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Review

Psyllium as therapeutic and drug delivery agent

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Abstract

There is no doubt that fibers, in particular viscous dietary fibers, have positive effects on human health, both in the prevention and in treatment of chronic diseases. Dietary fibers from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight control, to regulation of glucose control for diabetic patients and reducing serum lipid levels in hyperlipidemics. Keeping in view, the pharmacological importance of psyllium polysaccharide and its gel-forming nature, this article discusses the therapeutic value of psyllium for the treatment of constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia and exploitation of psyllium for developing drug delivery systems.

Keywords: Psyllium; Hydrogels; Controlled drug delivery devices; Therapeutic agent

Contents

1. Introduction

Psyllium is the common name used for several members of the plant genus *Plantago*. Psyllium and ispaghula husk

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(similar uses differ in doses) terms interchangeably used in the text, psyllium is derived from the dried, ripe seeds of *Plantago psyllium* (synonym for *Plantago afra* L.) and from *Plantago indica* L., but ispaghula husk is derived from the ripe seeds of *Plantago ovata Forsskaol* (synonym for *Plantago isphagula Roxburgh*) (Blumenthal et al., 2000). The seeds of psyllium are used commercially for the production of mucilage. The mucilage obtained from the seed coat by mechanical milling/grinding of the outer layer of the seeds. It is a white fibrous hydrophilic material and forms the clear colorless mucilaginous gel by absorbing water. The gel nature and composition of the polysaccharides extracted from the seeds of the *P. ovata* has been reported in literature (Kennedy et al., 1979; Sandhu et al., 1981; Laidlaw and Purcival, 1950). Fischer et al. have studied the physiologically active, gel-forming fraction of the alkali-extractable polysaccharides of *P. ovata Forsk* seed husk (psyllium seed) and some derived partial hydrolysis products by compositional and methylation analysis and NMR spectroscopy. Chemical and physical studies of the active fraction of psyllium mucilage shows that it has arabinose 22.6%, xylose 74.6%, molar basis; only traces of other sugars. With about 35% of non-reducing terminal residues, the polysaccharide is highly branched. The data are compatible with a structure consisting of a densely substituted main chain of β-(1 → 4)-linked D-xylopyranosyl residues, some carrying single xylopyranosyl side chains at position 2, others bearing, at position 3, trisaccharide branches having the sequence L-Araf-α-(1 → 3)-D-Xyl*p*-β-(1 → 3)-L-Ara*f*. The presence of this sequence is supported by methylation and NMR data, and by the isolation of the disaccharide 3-*O*-β-D-xylopyranosyl-L-arabinose as a product of partial acid hydrolysis of the polysaccharide (Fischer et al., 2004).

Psyllium has been reported as a medicinally active natural polysaccharide. It has been used for the treatment of constipation (Bouchoucha et al., 2004; Ramkumar and Rao, 2005), diarrhea (Washington et al., 1998), inflammation bowel diseases-ulcerative colitis (Fernandez-Banares et al., 1999), obesity in children and adolescents (Pittler and Ernst, 2004), high cholesterol (Rodriguez-Moran et al., 1998; Moreyra et al., 2005; Romero et al., 2002; Anderson et al., 1995, 1999, 2000a,b) and diabetes (Anderson et al., 1999; Florholmen et al., 1982; Fagerberg, 1982; Gupta et al., 1994; Fukagawa et al., 1990; Pastors et al., 1991). Keeping in view, the pharmacological importance of psyllium polysaccharides, this article review the therapeutic importance of psyllium for the treatment of constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia. This article also discusses the drug release studies carried out from the psyllium and psyllium based drug delivery devices.

2. Psyllium as therapeutic agent

Psyllium has been reported for the treatment of constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia.

2.1. Constipation

Constipation can be defined as infrequent or hard pellet stools or difficulty in evacuating stool. Passing one or more soft, bulky stools every day is a desirable goal. The stomach churns and mixes food for digestion and the near-liquid food then enters the small intestine, which ends in the right-lower abdomen where it enters the colon. The colon withdraws water from the liquid stool, so that by the time it reaches the rectum, there is a soft formed stool. If an excessive amount of water is extracted, the stool can become hard and difficult to expel. Constipation is often caused by colon that does not contract properly and fails to move the stool to the rectum. After serious problems are excluded, chronic constipation usually responds to simple measures, such as adding fiber, bran or a bulking agent to the diet. Psyllium is one of the most widely used bulking agents worldwide. This drug increases the frequency and weight of stools, softens hard stools, and reduces pain at defecation. A recent study demonstrated its superior effect compared with sodium docusate (Reynolds and Martindale, 1993; Ashraf et al., 1995; J.W. McRorie et al., 1998; J. McRorie et al., 1998).

Psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight (Kumar et al., 1987) and ameliorating chronic diarrhea (Qvitzau et al., 1988). Psyllium is a common ingredient in bulk laxative products, and several studies suggest that psyllium may provide benefits for treating constipation (Fernandez-Banares, 2006). There is a scientific basis for psyllium working as a mild laxative. This evidence, combined with the available research in humans, suggests that psyllium decreases the time necessary to pass bowel movements, increases the number of bowel movements per day and increases the amount of stool passed. Psyllium is renowned for its mucilaginous properties and, when the seeds are soaked in water, they increase, from 8 to 14 times, their original size. This gelatinous mass promotes peristalsis, hydration of the feces, provides a laxative exertion, relieves chronic constipation and produces a soft stool: as it lubricates, softens and increases fecal volume and viscosity. It may also relieve irritable bowel syndrome, diverticulitis, mucus colitis, cystitis, gastrointestinal ulcers and diarrhea (Thompson et al., 1999; Stevens et al., 1988; J. McRorie et al., 1998; Burton and Manninen, 1982). Psyllium is an excellent source of fiber, which also has direct action on the bowel. Acting like a bottle-brush, psyllium cleanses the bowel and by promoting peristaltic action of the muscles, motivates bowel movement. When using psyllium it is essential to drink plenty of water, so that the psyllium is able to swell, absorbing water to develop the mucilage action. Studies have shown that psyllium is more beneficial than bran, in maintaining regularity. First-line treatment for patients complaining of chronic constipation may involve the use of osmotic laxatives, lubricating agents, dietary fiber, bulk-forming agents or rectal evacuants (Krammer et al., 2005; Wang et al., 2005; Ramkumar and Rao, 2005; Bouchoucha et al., 2004). The choice depends on whether the clinical context is suggestive of slow transit or evacuation disorders (Degen and Phillips, 1996; Heaton et al., 1991; Heaton and O'Donnell, 1994; Koch et al., 1997).

