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(54) Title: LAXATIVE FORMULATION

(57) Abstract: The present invention relates to an herbal laxative formulation containing psyllium husk, semi-purified calcium sennosides and triphala extract and methods for treating constipation by ingesting the formulation of the present invention.

LAXATIVE FORMULATION

Field of the invention

The present invention relates to an herbal laxative formulation containing psyllium husk, calcium sennosides and triphala extract and methods for treating constipation by ingesting the formulation of the present invention.

Background of the invention

Constipation is a very complicated problem. Very few options are available from the synthetic drugs. Safe and effective drugs are available from herbal origin. Laxative is a synchronized process involving physical and physiological processes. The use of drugs with different mechanism of action leading to laxation will be beneficial for treating constipation.

There are two primary types of herbal laxatives. One is called a purgative, which includes herbs such as senna, rhubarb, leptandra, buckthorne and cascara. These often contain bitter principles in the form of anthraquinones which work by stimulating the peristaltic action of the intestinal lining, either directly or by promoting the secretion of bile through the liver and gall bladder.

The second type of laxative is a lubricating bulk laxative, which includes demulcent herbs such as psyllium and flax seed. This is more nutritional and usually does not have any significant direct effect on either the liver or the gall bladder. Rather, these work like a sponge by swelling and absorbing fluid, thus acting as an intestinal broom.

Currently used preparations of psyllium seed husks have certain disadvantages. Laxative preparations of psyllium seed husks are generally composed of ground husk and have coarse and unpleasant mouth feel when administered in drinks. Psyllium seed husks have been incorporated into cookies, crackers and similar products; however, these products have a tendency to begin to gel unpleasantly in the mouth. More significantly, though, psyllium seed husks can swell in the esophagus, producing an esophageal obstruction that can cause choking. For this reason, psyllium seed husk preparations are not recommended for ingestion by persons who may have difficulty swallowing (e.g., elderly persons). Finally, the recommended daily dose of psyllium husk of 3.5-11 g per day is inconvenient to ingest in any form. What is needed is a form of psyllium husk that is convenient and pleasant to use.

However, due to its mucilaginous nature, psyllium acquires a slimy or adhesive texture and mouth feel upon hydration. Psyllium normally forms a gelatinous mass when contacted with water and exhibits poor dispersibility and mixability in water. Psyllium also develops a distinctive, undesirable flavor in the presence of heat and moisture which further limits its use in food products. This slimy mouth feel is unpalatable and various additives have been incorporated in psyllium-containing ingestible compositions in order to mask the undesirable texture and mouth feel of the psyllium.

The herb Senna comprises dried leaflets of Cassia acutifolia, which is generally known as Alexandrain senna or Cassia angustifolia, known in commerce as Tinnevelly senna, or a mixture of both the species. Senna leaf contains not less than 2.5% of hydroxyanthracene glycoside, calculated as Sennoside B. Sennosides are partially purified natural complex of anthraquinone glycosides found in senna, isolated form C. angustifolia or C. acutifolia as calcium salts.

Negative aesthetics and performance attributes are recognized with using senna-containing laxative compositions. US 4,511,561 reports that undesirable side effects may be observed with the use of sennosides. This patent describes certain compositions containing psyllium and senna resulting from a specific granulation procedure. It also describes the use of peppermint oil as flavour oil.

There is a need for laxative composition with sennosides having improved aesthetics, reduced undesirable side effects (e.g., reduced cramping, reduced gas, reduced bloating, etc.) and an improved consumer acceptability to encourage regular compliance for treating constipation. Further, laxatives should be in convenient dosage forms that are effective as laxatives. In order to overcome these side effects US 5397573 discloses a formulation wherein the use of higher levels of menthol, preferably as part of peppermint oil, delivered to the lower gastrointestinal tract in combination with sennosides.

A study to evaluate antimutagenic potential of water, chloroform and acetone extracts of triphala has been made in an Ames histidine reversion assay using TA98 and TA100 tester strains of salmonella typhimurium against the direct-acting mutagens, 4-nitro-o-phenylenediamine (NPD) and sodium azide, and the indirect-acting promutagen, 2-aminofluorene (2AF), in the presence of phenobarbitone-induced rat hepatic S9. A combination drug 'Triphala' - a composite mixture of Terminalia bellerica, T. chebula and

Emblica officinalis, has been used in traditional system of medicine for the treatment of many malaises, such as heart ailments and hepatic diseases. The drug was sequentially extracted with water, acetone and chloroform at room temperature. The study revealed that water extract was ineffective in reducing the revertants induced by the mutagens. The results with chloroform and acetone extracts showed inhibition of mutagenicity induced by both direct and S9-dependent mutagens. A significant inhibition of 98.7% was observed with acetone extract against the revertants induced by S9-dependent mutagen, 2AF, in co-incubation mode of treatment (Kaur, S., Arora, S., Kaur, K., Kumar S. The in vitro antimutagenic activity of Triphala--an Indian herbal drug. Food Chem Toxicol 2002 Apr; 40(4):527-34).

Crude alcoholic extracts of T. chebula, T. bellirica and P. embelica were found to lack cellular toxicity in an assay using fresh sheep erythrocytes. (Ahmed I, Mehmood Z, Mohammad F. Screening of some Indian medicinal plants for their antimicrobial properties. Journal of Ethnopharmacology 1998: 68: 183-193.)

The aqueous extract of T. bellirica fruit was found to be non-toxic when administered orally to mice, whereas the LD50 of the alcoholic extract was equivalent to 4.25g crude drug per kilo body weight (Siddiqui, H. H., Studies on Terminilia bellirica Roxb; Effect on bile secretion and pharmacodynamic properties, Indian Journal of Pharmacy 1963: 297).

