

Fig. 1

Schematic representation of the cross-section of the enteric-coated colon-targeted drug delivery system

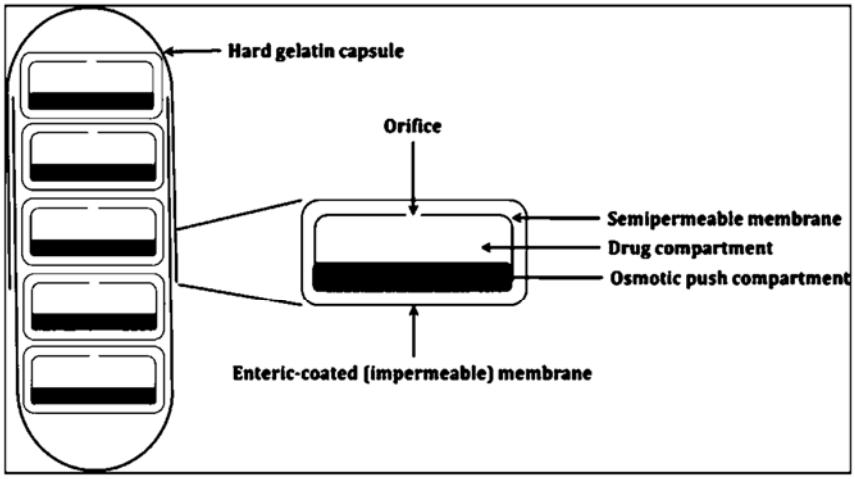

Fig. 2

Schematic representation of the cross-section of the OROS-CT colon-targeted drug delivery system

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Application No.	**Sheet no.: 01 of 02**

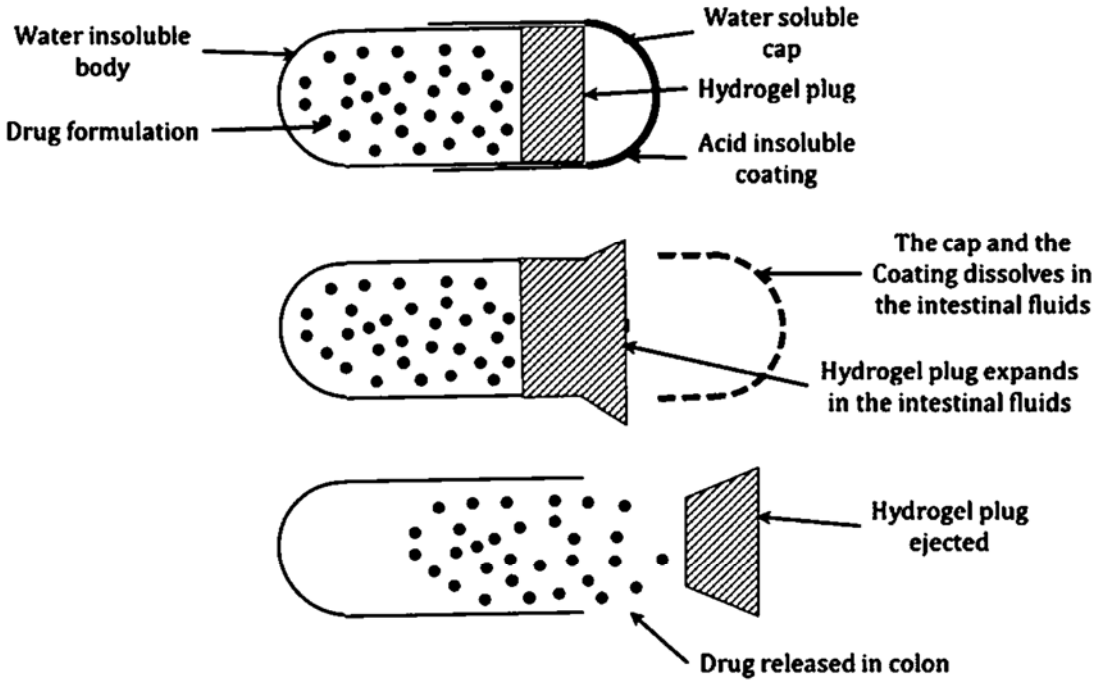

Fig. 3

Schematic representation of the mechanism of the *pulsincap* colon-targeted drug delivery system

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FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

AND

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See Section 10; Rule 13)

1. TITLE OF THE INVENTION:

"A COLON TARGETED PREBIOTIC AND PROBIOTIC TO IMPROVE THE MICROBIOME FUNCTIONING"

2. APPLICANT:

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4.PREAMBLE TO THE DESCRIPTION:

The following specification particularly describes the invention and the manner in which it is to be performed.