During one study, it was found that the majority of the stool collected after psyllium dose, was gelatinous and the gel fraction isolated from stool contained 75% carbohydrate; most of this carbohydrate was xylose (64%) and arabinose (27%), the same two sugars that account for the majority (79%) of the carbohydrate in psyllium (Marlett et al., 2000). This gel provided lubrication that facilitated propulsion of colon contents and produced a stool that was bulkier and moister than were stools resulting with use of comparable amounts of other bowel-regulating fiber sources. Most dietary fiber sources promote laxation by increasing colonic contents, which stimulates propulsion. Unlike most other fibers that affect large bowel physiology, psyllium increases the concentration of water in stool and produces a "slick" stool that is easy to pass (Eastwood et al., 1980; Spiller et al., 1979; Stevens et al., 1988; Marteau et al., 1994).

In contrast with other viscous fibers that are fermented completely in the colon, a component of psyllium is not fermented. Unfermented or incompletely fermented fiber and the accompanying moisture it holds, are two contributors to increased stool mass (Cummings, 1993) and providing substrate for microbial growth. The greater bacterial mass and accompanying water further increase stool weight (Stephen and Cummings, 1980; Chen et al., 1998). In most of the studies, the additional stool mass produced by consumption of more dietary fiber contains the same proportion of moisture as do low-fiber stools (Eastwood et al., 1980; Prynne and Southgate, 1979). It is also reported that psyllium increases stool frequency, weight and decreases stool consistency in constipated patients. These effects are not associated with significant changes in colorectal motility. The clinical parameters were not significantly affected by treatment with psyllium although there was a significant decrease in transit time (Mamtani et al., 1990; Heaton et al., 1992; Lederle, 1995; Karaus and Wienbeck, 1991; Bassotti et al., 1994). People with neurological disease have a much higher risk of both fecal incontinence and constipation than the general population. There is often a fine line between the two conditions, with any management intended to ameliorate one risking precipitating the other. Bowel problems are observed to be the cause of much anxiety and may reduce quality of life in these people (Coggrave et al., 2006).

2.2. Diarrhea

In case of diarrhea, one liquid stool each day or several soft, semiformed stools each day or frequent watery stools throughout the day and even the night or stool is made up mostly of water happen. There are many causes of diarrhea such as food (hot pepper, milk sugar lactose fatty foods), chemical laxatives (magnesium, phenolphthalein, sorbitol), new drug (antibiotics) and infection (bacteria, virus). Several studies suggest that psyllium may provide benefits for people with diarrhea, especially for patients being tube-fed. There is a scientific basis for psyllium working to increase the bulk of stools. This evidence, combined with the available research in humans, suggests that psyllium increases the number of normal stools and decreases the number of liquid stools (Belknap et al., 1997). Wenzl and coworkers have concluded that the normal intestine delivers stools that differ widely in quantity but maintains percent fecal water within a narrow range. Stool looseness in diarrhea is determined by the ratio of fecal water-to-water-holding capacity of insoluble solids. In patients with diarrhea with normal stool weight, loose stools are due to low output of insoluble solids without the concomitant reduction in water output that occurs in normal subjects when insoluble solids are low (Wenzl et al., 1995).

Psyllium has been reported to inhibit lactulose-induced colonic mass movements and to benefit patients with irritable bowel syndrome, improving both constipation and diarrhea. Psyllium delays gastric emptying, probably by increasing meal viscosity, and reduces the acceleration of colon transit, possibly by delaying the production of gaseous fermentation products (Washington et al., 1998). A combination of psyllium and calcium seems to be a cheap and effective alternative to conventional treatment of chronic diarrhea (Qvitzau et al., 1988). Dairy calves under 14 days of age with naturally occurring, uncomplicated diarrhea were treated for 3 days with a hypertonic oral electrolyte solution with or without psyllium. Fecal consistency was markedly different in psyllium-fed calves as compared with control calves within 24 h of psyllium supplementation (Cebra et al., 1998). Infection with enterotoxigenic *E. coli* (ETEC) induces secretory diarrhea by stimulating net secretion of fluid and electrolytes. Psyllium ameliorates ETEC-induced diarrhea and prevents the enhanced secretory responses to calcium-mediated agonists that occur in ETEC-infected piglet jejunum (Hayden et al., 1998).

A major placebo effect occurs in patients with painful irritable bowel syndrome and is probably responsible for the efficacy of psyllium (Longstreth et al., 1981). Supplementation with dietary fiber from psyllium or gum arabic was associated with a decrease in the percentage of incontinent stools and an improvement of stool consistency. Improvements in fecal incontinence or stool consistency did not appear to be related to unfermented dietary fiber (Bliss et al., 2001). Nutritional counseling of patients nelfinavir-associated diarrhea with lactase/psyllium, calcium carbonate, and loperamide has improved stool-form consistency, bowel movement frequency, and incidents of associated morbidity (urgency, incontinence) daily. Diarrhea is a common and often inadequately treated complication in patients with human immunodeficiency virus infection. Diarrhea has a significant impact on quality of life and can contribute to malnutrition, weight loss, immunosuppression, and mortality. In addition, diarrhea may have a significant impact on compliance with antiretroviral therapy. Medications, including protease inhibitors (PIs), are recognized as a common cause of diarrhea. Treatment of PI-associated diarrhea is largely nonspecific. Agents for which some efficacy has been shown for treatment of PI-associated diarrhea include oat bran, psyllium, loperamide, calcium carbonate, SP-303, and pancrelipase (Rachlis et al., 2005). The etiology and treatment of chronic nonspecific diarrhea of childhood is still poorly understood. Smalley et al. have evaluated children with this disorder in whom other etiologies of chronic diarrhea had been ruled out. Treatment with normalization of the diet and psyllium bulk agents seems to be an effective mode of therapy for chronic nonspecific diarrhea of