A water soluble fraction of T. bellirica showed no signs of toxicity in mice at oral doses up to 3.2g/kg bodyweight. (Anand, K. K. et al. - Hepatoprotective studies of a fraction form of the fruits of T. bellirica Roxb on experimental liver injury in rodents Phytotherapy Research. 1994: 8: 287-292.)

US 5,320,847 teaches a high-fibre, consumable bulk fibre composition, which may be used as a laxative, comprises powdered psyllium husks agglomerated with a water soluble, low viscosity gum, preferably gum acacia, to form a dry, free-flowing and water dispersible dietary fibre combinate. To form the dietary fibre combinate, the powdered psyllium husks are mixed with an aqueous solution of the water soluble, low viscosity gum, preferably by fluid bed agglomeration, and dried. The composition is employed to treat constipation by ingesting an effective amount of the dietary fibre combinate dispersed in water.

US 5,397,573 discloses a laxative composition comprising: (a) from 0.01%-75% of sennoside; (b) from 1%-99% menthol, pharmaceutically-acceptable esters of menthol, or mixtures thereof; and (c) from 1%- 99% carrier material. This patent further discloses laxative compositions containing sennoside and menthol, preferably as peppermint oil. This patent also teaches a method for treating constipation by orally and concurrently administering sennoside and menthol to the lower gastrointestinal tract of a person in need of such treatment.

US 5,514,663 relates to a pharmaceutical laxative composition in unit dosage form, for peroral administration of sennosides to a human or other animal subject, comprising a safe and effective amount of sennosides in a rapidly dissolving matrix; and a proximal colonic delivery carrier which effects release of said sennosides substantially near the junction between the small intestine and the colon or within the colon of said subject. This invention also involves methods for providing laxation for humans and other animals in need thereof by peroral administration of such compositions. The patent involves a novel dosage form of senna, or sennosides, for providing laxation in the colon.

The sennosides themselves have little direct laxative activity. Rather, they are convened to the derived active moiety, rhein-9-anthrone, by colonic bacteria. Pharmacology studies demonstrate that rhein-9-anthrone has the greatest purgative action associated with use of sennosides. Senna extracts and sennosides are water soluble. Sennosides are poorly absorbed from the small intestine, but the hydrolysis products generated in the colon (e.g., rhein or rhein-9-anthrone) are readily absorbed from both the small intestine and the colon.

US 5,232,699 relates to laxative compositions comprising psyllium and sennoside wherein sennoside is dispersed in a palatable food grade fat having a melting point within the range of from about 30°C to about 50°C.

US 4,857,331 teaches ingestible gels confectionary delivery system which is said to include a pectin gel component, an algin gel component and a polymer network gel component, as well as an active ingredient. It is stated therein that sennosides are known to cause an unpleasant taste.

US 4,766,004 describes dietary fibre supplement compositions said to be crunchy and highly palatable containing whole psyllium husk having particle size of 12 to 70

mesh. Also required is palatable food grade vegetable fat, which is solid at room temperature, a sweetening agent, and at least one flavoring agent.

US 4,842,865 relates to the use of glycofurol for liquidization of pharmaceutical preparations containing more than 50% phosphatidyl choline with a high content of unsaturated fatty acid, which preparations can contain another active ingredient, one of which is stated to be senna extract.

US 4,595,592 relates to a process for obtaining laxative compounds from the extraction of senna.

US 4,476,121 relates to orally administered compositions useful for treating constipation comprising a synergistic mixture of fruits, glycerin and compound senna.

US 4,402,944 relates to polysulfonated sennoside A and B derivatives. The Example 10 of the patent describes an injectable oil comprising the active compound and sesame oil.

US 4,256,875 relates to a process for extraction of sennoside from senna.

There are formulations available wherein psyllium seeds as well as husk along with other ingredients like senna powder, senna pods, cascara sagrada, aloe vera, croton tiglum, ipomea turpeth, etc. are used. However, all such formulations are non-specific, non-dose controlled and poly-herbal in nature. There are also formulations available comprising senna, gum, karaya and isabgol. Further, formulations are also available with Isabgol husk, gum tragacanth, senna extract, fennel and cumin.

Formulations containing only senna and ispaghula are available in the market, none is available in combination with the triphala and have employed either crude powders or extracts. Dosage is very large when powders are employed. These combinations have the disadvantages such as non-dispersibility and non-availability for pharmacological action.

Therefore, there is a need to provide an herbal laxative product derived from herbal extracts with no recognized side effects and in convenient dosage forms. There is also a need to provide a laxative formulation with better dispersibility and availability for pharmacological action compared to crude herbal leaf powders.

Objects of the invention

An object of the present invention is to provide an herbal laxative formulation comprising isabgol (psyllium husk), calcium sennosides, triphala extract, colouring, dispersing, sweetening and flavouring agents.

Another object of the present invention is to provide convenient dosage forms containing psyllium husk, calcium sennosides and triphala extract, which are effective for treating constipation.

Yet another object of the present invention is to provide the dosage in granules.

Brief description of the diagrams

Figure 1 depicts *In-vitro* release of sennosides by using herbal laxative formulation of the present invention.

Figure 2 depicts Tannin content in different Triphala ingredients as used in the laxative formulation of the present invention.

Figure 3 is a graphical representation of Orocecal Transit Time (Sulfapyridine appearance time) of the laxative formulations of the present invention vis-à-vis placebo and senna.

Figure 4 is a graphical representation of stool frequency during 24 hours of the formulation of the present invention vis-à-vis placebo and senna.