Field of Invention:

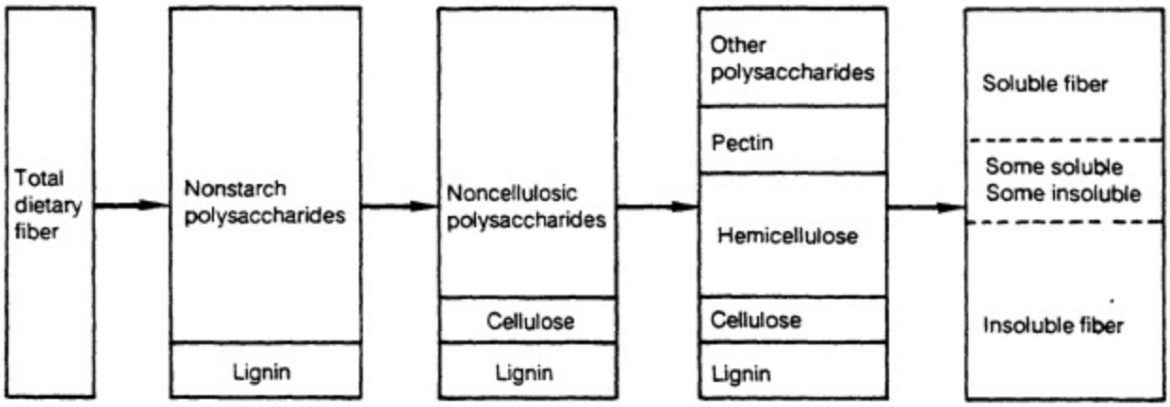
The present invention relates to Nutraceutical compositions comprising a combination of Prebiotic, Probiotic and optionally Vitamins and Minerals for colon targeted drug delivery and methods of preparation thereof. More particularly the invention relates to Nutraceutical compositions comprising a combination of Prebiotic, Probiotic and Vitamins and Minerals for colon targeted drug delivery and methods of preparation thereof wherein one of the Prebiotic is Inulin obtained from Chicory.

Background of Invention:

Health and diet have become the prime concern in the living world and the secret to good health has been a widely researched topic over the years. Good health comes from a good healthy gut. The transition from suckling on to breast milk onto eating processed foods, whatever we eat is absorbed into the bloodstream through our intestines. Therefore, our overall health depends on the health of our intestines. There are billions of bacteria present in the large intestine which are referred to as microbiome of the human body. The small intestine absorbs carbohydrates, lipids, proteins with the help of enzymes. But water-soluble nutrients are absorbed along with water in the human large intestine with the help of the microbiota/Microbiome. It is of utmost importance to understand that both water and water-soluble vitamins are absorbed in the large intestine with the help of the microbiome.

Roughage from food source is important for the beneficial bacteria in the gut and is generally obtained from high fiber diet. High fiber diet is of utmost importance for a healthy living Fiber has been known to produce roughage and help in formation of the bulk of human stools. Given that there are billions of bacteria in the gut, the primary source of food for these bacteria is dietary fiber.

Dietary fiber is of two kinds: soluble fiber and insoluble fiber.



To get a healthy human gut, it has to be ensured that these billions of bacteria are well fed. When these bacteria are well fed, they symbiotically release a by-product of digestion called butyrate. Butyrate can be understood as a simple jelly which seals micro traumas in the gut which leak out harmful materials into the bloodstream. If a gut is healthy, it has a high quantity of Butyrate which improves sleep and overall wellbeing also decreasing many metabolic disorders and prevents gut inflammation. Butyrate helps prevent athero-sclerosis and cardiovascular disease. In the study of blue zones, communities that lived longest had higher butyrate content in their colon.

The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery.