childhood (Smalley et al., 1982). Various studies on use of psyllium for the treatment of diarrhea have been reported in animals (Cebra et al., 1998). Fecal consistency of two 6-year-old male sibling Amur leopards (*Panthera pardus orientalis*) suffering from the acute diarrhea steadily improved after treatment with oral metronidazole, tylosin tartrate, and psyllium fiber (Neiffer, 2001). Treatment of chronic idiopathic large bowel diarrhea in dogs with a highly digestible diet and soluble fiber has been reported (Leib, 2000).

2.3. Irritable bowel syndrome

Medically, irritable bowel syndrome (IBS) is known by a variety of other terms: spastic colon, spastic colitis, mucous colitis and nervous or functional bowel. Usually, it is a disorder of the large intestine (colon), although other parts of the intestinal tract, even up to the stomach can be affected. The colon, serves two functions in the body, first, it dehydrates and stores the stool so that, normally, a well-formed soft stool occurs and second, it quietly propels the stool from the right side over to the rectum, storing it there until it can be evacuated. This movement occurs by rhythmic contractions of the colon. When IBS occurs, the colon does not contract normally, instead, it seems to contract in a disorganized, at times violent, manner. The contractions may be terribly exaggerated and sustained, lasting for prolonged periods. These abnormal contractions result in changing bowel patterns with constipation being most common. A second major feature of IBS is abdominal discomfort or pain. This may move around the abdomen rather than remain localized in one area. These disorganized, exaggerated and painful contractions lead to certain problems. The cause of most IBS symptoms, diarrhea, constipation, bloating, and abdominal pain, are due to this abnormal physiology. Being a structural component of the plant, psyllium forms a matrix that resists hydrolysis so that absorption of free arabinose during passage through the stomach and small intestine amounts to less than 5%. Similarly, psyllium also resists colonic bacterial degradation (Marteau et al., 1994).

Chronic constipation is defined as a symptom-based disorder, for at least 3 months in a year for the unsatisfactory defecation and characterized by infrequent stools, difficult stool passage, or both. On the other hand, the presence of clinically important abdominal discomfort or pain associated with constipation defines IBS with constipation. Intake of psyllium may be effective in alleviating chronic constipation in patients without slow colonic transit or disordered constipation. On the other hand, fiber with lactulose may improve stool consistency in patients with IBS with constipation (Fernandez-Banares, 2006). In addition, treatment with a combination of psyllium and propantheline was effective, both in relieving symptoms and in the maintenance of remission (Misra et al., 1989)

The treatment of IBS is directed to both the gut and the psyche. The diet requires review, with those foods that aggravate symptoms being avoided. Large amounts of beneficial fiber can be obtained by taking over-the-counter bulking agents such as psyllium mucilloid or methylcellulose. Multiple studies have examined the use of psyllium for IBS (Arthurs and Fielding, 1983; Greenbaum and Stein, 1981; Agarwal, 1990; Tomas-Ridocci et al., 1992). Bulking agents probably relieve constipation, spasmolytics may alleviate pain and anti-diarrhoeals help control urgency and diarrhea. With a combination of reassurance and therapeutic intervention up to 75% of patients can be expected to improve. For the 25% who do not, alternative therapies such as stress management, psychotherapy or hypnotherapy may prove effective (Prior and Whorwell, 1986). Both high-fiber dietary advice and the prescription of fiber as a bulking agent are very common in primary and secondary care management of IBS. IBS patients with constipation may have delayed intestinal transit. Therefore, fibers that accelerate intestinal transit may be beneficial in these patients. The uncertain benefits reported in several clinical studies, however, have led us to reappraise the value of fiber in IBS management (Bijkerk et al., 2004). Psyllium seeds showed to be superior to wheat bran with respect to stool frequency and abdominal distension so that it should be preferred in treatment of IBS and constipation (Hotz and Plein, 1994). Prior and coworkers have found the optimum dose of psyllium in IBS, 20 g per day (Prior and Whorwell, 1987). Personality factors influence the magnitude of therapeutic response of the psyllium (Longstreth et al., 1981). The easing of bowel dissatisfaction appears to be a major reason for the therapeutic success of psyllium in IBS (Jalihal and Kurian, 1990). There is some correlation between the increase in stool weight and the improvement in symptom score but the whole gut transit time remains unchanged despite alterations in stool weight and patients' symptoms. It was suggested that psyllium might modify the response to rapidly fermentable, poorly absorbed dietary carbohydrates such as lactose, fructose, and sorbitol, which have been implicated in some studies of IBS (Andersson and Nygren, 1978; Symons et al., 1992; Friedman, 1991). The well-recognized benefit of psyllium in IBS is partly due to its treatment of constipation but psyllium also benefits those with diarrhea and pain (Kumar et al., 1987)

2.4. Inflammatory bowel disease-ulcerative colitis (Crohn's disease)

Crohn's disease is a chronic, recurrent inflammatory disease of the intestinal tract. The intestinal tract has four major parts: the esophagus, or food tube; the stomach, where food is churned and digested; the long, small bowel, where nutrients, calories, and vitamins are absorbed; and the colon and rectum, where water is absorbed and stool is stored. The two primary sites for Crohn's disease are the ileum, which is the last portion of the small bowel (ileitis, regional enteritis), and the colon (Crohn's colitis). The condition begins as small, microscopic nests of inflammation, which persist and smolder. The lining of the bowel can then become ulcerated and the bowel wall thickened. Eventually, the bowel may become narrowed or obstructed and surgery would be needed. A small number of studies have examined the ability of psyllium to maintain remission in ulcerative colitis (Kanauchi et al., 2003; Mitsuyama, 2005; Hallert et al., 1991). Dietary fiber has been proven to be beneficial in maintaining remission in human ulcerative colitis, an effect related with an increased luminal production of short-chain fatty acids (SCFA). Dietary fiber supplementation ameliorated colonic damage in HLA-B27

transgenic rats. This effect was associated with an increased production of SCFA, which can act synergistically in inhibiting the production of pro-inflammatory mediators (Rodriguez-Cabezas et al., 2003). *n*-Butyrate enemas may be effective in the treatment of active distal ulcerative colitis. Because colonic fermentation of psyllium yields *n*-butyrate, a significant increase in fecal *n*-butyrat levels was observed after *P. ovata* seed administration. Hence, psyllium might be as effective as mesalamine to maintain remission in ulcerative colitis (Fernandez-Banares et al., 1999).

