Review Article

Pharmaceutical Applications of *Ispaghula Husk*: Mucilage

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ABSTRACT

Natural carbohydrates have been popularly used as a material for centuries in all kinds of pharmaceutical applications. It is the world's most abundant renewable and biodegradable polymer. Isabgol has been popularly used as therapeutic agent for the treatment of constipation, diarrhea, irritable syndrome, inflammatory bowel disease, ulcerative colitis, colon cancer, diabetes, and hypercholesterolemia The uniqueness of the chemical structures and macromolecular configurations of mucilage obtain from the Isabgol (plantago ovata forskal) has attracted Carbohydrate chemists in last decade, as the hydrogel produced by it is rigid, difficult to brake, to dissolve. Ironically solubility, flexibility is very important criteria for materials to be used in pharmacy. To meet these criteria chemical modifications of isabgol husk mucilage is indispensable so that it can be transformed into carrier for new drug delivery system, as a low cost non –conventional source for the using pharmaceutical formulations as an "Excipient", which can improve its procesability and performance for specific application in the broad field of pharmacy. Exploitation of Isabgol husk mucilage as an "Excipient" and its innovative, non-conventional applications, chemical derivatization, use of its derivative in modern fashion of drug designing has become a room for inventions for research scholar. Gums and Mucilage are naturally occurring biopolymers, finding increasing applications in pharmaceutical and biotechnology industry. It has been used successfully for many years in the food and pharmaceutical industry as a thickening agent, as a gelling agent, and as a colloidal stabilizer. Mucilage also has several unique properties that have enabled it to be used as a matrix for entrapment and/or delivery of variety of drugs, proteins, and cells. .Being a naturally occurring polysaccharide, in recent year it has gained increased importance in industrial applications. The benefits of natural carbohydrates are also more and more appreciated by the scientists and consumers from various industries due to its inertness, biocompatibility, and biodegradability.

Keywords: *Plantago ovata*, Natural carbohydrate, Mucilage, Chemical modification, Excipient.

INTRODUCTION

Since ancient age systems of medicines, ISBGOL: The word *'Ispaghula'* is derived from Persian language, there the word '*ISAP'* means 'horse' and '*GHULA*' means 'ear', as the seeds of the genus *Plantago* (includes more than 200 species) is looks like shape of the ear of the horse, the dried ripe seeds of *Plantago Afra (Plantago* Psyllium*), Plantago Indica (Plantago Arenaria)* And *Plantago Ovata* belongs to family *Plantaginaceae* are used in medicine. (Fig. 1,2,3)

Figure 1: Isabgol whole plant

A traditional plant known as *'ISABGOL'* is widely used as home remedy in all cultures, in various kinds of diseases, Conditions like chronic constipation, diarrhea, inflammation of mucous membrane of GI and genitourinary tracts, duodenal ulcer, gonorrhea, piles, etc., as bulk forming, non-irritant laxative drug, demulcent, as a cervical dilator etc[1-2]. Drugs are rarely administered solely as pure chemical substances, but are almost given in the form of drug delivery system [3](DDS).

Figure 2: Isabgol seed

The DDS consist of active pharmaceutical ingredient in association with excipients or inert substances. Drugs are converted to dosage forms using one or more materials which are referred as EXCIPIENTS, basically these materials are Pharmacologically inert, used to achieving certain goals like modifying appearance, improving handling property, physical property, ability, packaging characteristics, etc. so, the drug delivery systems or

dosage forms consists of active pharmaceutical ingredient in association with excipient play vital or pivotal role in drug products and hence the quality of drug products can be no higher than the quality of drug(s), and excipients (non-drug additives/adjuvants)from which the product is made.

Figure 3: Isabgol husk

A large numbers of carbohydrate containing excipients are available from natural Sources have their own place due to variety of properties offers by them, as they are widely used as binding agents, coating materials, suspending agents, granulating agents, easily dispersible material, increasing viscosity of aqueous solution in pharmaceutical industry. Natural carbohydrates, polymers are hydrocolloids, used as gel forming components, sweetener, binder, flavoring agents, lubricants, taste masking agents to prepare easy to swallow compositions[4]. One of the trends in this area is of study the useful substances of natural origin, for such substances tend to be biodegradable, biocompatible and non-toxic[5].The literature survey reveals that 'Mucilage' obtained from *plantago ovata* husk has greatly attracted the attention of Researcher workers, in this area during last decades.