The colon contains many species of anaerobic bacteria which obtain their energy by fermenting substrates such as polymers which have not yet been digested. Bacteroides, eubacteria, clostridia, enterococci, and enterobacteria are some examples of these colon-specific species, and they produce numerous enzymes such as glucuronidase, xylosidase, nitroreductase, and azoreductase to ferment these polymers.

Spore-forming bacteria have recently received an increasing amount of scientific and commercial attention for their therapeutic qualities. Spore based probiotics are soil-based microorganisms that are formed from spores and found in dirt and vegetation. Unlike most traditional probiotics which are similar to those naturally found in the human GI tract such as lactobacilli and bifidobacteria, spore-based probiotics derived from Bacillus species are delivered as dormant spores. The endospores encapsulate the beneficial bacteria making them stable and highly resistant to stomach acid's low pH, resulting in the delivery of more usable probiotics to the small intestine where they revert to active, growing bacteria. Spore-based strains (e.g., Bacillus subtillis, Bacillus coagulans) are vital to the food chain as they have the intrinsic ability to produce a multitude of enzymes, secretory proteins, antimicrobial compounds, vitamins and carotenoids
For most patients suffering with gut issues, a probiotic has been proven to have immense benefits both on cardiovascular health and diabetic health.

For ages, human beings have consumed spore-based probiotics through the ingestion of fermented foods and raw vegetables that are contaminated with soil microflora. Probiotics are bacteria which are part of the microbiome. However very few probiotics pave the way to the large intestine since most of them are destroyed by the gastric acid Unfortunately, most of these probiotics are killed on the way to the into the small intestinal secretions. As mentioned in "Probiotics, Prebiotics & Synbiotics: Harnessing Enormous Potential," Nutraceuticals World (September 2001), a trend regarding probiotics is finding novel delivery systems, particularly because acidity in the stomach is detrimental to many probiotics and may destroy as much as 90-95% of such probiotics during their passage through the stomach. To date, improving the protection of probiotics from stomach acid has included using enteric coated capsules and microencapsulation. Such types of microencapsulation include technology known as Probiocap™ by Institut Rosell.

Thus, over the years, probiotics have been demonstrated as efficacious, but there has been only limited exposure on the concept of prebiotics. Prebiotics can be

simply understood as food for intestinal bacteria most of which comes from plant-based foods. Prebiotics are a component of some foods that the body cannot digest. They serve as food for bacteria and other beneficial organisms in the gut. Health of the gut is directly proportional to the quantity of production of Butyrate. Prebiotics have tremendous benefits on cardiovascular health. Prebiotics has been proven by numerous independent scientific studies to increase the number of healthy bacteria in the colon, the benefits of which are impressive and essential to overall health and wellbeing.

US20150290262A1 relates to a technology which may include a stabilized mass of highly Refined cellulose fiber as a prebiotic composition alone or with a Probiotic composition. The mass may flow as a liquid, may be in a frozen state or may be in a dried solid mass.

US20100189767 (Shimoni) provides solid compositions of bioactive agents, in particular of probiotic microorganisms.

During the research the inventors of the invention found that into high fiber foods are the best of all health foods thus on their further research on the benefits and harmful effects of Chicory, the inventor of the present invention has surprisingly found that Chicory is the world's most potent pre-biotic with 65% of Inulin fiber specifically useful to the bacteria in the human gut. Inulin is a dietary fiber that benefits gut health. Inulin is a water-soluble storage polysaccharide and belongs to a group of non-digestible carbohydrates called fructans. Inulin has attained the GRAS status in USA and is extensively available in about 36,000 species of plants, amongst which chicory roots are considered as the richest source of Inulin. Commonly, Inulin is used as a prebiotic, fat replacer, sugar replacer, texture modifier and for the development of functional foods in order to improve health due to its beneficial role in gastric health. Filter coffee is known to have 70% coffee and 30% Chicory.

Prebiotics serve as food for probiotics, which are tiny living microorganisms, including bacteria and yeast. Both prebiotics and probiotics may support helpful bacteria and other organisms in the gut.

The basis of the invention can be understood that water soluble vitamins are predominantly absorbed with the help of water in the Colon, which is the most distal part of the human gut.