Because the intestinal microflora plays an important role in the development of inflammatory bowel disease (IBD), there is currently some interest in the manipulation of the composition of the microflora towards a potentially remedial community. Kanauchi et al. have summarized the clinical and experimental efficacy of the manipulation of microflora by the use of prebiotics, probiotics, synbiotics, and antibiotics in IBD. Prebiotics, defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of bacterial species already resident in the colon, can modulate the colonic microbiota by increasing the number of specific bacteria and thus changing the composition of the microbiota. Prebiotics for IBD include lactosucrose, oligofructose, insulin, bran, psyllium, and germinated barley foodstuff (Kanauchi et al., 2003; Mitsuyama, 2005). The efficiency of psyllium in relieving gastrointestinal symptoms in patients with ulcerative colitis in remission was studied in a placebo-controlled trial running for 4 months. Grading of symptoms judged psyllium consistently superior to placebo and associated with a significantly higher rate of improvement (69%) than placebo (24%) (Hallert et al., 1991).

2.5. Colon cancer

Cancer of the colon is a major health problem and it ranks as a leading form of cancer, along with lung and breast cancer. Importantly, colon cancer is also one of the most curable forms of cancer. When detected early, more than 90% of patients can be cured. This disease begins in the cells that line the colon. There now is strong medical evidence that there are abnormal genes for colon polyps and cancer that can be passed from parent to child. The genes within each cell are the hereditary structures that tell the cell what it should do. When these controlling genes are absent, there is a tendency to grow polyps. The cells in the polyp eventually become uncontrolled and turn into a cancer. Colon cancer also can develop with other conditions, such as ulcerative colitis, a chronic inflammation in the colon. The human epidemiology indicates an inverse correlation between high-fiber consumption and lower colon cancer rates. Possible mechanisms by which fibers may inhibit colon tumorigenesis include dilution and adsorption of any carcinogens and/or promoters contained within the intestinal lumen, the modulation of colonic microbial metabolic activity, and biological modification of intestinal epithelial cells. Dietary fibers not only bind carcinogens, bile acids, and other potential toxins but also essential nutrients, such as minerals, which can inhibit the carcinogenic process. Fermentation of fibers within the large bowel results in the production of SCFA, which in vivo stimulate cell proliferation, while *n*-butyrate appears to be antineoplastic in vitro (Jacobs, 1986). SCFA (C2–C6) are produced in the colon through bacterial fermentation of mainly dietary fiber. *n*-Butyrate possesses antineoplastic effects on human colon carcinoma cells. The role of dietary fiber during colorectal carcinogenesis might therefore be related to its fermentation to *n*-butyrate. The ratio of *n*-butyrate production to total SCFA production from fiber, however, was reduced in patients with colonic cancer and adenomas compared with healthy controls. It may be that the low ratios of colonic *n*-butyrate formation combined with low-fiber diets increase the risk of colonic neoplasia (Clausen et al., 1991).

Fecal *n*-butyrate concentrations of patients with colorectal cancer were reported to be lower than those of healthy controls. Psyllium delayed the fermentation rate of high-amylose cornstarch in the cecum and shifts the fermentation site of starch toward the distal colon, leading to the higher *n*-butyrate concentration in the distal colon and feces (Morita et al., 1999). The presence of *n*-butyrate in the distal colon may be important in the prevention of colon cancer because the majority of tumors in both humans and experimentally induced rodent cancer models occur in the distal colon (Bufill, 1990; Holt et al., 1996). The end products of microbial carbohydrate fermentation in the large bowel include SCFA, among which acetate, propionate and *n*-butyrate are quantitatively most important. SCFA have a range of effects that may be relevant to colonic health (Cummings, 1981; Pouillart, 1998). Of these, *n*-butyrate is of particular interest because it exerts a concentration-dependent slowing of the rate of cancer cell proliferation and promotes expression of differentiation markers in vitro, leading to reversion of cells from a neoplastic to a non-neoplastic phenotype (Kim et al., 1980; Whitehead et al., 1986; Willson, 1989). Fermentation is normally more active in the cecum and proximal colon than in the distal colon (Cummings and Englyst, 1987; Mitchell et al., 1985). For these reasons, highly fermentable dietary fibers such as pectin, guar gum and oat bran are fully fermented in the cecum and proximal colon and do not contribute *n*-butyrate to the distal colon (Lupton and Kurtz, 1993; McIntyre et al., 1991). This also might be the case for resistant starches such as high-amylose cornstarch (HAS) which has a fast fermentation rate (Topping et al., 1997; Morita et al., 1998, 1999). Therefore, it should be meaningful to establish a method by dietary manipulation to shift the fermentation site of HAS and to increase *n*-butyrate production in the distal colon and feces. Such delivery system of starch to the site where the incidence of colon cancer is higher might be of value to better understand the effects of *n*-butyrate on the large bowel physiology. Physical exercise, use of psyllium and aspirin, reduced risk of colon cancer (Juarranz et al., 2002). Psyllium strongly reduced the tumorigenicity of 1,2-dimethylhydrazine and psyllium-fed rats had the highest fecal aerobic counts, lowest beta-glucuronidase, and highest 7-alpha-dehydroxylase activities (Roberts-Andersen et al., 1987). Psyllium fiber provided colonocytes some protection from deoxycholic acid-induced lysis. Propionic acid, a product of fiber breakdown, was a potent colonocyte mitogen, suggesting that fiber could indirectly pro-

tect the colon by providing colonocyte nutrients (Friedman et al., 1988).