Summary of the invention

The present invention relates to a herbal laxative formulation for a immediate dissolution in gastric fluids comprising a safe and effective amounts of psyllium husk powder from about 59-61% w/w, senna alkaline earth metal salt of sennosides from about 9-10% w/w, triphala extract from about 29-31% w/w with an enhanced tannin, dispersing agent from about 4.0-5.0 %w/w, and carrier materials suitable for ingestion from about 1-2% w/w.

The present invention further relates to a method for treating constipation in humans. These methods comprise orally administering to a human in need of such a treatment an effective amount of herbal laxative formulation according to the present invention. Further, the present invention also relates to method for manufacturing the herbal laxative formulation of the present invention, said method comprising the steps of by passing the ingredients through a stainless steel mesh, weighing the psyllium husk, calcium sennosides and triphala extract along with dispersing and sweetening agents and

mixing them in a mixer for about 20 minutes, adding ethyl alcohol 5-8% v/w and demineralized water 8-10% v/w and mixing the wet mass in a mass mixer, passing the wet mass through another mesh, spreading the wet granules and drying at temperature of 40-50°C in a hot air oven for about 45 minutes, passing the dried granules through another mesh and retaining about 89% of the total granules on the mesh, and adding flavouring agents slowly while rotating the granules at a low speed in a coating pan and packing the formulation.

Detailed description of the invention

The present invention provides a herbal laxative formulation, said formulation comprising: (a) psyllium husk powder from about 59-61% w/w, (b) calcium sennosides from about 9-10% w/w, (c) triphala extract from about 29-31% w/w with an enhanced tannin content suitable, (d) dispersing agent from about 4.0-5.0 %w/w, and (e) carrier materials suitable for ingestion from about 1-2% w/w.

(a) **Psyllium husk**

The present laxative formulation comprises psyllium husk. The term "psyllium husk", as used herein, means the seed coat of psyllium seed (either intact or macerated or otherwise comminuted). Psyllium husk comes from psyllium seed, from plants of the Plantago genus. Various species such as Plantago lanceolate, P. rugelii, and P. major, are known. Commercial psyllium includes the French (black; Plantago indica), Spanish (P. psyllium) and Indian (blonde; P. ovata). Indian (blonde) psyllium is preferred for use herein.

Intact or macerated seeds can be used in the practice of this invention. However, it is typical to remove the seed coats from the rest of the seed by, for example, slight mechanical pressure, and then to use only the seed coat. In the practice of the present invention it is convenient and desirable to use macerated seed coat in the final composition. The seed coat is therefore preferably removed and sanitized by methods known in the art prior to use in the present composition. Furthermore, the psyllium husk utilized preferably has high purity, being about 85% to about 100% pure, and more preferably being about 95% to about 100% pure.

Psyllium is a fibre rich, highly mucilaginous, poorly absorbed laxative. The hydrated mucilage of psyllium reduces irritation of the large intestine and also prevents

depletion of mucosal lining of the large intestine. The stool becomes soft and slippery and hence less strain is required for evacuation of the bowels especially in patients suffering from hemorrhoids.

While for purposes of the present invention it is possible to have the psyllium husk dispersed in the dispersing agent and carrier materials along with the other ingredients of the formulation.

The laxative formulation of the present invention comprise a safe and effective amount of psyllium husk, typically from about 59% to about 61% by weight of the laxative formulation.

(b) **Calcium sennoside**:

Sennosides are plant-derived compounds that belong to the anthraquinone group of stimulant laxatives. Sennosides are derived from the leaves or pods of various species of the Cassia plant. Commercial sources include the species Cassia angustifolia (Tinnevelly senna) and Cassia acutifolia (Cassia senna or Alexandria senna). Commercially, sennosides are available as pods, leaves, or concentrates of the leaves and/or pods, and therefore, as used herein, sennoside includes not only the pure or concentrated sennoside compounds having laxative properties but also senna plant materials, which have laxative properties. Frequently sold concentrates range from 20%-95% calcium sennosides. The remaining components in the concentrate also originate from the plant, or are formed during extraction. Sennosides supplied from concentrates of senna pods are preferred. Such concentrates have ranges of sennoside content typically from about 20% to about 80%. Obviously, the higher the sennoside level in such concentrates, the less concentrate needed for the laxative compositions. Sennosides are also described in detail in The Merck Index, 10th Edition (1983), No. 8298 ("Senna") incorporated by reference herein in their entirety.

Senna extracts are gummy semisolid concentrates obtained after evaporation/recovery of the solvents. This also contains lot of chlorophyll. The extractive values are generally 10-15% w/w of the leaf powder taken. The extract contains up to 10%w/w sennosides.

Semi-purified sennosides are calcium salts precipitated from the extract before evaporation/recovery of the solvent. Calcium salts of sennosides as precipitates are taken

out leaving behind chlorophyll and other soluble material. These semi-purified calcium sennosides contain 20%w/w sennosides. These calcium sennosides i.e., semi-purified extracts are different from the extracts, which are known as crude extracts.

For purposes of the present invention, it is necessary that sennosides be dispersed in part in the carrier material.

The laxative compositions of the present invention comprise a safe and effective amount of sennosides, typically from about 9% to about 10%, and more preferably about 10% by weight of the laxative composition. Sennosides are present in the form of their alkaline earth metal salts, preferably 20% w/w calcium salt of sennoside. The sennosides used in the present formulation relieves constipation by stimulating the colon and has stool-softening action.

Safety of senna

Senna products as laxatives and several of their specific components have been submitted to a large number of genetic tests. (Assessment of the genotoxic risk from laxative senna products. Brusick, D. et al., Environ. Mol. Mutagen. 1997, 29(1):1-9). While most studies gave negative responses, results from some of the studies suggest that components of senna products, particularly emodin and aloe-emodin, have genotoxic activity. Assessment of the genotoxicity profile of these substances, in light of other data from animal and human metabolism, kinetic studies, human clinical trials and rodent carcinogenicity studies do not support concerns that senna laxatives pose a genotoxic risk to humans when consumed under prescribed use conditions.