India is a major source of the global supplier/production of Isapghula as its cultivated variety consists of more mucilage percentage than the wild variety (Fig.4). It is mainly cultivated in North-Gujarat, North –West Rajasthan covering an area of approximately 16,000 hectares. In India, approximately 50,000 hectares of land used for its cultivation. Till date natural carbohydrate are used in modern dosage form for release control, also in the form of matrix material, encapsulating excipients, coating material, on as a carrier to the target the drug to tissue or site-specific drug delivery system[6-7].

Figure 4: India Global supplier/production of Isapghula

MEDICINAL EFFICACY OF PSYLLIUM / ISPAGHULA

Psyllium has been reported for the treatment of constipation, diarrhea, and irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia[8].

Constipation

Psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight and ameliorating chronic diarrhea. Several studies suggest that psyllium may provide benefits for treating constipation. There is a scientific basis for psyllium working as a mild laxative. 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 the choice depends on whether the clinical context is suggestive of slow transit or evacuation disorders[9-10].

Diarrhea

Wenzl and co-workers have concluded that the normal intestine delivers stools that defer widely in quantity but maintain percent fecal water within a narrower range. Stools looseness in diarrhea is determined by the ratio of fecal water too water holding capacity of insoluble solids. Psyllium increases the number of normal stools and decreases the number of liquid stools. A combination of psyllium and calcium seems to be cheap and effective alternative to conventional treatment of chronic diarrhea. Fecal consistency was markedly different in psyllium calves as compare with control[10-11].

Ulcerative colitis (Crohn's disease)

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). A small number of studies have examined the ability of psyllium to maintain remission in ulcerative colitis. 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[12].

Irritable Bowel Syndrome

Constipation is defined as a symptom chronic constipation -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. Personality factors influence the magnitude of therapeutic response of the psyllium. The

easing of bowel dissatisfaction appears to be a major reason for the therapeutic success of psyllium in IBS[13-15].

Diabetes

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 .Water-soluble dietary fibers decrease postprandial glucose concentrations and decrease serum cholesterol concentrations to men with type 2 diabetes. Early or uncontrolled studies suggested that psyllium improved glycemic and lipid control in individuals with type-2 diabetes. 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 non-diabetic individuals[18-19].

Cholesterol lowering

It has been observed that there is a positive association with plasma LDL cholesterol levels and coronary heart disease risk. Intake of dietary fibers known to lower the concentration of LDL in plasma is considered to be highly beneficial. Psyllium intake has consistently shown significant reductions in plasma LDL cholesterol levels ranging from 10 to 24%. Reports of the use of psyllium, largely in hypercholesterolemia 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. The mechanism of action of psyllium's hypercholesterolemia effects has not been fully elucidated. Psyllium was shown to stimulate bile acid synthesis by increasing the hydroxylase activity in animal and humans models[20-21].

Psyllium and its safety aspects

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. U.S.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. 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. The Efficacy and safety of traditional medical therapies for chronic constipation. Reactions may also occur from breathing in the dust or from skin contact it is said that it is boon for patients and bane for providers[21-22].

Psyllium as drug delivery agent

A number of drug delivery devices have been proposed to deliver the drug for efficient therapy. Among them, hydrogels, specially based on polysaccharides, have attracted considerable attention as excellent candidates for controlled release devices or targetable devices of the therapeutic agents. 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 Singh and coworkers have modified the psyllium to prepare the hydrogels for the specialty applications[23-24].

SYNTHESIS OF PSYLLIUM BASED POLYMER MATRIX

Psyllium based polymeric networks were synthesized by chemically induced polymerization through free radical mechanism. In the presence of crosslinker NN-MBAAm (CH2 CHCONHCH2 NHCOCH CH2), 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. Reaction was carried out with definite amount of psyllium husk, APS, monomer and *N*,*N*-MBAAm in the aqueous reaction system at 65^{0}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^{o}C. Psyllium cross linked poly (*N*-hydroxymethylacrylamide) [Psy-*cl*-poly (HMAAm)] and psyllium crosslinked poly (acrylamide) [Psy-*cl*-poly (AAm)] (based hydro gels have been prepared by above mentioned method) [25-26].

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^{0}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[26]. (Fig.5)

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^{0}C temperature. The drug release was measured after fixed interval of time and release dynamics of model drugs were calculated[26].

Effect of pH, on Drug Release

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. 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. The modified ispaghula husk powder showed superior swelling and gelling as compared to untreated powder[27-28-29-30].