2.6. Diabetes

The human body needs blood glucose to be maintained in a very narrow range. Insulin and glucagons are the hormones, which make this, happen. It is the production of insulin and glucagons by the pancreas, which ultimately determines if a patient has diabetes, hypoglycemia, or some other sugar problem. Psyllium has been proposed as a possible treatment for high blood sugar levels. Studies in humans suggest moderate reductions in blood sugar levels after a single dose of psyllium, with unclear long-term effects (Jenkins et al., 2000; Wolever et al., 1991; Watters and Blaisdell, 1989; Uribe et al., 1985; Clark et al., 2006; Ziai et al., 2005; Brennan, 2005). Water-soluble dietary fibers decrease postprandial glucose concentrations and decrease serum cholesterol concentrations to men with type 2 diabetes (Anderson et al., 1999; Florholmen et al., 1982). Early or uncontrolled studies suggested that psyllium improved glycemic and lipid control in individuals with type-2 diabetes (Gupta et al., 1994). In a carefully controlled crossover study of the effects of psyllium taken immediately before breakfast and dinner compared with the effects of cellulose placebo supplementation in individuals with type 2 diabetes, postprandial serum glucose values were 14% lower after breakfast, 31% lower after lunch, and 20% lower after dinner with psyllium (Pastors et al., 1991). High-fiber diets increase peripheral insulin sensitivity in healthy young and old adults (Fukagawa et al., 1990). Psyllium has also been shown to significantly reduce postprandial serum glucose and insulin concentrations in non-diabetic individuals (Jarjis et al., 1984). The diabetes control and complications trial convincingly showed that maintaining good glycemic control delayed the onset and slowed the progression of complications in individuals with type 1 diabetes. Many healthy individuals with type 2 diabetes may also benefit from improved glycemic control. Furthermore, type 2 diabetes dramatically increases the risk of atherosclerotic cardiovascular disease and reductions in atherogenic lipids could greatly reduce mortality and morbidity from cardiovascular disease in individuals with type 2 diabetes (Laakso, 1996; Savage, 1996).

The ability of soluble fibers to reduce the postprandial glucose response to meals eaten several hours after fiber ingestion (second meal effect) was shown previously in nondiabetic individuals (Jenkins et al., 1980; Wolever et al., 1988; Nuttall, 1993; Riccardi and Rivellese, 1991). Several studies indicate that high-fiber diets or diets supplemented with soluble fibers such as guar gum, soy, or pectin improve metabolic control in many individuals with type 2 diabetes (Anderson and Ward, 1986; Anderson et al., 1987; Jenkins and Jenkins, 1995; Brad et al., 1995; Groop et al., 1993; Librenti et al., 1992; Vinik and Jenkins, 1988). In children and adolescents from developed countries, obesity prevalence has strongly increased in the last decades and insulin resistance and impaired glucose tolerance are frequently observed. Some dietary components such as low glycemic index foods and dietary fiber could be used in order to improve glucose homeostasis in these children (Frati Munari et al., 1998). After psyllium supplementation, the percentage change in postprandial glucose in type 2 diabetes patients, ranged from −12.2 to −20.2% (Moreno et al., 2003).

2.7. Cholesterol lowering

It has been observed that there is a positive association with plasma LDL cholesterol levels and coronary heart disease risk (Anderson et al., 1987, 1994; Anderson, 1987). Intake of dietary fibers known to lower the concentration of LDL in plasma is considered to be highly beneficial. Of the viscous soluble fibers, psyllium husk fiber appears to be one of the most effective with the least adverse effects (Bell et al., 1989, 1990). Psyllium intake has consistently shown significant reductions in plasma LDL cholesterol levels ranging from 10 to 24% (Davidson et al., 1991, 1996; Fernandez et al., 1997; McCall et al., 1992a,b).

Reports of the use of psyllium, largely in hypercholesterolemic men, have suggested that it lowers serum cholesterol as a result of the binding of bile acids in the intestinal lumen and reduced risk of coronary heart disease (Van Rosendaal et al., 2004). The mechanism of action of psyllium's hypocholesterolemic effects has not been fully elucidated. Psyllium was shown to stimulate bile acid synthesis by increasing the 7α-hydroxylase activity in animal and humans models (Horton et al., 1994; Matheson et al., 1995). The diversion of hepatic cholesterol for bile acid production has long been established as a mechanism for reducing serum cholesterol. Synthesis of bile acids from cholesterol is regulated by feedback inhibition of the rate limiting enzyme cholesterol 7α-hydroxylase by bile acids returning to the liver via the enterohepatic circulation (Buhman et al., 1998). Hepatic 7α-hydroxylase activity, protein mass, mRNA levels and the rate of transcription are all higher in rats fed cholestyramine (CHY), a bile acid sequestrant, and lower in rats fed bile acids (Chiang et al., 1990; Chiang and Stroup, 1994; Heuman et al., 1988, 1989; Heuman, 1989; Jelinek and Russell, 1990; Donkin et al., 1996). It was demonstrated that 7α-hydroxylase activity and bile acid pool size were greater in rats fed a diet containing 5% psyllium compared with rats fed a diet containing 5% cellulose. In addition, psyllium has been shown to coordinately increase 7α-hydroxylase activity and mRNA levels in hamsters (Horton et al., 1994). A bile acid response element has been identified in the promoter of the 7α-hydroxylase gene, suggesting a molecular mechanism involved in transcriptional regulation of 7α-hydroxylase (Hoekman et al., 1993; Sundseth and Waxman, 1990). The magnitude of the hypocholesterolemic effect is consistent with findings from a number of studies using hamsters, guinea pigs and rats (Arjmandi et al., 1997; Daggy et al., 1997; Fernandez et al., 1995a,b; Fernandez, 1995; Trautwein et al., 1993, 1998, 1999; Turley et al., 1991, 1994, 1996; Turley and Dietschy, 1995). Suggested mechanisms for this hypocholesterolemic effect have focused on greater excretion of bile acids and total steroids leading to an up-regulation of bile acid biosynthesis (Arjmandi et al., 1992a, 1992b; Matheson and Story, 1994; Matheson et al., 1995; Vahouny et al., 1987). It is proposed that feeding psyllium causes greater viscosity in the intestine, thus preventing absorption of bile acids and neutral steroids, a phenomenon that has been observed for other vis-

cous sources of dietary fiber (Carr et al., 1996; Gallaher et al., 1993a,b).