Triphala extract:

According to the Ayurvedic Formulary of India, Triphala is prepared by mixing equal parts of *Phyllanthus eblica* (Amla), *Terminalia bellirica* (Behda) and *Terminalia Chebula* (Harda). It is taken in dosages of 3- 6 g, twice daily in the treatment of flatulence, constipation, diabetes and eye disease. Triphala is an effective blood purifier that stimulates bile secretion as it detoxifies the liver, helps digestion and assimilation and significantly reduces serum cholesterol and lipid level through out body. Triphala is also known to have a general strengthening effect of the body system and the bowels. Due to its strong anti-oxidant activities, triphala gives protection from the xenotoxic activity of senna that has been suspected.

In the present invention an extract such as an alcoholic extract (95%) of triphala containing tannins is used in the present formulation. By way of employing the extract the large dose of triphala powder is reduced. Further, an aqueous extract of triphala can also be suitably used. The laxative formulation of the present invention comprises an amount of triphala extract from about 29-31% w/w.

The addition of triphala extract along with calcium sennosides brings about a better laxative effect, which is further enhanced by the swelling effect of psyllium husk powder.

The advantages of having triphala extract in the present formulation acts as a gentle cleanser without any recognized side effects. Further, the triphala also strengthens entire gastrointestinal system. This laxative application is generally safe and effective even for geriatric and pediatric use because the rejuvenative properties of triphala offset the potentially debilitating effects. Further, triphala will not cause dependence unlike other laxatives, because it strengthens and tones up the musculature of the bowel.

Tannin content in Triphala ingredient is determined by the titrimetric method described in A.O.A.C 1970, the procedure is as written below:

Chemicals Required

Oxalic acid ($C_2H_2O_4$), Potassium permanganate ($KMnO_4$), Indigo solution, Ether

Reagents:

Oxalic acid 0.1 N solution - 1ml = 0.006235 gm of quarcitannic acid or 0.0008 gm of 'O' absorbed.

Potassium permanganate standard solution – Dissolve 1.333 gm of KMnO4 in 1-liter water and standardize against 0.1N oxalic acid solution.

Indigo solution – Dissolve 6 gm sodium indigotin disulfonate in 500 ml water by heating. Cool the solution and add 50 ml sulphuric acid. Make the volume to 1 liter with water and filter the solution.

Method:

Extract 2 gm sample for 2 hour with anhydrous ether. Boil residue for 2 hour with 300 ml water, cool and dilute to 500 ml and then filter the solution. Measure 25 ml of this infusion into 2 L porcelain dish and add 20 ml indigo solution and 750 ml water. Add potassium permanganate 1 ml at a time until blue solution changes to green and add few

drops at a time until solution becomes golden yellow. Similarly titrate mixture of 20 ml indigo solution and 750 ml water. Multiply difference between two titrates by desired factor to obtain quercitannic acid (tannin). The percentage of tannin content in each ingredient is recorded and tabulated in the following Table. The results are plotted to obtain **Fig 2**, which clearly shows the higher content of tannin in Triphala extract.

TANNIN CONTENT IN DIFFERENT TRIPHALA INGREDIENT

	Amla (%)	**Baheda(%)**	**Hardae(%)**
Powder	29.0	32.2	26
Extract	58.0	89.3	47.8

Dispersing agent:

The dispersing agent is preferably polyvinyl pyrrolidone $[(C_6H_9NO)_n]$. Cross-linked PVP is non-ionic, water insoluble, swellable homopolymer, white free flowing powder. It is a super disintegrant, which readily disintegrates in water and form homogenous mixture. Other dispersing agents used in pharmaceutical industry are Starch, Sodium bicarbonate and citric acid

Carrier materials

Colouring agent:

The colouring agent is preferably natural red from beetroot. Beet root color is used as coloring agent because it is natural, easily available and gives good reddish brown color to the granules. Other coloring agents used in pharmaceutical industry are chlorophyll, amaranthus red, sunset, brilliant blue or β-carotene.

Sweetening agent:

The present compositions comprise a sweetening agent. Water-soluble sweetening agents such as monosaccharides, disaccharides, and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof; water-soluble artificial sweetners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, acesulfam-K and the like, and the free acid form of saccharin; or dipeptide based sweeteners such as L-aspartyl-L-phenylalanine methyl ester and the like. In general, the amount of sweetener is

primarily a matter of taste preference and will vary with the sweetener selected and with the ingredients in the composition being prepared. Preferred are non-nutritive artificial sweeteners such as aspartame, acesulfame, saccharin, cyclamate and a sugar component such as sucrose, invert sugar syrups, corn syrup solids, fructose, dextrose (glucose), honey, molasses, maple syrup and the like. Preferable sugar components are fructose, glucose, sucrose and corn syrup solids.

The compositions of the present invention preferably comprise from about 0.5% about 1% of a sweetening agent, and more preferably from about 0.5% to about 1% of a sweetening agent by weight of the laxative formulations.

Flavouring agent:

Flavouring agents such as vanilla, strawberry, raspberry and orange the like, are preferred optional components and typically comprise from about 0.2% to about 0.5% by weight of the laxative formulations. Flavour can be modified as per the requirement of the end user. Colours and flavours are added to improve the organoleptic properties of the formulation.

There is a general belief that mucilage of psyllium on absorption of water forms a barrier coat and hence interferes with the release of sennosides and tannins of triphala. The dispersible granules ensure that sennosides and triphala ingredients become immediately dispersible and soluble in water the moment they are placed in water just before taking the granules. Since, calcium sennosides and triphala extract are employed in place of crude powders, the extracts dissolve immediately in gastric fluids even before isabgol starts swelling.