Prebiotics and Probiotics are available in a number of Nutraceuticals and food products but there still remains an unmet need for improved formulations comprising a combination of both Prebiotic as well as Probiotic optionally along with multivitamins having targeted colon delivering technologies keeping in view their beneficial effect in the large intestine.

Summary of Invention:

The present invention relates to Colon targeted Nutraceutical compositions comprising Prebiotics and Probiotics optionally along with multivitamins and minerals and method of preparation thereof.

In the main aspect, the invention provides compositions which include one or more Prebiotic wherein one of the Prebiotic is Inulin, one or more Probiotic optionally along with Vitamins and Minerals and nutraceutical acceptable excipients.

In another aspect, the invention provides composition in which the delivery of the Prebiotic, Probiotic and Vitamins and Minerals is targeted to the colon.

In one aspect the most preferred prebiotic according to the invention comprises Inulin obtained from Chicory.

In yet another aspect, the invention provides a process for preparing compositions comprising the Prebiotic and Probiotic for colon targeted drug delivery.

In a further aspect, the invention provides compositions proposed for use during treatment of Irritable Bowel Syndrome, Diabetics, Hypertensives, Dehydrated patients, Patients receiving chemotherapy and antibiotics, Dyslipidemia , Pancreatitis, Gastritis, Inflammatory Bowel Disease and Vitamin deficiencies.

Brief Description of the Drawing:

Fig 1 shows Schematic representation of the cross section of the **enteric coated** colon targeted drug delivery system.

Fig 2 shows Schematic representation of the cross section of the **OROS-CT** colon targeted drug delivery system.

Fig 3 shows Schematic representation of the mechanism of the **Pulsincap** colon targeted drug delivery system.

Detailed Description of Invention:

Prebiotics and Probiotics have flooded the markets in the health-conscious world. Though a number of nutraceuticals are currently available there still remains an unmet need where both the Probiotics, Prebiotics and optionally the Vitamins and Minerals are combined in the same composition and delivered at the targeted site of action efficiently.

Thus, the present invention describes a colon targeted Nutraceutical composition comprising the following: i) One or more Prebiotic wherein one of the Prebiotic is Inulin ii) One or more Probiotic iii) Optionally One or more Vitamins and Minerals iv) acceptable excipients. The nutraceutical composition of the invention exhibits a colon specific targeted delivery. The Prebiotic, Probiotic and Vitamins are delivered directly into the large intestine where water is absorbed.

For the purpose of the present invention as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include both the singular and the plural unless the context clearly dictates otherwise. For example, a

composition containing “a probiotic” includes a composition having one probiotic or two or more probiotics, and “a prebiotic” includes a prebiotic or two or more prebiotics. Each of the terms “includes,” “include,” “comprises” and “comprise” means “includes at least.”

In an embodiment, the composition of the present invention comprises Inulin obtained from Chicory root.

In another embodiment, the composition of the present invention comprises Inulin obtained from Chicory root along with another Prebiotic.

In yet another embodiment the composition of the present invention comprises one or more Probiotics along with Prebiotics.

In still further embodiment the composition of the present invention comprises one or more Probiotics and Prebiotics along with one or more Vitamins and Minerals.

In yet further embodiment the composition of the present invention is provided for colon targeted delivery.

In a preferred embodiment the composition of the present invention is provided as a hard gelatin capsule with enteric protective micro spherules for delivery at the targeted site of action.

In a further preferred embodiment, the composition of the present invention is provided as an enteric coated tablet for delivery at the targeted site of action.

In yet another preferred embodiment, the composition of the present invention is delivered to the targeted site of action through the osmotic-controlled release oral delivery (OROS -CT) system.

In yet another preferred embodiment, the composition of the present invention is delivered to the targeted site of action through the Pulsincap mechanism.

In an alternative embodiment, the composition of the present invention is proposed for use during treatment of Irritable Bowel Syndrome, Diabetics, Hypertensives, Dehydrated patients, Patients receiving chemotherapy and antibiotics, Dyslipidemia , Pancreatitis, Gastritis, Inflammatory Bowel Disease and Vitamin deficiencies.