Psyllium and CHY normalized the lithogenic index and prevented cholesterol gallstone formation compared with controls. Daily fecal bile acid excretion was ~400% greater in hamsters fed 6% psyllium, whereas CHY caused an 11-fold increase. Daily neutral sterol excretion did not differ in psyllium-fed hamsters but was >100% greater in those fed-CHY than in controls (Bergman and van der Linden, 1967). The mechanism of this protection is not fully elucidated but seems to relate to changes in the bile acid profile affecting the hydrophobicity of the bile acid pool. Psyllium and CHY caused distinct alterations in the bile acid profile. Psyllium caused a selective reduction of taurine-conjugated bile acids, especially of taurochenodeoxycholate. As a result, the glycine:taurine conjugation and the cholate:chenodeoxycholate ratios were significantly higher in psyllium-fed hamsters. There is consistent evidence from a number of studies that psyllium, like CHY, leads to an increase in cholesterol 7α-hydroxylase activity in parallel with 7α-hydroxylase mRNA (Fernandez et al., 1995a; Fernandez, 1995; Matheson and Story, 1994; Matheson et al., 1995).

3. Safety aspects of psyllium

In order to find the safety and tolerability aspects of ispaghula husk various studies have been carried out. In one study the nutritional, biochemical and haematological effects of ispaghula has been untaken. It was observed that a daily dose of 10.5 g of ispaghula was well tolerated and the majority of adverse events recorded were minor, of short duration and either unrelated or possibly related to the study treatment. The results from the study suggested that ispaghula husk could be used with confidence for the long-term treatment of mild-to-moderate hypercholesterolemia (Oliver, 2000). US Food and Drug Administration recently authorized the use of health claims on food products containing soluble fiber from psyllium that state that they are associated with a decreased risk of coronary heart disease (Anderson et al., 2000b). The addition of psyllium to a traditional diet for persons with diabetes is safe, is well tolerated, and improves glycemic and lipid control in men with type 2 diabetes and hypercholesterolemia (Anderson et al., 1999). Medical nutrition therapy in type 2 diabetes must be individualized to reflect personal lifestyle and management goals. Because type 2 diabetes markedly increases the risk of atherosclerosis and its complications, achievement and maintenance of normal serum lipid concentrations is a primary goal of diabetes management that could greatly reduce death and disability in this population. It was suggested that the addition of psyllium to a standard diet for diabetes is safe, is well tolerated, and offers an additional dietary tool to improve metabolic control in individuals with type 2 diabetes and hypercholesterolemia. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults (Fukagawa et al., 1990). Ramkumar and coworkers have undertaken a systematic review of the efficacy and safety of traditional medical therapies for chronic constipation with the intention to make evidence-based recommendations. In their study they have found good evidence to support the use of tegaserod, lactulose, and psyllium for constipation (Ramkumar and Rao, 2005).

Workers in the healthcare and pharmaceutical industries can become sensitized and develop allergic respiratory (breathing) symptoms due to handling bulk laxatives containing psyllium powder. Occupational asthma associated with psyllium exposure has been observed. Reactions may also occur from breathing in the dust or from skin contact (Freeman, 1994; Marks et al., 1991; Schwartz et al., 1989). It is said that it is boon for patients and bane for providers (Hoffman, 2006).

4. Psyllium as drug delivery agent

A number of drug delivery devices have been proposed to deliver the drug for efficient therapy (Chourasia and Jain, 2003). Among them, hydrogels, specially based on polysaccharides, have attracted considerable attention as an excellent candidates for controlled release devices or targetable devices of the therapeutic agents (Chourasia and Jain, 2004). The release rate of drugs from hydrogels was primarily determined by the swelling extent, which further enhanced by addition of enzyme in the buffer solutions (Chiu et al., 1999) whereas swelling of polymeric networks was depended on composition of copolymer and pH of the surrounding medium (El-Hag Ali Said, 2005). Modification of the psyllium to develop the hydrogels is not much reported in the literature. Singh and coworkers have modified the psyllium to prepare the hydrogels for the specialty applications (Singh et al., 2006a).

4.1. Synthesis of psyllium based polymeric matrix

Psyllium based polymeric networks were synthesized by chemically induced polymerization through free radical mechanism. Ammonium persulphate (APS) has generated the reactive sites, both on the psyllium and monomer, leading to the propagation of the reaction. In the presence of crosslinker NN-MBAAm (CH_2=CHCONHCH$_2$ NHCOCH=CH_2), because of its polyfunctionality, a new macro-radical get formed that has four reactive sites and these sites can be linked both with the radical on the psyllium and the monomers This will resultant into the formation of three-dimensional networks, which were used to study the in vitro release of the model drugs (Singh et al., 2006b). Reaction was carried out with definite amount of psyllium husk, APS, monomer and *N*,*N*-MBAAm in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for 2 h in distilled water and for 2 h in ethanol to remove the soluble fraction and then were dried in air oven at 40°C. Psyllium crosslinked poly(*N*-hydroxymethylacrylamide) [Psy-*cl*-poly(HMAAm)] (Singh et al., 2006b) and psyllium crosslinked poly(acrylamide) [Psy-*cl*-poly(AAm)] (Singh et al., 2007a) (based hydrogels have been prepared by above mentioned method).

