol tartrate a model drug with high solubility. The results indicated that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as metoprolol tartrate. Another water-soluble drug, diltiazem HCl has been given controlled release comparable with marketed sustained release diltiazem HCl tablets (D-SR tablets), which are prepared in the form of matrix tablets with guar gum using the wet granulation technique.

Gum acacia:

Gum acacia or gum arabic is the dried gummy exudate obtained from the stem and branches of Acacia senegal (Linne) Willdenow and other related species of acacia (Family Leguminosae). The gum has been recognized as an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges and as a tablet binder. Sustained release of ferrous sulfate was achieved for 7 h by preparing gum arabic pellets. Release was further sustained for more than 12 h by coating the pellets with polyvinyl acetate and ethylene vinyl acetate, respectively. An increase in the amount of gum Arabic in the pellets decreased the rate of release due to the gelling property of gum arabic. The gel layer acts as a barrier and retards the rate of diffusion of FeSO4 through the pellet. Gum arabic was used as an osmotic, suspending and expanding agent in the preparation of a monolithic osmotic tablet system (MOTS) with two orifices on both side surfaces. Water-insoluble naproxen was selected as the model drug. The optimal MOTS was found to be able to deliver naproxen at a rate of approximately zero order up to 12 h in pH 6.8. Cumulative release at 12 h is 81%, and is independent of environment media and stirring rate. Therefore, these MOTS can be used in the oral drug-controlled delivery field, especially for water-insoluble drugs.

Karaya gum:

Karaya gum is obtained from Sterculia urens (Family sterculiaeae) is a partially acetylated polymer of galactose, rhamnose, and glucuronic acid. Swellable hydrophilic natural gums like xanthan gum and karaya gum were used as release-controlling agents in producing directly compressed matrices. Caffeine and diclofenac sodium, which are having different solubilities in aqueous medium were selected as model drugs. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds. In case of xanthan gum neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the lower proportion of gum produced a lesser degree of hydration. In contrast, karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Hence it was concluded that drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of drug. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices. Park et al. showed that mucoadhesive tablets prepared by karaya gum for buccal delivery, had superior adhesive properties as compared to guar gum and was able to provide zero-order drug release, but concentrations greater than 50% w/w may be required to provide suitable sustained release.

Xanthan gum:

Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone ($\beta$-D-glu-
Fig. 3: Structure of alginic acid.

Fig. 4: Structure of guar gum.

Fig. 5: Structure of xanthan gum.

Fig. 6: Structure of Locust bean gum
Tamarind gum

Tamarind gum is obtained from endosperm of seeds of the tamarind tree, which is a seed gum. Chemically tamarind kernel powder is highly branched carbohydrate polymer. Its backbone consists of D-glucose units joined with (1→4) b-linkages similar to that of cellulose. It consists of a main chain of b-D-(1→4)-galactopyranosyl unit with a side chain of single xylopyranosyl unit attached to every second, third and fourth of D-glucopyranosyl unit through a-D-(1→6) linkage (as shown in Fig 1). Tamarind kernel powder disperses and hydrates quickly in cold water but does not reach maximum viscosity unless it is heated for 20-30 mins.

Locust bean gum

Locust bean gum is extracted from the endosperm of the seeds of the carob tree Ceretonia siliqua, composed of a 1-4-linked b-D-mannan backbone with 1-6-linked a-D-galactose side groups which may be described chemically as galactomannan. The physicochemical properties of galactomannan are strongly influenced by the galactose content and the distribution of the galactose units along the main chain. Longer galactose side chains produce a stronger synergistic interaction with other polymers and greater functionality. It is dispersible in either hot or cold water, forming a solution having a pH between 5.4 and 7.0. Locust Bean Gum used as a granulating and binding agent for tablets 41. Locust bean gum is the controlled reversion excipient and it is used in oral solid dosage forms 42. By utilizing retention properties of xanthan gum and releasing properties of galactomannan, desire release profile was achieved in delivery of theophylline. Hydrophilic. The matrices prepared by combination of both gums were able to produce near zero-order drug release. The XG (conc 8%) tablets provided the required release rate (about 90% at the end of 8 h), with zero-order release kinetics.

Venkataraju et al., prepared matrix tablets for oral controlled delivery of propranolol hydrochloride containing Xanthan and locust bean gum. The result shows that locust bean gum has a synergistic action with the xanthan gum to produce a controlled release effect. The formulation was found to provide the required release rate, with zero-order release kinetics.

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It is used as potential polysaccharide having high drug holding capacity for sustained release of verapamil hydrochloride. The release pattern was found to be comparable with matrices of other polysaccharide polymers such as ethyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose, as well as the commercially available sustained release tablets (isoptin SR). It is also used as suitable polymer for sustained release formulations of low drug loading. Sustained release behaviors of both water soluble (acetaminophen, caffeine, theophylline and salicylic acid) and water insoluble (indomethacin) drugs on tamarind seed polysaccharide was examined. Studies showed that tamarind seed polysaccharide could be used for controlled release of both water-soluble and water insoluble drugs. Zero order release can be achieved taking sparingly soluble drugs like indomethacin from tamarind seed polysaccharide. The rate of release can be controlled by using suitable diluents like lactose and microcrystalline cellulose. For water-soluble drugs, the release amount can also be controlled by partially crosslinking the matrix. The extent of release can be varied by controlling the degree of crosslinking. The mechanism of release due to effect of diluents was found to be anomalous and due to crosslinking was found to be supercase II.
a period of 7.5 hour. A credible correlation was obtained amongst swelling index, viscosity, and surface roughness of the polysaccharide particles and in vitro dissolution profile of spheroids. In the comparative bioavailability study the developed spheroids have able to sustained drug release and also was found to improve the extent of absorption and bioavailability of drug.28

Tragacanth:

This gum is obtained from the branches of Astragalus gummifer, Family Leguminosae. Tragacanth when used as the carrier in the formulation of 1- and 3-layer matrices produced satisfactory release prolongation either alone or in combination with other polymers.34

CONCLUSION

Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of CDDS. As the natural excipients are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition natural excipients are non-toxic, freely available, and less expensive compared to their synthetic counterparts. Therefore, in the years to come, there is going to be continued interest in the natural excipients to have better materials for controlled drug delivery systems.

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