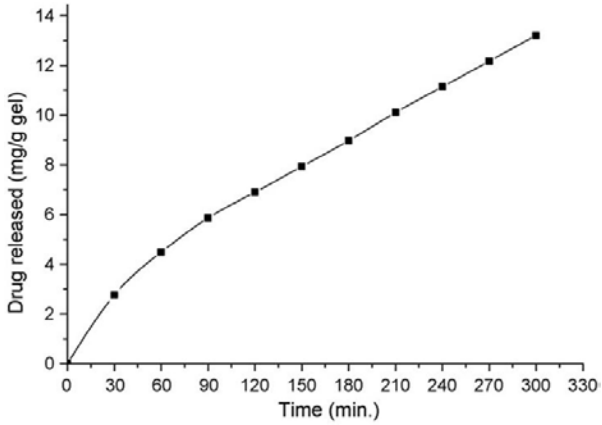


Figure 5: Release dynamics of salicylic acid from drug loaded sample of Psy-clpoly (*N*-HMAAm) in distilled water at 37◦C.

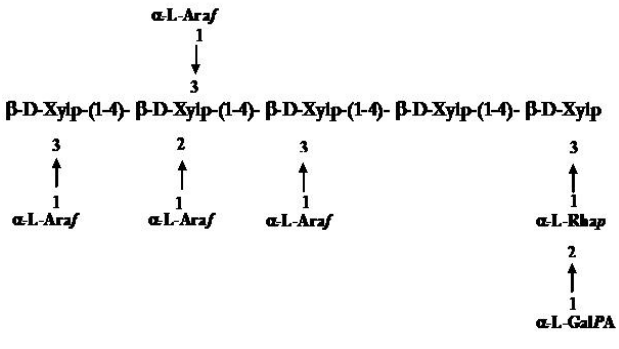
LITERATURE SURVEY ON ISPAGHULA

U.S. Patent 5248502 describes a method for reducing the allergenicity of psyllium seed husk by alkaline treatment. A process of for purification of psyllium husk has been described in U.S. Patent 5085785.U.S Patent 4813613 describes mechanical method for obtaining high purity mucilage from *plantago psyllium* seeds U.S. Patent 4459280 describes a method for increasing the dispersibility and mixability of psyllium hydrophilic mucilloid U. S. Patent 6337048 describes process for sterilization of psyllium husk A process of sterilization seed husk using isopropyl alcohol has been described in U.S. Patent 3992147. The husk are then filtered and dried[31-32]. A sample of husk containing a count of one million /gram was reduced to zero by this method. U.S. Patent 6248373 describes the enzymatic modification of psyllium husk. U.S. Patent 6287609 describes a procedure for purification of psyllium seed husk by treatment with alkali. U.S. Patent 5641511 described timed release granular dosage form of aspirin, acetaminophen or ibuprofen using psyllium husk. U.S. Patent 5713852 describes an osmotic delivery system for delivering an anti-inflammatory agent to the site of a painful condition in the oral cavity[33-34]. U.S. Patent described an improved osmotic system for the controlled and continuous delivery of a steroid drug. U.S. Patent 5533995 described a transdermal device for the controlled administration of a drug to the skin. U. S. Patent 5827528 described a medical adhesive composition of psyllium. U. S. Patent 5776887 describes solid matrix nutritional mix, designed for persons with diabetes. U.S. Patent 6251421 describe an invention that provides orally administrable pharmaceutical. U.S. Patent 5891441 describes a chemical composition to aid in absorbing and binding fat, prior to its being digested[35-36]. U.S. Patent 5601837 describes an invention that relates to pharmaceutical compositions. U.S. Patent 5356467 describes method for preparation of controlled release coating of zein. U. S. Patent 5445826 describes a prolonged delivery system with psyllium. U.S.Patent 5445831 describes a psyllium containing oral product with improved aesthetics using psyllium husk of specific particular size : 80# <15%, 80-200# ≥ 45%, > 200# < 40%.U.S. Patent 4666716 describes a formulation containing psyllium and ibuprofen /indomethacin/aspirin in the ratio of 1:30 to 1:40 for treatment of diarrhea**.** U.S. Patent 5059416 describes a delivery system containing hydrophilic material (psyllium) U.S. Patent 5759520 describes an aqueous foamable composition having a delayed foaming action on expulsion U.S. Patent 4514318 describes a method for stabilizing polysaccharide thickened aqueous medium and stable psyllium gels. U.S. Patent 20010026809 and 024982 describes sustained release tablets comprising of immediate release cores and sustained release coating. U. S. Patent 5874418 describes sustained release formulations for oral use. U.S. Patent 5914132 relates to a pharmaceutical composition for colonic delivery[37-38]