4.2. Drug loading to the psyllium based polymeric matrix

The loading of a drug onto hydrogels was carried out by swelling equilibrium method. The hydrogel was allowed to swell

in the drug solution of known concentration for 24 h at 37 °C and then dried to obtain the release device. The concentration of the rejected solution was measured to calculate percent entrapment of the drug in the polymer matrix (Singh et al., 2006b).

4.3. Drug release from polymer matrix

In vitro release studies of the drug were carried out by placing dried and loaded sample in definite volume of releasing medium at 37 °C temperature. The drug release was measured after fixed interval of time and release dynamics of model drugs were calculated (Singh et al., 2006b).

4.4. Mechanism for drug release from polymer matrix

In the hydrogels system, absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus the drug release kinetics. A model based on the work of Alfrey et al. describes the swelling membrane, which consists of three zones. Adjacent to the bulk water is a layer of completely swollen gel. Then there is a fairly thin layer in which the polymer chains are slowly hydrating and relaxing. The third zone is a matrix of unswollen, completely dried, rigid polymer. The diffusion of water in hydrogels was classified into three different types based on the relative rates of diffusion and polymer relaxation (Alfrey et al., 1966). This classification of the diffusion of water in hydrogels can also be used to classify the drug release profiles from the swelling polymer (Peppas and Korsmeyer, 1987) and mechanism of release can be Fickian, non-Fickian and Case II diffusion.

4.5. Mathematical modeling of drug release (Singh et al., 2006b)

Although there are a number of reports dealing with mathematical modeling of drug release from swellable polymeric systems, no single model successfully predicts all the experimental observations (Bamba et al., 1979; Peppas et al., 1980; Korsmeyer et al., 1986; Lee, 1980; Brannon-Peppas and Peppas, 1989). Fickian, non-Fickian and Case II diffusion mechanism of the drugs from the polymeric matrix can be calculated from the following equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fractional release of drug in time t, 'k' the constant characteristic of the drug–polymer system, and 'n' is the diffusion exponent characteristic of the release mechanism. For normal Fickian diffusion the value of $n = 0.5$, Case II diffusion $n = 1.0$ and non-Fickian $n = 0.5$–1.0. Initial diffusion coefficient, average diffusion coefficient and late diffusion coefficient can be calculated from the following equations (Alfrey et al., 1966; Ritger and Peppas, 1987a,b):

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi \ell^2}\right)^{0.5} \tag{2}$$

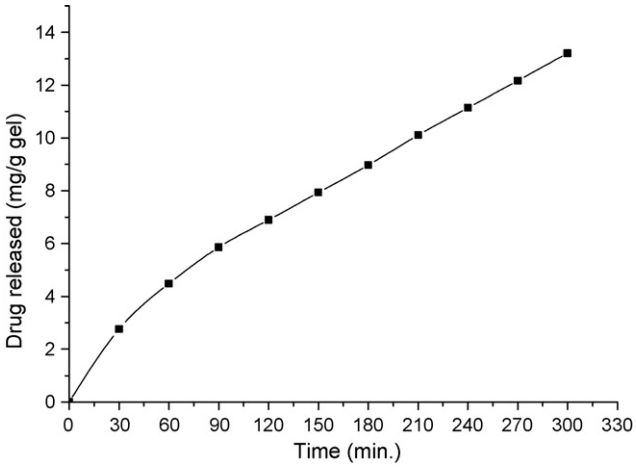

Fig. 1. Release dynamics of salicylic acid from drug loaded sample of Psy-cl-poly(*N*-HMAAm) in distilled water at 37 °C.

$$D_A = \frac{0.049\ell^2}{t^{1/2}} \tag{3}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right) \exp\left[\frac{-\pi^2 Dt}{\ell^2}\right] \tag{4}$$

where (M_t/M_∞) is the fractional release and M_t and M_∞ is drug released at time 't' and at equilibrium, respectively, D is the diffusion coefficient and λ is the thickness of the sample.

4.6. Release dynamics of the drugs

The release of water-soluble drugs, entrapped in a hydrogels, occur only after water penetrates the polymeric networks to swell and dissolve the drug, followed by diffusion along the aqueous pathways to the surface of the device. The release of drug is closely related to the swelling characteristics of the hydrogels, which in turn, is a, key function of chemical architecture of the hydrogels. The release profile of salicylic acid and tetracycline hydrochloride from per gram of the drug loaded hydrogels

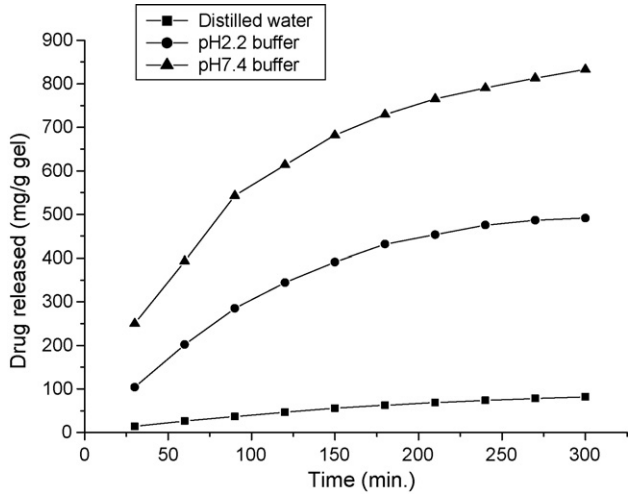

Fig. 2. Release dynamics of tetracycline from drug loaded sample of Psy-cl-poly(*N*-HMAAm) in different medium at 37 °C.