Prebiotics can be classified in the following 5 groups
1)Fructans (Include Inulin which produce Butyrate which improves overall health)
2)Galacto-oligosaccharides (Milk derived)
3)Starch and glucose derived oligosaccharides (Resistant starch)
4) Other oligosaccharides
5)Non carbohydrate oligosaccharides

The Prebiotic that may be used to practise the invention comprise Inulin, B glucans, pectins (Mucilage) and resistant starch.
Inulin obtained from Chicory root is the preferred source of Inulin used for the invention.

Probiotics that may be used to practice the invention are bacteria that benefit mammalian (particularly human) health, particularly gastrointestinal health.
Specific probiotics that may be used include, but are not limited to, one or more of Lactobacilli and Bifidobacteria and dormant spores of Bacillus species (Bacillus coagulans and bacillus subtilis. Preferably, the probiotic includes live colonies of Lactobacilli and Bifidobacteria, Saccharomyces Boulardii and dormant spores of Bacillus species (Bacillus coagulans and bacillus subtilis.

Most preferably, the Probiotic includes one or more of live colonies of Lactobacilli and Bifidobacteria Saccharomyces Boulardii and dormant spores of Bacillus species (Bacillus coagulans).

There is no published standard for the number of bacteria that should be in a probiotic product or dosage, only estimated figures ranging from 10^6 to 10^{10} bacteria per day, depending on the condition of the host, but what is important to understand is the Probiotic bacteria are harmless and susceptible to the acidic gastric acid, emulsifying bile juices and alkaline small intestine fluids. To overcome these barriers it is important to deliver the probiotic bacteria to the site where they actually live (Large intestine). It is also important to consider using probiotic spores along with live bacteria as spores are resistant to above mentioned barriers.

In an embodiment the one or more Prebiotic present in the composition is in the concentration range of 15%to 35%.

Determining whether a prebiotic is complementary to a probiotic may be done in a number of ways known to those skilled in the art. For example, the effect could be gauged by a plate count of probiotics present in a subject's faeces or the pH of a subject's chyme, a lowering of which would likely indicate an increased number of probiotics. Alternatively, a probiotic could be cultured in vitro with a selected prebiotic and without the probiotic. Tests could then be conducted to determine relative growth curves over time. Prebiotic stimulation of human colonic butyrate-producing bacteria and bifidobacteria, in vitro

In another embodiment the one or more Probiotic present in the composition is in the concentration range of 25%to 35%.

In yet another embodiment the Inulin present in the composition as a Prebiotic is present in the concentration range of 17% to 20%.

A preferred Prebiotic of the invention is Inulin obtained from Chicory root. The Prebiotic dosage range is between 10 mg to 3 grams of this range of Inulin and B glucan 100 mg to 2 grams.

The Vitamins and Minerals that may be used to practise the invention are as per acceptable standards and comprise Vitamin A no more than 5,000 IU , Thiamine (Vitamin B1) 0.7 mg to 1.5 mg , Riboflavin (Vitamin B2) 1mg to 2.0 mg , Niacin (Vitamin B3) 14mg to 35mg , Vitamin B6 2 to 100mg , Vitamin B12 6mcg to 250 mcg Vitamin C 60 to 1000mg , Vitamin D 400IU to 60,000 , Vitamin E 20 to 100 IU, Vitamin K 10mcg to 600 mcg , Folic Acid not more than 400mcg , Calcium 100 mg to 600 mg , Iron 10mg to 18 mg , Magnesium 50mg to 350mg , Zinc not more than 30 mg , Copper 0.5 mg to 10 mg , Selenium 20 to 110mcg , Chromium 35mcg to 80 mcg and Potassium 10 to 100 mg .

Potential advantages of such colon targeted Nutraceutical composition include efficacious delivery of the Prebiotic, Probiotic and optionally Vitamins and Minerals into the large intestine without any significant degradation or deterioration of the Probiotic, Probiotic and the Vitamins and Minerals. Further the Prebiotic and Probiotic act in compliance to each other where the Prebiotics serve as a food source of the living Probiotic.

According to an embodiment the composition of the present invention comprises Inulin, Beta Glucan, Lactic acid bacillus, Bifidobacterium BB12, Saccharomyces Boulardii, water soluble vitamins and Minerals along with nutraceutical acceptable excipients.