Ispaghula is the major ingredient, which is a non-habit forming, fibre rich bulk laxative. It is slow in action. So, therefore, by adding sennosides, the laxative effect of ispaghula is enhanced.

The combination of above ingredients is made into a dispersible granule formulation with colour and flavour to improve taste of the formulation. Hence, the three main ingredients acting through different modes bring about a more synergistic and harmonious results for subjects suffering from constipation.

Standards

The combination of psyllium husk, senna as semi-purified sennosides and triphala extract is unique and has been clinically proven to be effective and safe. Formulation is evaluated for its physical characteristics and in vitro dissolution behavior. All the important physical characteristics of the formulation like moisture content, swelling index, particle size distribution, flowability and microbial limit are evaluated.

In-vitro dissolution study is carried out using USP dissolution apparatus. Dissolution study is carried out as per I.P. /B.P. Percent release of sennosides and total tannins is carried out using spectrophotometric method and titrimetric methods respectively.

Conditions:

Medium	900 mL of 0.1N hydrochloric acid
Rotation speed	50 rpm
Apparatus	U.S.P Paddle Assembly
Time	120 min
Filters	0.45 μm

Sample Preparation:

5 g granules are placed into each of the six dissolution vessels to form an assembly. The assembly is lowered into the medium and the paddles are rotated at 50 rpm. The samples of 20 ml are withdrawn through filters after 120 minutes. Assay experiments for the determinations of Sennosides and tannins are done according to the method of IP, 1996 and AOAC, 1970 method respectively.

In vitro dissolution study is carried out using USP dissolution apparatus and the percentage release of sennoside is determined and the results are plotted as shown in Figures **1**. It can be seen from **Fig 1** that by administering the laxative formulation of the present invention, the release of sennosides is about over 80% within a span of 45 minutes from the time ingestion.

Pre-formulation and post formulation parameters have been generated meticulously planned and data generated to the extent possible. Laxative action of the ispaghula is due to its swelling power. It may entrap other active principles of the formulation leading to poor release of sennosides from senna and tannins from triphala. Hence, the formulation of the present invention is made into easily dispersible granules. Formulation is also evaluated for its physical characteristics and *in vitro* dissolution

behavior. The percentage of release of calcium sennoside granules of the present invention vis-à-vis prior art formulations are provided in Table 1.

Standardization methods adopted in preparing the formulation of the present invention includes (a) estimation of sennosides for Senna (b) estimation of total tannins for Triphala, and (c) estimation of swelling index for Ispaghula (Psyllium husk).

The results of the dissolution study are tabulated in Table 1, which clearly demonstrate the dispersibility and availability of senna and tannins of the laxative formulation of the present invention as compared to crude leaf powder and extracts.

The **Tables 1 and 2** are furnished to show the richness of calcium sennosides over senna powder and senna extract with respect to sennoside content. The tables also show that calcium sennosides have better dissolution profile and bioavailability.

Table 1: Percentage release of sennoside and total tannins from different formulations

Formulation	Sennoside release (%)	Tannins release (%)
Granules with senna leaf powder	33.6	77.75
Granules with senna extract	85.47	84.17
Granules with calcium sennoside (semi-purified sennosides)	98.95	88.30

The availability of correct dose of sennoside for pharmacological activity will ensure the consistent quality of the product over other products, which use crude leaf powder and extracts.

Further, studies have been conducted to determine the availability of Senna in powder, extract and semi-purified forms and results are compiled in Table 2.

Table 2: Composition of sennosides in senna powder, senna extract and calcium sennosides

Senna powder (%)	Senna extract (%)	Calcium Sennoside(%)
1.6	10.6	18.46

The values in **Table-2** describe the percentage of sennosides present in senna leaf powder, senna extract and calcium sennosides. Ingredients in the **Table-2** are used to indicate the superiority of the use of calcium sennosides over senna leaf powder and senna extract. Sennosides content in calcium sennosides is about 18.46% where as it is much less in senna leaf powder or senna extract i.e 1.6 and 10.6% respectively. Accordingly, calcium sennosides are used in the laxative formulation of the present invention.

It can also be seen from Table 2 that the powder formulations provide very poor quantities of senna for pharmacological activity.

Table 2 also clearly indicates the superiority of using semi-purified sennoside (as calcium sennoside) over senna leaf powder and crude extract of senna.

All the important physical characteristics of the formulation like moisture content, swelling index, particle size distribution, flowability and microbial limit were evaluated and the data were provided in Table 3.

Table 3: The physical characteristics of the granules.

Sl. No.	Parameter	Value
1	Particle size distribution IQCS value	0.09
2	Bulk density	0.518
3	Tapped density	0.553
4	Carr's index	6.83
5	Housner's ratio	1.06
6	Moisture content	5.2%
7	Microbial limit	<300 cfu
8	Swell volume	34

A comparative clinical study has been conducted to compare the laxative effect of senna and senna and ispaghula combination. Both laxatives increased defecation frequency and wet and dry stool weights although the added effect of the senna is clearly evident. Only the psyllium with senna increased stool moisture. Two distinct responses to the psyllium plus senna are evident; the subpopulation of high responders (n = 7) is responsible for most of the increase in stool frequency and dry weight in this group, and

laxation in the subpopulation of normal responders (n = 12) was similar to that observed in those receiving psyllium alone. Both laxatives provided a similarly high degree of subjective relief and improvement in stool consistency. When constipation is assessed objectively by stool frequency and weight, laxation is attained by 63% of the psyllium plus senna group and 48% of the psyllium group (*Marlett JA, Li BU, Patrow CJ, Bass P. Comparative laxation of psyllium with and without senna in an ambulatory constipated population. Am J Gastroenterol 1987 Apr; 82(4):333-7*)