Table 1
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the release of salicylic acid and tetracycline hydrochloride from drug loaded hydrogels samples of Psy-*cl*-poly(*N*-HMAAm) and Psy-*cl*-poly(AAm) (Singh et al., 2006b, 2007b)

Drug in releasing medium	Diffusion exponent, '*n*'	Gel characteristic constant, '*k*' × 10^2	Diffusion coefficients (cm^2/min)		
			Initial, $D_i \times 10^4$	Average, $D_A \times 10^4$	Late time, $D_L \times 10^4$
Psy-*cl*-poly(*N*-HMAAm)					
Salicylic acid	0.67	1.626	4.00	3.364	0.57
Tetracycline hydrochloride					
Distilled water	0.71	1.552	5.01	3.76	0.67
pH 2.2 buffer	0.67	2.291	10.30	9.11	1.71
pH7.4 buffer	0.52	5.309	6.38	8.52	1.52
Psy-*cl*-poly(AAm)					
Salicylic acid	0.68	1.626	9.74	8.84	1.42
Tetracycline hydrochloride					
Distilled water	0.74	1.272	21.44	19.5	2.95
pH 2.2 buffer	0.6	2.754	7.60	8.70	1.16
pH7.4 buffer	0.56	3.639	15.97	17.37	2.81

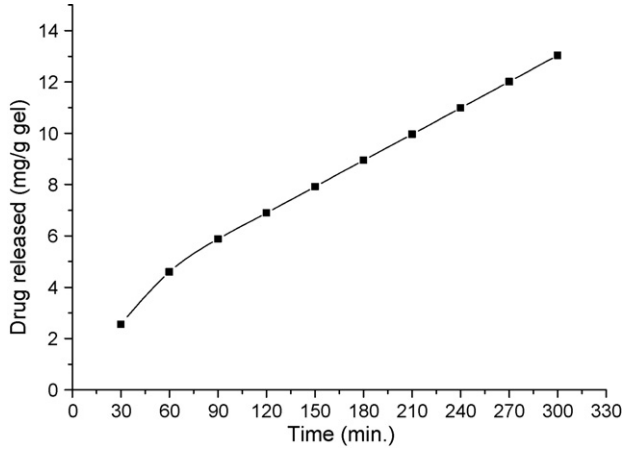

Fig. 3. Release dynamics of salicylic acid from drug loaded sample of Psy-cl-poly(AAm) in 20 ml distilled water at 37 °C.

has been studied from the from the [Psy-*cl*-poly(HMAAm)] and [Psy-*cl*-poly(AAm)] has been shown in Figs. 1–4 and values for

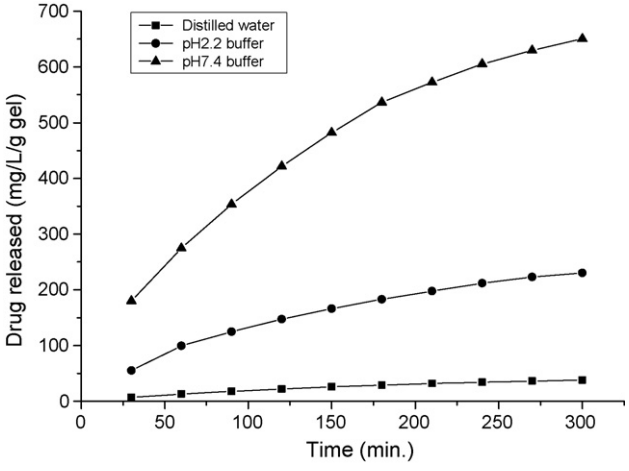

Fig. 4. Release dynamics of tetracycline from drug loaded sample of Psy-cl-poly(AAm) in different medium at 37 °C.

the diffusion exponent '*n*', gel characteristic constant '*k*' and diffusion coefficients shown in Table 1 (Singh et al., 2006b, 2007b). The effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. In release medium of pH 7.4 buffer the release pattern of tetracycline drastically changes to the extent that mechanism of drug diffusion shifted from non-Fickian diffusion to Fickian diffusion.

Oral sustained release gastroretentive dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new gastroretentive sustained release delivery system for ofloxacin was developed by Chavanpatil and coworkers with release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crosspovidone. Formulations were evaluated for in vitro drug release profile, swelling characteristics and in vitro bioadhesion property. The in vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. For the developed formulation, the value of '*n*' was found to be 0.5766 while for the marketed formulation the value was 0.5718 indicating the anomalous transport. The swelling properties were increased with increasing crosspovidone concentration and contributed significantly in drug release from the tablet matrix (Chavanpatil et al., 2005, 2006).

Gohel and coworkers have prepared the succinic acid treated and tartaric acid treated ispaghula husk powder for the development of modified release tablets of diltiazem HCl by adopting direct compression technique. The modified ispaghula husk powder showed superior swelling and gelling as compared to untreated powder. Addition of compaction augmenting agent such as dicalcium phosphate was found to be essential for obtaining tablets with adequate crushing strength. In order to improve the crushing strength of diltiazem HCl tablets, to modulate drug release pattern, and to obtain similarity of dissolution profiles in distilled water and simulated gastric fluid (pH 1.2), modified guar gum was used along with modified ispaghula husk

powder and tartaric acid and succinic acid (Gohel et al., 2000, 2003).

Dietary fibers are widely used in hypoglycemic, hypolipidemic, and slimming diets. It is probable that their ingestion coincides with the oral administration of drugs and a modification of their pharmacokinetics can appear. Garcia and coworkers have studied the influence of two soluble fibers (guar gum and psyllium) on the pharmacokinetics of ethinyloestradiol (EE) when they were administered together to female rabbits via the oral route. Three groups of rabbits were used. All animals received 1 mg/kg of EE; this compound was administered alone in the control group and with 3.5 g of guar gum or psyllium in the other two groups. When guar gum was administered, there was a decrease in the extent of EE absorbed, but no change was observed in the rate of absorption. When psyllium was administered, the extent of EE absorbed increased slightly and the rate of absorption was slower (Garcia et al., 2000).

5. Conclusion

It is concluded from the foregone discussion that because of therapeutic importance of psyllium and its gel-forming nature, hydrogels developed from it can act as double potential drug delivery devices, that to colon targeted, indicated from the drug release profile in different release medium reported in the literature. For example, psyllium has been shown to be significantly reduce serum glucose when taken as dietary fiber and, if it will suitably tailored to develop the hydrogels for controlled release of insulin; it can act as double potential candidate for cure of diabetes mellitus. Therefore, it is concluded that psyllium has very high potential to develop novel formulation for the delivery of therapeutic agents and it has to be exploited out.

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