Mucilages of *Isabgol*

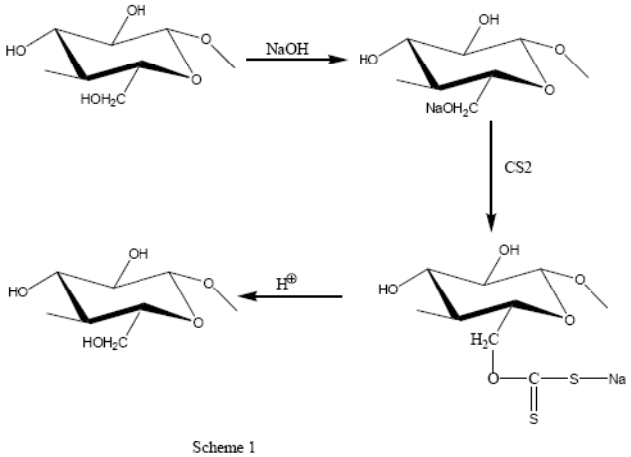
Mucilage that is responsible for the laxative action since D-xylan polymers are insoluble in water, it is proposed[39]. The physiologically active, gel-forming fraction of the alkali-extractable polysaccharides of *plantago ovata* Forsk seed husk (*Ispaghula* seed) and some derived partial hydrolysis products were -studied by compositional and methylation analysis and NMR spectroscopy. Resolving the conflicting claims of previous investigators, the material was found to be a neutral arabinoxylan (arabinose 22.6%, xylose 74%, 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 3, trisaccharide branches having the sequence L-Araf-a-(1-3)-D-Xylp-B (1-3)-L-Araf. The presence of this sequence is supported by methylation and NMR data, and by the isolation of the disaccharide 3-O-B-D- Xylopyranosyl-L-arabinose as a product of partial acid hydrolysis of polysaccharide[40]. (Fig-6)

Fig 6. Structure consisting of a densely substituted main chain of 3, trisaccharide branches having the sequence L-Araf-a-(1-3)-D-Xylp-B (1-3)-L-Araf.

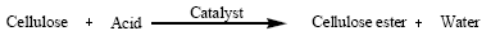


Chemical Modification

The biological & biomedical applications of polymeric material have greatly increased recently. Of these, bio-based materials, or biopolymers, are used to repair, restore, or replaced damaged or diseased tissue or to interface with the physiological environment. Well known examples of this chemicals modifications are cross-linked dextrans (Sephadex) and agaroses (Sepharose) (Yalpani, polysaccharides, synthesis, Modifications and structure/property relations. The possible reactions, sites for this type of chemical modifications are explains here by taking one of the example of naturally occuring biopolymeric material cellulose as follow (figure-7). The chemical reactivity of cellulose is determined to a large extent by the structure of its solid state. Cellulose possesses one primary and two secondary hydroxyl groups. Like any hydroxyl – containing compound, these hydroxyl groups can undergo addition, substitution, and oxidation reaction. Once the hydroxyl groups on the chain unit are made accessible, they offer a verity of possibilities for making useful derivatives. These derivatives can be made by etherification, esterification, cross-linking, or graft copolymerization. There are various schemes for the derivatization is as per figure shown below by taking one of the examples of polysaccharide-cellulose. Consequently chemical modification of starch has become important to tool to over come the problems and creates starches having altered characteristics, compare to native starch. Common treatments are acid treatments oxidation, etherification, quaternization, grafting, cross-linking, preparation of poly-vinyl-starch composites[41], etc. There are thus an increasing interest in and used for methods capable of introducing oxidative changes of various kinds in polysaccharides, by using aqueous medium, phenol oxidizing enzyme enhancing agent, peroxidase enzyme etc.