It is interesting to note here that crude senna powder and senna extract as used in the prior art formulations, do not contain sufficient amount of sennosides as that is required, to elicit the activity of laxation. The sennosides (20 mg per day) can show the activity within 8 hours. This activity causes slight griping and peristaltic movement of the intestines. Further, this activity also contains certain undesirable side effects. It is also to be noted here that to produce psyllium husk bulk, about 5 to 7 g of husk is required. Even then, to produce movements of the large intestine sennosides and triphala are essential. Triphala powder dose recommended in the ayurvedic literature is quite high. Hence, the concentrated extract of the present invention is about 3.5 times more concentrated than the powders as used in prior art formulations. Hence, the end result is faster laxative effect devoid of strain on the bowels and undesirable side effects. Bowel frequency was greater in comparison to senna alone.

Method for making laxative formulation

Method according to the present invention is to provide a process for the preparation of the laxative formulation according to the present invention comprises the steps of: (a) passing the ingredients through a stainless steel mesh, (b) weighing the psyllium husk, calcium sennosides and triphala extract along with dispersing and sweetening agents and mixing them in mixer for about 20 minutes, (c) adding ethyl alcohol 5-8% v/w and demineralized water 8-10% v/w and mixing the wet mass in a mass mixer, (d) passing the wet mass through another mesh, (e) spreading the wet granules and drying at temperature of 40-50^{0}C in a hot air oven for about 45 minutes, (f) passing the dried granules through another mesh and retaining about 89% of the total ranules on the mesh, and (g) adding flavouring agents slowly while rotating the granules at a low speed in a coating pan and packing the formulation.

Method of treatment

The present invention also relates to a method for treating constipation in humans (subjects) in need of such treatment. This method comprises orally administering to a human in need of such treatment a safe and effective amount of a composition of the present invention.

The dosage range of the formulation of the present invention is as follows:

Ingredients	**g per day/ person**
Psyllium husk powder:	5-10
Semi-purified sennosides i.e., Calcium sennosides (20%):	0.065-0.125
Triphala extract:	1.5-2.5

Ingestion of the formulation in the above-cited dosage form is administered into mouth followed by washing granules down with sufficient amount of water.

The pharmacodynamics of the herbal formulation of the present invention is investigated vis-à-vis placebo (double blind) and senna.

The investigation is a randomized, double blind, placebo controlled, phase I, cross-over pharmacodynamic study (orocecal transit time) and safety evaluation of the present herbal formulation in healthy male human subjects under fasting condition with a single dose of 5 g administered stat. Patients enrolled into the study are normal healthy subjects and are screened by physician for eligibility.

A single dose of 5 g of the present herbal formulation or placebo or senna is administered by oral route after 10 hour over night fasting. During the study, adverse events, if any are recorded. Blood pressure, heart rate, pulse rate and physical assessment are carried out.

Sulfasalazine tablets are ingested by the subjects along with the formulation or the Placebo and senna. After oral administration, Sulfasalazine is bio-transformed in the cecum by bacterial azoreductase (reduction of azo bond) into Sulfapyridine and 5-aminosalicyclic acid. The released Sulfapyridine is immediately absorbed into the blood and the time necessary for its appearance in the blood provides a measure of the orocecal

transit time. The method has high significant correlation between orocecal transit time and Sulfapyridine appearance time.

(Staniforth DH, Comparison of orocaecal transit times assessed by the lactulose/breath hydrogen and the sulphasalazine/sulphapyridine methods. Gut. 1989, 30:978-82)

The pharmacodynamics of the present herbal formulation, placebo (double blind) and senna are shown in Tables 4 to 7.

Table 4: Summary statistics of mean orocecal transit time (minutes) data of the present herbal formulation, placebo and senna.

Statistic	Present herbal formulation	Placebo	Senna
Mean	248.5	351.43	318
Minimum	210	300	280
Maximum	300	480	420
S.D.	24.76	50.51	42.6
n	14	14	14

S.D. - Standard deviation; n – Number of subjects

The comparison between the present formulation, placebo and senna are shown in Table-4, and the results of Sulphapyridine appearance time as tablulated in Table 4 are plotted to obtain **Fig 3**, which shows that Sulfapyridine time appearance is significantly lower in the laxative formulation of the present formulation. Therefore, formulation of the present invention is more effective in overcoming constipation when compared to Senna alone or placebo.

The effect of laxative formulation of the present invention on the stool frequency as compared with a placebo and senna is tabulated in **Table 5**.

Table 5: Summary statistics of mean stool frequency data of the present herbal formulation, placebo and senna.

Statistics	Laxative formulation of the present invention	Placebo	Senna
Mean	1.86	0.21	0.68

Minimum	01	00	01
Maximum	03	01	01
S.D.	0.66	0.42	0.36
n	14	14	14

S.D. - Standard deviation; n – Number of subjects

As can be seen from Table5, with the formulation of the present invention the stool frequency in the subjects increased and significantly higher when compared to Senna or placebo.

The results as obtained in Table 5 are plotted in the form of a **Fig 4**, which clearly shows the enhanced stool frequency when the laxative formulation of the present invention is administered.

Table 6: Summary table of the main study results for the present herbal formulation and placebo.

Parameter	**Present herbal formulation**		**Placebo**		**F (treatment)**	**Inference**	**P**
	Mean	**CV%**	**Mean**	**CV%**			
Orocecal transit time	248.7	9.9	351.4	14.4	51.59	Significant	1.25e-007***

CV% - Co-efficient of variation; F – Fisher test (Variance ratio); P – Probability value

Table 7: Summary table of the main study results for the present herbal formulation and senna.