According to another embodiment the composition of the present invention comprises Inulin, Lactic acid bacillus, Bifidobacterium BB12, Saccharomyces Boulardii along with bacillus spores as nutraceutical expectable excipients.

The Nutraceutical composition according to the present invention may be administered orally through unit dosage forms including tablets, capsules flavoured or plain (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, multiple unit pellet systems (MUPS), microspheres, multiarticulates), sachets (filled with powders, pellets, beads, mini- tablets, pills, micro-pellets, small tablet units, MUPS, microspheres, multiarticulates. Sprinkles), dry syrups / dry powders for reconstitution, however, other dosage forms such as controlled release formulations, enteric coated formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended-release formulations, osmotic drug delivery formulations, pulsatile release formulations, dual release formulations are also included in the prime scope of the invention.

Such solid dosage form protects the Prebiotic, Probiotic and the Vitamins as they travel through the digestive tract into the large intestine.

Technology and methods which resists the release of the drug in the stomach and targets the release in the large intestine or colon may be utilised to achieve the colon targeted drug delivery composition of the present invention.

The well-known and commonly known technologies in art include the enteric coating of microspheres or tablets, Osmotic tablet technology which involves the osmotic/hydrostatic pressure-driven dosage form and comprise of bi- and tri-layered matrix tablets and capsule-in-capsule approaches for combination products utilised to achieve dual or multiple active release profiles, Pulsincap system comprises of a water-insoluble capsule enclosing the drug reservoir. The active content is sealed into the capsule body, a swellable hydrogel plug swells, when the capsule comes in contact with the intestinal fluid and after a lag time, the plug pushes itself outside the capsule and rapidly releases the active.

Suitable excipients such as fillers, binders, polymers, enteric coating polymers, diluents, disintegrants, lubricants, and wetting agents, Flavouring agents may be

used to form the core. Suitable polymers which form hydrogels such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, polyvinylpyrrolidone, polyethylene oxide, and mixtures thereof may be used which would form the gel plugs. Further Hydrophilic polymers, Osmotic agents, swellable polymers and other excipients known in the art may be substituted for the preferred formulations to achieve the desired targeted delivery through the desired technology which has been discussed hereinbefore and includes enteric coating, OROS technology, targeted release achieved by Pulsincap mechanism and the like. Capsule shells utilised for the capsule formulation may be flavoured or plain to enhance the acceptability of the final formulation.

The invention will now be exemplified by below non-limiting examples. It may, however, be noted that the below examples in no way limit the scope of the invention. Further, a person of ordinary skill in this art would recognize that certain modifications would come within the scope of this invention. For that reason, the appended claims should be studied to determine the true scope and content of this invention.

Examples:

Example 1:

Ingredients	**Quantity**
Inulin from Chicory	250 mg per pill
Beta glucan from baker's yeast `	200 mg per pill
Cellulose powder	100mg per pill
Lactic acid bacillus	120 million CFU
Bifidobacterium BB12	1 Billion colony forming unit
Saccharomyces Boulardii	30 million CFU
Lactic Acid Bacillus	100 million CFU
Water soluble Vitamins:	

Vitamin A, Thiamine (Vitamin B1) , Riboflavin (Vitamin B2), Niacin (Vitamin B3), Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Folic Acid

Minerals:

Calcium, Iron, Magnesium, Zinc, Copper, Selenium, Chromium, Potassium

Example 2:

Ingredients	**Quantity**
Inulin	1000mg
Lactic acid bacillus	120 million spores
Bifidobacterium BB12	1 Billion colony forming unit
Saccharomyces Boulardii	30 million spores
Lactic Acid Bacillus	100 million spores