Scheme 1



Scheme2

Figure 7: The possible reactions, sites for this type of chemical modifications are explains here by taking one of the example of naturally occurring biopolymer material cellulose as follow

Much emphasis has been placed on the chemical modifications of naturally occurring bioadhesive materials now a days, as it is useful material from the view point of the high potential of these polysaccharide. In many cases, the chemically modified molecules show greater activity than the original polymeric material. Acetylation of partially methylated alditols with acetic anhydride for 2–4 h at ambient temperature using 4-*N,N′*-dimethylaminopyridine as a catalyst and the reaction was free from generating non-sugar reaction artifacts Utility of these simple methods for rapid methylation analysis was demonstrated in the characterization of oligosaccharides isolated in small amounts using a carbohydrate analyzer. which can be an influential role in the preparation of mucilage derivatives, as shown in the figure mucilage possesses one primary hydroxyl group per unit of beta dexto xylopyranose units, these hydroxyl group can undergo reaction like oxidation, reduction, methylation, sulfonation, Esterification, etherification, attachment of cystein etc. Modified derivatives can be used in the fields of pharmacy, medicine, cosmetics, and food. Practical applications of such kinds of natural carbohydrates like cellulose, starch, etc. are widely used in the same manners and the same industries. Asystematic flowchart for mucilage derivative preparations can form a new window for research scholars. A new drug delivery modality can developed based on drug encapsulation in polymeric miscelles followed by a controlled release at the site of triggered by ultra sound focused on the tumor[42]. The results of the in vitro studies of the above technique and summarised and the first in vivo experiments using colon cancer in rats are reported /measured using doxorubicin (DOX) and ruboxyl (RB) release from micelles under continuous wave (CW) or pulsed ultrasound in the frequency range of 20 kHz to 3 MHz. The measurements were based on the decrease of the fluorescence intensity when drug was transferred from the micelle core to aqueous environment. Native natural carbohydrate may not be suitable in some controlled drug delivery system, as many drugs are released too fast from system based on this, due to substantial swelling, enzymatic degradation of native carbohydrate in biological systems. Various kinds of polysaccharides in particularly starch. Starch is utmost important as sizing agent in the textile industry, pharmaceutical industry, printing industry and for the finishing in various industries. However the properties of natives starch is not always optimal compared to the properties required for the particular applications. One of the problems is the very large molecular size instability of viscous solution, under varying temperature and its susceptibility to microbial degradation[43]. Consequently chemical modification of starch has become important to tool to over come the problems and creates starches having altered characteristics, compare to native starch. Common treatments are acid treatments oxidation,

etherification, quaternization, grafting, cross-linking, preparation of poly-vinyl-starch composites, etc. The relevance of studying the effect of chemical modification on the functional and structural properties of polysaccharides lies in the design of new molecules with altered physicochemical properties[44]. The modified molecule can be use in designing new drugs delivery system which has ability to modify the rheological properties of the parent native polysaccharide in aqueous or organic solution. Though the derivatization has become popular in practice carbohydrate, research chemists has to increase more resistance towards hydrolysis and enzymatic lysis than native plain carbohydrate. The present invention 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[45].

CONCLUSION

Mucilage, a non-toxic biomaterial, is abundant in nature. It has an unusual combination of biological activity plus mechanical and physical properties chemical modification can convert them into various derivatives. This unique characteristic makes them in important bio material for biochemical, pharmaceutical, and surgical applications. The conception and development of this supra molecules and their derivatives as pharmaceutical excipients material is an innovative idea from technological point of view, and advancement in many fields including chemistry, biochemistry, and physical chemistry. On, Broadly speaking, this review article point out that in the past few years, especially in patent literature, invention in the direction to prepare chemical derivative and it's pharmaceutical applications towards the development of cost effective technology and establishing their standard of *plantago ovata* Forsk., to develop its chemical modification technique, to obtain diversified physico-chemical properties of the native mucilage of *plantago ovata*, and it's derived derivative to apply this in conventional pharmaceutical applications, as well as non-conventional pharmaceutical application in formulations, new drug design, drug delivery System and if possible to developed suitable dosage form design not only for sustained release or targeting d rug delivery but also for modern time and Modern fashion as a carrier of wide variety of biologically active agents, either for local treatment or for specific site delivery system. By selection of its appropriate type of modification as per the requirement of industry, gelating condition, added excipients, and coating agents, the dosage forms of various morphology and characteristics can be fabricated. It is observed from all the work done and the research literature survey, that the medicinal values of Isapghula is still their in practice as home remedy famous as "Dadima's drug/ dava" there for it is concluded that *Isapghul* has high potential in developing an unconventional source as an 'excipient' and very high potential in developing a new formulations and in design of dosage forms. As research and development continues with drug delivery system using biopolymers, one can expect to see many innovative and exciting applications.

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