Parameter	Present herbal formulation		Senna		F (treatment)	Inference	P
	Mean	CV%	Mean	CV%			
Orocecal transit time	248.7	9.9	318	13.3	27.27	Significant	1.87e-005***

CV% - Co-efficient of variation; F – Fisher test (Variance ratio); P – Probability value

From the statistics data in table 6 and 7 it can be conclusively stated that in terms of pharmacodynamic parameter (Oracecal transit time) present formulation is better than placebo or senna.

Further, it was assumed before that gel formation of isabgol interferes in the release of sennosides and triphala for the activity in the stomach. The above limitation has been overcome in the formulation of the present invention, wherein this formulation completely releases senna (sennosides) and triphala (tannins) ingredients into solution instantaneously. The granules of the formulations are dispersible employing extracts rather than the crude powders of the ingredients.

Mechanism of Action

The present formulation has three-pronged activity sennosides bring about rapid spasmodic movements of the large intestine and prevent re-absorption of water thereby making the stool soft. Ispaghula, due to its hydrophilic nature rapidly absorbs water, swells and forms a bulky mucilaginous mass, which acts as a mechanical bulk laxative in addition to rendering protection to the mucosal lining of the colon and large intestine. Triphala is a reputed Ayurvedic drug, which is a detoxifier and strengthens the tonicity of the intestinal musculature. The present herbal formulation is a judicious blend of highly effective, semi-purified plant based drugs that successfully treat the problem of chronic and habitual constipation.

Exclusivity of the present herbal formulation:

The combination of extracts of Senna, Triphala and Ispaghula is unique. The formulation has been clinically proven to be highly effective and very safe. The present

herbal formulation shows 98% release of Sennosides as compared to other products, which contain Senna leaves, and show only 35% release of Sennosides. Similarly tannin percentage is much higher in Triphala Extract as compared to Triphala powder. Clinical studies have proven that Senna equivalent to 100 mg Sennosides do not cause any discomfort or uneasiness. Our clinical studies show that this dose is optimally effective in providing laxation. It is in the granular form, which makes it easy to take.

The following example further describes an embodiment of the present invention. This example is solely for the purpose of illustration and not to be construed as limiting the scope of the present invention, as many variations are possible without departing from the spirit and scope of the present invention.

EXAMPLE

The granular composition according to the present invention containing psyllium husk powder, senna alkaline earth metal salt of sennosides, triphala extract is prepared as follows having the following composition.

Ingredients	Weight %
Psyllium husk powder	**59.0-61.0**
Senna alkaline earth metal salt of sennosides	**9.0-10.0**
Triphala extract	**29.0-31.0**
Dispersing agent, polyvinyl pyrrolidone	**4.0-5.0**

Carrier material	Weight %
Colouring agent, natural red from beetroot	**2.0**
Sweetening agent, glucose	**2.0**
Flavouring agent, raspberry flavour	**1.0**

Advantages of the herbal formulation of the present invention

1. The present formulation is a scientifically evaluated and clinically proven herbal laxative formulation.
2. The ingredients of the formulation are most effective and safest among plants with similar claims. It has minimum number of ingredients, which have a broad spectrum of activity.

3. Dosage and quantities of ingredients are decided with scientific rationale.
4. It is completely standardized and ensures uniformly high quality of the product.
5. It has superior dissolution profiles and ensures optimal availability of the drugs for eliciting the activity.
6. Heavy metal content (Lead, Mercury and Arsenic) in the present formulation are below the permissible limits Lead 7.635 ppm, Arsenic 0.585 ppm and Mercury 0.725 ppm.
7. The present herbal formulation is 100% natural as it has no artificial colour or flavour.
8. This laxative application is safe and effective even for geriatric and pediatric use because the rejuvenative properties of Triphala offset the potentially debilitating effects.
9. The formulation comprising triphala will not cause dependence unlike many laxatives, because it also strengthens and tones up the musculature of the bowel.

We claim:

1. An herbal laxative formulation comprising:
   a) psyllium husk powder from about 59-61% w/w,
   b) calcium sennosides from about 9-10% w/w,
   c) triphala extract from about 29-31% w/w with an enhanced tannin content,
   d) dispersing agent from about 4.0-5.0 %w/w, and
   e) colouring, sweetening and flavouring agents suitable for ingestion from about 1-2% w/w.
2. The formulation as claimed in claim 1, wherein the triphala extract is a spray dried water extract or an ethanolic extract.
3. The formulation as claimed in claim 1, wherein the enhanced tannin content is in the range of 65-75%.
4. The formulation as claimed in claim 1, wherein the dispersing agent is selected from starch, sodium bicarbonate, citric acid and polyvinyl pyrrolidone $[(C_6H_9NO)_n$ preferably polyvinyl pyrrolidone $[(C_6H_9NO)_n$.
5. The formulation as claimed in claim 1, wherein the colouring agent is natural red from beetroot, chlorophyll, Amaranthus red, sunset, brilliant blue or β-carotene
6. The formulation as claimed in claim 1, wherein the formulation is in dispersible granular form.
7. The method of treating constipation in a subject, said method comprising orally administering herbal laxative formulation comprising psyllium husk powder from about 59-61% w/w, senna alkaline earth metal salt of sennosides from about 9-10% w/w suitable for immediate dissolution in gastric fluids, triphala extract from about 29-31% w/w with an enhanced tannin content suitable for immediate dissolution in gastric fluids, dispersing agent from about 4.0-5.0 %w/w, and carrier materials suitable for ingestion from about 1-2% w/w.