The above formulations of the composition of the present invention can be formulated using excipients known in art and by technologies as discussed here in before. The Figures 1, 2 and 3 well illustrate the schematic representation of these technologies. This invention is more easily comprehended by reference to the specific embodiments recited hereinabove which are representative of the invention. It must be understood, however, that the specific embodiments are provided only for the purpose of illustration, and that the invention may be practiced otherwise than as specifically illustrated without departing from its spirit and scope. The compositions, processes and technologies of the appended claims are not limited in scope by the specific compositions and technologies described herein, which are intended as illustrations of a few aspects of the claims and any compositions and methods that are functionally equivalent are intended to fall within the scope of the claims. Various modifications of the compositions and methods in addition to those shown and described herein are intended to fall within the scope of the appended claims. Other combinations of the compositions and method steps also are intended to fall within the scope of the appended claims, even if not specifically recited. Thus, a combination of steps, elements, components, or

constituents may be explicitly mentioned herein or less, however, other combinations of steps, elements, components, and constituents are included, even though not explicitly stated. The term "comprising" and variations thereof as used herein is used synonymously with the term "including" and variations thereof and are open, non-limiting terms. Although the terms "comprising" and "including" have been used herein to describe various embodiments, the terms "consisting essentially of" and "consisting of" can be used in place of "comprising" and "including" to provide for more specific embodiments of the invention and are also disclosed.

We Claim,

1. A colon targeted nutraceutical composition comprising
   a) one or more Prebiotics in the concentration range of 15%to 35% wherein one of the Prebiotic is Inulin in the concentration range of 17%to 20%
   b) one or more Probiotics in the concentration range of 25%to 35%
   c) optionally one or more Vitamins and Minerals
   d) acceptable excipients

2. The colon targeted nutraceutical composition as claimed in claim 1 comprising Inulin obtained from Chicory root.

3. The colon targeted nutraceutical composition as claimed in claim 1 wherein the other Prebiotic is selected from the group consisting of Inulin and combinations thereof.

4. The colon targeted nutraceutical composition as claimed in claim 1and 2 wherein the Probiotic is selected from the group consisting of Inulin from Chicory B glucans from bakers yeast and combinations thereof.

5. The colon targeted nutraceutical composition as claimed in claim 1 comprising Inulin from Chicory 250 mg per pill, Beta glucan from baker's yeast 200 mg per pill, Cellulose powder 100mg per pill, Lactic acid bacillus 120 million spores, Bifidobacterium BB12 1 Billion colony forming unit, Saccharomyces Boulardii 30 million spores, Lactic Acid Bacillus 100 million spores, Water soluble Vitamins and Minerals

6. The colon targeted nutraceutical composition as claimed in claim 1 comprising Inulin 1000mg, Lactic acid bacillus 120 million spores, Bifidobacterium BB12 1 Billion colony forming unit, Saccharomyces Boulardii 30 million spores, Lactic Acid Bacillus 100 million spores.

7. The colon targeted nutraceutical composition as claimed in claim 1 wherein the said composition is provided in the form of an enteric coated tablet.

8. The colon targeted nutraceutical composition as claimed in claim 1 wherein the said composition is provided in the form of a hard gelatin capsule comprising an enteric coated tablet.

9. The colon targeted nutraceutical composition as claimed in claim 1 wherein the said composition is formulated using OROS technology.

10. The colon targeted nutraceutical composition as claimed in claim 1 wherein the said composition is formulated using Pulsincap technology.

Dated this 13th day of May, 2021

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A COLON TARGETED PREBIOTIC PROBIOTIC NEUTRACEUTICAL COMPOSITION

ABSTRACT:

The invention provides a colon targeted composition comprising Prebiotics, Probiotics and optionally vitamins and minerals along with nutraceutically acceptable excipients. More particularly the composition of the present invention essentially comprises of Inulin as Prebiotic which is obtained from Chicory root. The composition may be provided in the form of an enteric coated tablet, Hard gelatin capsule comprising the enteric coated tablet or may utilise the OROS or PULSINCAP technology. The said composition specifically refers to a Colon targeted composition essentially delivering the Prebiotic, Probiotic and optionally vitamins and minerals at the targeted site of action.

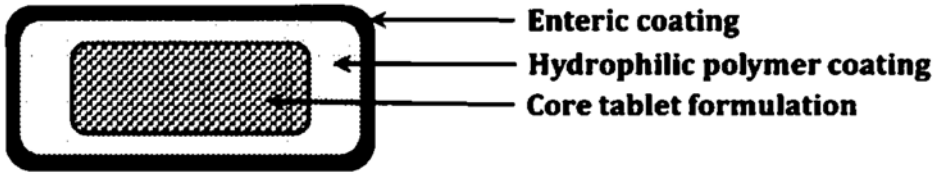

Fig. 1

Schematic representation of the cross-section of the enteric-coated colon-targeted drug delivery system

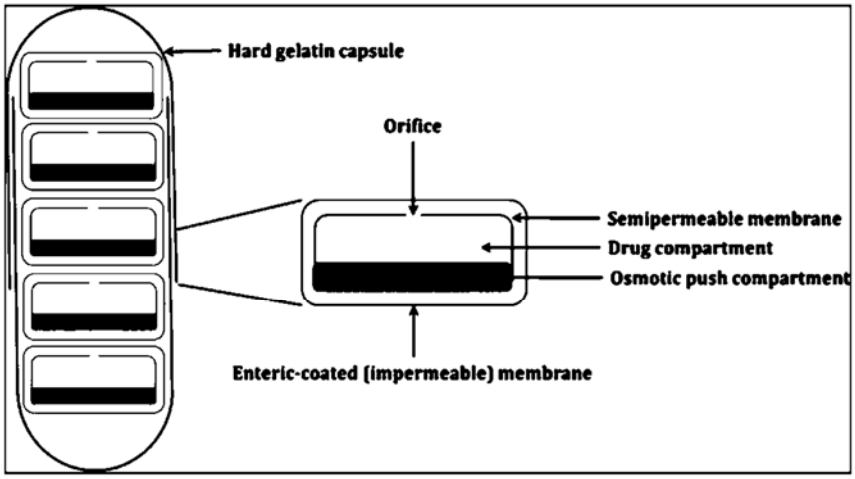

Fig. 2

Schematic representation of the cross-section of the OROS-CT colon-targeted drug delivery system

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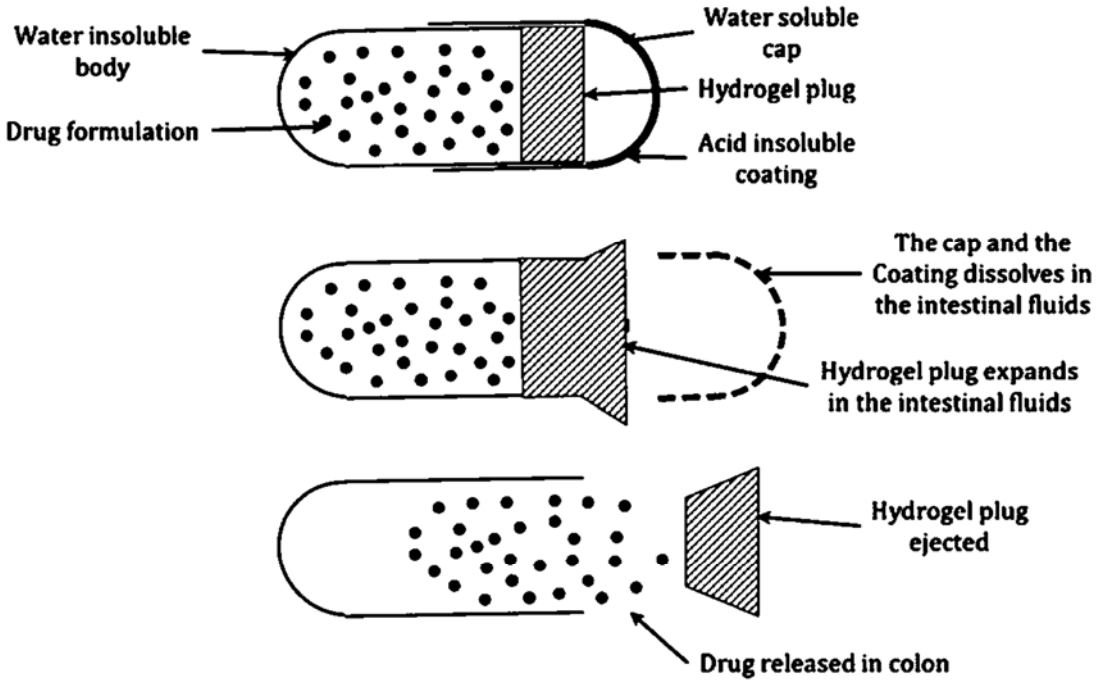

Fig. 3

Schematic representation of the mechanism of the *pulsincap* colon-targeted drug delivery system

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