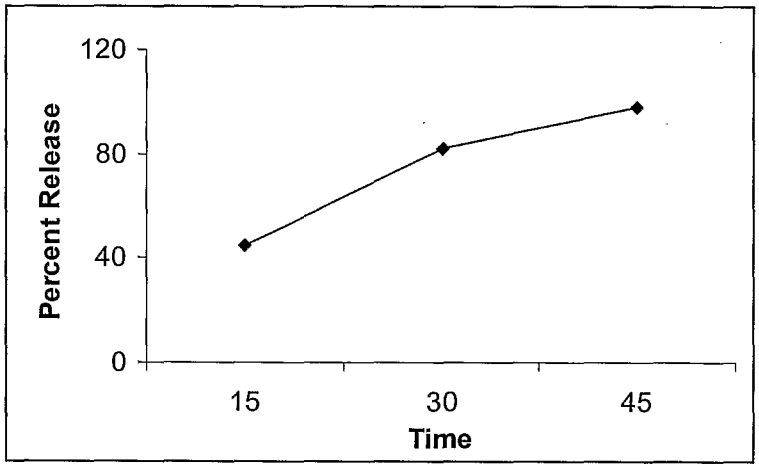

Figure 1

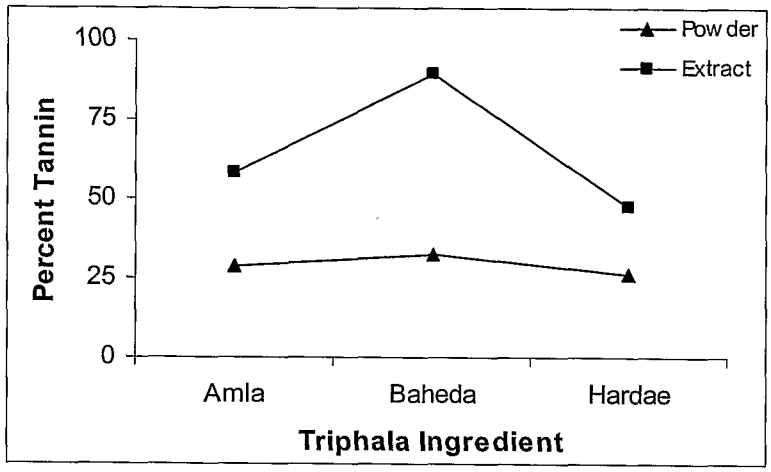
Pow der
Extract
100
75
50
25
0
Percent Tannin
Amla
Baheda
Hardae
Triphala Ingredient

Figure 2

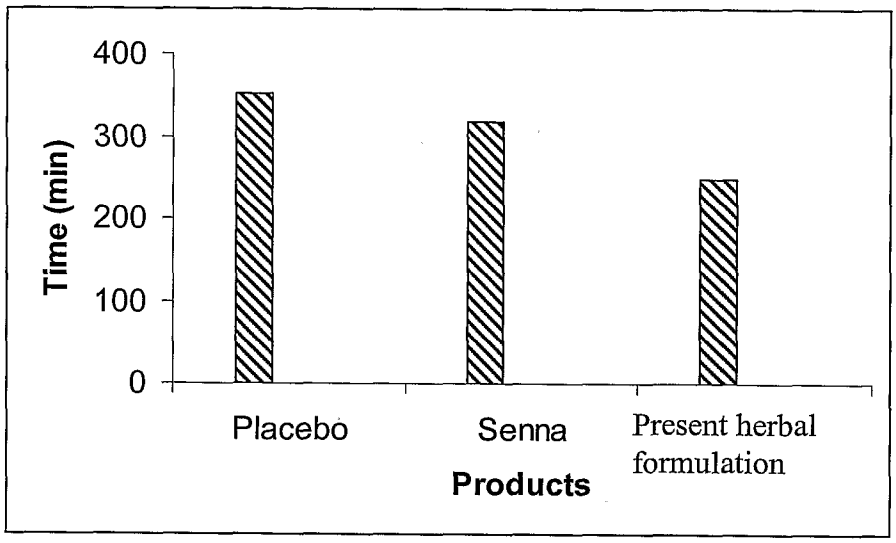
400
300
200
100
0
Time (min)
Placebo
Senna
Present herbal formulation
Products

Figure 3

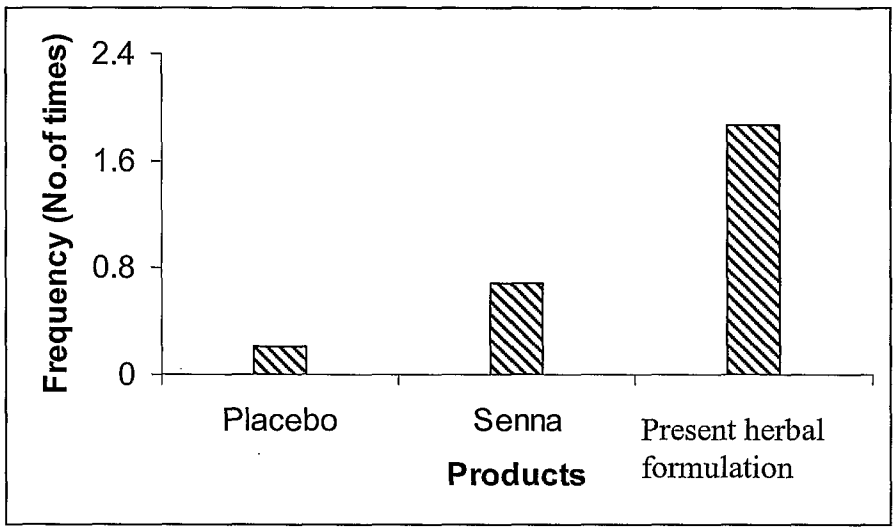
Frequency (No.of times)
2.4
1.6
0.8
0
Placebo
Senna
Present herbal formulation
Products

Figure 4